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Regulation and Effects of FGF23 in Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a global health epidemic that accelerates cardiovascular disease, increases risk of infection, and causes anemia and bone disease, among other complications that collectively increase risk of premature death. Alterations in calcium and phosphate homeostasis have long been considered nontraditional risk factors for many of the most morbid outcomes of CKD. The discovery of fibroblast growth factor 23 (FGF23), which revolutionized the diagnosis and treatment of rare hereditary disorders of FGF23 excess that cause hypophosphatemic rickets, has also driven major paradigm shifts in our understanding of the pathophysiology and downstream end-organ complications of disordered mineral metabolism in CKD. As research of FGF23 in CKD has rapidly advanced, major new questions about its regulation and effects continuously emerge. These are promoting exciting innovations in laboratory, patient-oriented, and epidemiological research and stimulating clinical trials of new therapies and repurposing of existing ones to target FGF23.

INTRODUCTION

A diverse set of genetic, metabolic, autoimmune, malignant, toxic, and environmental factors can activate multiple molecular mechanisms of kidney injury. While these injuries culminate in different patterns of vascular, glomerular, and tubulointerstitial kidney diseases, reduced kidney function itself, virtually regardless of its underlying cause, triggers a host of final common pathway complications. In many cases, these are initially appropriate compensatory adaptations to reduced kidney function, but they eventually devolve into the pathophysiological cascades that contribute to the syndrome and complications of chronic kidney disease (CKD).

Fibroblast growth factor 23 (FGF23) is a bone-derived endocrine hormone that regulates phosphate and calcium homeostasis. After its discovery as the previously elusive phosphatonin that causes syndromes of vitamin D-resistant, hypophosphatemic rickets, FGF23 emerged as a central regulator of normal mineral metabolism. It also emerged as a critical component of the aberrant mineral metabolism that complicates CKD, which wreaks havoc on the skeleton, heart, and vessels as it progresses to end-stage renal disease (ESRD) (1, 2). In this review, we describe FGF23 regulation and effects in health, in progressive CKD, and in related disorders. We review the links between FGF23 excess and adverse clinical outcomes in CKD, discuss the potential underlying mechanisms of these off-target complications, and provide an update on therapeutic strategies aimed at lowering FGF23 in CKD.

MINERAL METABOLISM: THE PRE-FGF23 PARADIGM

For decades, mineral metabolism was understood through the lens of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D and their effects on the parathyroid glands, intestine, kidney, and bone. In response to hypocalcemia, which is detected by the calcium-sensing receptor (CaSR), PTH stimulates bone resorption, which releases calcium and phosphate into circulation (3), and increases circulating concentrations of 1,25-dihydroxyvitamin D, which facilitates entry of dietary calcium and phosphate into circulation (4). PTH increases 1,25-dihydroxyvitamin D in two ways: (*a*) by enhancing conversion of 1,25-hydroxyvitamin D substrate into the activated form by stimulating *CYP27B1* (1α-hydroxylase) and (*b*) reducing 1,25-dihydroxyvitamin D inactivation by inhibiting *CYP24A1* (24-hydroxylase) (4). In the kidney, PTH also increases distal tubule calcium reabsorption and downregulates the proximal tubular sodium-phosphate cotransporters, NPT2a and NPT2c, which increases urinary phosphate excretion (5). By increasing tubular reabsorption of calcium and tubular excretion of phosphate that entered the circulation from the bone and gut under the influence of PTH, the net effect of PTH pulses in response to hypocalcemia is to increase serum calcium while maintaining normal serum phosphate. Hypercalcemia reverses each of these steps starting with suppression of PTH secretion.

The main effects of 1,25-dihydroxyvitamin D on mineral homeostasis include (*a*) augmenting dietary calcium absorption, which is mediated primarily by vitamin D–dependent active transport; (*b*) augmenting dietary phosphate absorption, although the majority of phosphate is passively absorbed between enterocytes via paracellular transport rather than across enterocytes via vitamin D–dependent stimulation of the active transporter, NPT2b; and (*c*) potentiating PTH-mediated bone resorption and renal calcium reabsorption (6). The net effects of these actions of 1,25-dihydroxyvitamin D are to increase both serum calcium and phosphate.

