


## Fibroblast Growth Factor 23 and the Last Mile

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### Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphorus balance by enhancing urinary phosphorus excretion and inhibiting the synthesis of 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ] (1). Its discovery and characterization could be considered a triumph for precision medicine in that it revolutionized our understanding of phosphorus and vitamin D metabolism and led to the development of a targeted treatment (burosumab) to relieve debilitating hypophosphatemia and associated bone and muscle disease from rare disorders of phosphorus wasting. Beyond these rare diseases, FGF23 plays a broader role in maintaining phosphorus balance in states of phosphorus excess, such as CKD. FGF23 concentrations increase early in kidney failure and steadily rise with kidney function decline. Although this represents an appropriate physiologic response to maintain normal phosphorus balance, an important consequence is progressive  $1,25(\text{OH})_2\text{D}$  decline. Thus, increased FGF23 secretion seems to be critical for avoiding phosphorus overload in early CKD but with the tradeoff of lower  $1,25(\text{OH})_2\text{D}$ , supporting the notion that increased FGF23 may be the key factor underlying the genesis of secondary hyperparathyroidism in CKD.

If the story had ended there, the discovery of FGF23 would have made an immeasurable contribution to our understanding of the pathophysiology of mineral bone disease in CKD. However, epidemiologic data have established that higher FGF23 concentrations are independently associated with higher risk of cardiovascular disease events and death in individuals across the spectrum of kidney function (2). Although the mechanisms for these associations remain under investigation, higher FGF23 concentrations are strongly associated with higher left ventricular mass independently of BP and kidney function (3). In addition, FGF23 induces hypertrophy of cardiomyocytes *in vitro* and *in vivo* (3), both through fibroblast growth factor receptor (FGFR)-mediated stimulation of hypertrophy (3) and through disturbances in calcium handling in cardiac cells (4). More recent data show that FGF23 can adversely affect cardiovascular health by stimulating sodium retention, upregulating the renin-angiotensin-aldosterone system, and enhancing the arrhythmogenic potential of heart cells *via* disruption of calcium trafficking (4). Although phosphorus excess and Klotho deficiency may play some role in explaining these findings, in

the aggregate, these data provide both clinical evidence and mechanistic evidence for a direct link between higher FGF23 and cardiovascular disease and a roadmap for blocking the prohypertrophic effects of FGF23 in patients with CKD.

### FGF23 and Cardiovascular Disease: More Questions Than Answers

However, this is all a familiar story. For example, parathyroid hormone (PTH) originally rose as a key player in disordered bone and mineral metabolism, with subsequent data showing a potential role in cardiovascular risk factors (anemia, hypertension, and endothelial function) and left ventricular hypertrophy. Yet, randomized trials have shown little, if any, efficacy for reducing cardiovascular disease *via* lowering PTH concentrations. FGF23 is at a similar crossroad. Although FGF23 seems to be a robust biomarker of cardiovascular disease risk, it is not clear that it represents a major advance from other available biomarkers or that it has panned out as a useful marker for other outcomes, such as bone disease or CKD progression. Furthermore, some data do not support a role of FGF23 in the development of cardiovascular disease, indicating genuine uncertainty about this issue that will not be resolved by conducting more observational or experimental studies, no matter how well designed. For FGF23 to claim a durable role in clinical practice, clinical trials are needed to demonstrate that disrupting adverse effects of FGF23 improves cardiovascular health. To this end, there are a number of potential approaches:

### Reduction in FGF23 Concentrations

Given that dietary phosphorus intake stimulates FGF23, the most common approach to reducing FGF23 has centered on using drugs to diminish gastrointestinal phosphorus absorption—*via* dietary phosphorus restriction, oral phosphorus binders, or inhibitors of sodium-proton exchange transporters or sodium-phosphorus cotransporter 2b in gut epithelial cells (5). In general, these approaches have had modest effects on reducing FGF23 concentrations in patients with CKD, with long-term concerns about adherence. Furthermore, no randomized, controlled trials have shown that reducing FGF23 through restriction of gastrointestinal phosphorus absorption improves meaningful clinical outcomes in CKD.

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Calcimimetics are more effective in lowering FGF23, reducing FGF23 concentrations by approximately 30%–50% in patients with ESKD (6). Furthermore, in a *post hoc* analysis, a greater reduction in FGF23 concentrations in response to cinacalcet was strongly associated with lower mortality and cardiovascular disease events (particularly heart failure) in patients on hemodialysis (6). These data provide some evidence that a strategy of lowering FGF23 using calcimimetics may improve outcomes in patients with ESKD.

Given the efficacy of anti-FGF23 antibodies in reducing FGF23 concentrations and improving symptoms in individuals with phosphorus wasting disorders, a similar approach may be feasible in CKD. Enthusiasm for this needs to be counterbalanced by experimental data showing poor outcomes in animals with CKD exposed to anti-FGF23 antibodies due to the development of hyperphosphatemia and accelerated mortality when FGF23 concentrations were drastically reduced (7). In light of these data, it is likely that the use of anti-FGF23 antibodies may be most relevant for those with ESKD, and even then, those with little to no residual kidney function.

