Fibroblast growth factor 23 and heart failure: the plot thickens

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From its humble beginnings as a hormone regulating phosphorus and vitamin D metabolism, fibroblast growth factor 23 (FGF23) has evolved into one of the most intensively studied proteins, implicated in the nexus between cardiovascular disease (CVD) and chronic kidney disease (CKD). Prospective studies have shown that higher FGF23 concentrations are associated with higher risk of incident CVD events independently of established risk factors, particularly in CKD [1–4]. Moreover, this association has been most consistently observed for CVD events linked to heart failure, one of the most common presentations of heart disease in individuals with CKD [2, 4–7].

The reason why elevated FGF23 appears to demonstrate greater specificity for heart failure-related CVD phenotypes is unclear. However, one possibility may be that FGF23 either directly or indirectly promotes adverse left ventricular remodeling. Observational studies have shown that higher FGF23 concentrations were independently associated with greater left ventricular mass and higher prevalence of left ventricular hypertrophy (LVH) [8–10]. Animal studies have shown that FGF23 can activate FGF receptor 4 (FGFR4)-dependent, Klotho-independent signaling via the phospholipase C (PLC) γ/calcineurin/NFAT pathway, leading to pathological LVH [8, 11]. Further, the development of LVH was abrogated by blocking FGF23 binding to FGFR4 in rat models of CKD despite the development of severe hypertension [8, 11, 12]. Other studies have suggested that FGF23 can promote LVH by altering calcium trafficking in cardiomyocytes and atrial myocytes, resulting in increased contractility, hypertrophy and arrhythmogenesis [13, 14]. Further, FGF23 may contribute to cardiac disease via activation of the renin–angiotensin–aldosterone system [15]. In the aggregate, these data support excess FGF23 as a causal mechanism for adverse cardiac remodeling and heart failure. To date, however, no studies have shown that lowering FGF23 improves CVD outcomes in individuals with or without CKD. Thus, while early returns are promising, the clinical potential of these findings remains hypothetical and requires further investigation.

One area that deserves particular attention is the prognostic role of FGF23 in individuals with heart failure. Studies have shown that circulating FGF23 concentrations are elevated in heart failure patients, correlate with heart failure severity and independently predict poor outcomes, even among individuals with preserved kidney function [defined as an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m2] [16–22]. Recognizing that FGF23 is expressed in heart tissue [23], these findings have prompted investigators to examine whether high FGF23 concentrations in the setting of heart failure are solely a product of increased bone synthesis or perhaps direct release of FGF23 from diseased cardiac tissue. Andrukhova et al. examined FGF23 expression and tissue distribution in myocardial tissue after induction of experimental myocardial infarction in rats [24]. They found that secretion of FGF23 markedly increased after induction of myocardial infarction. Further, they showed strong up-regulation of FGF23 in bone cells and to a lesser extent, in ventricular cardiomyocytes following infarction. Richter et al. compared the quantity and distribution of FGF23 in heart tissue samples obtained from individuals with end-stage heart disease undergoing heart transplantation to tissue from healthy controls [25]. They showed that FGF23 was detectable in cardiomyocytes of individuals with heart failure but not in healthy control samples. In addition, FGF23 has been detected in coronary arteries from human hearts [26]. To date, no other studies have examined myocardial production of FGF23 in humans with heart disease. For this reason, the study by Andersen et al. [27] in this issue of Nephrology Dialysis Transplantation provides important new insights into this story.

These investigators compared circulating intact FGF23 in 21 patients hospitalized with acute decompensated heart failure (ADHF) with 19 healthy controls. In addition, they assessed FGF23 mRNA expression in heart tissue obtained from 17 separate individuals with end-stage heart disease undergoing implantation of left ventricular assist device or transplant surgery and six normal control samples obtained from commercial sources. Frozen left ventricular tissue from a subset of this latter group was used to examine the cardiac tissue distribution of FGF23 via immunohistochemistry. The main finding of this study was that FGF23 concentrations were higher in ADHF patients than the healthy controls, even when restricting
the analysis to individuals with an eGFR of >60 mL/min/1.73 m². In addition, FGF23 was shown to be expressed in tissue from individuals with end-stage heart failure and healthy controls, with no differences in quantification between the groups. Similarly, immunohistochemical analysis showed that FGF23 protein was present in left ventricular tissue of heart failure patients and controls with no obvious difference in the distribution of FGF23 between the groups.