Based on this paradigm, secondary hyperparathyroidism in CKD was considered to be a trade-off to compensate for impaired renal phosphate excretion and relative deficiency of 1,25-dihydroxyvitamin D that was thought to be due to the inability of the ailing kidney to produce sufficient 1,25-dihydroxyvitamin D (7). However, physiological studies of dietary phosphate restriction suggested otherwise. Lowering dietary phosphate decreased PTH, as would be predicted,

but concomitantly increased circulating 1,25-dihydroxyvitamin D, the opposite of what would be expected based on a primarily PTH-centric paradigm (8). Instead, these results suggested that an additional upstream factor regulates vitamin D in response to changes in dietary phosphate consumption and secondarily affects PTH. The identity of this factor would remain unknown for almost 20 years.
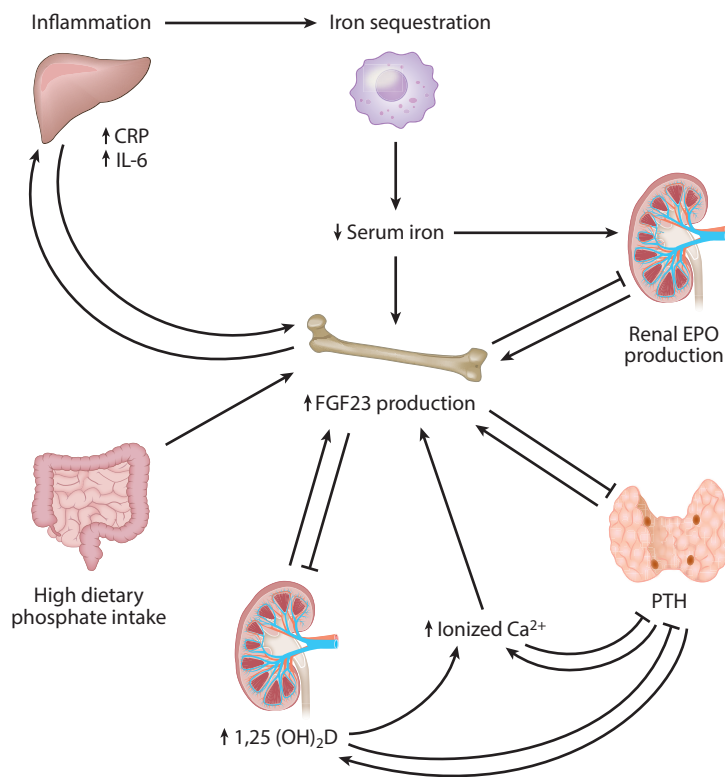
FGF23

The discovery that primary excess of FGF23 causes rare diseases of hypophosphatemic rickets or osteomalacia revolutionized our understanding of normal mineral homeostasis and its dysregulation in CKD (2, 9, 10). The *FGF23* gene encodes a 32-kDa glycoprotein composed of 251 amino acids that is secreted by osteocytes and bone marrow stromal cells (11). Unlike other autocrine FGFs, its lack of heparin binding motifs enables it to circulate freely as an endocrine hormone (11). Target-organ signaling by FGF23 is mediated by its binding to heterodimeric complexes of FGF receptors (FGFRs) and α-Klotho (hereafter, referred to as Klotho) coreceptors that are prominently expressed in the kidney, parathyroid gland, bone, and perhaps other tissues (12).

