

Fibroblast Growth Factor 23 and Disordered Vitamin D Metabolism in Chronic Kidney Disease: Updating the “Trade-off” Hypothesis

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The discovery of fibroblast growth factor 23 (FGF23) has clarified much of our understanding of abnormalities in phosphorus and vitamin D metabolism in chronic kidney disease (CKD). FGF23 is a bone-derived hormone that promotes phosphaturia and decreases the synthesis of 1,25-dihydroxyvitamin D (1,25(OH)₂D). The primary systemic stimuli of FGF23 secretion are increased 1,25(OH)₂D levels and increased dietary phosphorus intake. In kidney failure, FGF23 levels increase early and steadily rise with progression of kidney disease, likely as an appropriate physiologic adaptation to maintain normal phosphorus balance by helping to augment urinary phosphate excretion in conjunction with increased parathyroid hormone levels and by decreasing gut phosphorus absorption through decreased 1,25(OH)₂D. In the long term, this compensation may become maladaptive by causing a progressive decline in 1,25(OH)₂D levels with attendant consequences such as secondary hyperparathyroidism. Moreover, excess FGF23 levels have been independently linked with cardiovascular disease and mortality, suggesting that chronically elevated FGF23 levels may directly contribute to adverse CKD outcomes. Together, these findings have sparked increased interest in elucidating the potential interconnections between dietary phosphorus intake, FGF23, and clinical outcomes in patients with CKD. In addition, given that treatment with activated vitamin D compounds stimulates FGF23, these data have raised important new questions about the optimal use of activated vitamin D compounds in the management of bone and mineral disorders in CKD.

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The discovery of fibroblast growth factor 23 (FGF23) was a seminal moment in our understanding of altered phosphorus and vitamin D metabolism in chronic kidney disease (CKD). Studies have shown that increased FGF23 plays a central role in the pathogenesis of 1,25-dihydroxyvitamin D (1,25(OH)₂D) deficiency in kidney failure (1,2). Furthermore, excess FGF23 has emerged as an independent risk factor for cardiovascular disease and mortality in CKD (3–7). These findings have not only clarified much of our current understanding of disordered vitamin D metabolism in kidney failure but also unveiled critical new insights into the role of abnormalities of phosphorus metabolism in adverse CKD outcomes, which together may force fundamental re-alignments in our current approach to the treatment of bone and mineral disorders in patients with CKD.

Historical Perspectives of Disordered Vitamin D Metabolism in CKD

Decreased levels of 25-hydroxyvitamin D (25(OH)D) and 1,25(OH)₂D are exceedingly common in CKD (8) and are associated with cardiovascular disease and mortality (9–13). The clinical relevance of these associations has been underscored by observational data showing a robust association between treatment with activated vitamin D compounds and improved survival in both end-stage and predialysis CKD populations (14–17). Collectively, these findings have led to increased recognition of the role of vitamin D deficiency in adverse kidney disease outcomes (18).

Because the kidney is the primary source of 25(OH)D-1 α -hydroxylase—the enzyme needed to convert 25(OH)D to its more active metabolite (19,20)—the pathophysiology of vitamin D deficiency in kidney failure has primarily focused on impaired 1,25(OH)₂D synthesis and its link to bone and mineral disorders. Decreased 25(OH)D-1 α -hydroxylase activity in kidney failure has traditionally been attributed to two main factors: diminished renal mass, leading to progressive loss of the enzyme in proximal tubule cells, and subsequent phosphate “retention,” which is thought to directly inhibit the enzyme via

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increasing intracellular phosphate (21–23). However, although these factors likely play an important role in contributing to decreased $1,25(\text{OH})_2\text{D}$ synthesis in moderate-to-severe kidney disease, on their own, they have proved inadequate to explain the initial decline in $1,25(\text{OH})_2\text{D}$ synthesis in early kidney disease for several reasons.

