FGF23: Fashion or Physiology?

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C hronic kidney disease (CKD) predisposes to cardiovascular disease (CVD), but the pathophysiologic mechanisms that drive this powerful association remain poorly defined despite intense investigation. The inability of randomized trials to demonstrate a benefit in patients with CKD of interventions that are known to reduce major cardiovascular events in the general population (1,2) has led experts to postulate the presence of CKD-specific mechanisms of CVD. Among numerous unproven, CKD-specific candidate risk factors for CVD that are currently most in vogue—anemia, inflammation, oxidative stress, uric acid, and uremic toxins—disordered mineral metabolism has garnered perhaps the most attention.

Guarded enthusiasm for disordered mineral metabolism as a novel CVD risk factor has a reasonable foundation. Many observational studies, far too numerous to cite here, reported that the alterations in mineral metabolism that are common in patients with CKD are associated with increased risk for CVD and mortality. In support of the human data, laboratory studies promoted plausible biological mechanisms, including accelerated atherosclerosis, uremic cardiomyopathy, and vascular calcification (3,4). In a bit of a reversal from the previous flow of research ideas, discovery in the area of CKD sparked ideas for cardiovascular research in the general population. Thus, whereas the roots of the disordered-mineral-metabolism-as-novel-cardiovascular-disease-mechanism fad can be traced to early studies of phosphorus, calcium, and calcium-phosphate product (incidentally, now out of vogue) in dialysis patients, this trend has spilled over into the general medical literature with numerous reports of CVD and death in association with increased phosphate and parathyroid hormone (PTH) levels and decreased vitamin D levels in non-CKD populations (5–7).

Fibroblast growth factor 23 (FGF23) is the latest mineral metabolite to be linked to CVD and death. Like phosphate, PTH, and vitamin D before it, altered FGF23 levels were first recognized as an independent risk factor for mortality in dialysis patients (8) but later were shown to be a risk factor for CVD and death in the general population (9). As a potential early biomarker of disordered mineral metabolism or as a directly toxic growth hormone, the trendy FGF23 now headlines numerous studies that aim to advance further the hypothesis that disordered mineral metabolism promotes CVD in CKD.

In this issue of CJASN, Kanbay et al. (10) provide the latest report on FGF23 and CVD. In a cross-sectional study, the authors analyzed coronary angiograms from 177 patients who had “mild CKD” and for whom standard mineral metabolites were measured along with FGF23 and fetuin A levels. Early CKD was defined as an estimated GFR (eGFR) of 30 to 90 ml/min per 1.73 m2, based on the Cockcroft-Gault formula. The patients were selected for coronary angiography because of symptoms of stable coronary artery disease (CAD) and an exercise tolerance test or stress echocardiogram that suggested a high probability of an occlusive lesion. Patients were excluded if they had severe congestive heart failure or had received medications that are known to influence FGF23 levels: Either vitamin D or phosphate binders. The main outcome variable was the Gensini score, which summarizes the total burden of coronary atherosclerosis by quantifying the severity of disease in each coronary artery and weighing the significance of individual lesions on the basis of the amount of distal myocardium at risk. The primary analysis used stepwise linear regression to examine predictors of more severe CAD, marked by a higher Gensini score.

A review of Table 1 reveals many expected findings for a population with CAD, including a high prevalence of smoking, diabetes, hypertension, and dyslipidemia. One third of the population was deficient of vitamin D, 12% had hyperphosphatemia, and 38% had abnormally high PTH levels; however, the median FGF23 level was only 21 RU/ml, and 75% of the patients had levels <39 RU/ml. These are low FGF23 levels in general and extremely low for a population with CKD, even one with early disease. For example, using the same FGF23 assay, previous investigators demonstrated a median FGF23 level of 43 RU/ml in a large study of patients without CKD (9).