There are three levels of FGF23 regulation in osteocytes: (*a*) *FGF23* transcription, (*b*) post-translational modification of nascent FGF23 peptides, and (*c*) cleavage of full-length FGF23 protein into N- and C-terminal fragments (13). The FGF23 N terminus (155 amino acids) contains a conserved FGFR binding domain, and the C terminus (78 amino acids) contains the Klotho binding domain (11). Between these, FGF23 contains an $R_{176}HTR_{179}$/S180 subtilisin-like pro-protein convertase cleavage motif that is not present in other FGF family members (14). When wild-type *FGF23* is expressed in osteocytes, biologically intact FGF23 (32 kD) and cleaved N- and C-terminal peptide fragments (20 and 12 kD, respectively) are secreted (13). In health, the secreted amount of full-length FGF23 is regulated by competing posttranslational modifications, which determine the biological half-life of the nascent peptide. *O*-glycosolation at Thr^{178} by polypeptide *N*-acetylgalactosaminyltransferase 3 (GalNT3) protects FGF23 from proteolytic cleavage (15). Conversely, phosphorylation at Ser^{180} via the secretory protein kinase family with sequence similarity 20, member C (FAM20C) inhibits GalNT3-mediated *O*-glycosylation, thus promoting proteolytic cleavage of FGF23 (16).

MINERAL METABOLISM: THE POST-FGF23 PARADIGM

Activation of FGFR-Klotho complexes in the kidney by FGF23 increases urinary phosphate excretion by downregulating NPT2a and NPT2c in the proximal tubule, mirroring the phosphaturic effects of PTH (17, 18). In contrast, FGF23 has the opposite effects of PTH on the enzymes that mediate vitamin D production and degradation. Unlike PTH, which increases circulating concentrations of 1,25-dihydroxyvitamin D, FGF23 lowers 1,25-dihydroxyvitamin D concentrations by inhibiting *CYP27B1* and stimulating *CYP24A1* (19).

Serum phosphate is maintained within a narrow range despite day-to-day dietary fluctuations because FGF23 levels rise and fall in parallel to the amount of dietary phosphate intake (**Figure 1**) (20). When phosphate intake increases, FGF23 levels rise to increase urinary fractional excretion of phosphate and, by lowering circulating 1,25-dihydroxyvitamin D levels, FGF23 indirectly attenuates gut absorption of phosphate. Low-phosphate diets have the opposite effects: FGF23 decreases, renal avidity for phosphate reabsorption increases, and 1,25-dihydroxyvitamin D levels rise, which enhances dietary phosphate absorption, thereby maintaining normal serum phosphate (20). Interestingly, the effects of dietary phosphate loading on circulating FGF23 occur independently of changes in serum phosphate (21), and cultured osteoblasts do not consistently increase

Stimulators of FGF23 production. Dietary phosphate loading, hypercalcemia, PTH, and 1,25(OH)$_2$D are the classic stimuli of FGF23 production. Circulating FGF23 induces phosphaturia and reduces circulating concentrations of 1,25(OH)$_2$D, thus lowering intestinal calcium and phosphate absorption. This effect of FGF23 opposes another feedback loop in which PTH stimulates 1,25(OH)$_2$D, and 1,25(OH)$_2$D inhibits PTH. FGF23 also exerts direct negative feedback on PTH, completing another classic negative endocrine feedback loop. FGF23 directly stimulates hepatic production of proinflammatory cytokines, which contribute to the chronic inflammation associated with CKD. Elevated hepcidin causes iron sequestration in the reticuloendothelial system and impairs enteric iron absorption, thus reducing serum iron. Inflammation, iron deficiency, and EPO are novel stimuli of FGF23 production. Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; CKD, chronic kidney disease; CRP, C-reactive protein; EPO, erythropoietin; FGF23, fibroblast growth factor 23; IL-6, interleukin 6; PTH, parathyroid hormone.

FGF23 expression in response to exogenous phosphate (22, 23). This suggests, seemingly para-doxically, that serum phosphate does not directly regulate FGF23 even though FGF23 has potent effects on serum phosphate. The mechanisms of how dietary phosphate loading modulates bone production of FGF23 independent of an intermediate increase in serum phosphate and, more gen-erally, how phosphate economy is sensed, have yet to be elucidated. Recent work suggests possible roles for FGFR1, Pit1/2, and CaSR, but additional research is needed (24).