First, $1,25(\text{OH})_2\text{D}$ levels begin to decline very early in the course of kidney failure (ranging from a creatinine clearance of 60 to 80 ml/min) (24–28) when there is unlikely to be sufficient loss of renal mass (and thus, renal $25(\text{OH})\text{D}$ - 1α -hydroxylase activity) to substantially impair $1,25(\text{OH})_2\text{D}$ synthesis. Indeed, studies have shown that dietary phosphorus restriction can significantly increase and, in some cases, normalize $1,25(\text{OH})_2\text{D}$ concentrations in both children and adults with mild-to-moderate CKD (22,29), suggesting that there remains sufficient nephron mass to sustain $1,25(\text{OH})_2\text{D}$ production in early CKD, but only under the appropriate physiologic conditions. In addition, although functional $25(\text{OH})\text{D}$ - 1α -hydroxylase inhibition due to increasing serum phosphate and/or intracellular phosphate is possible, overt hyperphosphatemia is a very late phenomenon in kidney failure (8). In fact, serum phosphate concentrations appear to decrease slightly in the earliest stages of CKD (22,30,31). Moreover, few studies have convincingly demonstrated that increased intracellular phosphate levels in renal proximal tubule cells inhibit $25(\text{OH})\text{D}$ - 1α -hydroxylase in early kidney failure (23). Thus, although decreased renal mass and phosphate retention likely contribute to decreased $1,25(\text{OH})_2\text{D}$ synthesis in late stages of kidney failure, additional pathophysiological mechanisms have been sought to explain the initial decline of $1,25(\text{OH})_2\text{D}$ in early CKD.

FGF23 and $1,25(\text{OH})_2\text{D}$ Deficiency in Early CKD: The Emerging Paradigm

With the discovery and subsequent characterization of FGF23, a novel mechanism for the early decline in $1,25(\text{OH})_2\text{D}$ synthesis emerged. FGF23 is secreted by osteoblasts and osteocytes and acts primarily in renal proximal tubules to increase urinary phosphorus excretion through downregulation of sodium-phosphate co-transporters and decrease $1,25(\text{OH})_2\text{D}$ levels through the inhibition of $25(\text{OH})\text{D}$ - 1α -hydroxylase and the upregulation of the catabolic $25(\text{OH})\text{D}$ - 24 -hydroxylase pathway (32). The primary systemic factors that stimulate FGF23 secretion appear to be increased serum $1,25(\text{OH})_2\text{D}$ levels and increased dietary phosphorus intake (32). $1,25(\text{OH})_2\text{D}$ directly stimulates FGF23 expression in osteocytes by binding to a vitamin D response element in the promoter region of the *Fgf23* gene (33). The mechanisms involved in the regulation of FGF23 secretion by dietary phosphorus are less clear (34,35). Interestingly, *in vitro* and *in vivo* studies have failed to show a consistent association between increased phosphate and increased FGF23 secretion (33,36,37), suggesting that phosphate itself may not directly regulate FGF23. Whether phosphate regulates FGF23 synthesis via indirect mechanisms remains to be determined.

FGF-23 concentrations increase early in kidney failure—perhaps as early as estimated glomerular filtration rates (eGFR) <90 ml/min per 1.73 m^2 (38)—and steadily rise with

progression of kidney disease, such that by the time patients reach end-stage renal disease, FGF23 levels can be up to 1000-fold above the normal range (4,5,39). Although this likely represents an appropriate physiologic response to maintain normal phosphorus balance by increasing urinary phosphate excretion and decreasing gut phosphorus absorption via decreased $1,25(\text{OH})_2\text{D}$ synthesis, an important consequence is progressive $1,25(\text{OH})_2\text{D}$ decline. Indeed, we and others showed that FGF23 was inversely associated with $1,25(\text{OH})_2\text{D}$ levels in patients with mild-to-moderate CKD (1,2), independently of key factors known to influence $1,25(\text{OH})_2\text{D}$, including serum phosphate, parathyroid hormone (PTH), $25(\text{OH})\text{D}$, and eGFR. Furthermore, in multivariable models simultaneously adjusted for these key variables, higher FGF23 was the strongest independent predictor of lower $1,25(\text{OH})_2\text{D}$ in these patients (1).

When taken together, these results suggest that increased FGF23 is among the earliest pathogenic factors associated with decreased $1,25(\text{OH})_2\text{D}$ synthesis in CKD. Moreover, these findings have provided crucial new insights into the classic “trade-off” hypothesis, which remains a valuable framework for understanding the pathogenesis of disordered mineral metabolism in CKD (Figure 1) (40–42). In general terms, this hypothesis postulates that the maintenance of phosphorus balance in the face of decreased