Among the markers of mineral metabolism, only FGF23 and fetuin A were associated with the Gensini score in univariate analyses. Indeed, the strikingly strong correlation between FGF23 and the Gensini score (R = 0.87) was by far the tightest of any covariate, followed at a distant second by fetuin A. In the multivariable-adjusted analyses, increased

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FGF23 remained the strongest independent predictor of a higher Gensini score, whereas lower fetuin A levels were the borderline of statistical significance. In another striking finding, traditional CAD risk factors contributed virtually nothing to the regression models. Perhaps the effects of traditional risk factors were minimized because the study analyzed the severity of CAD in a population with established disease rather than studying its presence or absence in an unselected population of patients with and without CAD.

The focus of the authors’ interpretation of the results is the independent association between increased FGF23 and, to a lesser extent, decreased fetuin A and higher Gensini scores in patients with “mild CKD”; however, it is not clear how the presence of CKD was ascertained in patients with eGFR between 60 and 90 ml/min per 1.73 m$^2$ because the authors do not mention how many patients carried a diagnosis of CKD. They also did not assess proteinuria. This is an especially important point because 2 SD above and below the mean of a normally distributed variable, such as the eGFR of 74.0 ± 9.5 ml/min per 1.73 m$^2$ in this case, encompasses 95% of the population; therefore, 97.5% of participants had an eGFR of ≥54 ml/min per 1.73 m$^2$. In other words, the majority of participants had eGFR of >60 ml/min per 1.73 m$^2$, yet they were nevertheless considered to have early CKD. This issue is compounded further after closer scrutiny of Table 1. Although the mean serum creatinine was listed as 1.1 mg/dl in the overall study population, the mean in each Gensini score tertile was ≤1.0 mg/dl. Recalculating the overall eGFR using a mean creatinine that was more likely 0.8 mg/dl yields a significantly higher value with even fewer participants at <60 ml/min per 1.73 m$^2$. The likelihood that few patients had significant reductions in eGFR probably explains the extremely low FGF23 levels that were observed.

The dearth of patients with CKD in the study may belie its title but may also represent its most significant finding. Could FGF23 be a novel risk factor for CAD in the general population? Could FGF23-associated CAD explain the increased risk for cardiovascular events and mortality in the general population with similarly subtle increases in FGF23 levels? It is interesting to note that when the authors repeated the main analyses after restricting the population to those with an eGFR of <60 ml/min per 1.73 m$^2$, the association between FGF23 and the Gensini score weakened relative to the findings in the overall population. This indicates that FGF23 was even more strongly associated with the severity of CAD in patients with the most preserved eGFR. Likewise, fetuin A fell out of the model as insignificant in the low eGFR subgroup.

Although important as the first report of an association between increased FGF23 and CAD, we must be extremely cautious in interpreting the results without additional validation. Like any cross-sectional study, reverse causality is an important limitation to consider. For example, could the presence of CAD lead to physiologic changes in bone that increases FGF23 secretion rather than FGF23 inducing coronary disease? Could the inflammatory state that characterizes CAD lower fetuin A levels rather than vice versa? Next, a plausible mechanism to link FGF23 to CAD must be established. The authors emphasize vascular calcification as a potential link, yet they studied luminal occlusive disease of the coronaries, not calcification. Animal models could be useful in determining whether any true causal relationship exists between FGF23 and atherosclerosis. If those hurdles can be surmounted, then the final, most challenging and costly test will lie in whether interventions that change FGF23 can change CAD severity or its outcomes. Until then, we are left to wonder whether the current intense focus on FGF23 represents an ephemeral fashion or the first scientific baby steps toward establishing novel paradigms for health and disease.

Disclosures

M.W. has served as a consultant or received honoraria from Abbott Laboratories, Amgen, Cytochroma, Davita, Genzyme, Shire, and Mitsubishi.

References


See related article, “Fibroblast Growth Factor 23 and Fetuin A are Independent Predictors for the Coronary Artery Disease Extent in Mild Chronic Kidney Disease,” on pages 1780–1786.