Unlike serum phosphate, *FGF23* transcription is potently activated by 1,25-dihydroxyvitamin D, which directly binds stimulatory vitamin D response elements within the *FGF23* promoter (**Figure 1**) (22). This establishes a classic negative endocrine feedback loop between FGF23 and 1,25-dihydroxyvitamin D that opposes the negative endocrine feedback loop between PTH and 1,25-dihydroxyvitamin D. Indeed, it has been postulated that the primary function of FGF23 is to

counterbalance the effects of PTH and serve as a brake against endogenous 1,25-dihydroxyvitamin D intoxication (22). Working in a separate negative endocrine feedback loop, PTH stimulates FGF23 directly and indirectly (via changes in 1,25-dihydroxyvitamin D and calcium), whereas FGF23 inhibits PTH (**Figure 1**) (25). The latter can be considered a component of the synchronized effects of FGF23 to suppress 1,25-dihydroxyvitamin D by reducing its main stimulus, PTH.

Studies of genetically modified mice and observations in humans with hypoparathyroidism demonstrate that calcium also regulates FGF23 (**Figure 1**). Unlike phosphate, exogenous calcium is capable of stimulating *FGF23* transcription in cultured osteoblasts (26). In mice lacking the vitamin D receptor (VDR), exposure to high dietary calcium increases circulating FGF23, supporting vitamin D-independent effects of calcium on FGF23 regulation (27). Mice with genetic ablation of PTH and humans with hypoparathyroidism develop hypocalcemia and low 1,25-dihydroxyvitamin D levels, but FGF23 is inappropriately low despite severe hyperphosphatemia (28). Intravenous calcium supplementation induced a significant phosphaturic response that normalized serum phosphate in patients with hypoparathyroidism, suggesting that it likely increased FGF23 (which had not been discovered at the time of this classic study) (29). More recently, 1,25-dihydroxyvitamin D supplementation increased FGF23 and normalized serum phosphate in patients with hypoparathyroidism (30). Collectively, these data suggest that normal serum calcium is required for other FGF23 regulatory pathways to function normally, perhaps to avoid life-threatening suppression of serum calcium by further FGF23-mediated reductions of 1,25-dihydroxyvitamin D and PTH.

MEASURING FGF23

Two different types of enzyme-linked immunoassays were developed to measure FGF23. The C-terminal assay is predicated on antibodies that target two epitopes in the C terminus of the peptide distal to its cleavage site (10). As a result, the cFGF23 assay can capture full-length FGF23 and its C-terminal fragments. Intact assays exclusively detect full-length FGF23 because they leverage antibodies that target two epitopes that flank the FGF23 cleavage site (31). In most instances, precise measurement of the biologically active form of a hormone is preferred. However, in the case of FGF23, the serendipitous development of the distinct cFGF23 and iFGF23 assays provided a powerful tool—a liquid bone biopsy for FGF23—that can substitute simultaneous measurements of both cFGF23 and iFGF23 in blood for invasive bone biopsies to infer the balance of FGF23 transcription and cleavage in bone in different clinical settings (32).

FGF23 ELEVATION IN CHRONIC KIDNEY DISEASE

Cross-sectional studies demonstrated that FGF23 levels rise as estimated glomerular filtration rate (eGFR) declines in both children and adults with CKD, but prior to the development of hyperphosphatemia, 1,25-dihydroxyvitamin D deficiency, hypocalcemia, or secondary hyperparathyroidism (33, 34). This temporal progression was confirmed in animals with CKD induced by administering anti-glomerular basement membrane antibodies (35). Within 10 days, only FGF23 and creatinine were significantly elevated; 1,25-dihydroxyvitamin D levels declined, and PTH rose only after day 20. Once CKD with secondary hyperparathyroidism was established, antibody neutralization of FGF23 fully normalized 1,25-dihydroxyvitamin D and precipitated severe hyperphosphatemia (35). This demonstrated that secondary FGF23 excess is critical to maintaining normal serum phosphate in CKD, and that the mechanism of 1,25-dihydroxyvitamin D deficiency in CKD is FGF23 excess rather than progressive loss of renal mass. These results also suggest that the trade-off hypothesis was correct, but FGF23 rather than PTH was the

principal ringleader of the response that suppresses 1,25-dihydroxyvitamin D and precipitates secondary hyperparathyroidism.