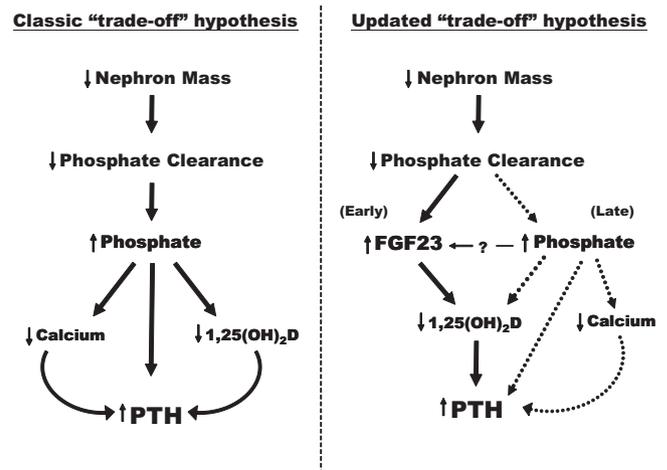


Figure 1. Classic versus more contemporary renditions of the “trade-off” hypothesis. In the original exposition (left side of figure), decreased nephron mass leads to decreased phosphorus clearance, resulting in phosphate retention, hypocalcemia, and decreased $1,25(\text{OH})_2\text{D}$ levels. These metabolic disturbances in turn stimulate increased PTH secretion to maintain normal mineral ion homeostasis, but with the trade-off of higher circulating PTH levels. In the updated rendition of the hypothesis (right side of figure), decreased phosphate clearance stimulates increased FGF23 secretion in early kidney failure to maintain normal phosphorus balance by increasing urinary phosphate excretion and inhibiting $1,25(\text{OH})_2\text{D}$ synthesis. Decreased $1,25(\text{OH})_2\text{D}$ levels in turn stimulate increased PTH levels in early kidney failure, with the effects of phosphate retention on increased PTH secretion being more prominent in later stages of kidney disease (denoted by the dashed lines). Whether increased serum phosphate levels also directly stimulate FGF23 is unclear.

ing renal clearance necessitates increased secretion of humoral factors (in the original exposition referring to PTH) that augment per nephron filtration of phosphorus, but with the trade-off of requiring higher circulating hormone levels (40). Although these core elements remain operative today, the emergence of FGF23 has added perhaps a new leading player. Indeed, increased FGF23 secretion appears to be critical for maintaining normal phosphorus balance in early CKD, but with the trade-off of progressive 1,25(OH)₂D deficiency. Thus, although decreased phosphorus clearance remains the major culprit in this updated version of the hypothesis, and secondary hyperparathyroidism a major consequence, increased FGF23 appears to play a novel, and perhaps preeminent, pathophysiologic role in early CKD.

FGF23 and Clinical Outcomes

Although an increased FGF23 appears to be maladaptive given its link with progressive 1,25(OH)₂D decline in CKD, it also appears to be vital for mitigating the development of hyperphosphatemia, which itself is strongly associated with adverse outcomes across the spectrum of kidney function (43–47). Thus, whether higher FGF23 levels are ultimately protective by attenuating the development of excess phosphate levels or harmful by exacerbating 1,25(OH)₂D deficiency in CKD was unclear.

To investigate this issue, we examined the relationship between FGF23 and mortality in a nested, case-control study of hemodialysis patients (4). Two hundred patients who died within the first year of dialysis and 200 control patients who survived the first year of dialysis were randomly selected from 10,044 participants in the Accelerated Mortality on Renal Replacement (ArMORR) study, a prospective cohort of incident hemodialysis patients with detailed demographic, laboratory, and outcomes data throughout the first year of hemodialysis (10). FGF23 levels were measured in stored blood samples collected within a week of starting hemodialysis, allowing us to analyze the risk of 1-year all-cause mortality as a function of baseline FGF23 in these patients. We found that increased FGF23 levels were strongly associated with increased risk of future mortality. These results were consistent across baseline quartiles of serum phosphate, were minimally confounded by other risk factors, and demonstrated a “dose-response” relationship, such that the risk of mortality increased linearly with ascending quartiles of FGF23. Interestingly, this relationship was not materially changed when adjusted for 1,25(OH)₂D levels in a subset of patients with available measurements, suggesting that the association between increased FGF23 and mortality was not primarily mediated by decreased 1,25(OH)₂D. These findings were largely confirmed in a subsequent analysis of prevalent hemodialysis patients undergoing long (5- to 8-hour) hemodialysis sessions in France (5), although in a more recent Swedish study, a consistent relationship between increased FGF23 and mortality was not found in a cohort of patients initiating either peritoneal or hemodialysis (48). Nevertheless, collectively, these results suggest that an increased FGF23 is a powerful, independent predictor of mortality on hemodialysis.