The findings of Andersen et al. confirm the findings of prior studies showing that FGF23 concentrations are elevated in individuals with heart failure [18, 22, 27, 28] and that FGF23 is expressed in human myocardial tissue [25]. Importantly, however, their results suggest that the quantitative expression of FGF23 in heart tissue of individuals with severe heart failure does not differ from normal controls, in contrast to other studies suggesting up-regulation of FGF23 transcription in diseased tissue [24, 25]. Together, Andersen’s data suggest that while cardiomyocytes have the capability to synthesize and secrete FGF23, heart failure per se does not up-regulate this process. For all these reasons, the findings of this study are a welcome contribution to understanding what role cardiac FGF23 expression may have in increasing circulating FGF23 concentrations in individuals with heart failure.

That being said, several results of this study deserve cautious interpretation. First, even though eGFR was lower in ADHF patients than controls, the authors argue that higher FGF23 concentrations in patients versus controls were at least in part independent of kidney function. They base this on a secondary analysis which showed that FGF23 concentrations were higher in ADHF patients than in controls even when restricting the analysis to individuals with an eGFR of >60 mL/min/1.73 m². However, creatinine is such an insensitive marker of early kidney injury, it is very difficult to tell whether individuals with ADHF had subtle declines in kidney function not evident using a single estimate of GFR. Indeed, elevated FGF23 appears to be a more sensitive biomarker of early kidney disease than creatinine [29]. In reality, the most likely reason for the higher FGF23 in individuals with ADHF versus controls was worsened renal hemodynamic parameters due to acute heart failure in the former when compared with the latter group. Another important limitation of this study is that the authors compare gene expression and immunohistochemical staining from one sample of human tissue with circulating parameters in a completely different sample of patients. These samples are sufficiently different that it is difficult to extrapolate expression differences in the heart tissue from one set of patients to explain differences in circulating FGF23 concentrations between ADHF and control patients from another set of individuals. To really draw any reasonable conclusions, it would have been ideal to use the same set of patients in both experiments.

At the end of the day, what can we take away from the work by Andersen et al.? First, as has been reported by others, circulating FGF23 concentrations are much higher in individuals with heart failure than in healthy controls. What still needs to be clarified is whether this is a simply a byproduct of kidney injury related to heart failure or perhaps a direct response of bone or myocardial cells to the failing heart. Second, cardiomyocytes seem fully capable of secreting FGF23. This begs the question of why? Determining the answer to this question may provide key insights into what role FGF23 may have in the development of LVH in CKD. There is increasing evidence that non-specific binding of FGF23 to FGFRs in myocardial cells has a bevy of adverse effects, not the least of which is the promotion of cardiomyocyte hypertrophy. While the physiological implications of these findings have mostly focused on excess circulating FGF23 due to either kidney disease or other states of phosphorus excess, it is intriguing to speculate whether FGF23 produced by cardiomyocytes may have adverse paracrine/autocrine effects that help to accelerate the development of adverse cardiac remodeling in the setting of heart disease. If so, this may impact the development of therapies directed at abrogating the adverse effects of FGF23 since it would suggest that lowering systemic FGF23 concentrations may be insufficient to protect against locally derived FGF23 production in myocardial tissue. To this end, the findings of Andersen et al. provide new incentive to further elucidate the full spectrum of ways that excess FGF23 impacts cardiac function and how this may ultimately contribute to the pathophysiology of heart failure in CKD.

CONFLICT OF INTEREST STATEMENT

None declared. The results of this paper have not been published previously in whole or part.


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