#### Inhibition of FGFR4

It is important to note that the classic effects of FGF23 in the kidney are mediated by binding to complexes of FGFR1 and Klotho, leading to activation of Ras/mitogen-activated protein kinase signaling (4). In contrast, the prohypertrophic effects of FGF23 on cardiomyocytes are mediated by binding of FGF23 to FGFR4, even in the absence of Klotho, which activates phospholipase C $\gamma$ /calcineurin/NF of activated T cells signaling. This is serendipitous in that it allows for a more targeted approach to inhibiting adverse effects of FGFR4 binding in the heart without at the same time blocking the FGFR1-specific effects of FGF23 in enhancing phosphaturia. The potential importance of this was demonstrated by studies showing that the adverse effects of elevated FGF23 on cardiac hypertrophy in animals with experimentally induced CKD were partially reversible through targeted blockade of FGF23 binding to FGFR4 without precipitating hyperphosphatemia (4).

In addition to cardiac hypertrophy, FGF23 binding to FGFR4 may promote cardiovascular disease by stimulating inflammation. In cultured hepatocytes, FGF23 induces secretion of inflammatory cytokines through binding to FGFR4. Additionally, injection of FGF23 in mice increased hepatic C-reactive protein (CRP) and IL-6 expression and raised serum CRP concentrations compared with mice injected with vehicle (8). Importantly, injection of anti-FGFR4 antibodies or cyclosporin A in 5/6-nephrectomized rats prevented the elevation of serum CRP compared with nephrectomized rats treated with vehicle, despite no differences in the degree of kidney function decline (8). These intriguing data suggest that blockade of FGFR4 or the calcineurin-dependent signaling pathway by which FGFR4 activation upregulates inflammatory cytokine secretion may be a novel therapy for reducing systemic inflammation in patients with CKD.

#### Treatment of Iron Deficiency

Iron plays a key role in regulating phosphorus metabolism (9). Experimental data have shown that iron

deficiency increases FGF23 expression by stabilizing hypoxia-inducible factor 1 $\alpha$ , which in turn, binds to a site in the *Fgf23* promoter to induce transcription. The hypoxia-inducible factor 1 $\alpha$ -induced increase in FGF23 expression is normally accompanied by increased cleavage of the intact FGF23 peptide into N- and C-terminal fragments of unclear physiologic significance, presumably to protect from developing systemic signs of excess FGF23. Thus, iron deficiency is typically characterized by high concentrations of C-terminal FGF23 (consisting of both C-terminal FGF23 fragments as well as the intact peptide) but normal or only slightly high intact FGF23. However, individuals with CKD have an impaired ability to cleave the intact FGF23 peptide, especially in ESKD, in which virtually all circulating FGF23 is the full-length peptide. Accordingly, iron deficiency may be a novel factor underlying excess intact FGF23 in patients with CKD, with attendant consequences such as cardiac hypertrophy and inflammation. Whether iron supplementation similarly lowers FGF23 in patients with CKD is an active area of investigation. Importantly, because the C-terminal FGF23 assay detects the intact peptide as well as circulating fragments, identifying individuals who might benefit from treatment of iron deficiency would require using FGF23 assays that detect the intact peptide exclusively.

#### Inhibition of the Renin-Angiotensin-Aldosterone System

FGF23 may also affect cardiovascular health *via* effects on the renin-angiotensin-aldosterone system. Elevated FGF23 was shown to increase the expression of renin-angiotensin-aldosterone system genes in cardiomyocytes (4). Furthermore, treatment with renin-angiotensin-aldosterone system inhibitors attenuated the effects of FGF23 on cardiomyocyte hypertrophy and fibrosis in *in vitro* models. This is important in that *post hoc* analyses of randomized controlled trials of angiotensin-converting enzyme inhibitors in the treatment of ischemic heart disease and heart failure showed that the benefit from treatment with an angiotensin-converting enzyme inhibitor was only observed in individuals with an elevated baseline FGF23 (10). Together, these data suggest that treatment with renin-angiotensin-aldosterone system inhibitors may attenuate the adverse effects of FGF23 on cardiac function.

#### FGF23 and Moving beyond the Hype

The discovery and characterization of FGF23 to this point have been a captivating tale of the power of science to address the unmet need of patients afflicted with rare conditions while unveiling basic pathophysiologic principles underlying more common diseases. However, where the story goes from here is very much up in the air. To complete the last mile needed to establish FGF23 as a viable target for improving cardiovascular outcomes, randomized trials that target pathways shown to be involved in the pathophysiology of FGF23-induced cardiovascular disease are necessary. The roadmap is there, and potential therapeutic targets are already identified. However, the scientific and clinical community must be willing to finish the task and conduct these trials. Otherwise, FGF23 will be relegated to a long list of clinical biomarkers of unclear utility or, even worse, fall into the trap of phosphorus and PTH—biomarkers that

we treat because that is what we have always done and not because we have empirical evidence to demonstrate efficacy.

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