To elucidate potential mechanisms that may underlie these findings, we subsequently performed a cross-sectional analysis

of 162 patients with predialysis CKD and 58 patients with preserved kidney function to examine the associations between FGF23 and echocardiographic indices of left ventricular structure and function (3). The rationale for this study was based in part on previous reports showing that elevated concentrations of FGF23 can nonselectively activate fibroblast growth factor receptors implicated in the development of cardiac hypertrophy (49–53), suggesting a biologic basis for an association between increased FGF23 and heart muscle disease. Increased FGF23 concentrations were associated with increased left ventricular mass index (LVMI) and greater likelihood of left ventricular hypertrophy (LVH), independently of classic risk factors, including age, diabetes, hypertension, body mass index, and eGFR. Moreover, in multivariable-adjusted models, FGF23 was among the strongest independent predictors of higher LVMI and greater odds of LVH in CKD participants. Interestingly, as we found with FGF23 and mortality on hemodialysis, adjusting for 1,25(OH)₂D concentrations in a subset of participants with available measurements had minimal effect on these relationships, suggesting a direct effect of FGF23 on cardiomyocyte hypertrophy independent of its effects on 1,25(OH)₂D. Alternatively, it is possible that increased FGF23 levels may inhibit extrarenal sites of 25(OH)D-1 α -hydroxylase, such as in cardiomyocytes and vascular endothelium (54,55), disrupting critical autocrine/paracrine actions of 1,25(OH)₂D in these tissues, and thereby contributing to cardiovascular disease. Further studies will need to determine whether FGF23 has effects on extrarenal 25(OH)D-1 α -hydroxylase, and if so, whether this may account for its association with left ventricular disease.

Subsequent studies have not only confirmed the association between FGF23 and LVH (7,56) but also demonstrated independent associations between FGF23 and faster kidney disease progression (57), higher atherosclerosis burden (58), vascular calcification (59,60), and impaired endothelial function and arterial stiffness (6). Importantly, several of these studies showed independent relationships between increased FGF23 and adverse outcomes in individuals with preserved kidney function (6,7,58), suggesting that excess FGF23 may be harmful for cardiovascular health across the spectrum of kidney function. Together, these data provide compelling evidence that although excess FGF23 may be important for maintaining normal phosphorus balance in states of phosphate excess (particularly kidney failure), long-term exposure to elevated FGF23 may be maladaptive by accelerating cardiovascular disease and mortality.

When again considered in the context of the trade-off hypothesis, these data allow us to further expand upon this venerable framework. As first speculated by one of its principal authors, it is possible that the unabated rise of a circulating humoral factor in response to decreased clearance of a filtered solute may produce a time when “the biologic activity of the substance is sufficiently great to spill over to cells of extrarenal organs and...conceivably have adverse effects that contribute to the uremic syndrome” (40). Although PTH was originally conceived as the humoral factor in this scenario, it seems that FGF23 may serve this bill just as well given that increased FGF23 levels are already evident early in the course of kidney

failure and are independently associated with cardiovascular disease and mortality.

Whether FGF23 exerts a direct toxic effect on end-organ tissues—which is possible given the presence of fibroblast growth factor receptors in cardiomyocytes and vascular endothelium (61)—or whether its link with adverse outcomes is mediated through an as-of-yet unidentified factor is a critical question with key implications for the management of patients with CKD. Indeed, FGF23 levels can be decreased using routine clinical interventions that limit gut phosphorus absorption (62–66). Hence, if FGF23 has direct toxicity, then early implementation of dietary phosphorus restriction—even before the development of overt hyperphosphatemia—may represent a novel approach for ameliorating the markedly high rates of cardiovascular disease and mortality in CKD. However, it is important to emphasize that a number of risk factors have been linked with adverse outcomes in large observational studies, only to be shown to have negligible effects on hard clinical endpoints when directly targeted in randomized, controlled trials (67–69). Thus, well-designed animal and human studies are first needed to establish a causal relationship between elevated FGF23 and cardiovascular disease, and if established, to determine whether lowering FGF23 levels may improve clinical outcomes in patients with CKD.

FGF23 and Activated Vitamin D Therapy in CKD: A Balancing Act?

Because activated vitamin D and its analogs stimulate FGF23 synthesis, and increased FGF23 is increasingly associated with adverse outcomes, there has been recent speculation about whether the stimulatory effect of activated vitamin D compounds on FGF23 may have long-term adverse consequences in CKD (70). Unfortunately, no studies have formally examined this issue, and so the answer remains unclear. Nonetheless, it is worth considering several insights from the existing literature.

Whereas activated vitamin D compounds strongly stimulate FGF23 secretion in animal models (33,71), and in humans with X-linked hypophosphatemia (72,73), other studies suggest that the effect of vitamin D on FGF23 may be more modest in patients with CKD. For example, in a prospective study of 30 chronic hemodialysis patients treated with intravenous calcitriol at doses ranging from 0.5 to 1.0 μg two or three times per week for 6 months, a statistically significant rise in FGF23 concentrations was only observed after 6 months of therapy, in contrast to concomitant PTH concentrations, which sharply fell within 1 month of starting therapy (74). Interestingly, there was a weak although statistically significant linear association between FGF23 and cumulative calcitriol dose ($r^2 = 0.143$, $P = 0.04$), suggesting that the use of lower calcitriol doses may have blunted the rise in FGF23 levels in these patients.

Similar results were recently reported in a secondary analysis from the ACHIEVE trial (70). In this study, longitudinal FGF23 measurements were obtained in 91 patients randomly assigned to treatment with Cinacalcet and low-dose vitamin D (2 μg of paricalcitol or 1 μg of doxercalciferol three times weekly) or treatment with escalating vitamin D to maintain PTH concentrations between 150 and 300 pg/ml. During the 27-week

course of therapy, FGF23 levels linearly decreased in the Cinacalcet and low-dose vitamin D arm, suggesting that Cinacalcet may help reduce FGF23 levels by allowing for lower vitamin D doses to control PTH. Interestingly, however, although FGF23 levels did not decrease in the escalating vitamin D arm, they did not significantly increase in these participants either, despite their receiving an average weekly dose of 14.8 $\mu\text{g}/\text{wk}$ (in paricalcitol equivalents). Moreover, in multivariable-adjusted models, mean vitamin D analog dose was not significantly associated with the percent change in FGF23 concentrations. Although larger studies need to confirm these findings in both end-stage and predialysis CKD populations, together these results suggest that activated vitamin D compounds may not markedly exacerbate FGF23 excess in CKD.

Furthermore, if the stimulatory effects of activated vitamin D compounds on FGF23 were particularly deleterious, then it is reasonable to assume that at least one study of hemodialysis patients—who not only are exposed to the highest dosages of vitamin D but also have the highest circulating concentrations of FGF23—would have demonstrated increased mortality associated with vitamin D therapy. That no such studies have been published to date despite the widespread use of vitamin D in these patients suggests that the potential benefits of vitamin D therapy on cardiovascular and immune function likely outweigh whatever deleterious effects vitamin D may have *vis-à-vis* increasing FGF23. Nevertheless, it is certainly possible that a strategy of Cinacalcet with low-dose activated vitamin D therapy represents the best of all worlds, that is, by reducing both PTH levels and FGF23 levels, while still allowing for some physiologic VDR activation. Whether this ultimately results in improved outcomes compared with therapy with activated vitamin D alone will need to be the focus of future investigations. However, given the current data, there is little evidence to support restricting activated vitamin D therapy because of fears of markedly exacerbating FGF23 excess, and thereby worsening health outcomes, in CKD.

Summary

The discovery of FGF23 has been a watershed moment in our understanding of disorders of mineral metabolism in CKD. Not only has this finding elucidated the pathogenic mechanisms underlying disturbances in vitamin D metabolism in early kidney failure, it has revealed critical new insights into the consequences of abnormal phosphorus metabolism, which together may fundamentally alter the management of bone and mineral ion disorders in CKD. Nonetheless, there remains much to be learned about how all of the pieces of this puzzle fit together, and future studies will need to further clarify several key issues.

For example, do markedly increased FGF23 levels have a direct toxic effect on end-organ tissues or is their link with adverse outcomes mediated through other mechanisms? Can interventions that limit dietary phosphorus absorption effectively suppress FGF23 levels in CKD patients in the long term, and if so, may this translate into improved clinical outcomes? What, if any, adverse effects does the stimulatory effect of activated vitamin D compounds on FGF23 have, and how may

this alter the way in which activated vitamin D compounds are utilized in CKD? As we await the answers to these and other crucial questions, it is clear that more human clinical studies will be critical for these efforts, and thus, should be among the top priorities for future research initiatives, with the ultimate goal of improving the markedly poor clinical outcomes in patients with CKD.

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Disclosures

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