Further confirmation of this pathophysiologic cascade can be gleaned from the response of patients with iron deficiency anemia and normal kidney function to intravenous ferric carboxymaltose, which acutely increases biologically active FGF23 via unclear mechanisms (36). This triggers a pathophysiological cascade of renal phosphate wasting with hypophosphatemia and acute 1,25-dihydroxyvitamin D deficiency, which precipitates hypocalcemia that is mitigated by secondary hyperparathyroidism (36, 37). Taken together, these observations support a pathophysiological cascade of disordered mineral metabolism in CKD that begins with gradually increasing FGF23 levels that suppresses circulating 1,25-dihydroxyvitamin D levels, by both reducing its production and accelerating its degradation, which leads to a tendency toward hypocalcemia that is compensated by secondary hyperparathyroidism (33, 38).
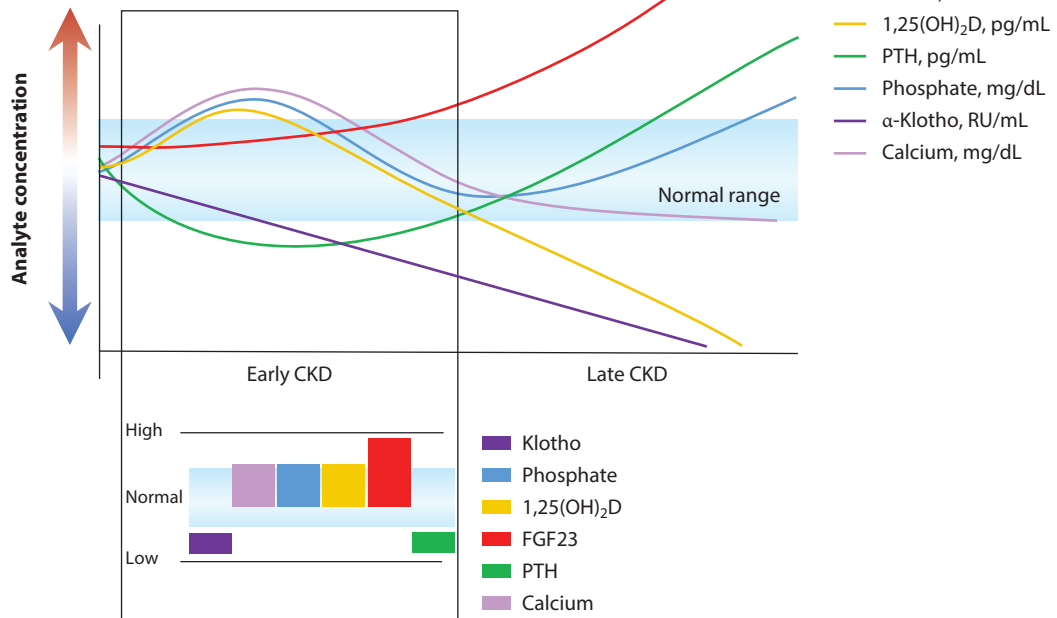
CHRONIC KIDNEY DISEASE: PRIMARY KLOTHO DEFICIENCY OR PRIMARY FGF23 EXCESS?

Why FGF23 rises beginning in early CKD before other alterations in mineral metabolism and where in the cascade Klotho deficiency fits are some of the most important unanswered questions in the field. The identical mineral metabolism phenotypes of mice lacking FGF23 or Klotho led to the discovery that they share a common physiological pathway as ligand and coreceptor (17, 39). Klotho exists in a full-length membrane form that forms heterodimeric receptors with FGFR for FGF23 and a soluble form that exerts pleiotropic functions, including perhaps acting as a portable coreceptor for FGF23 (12, 40, 41)
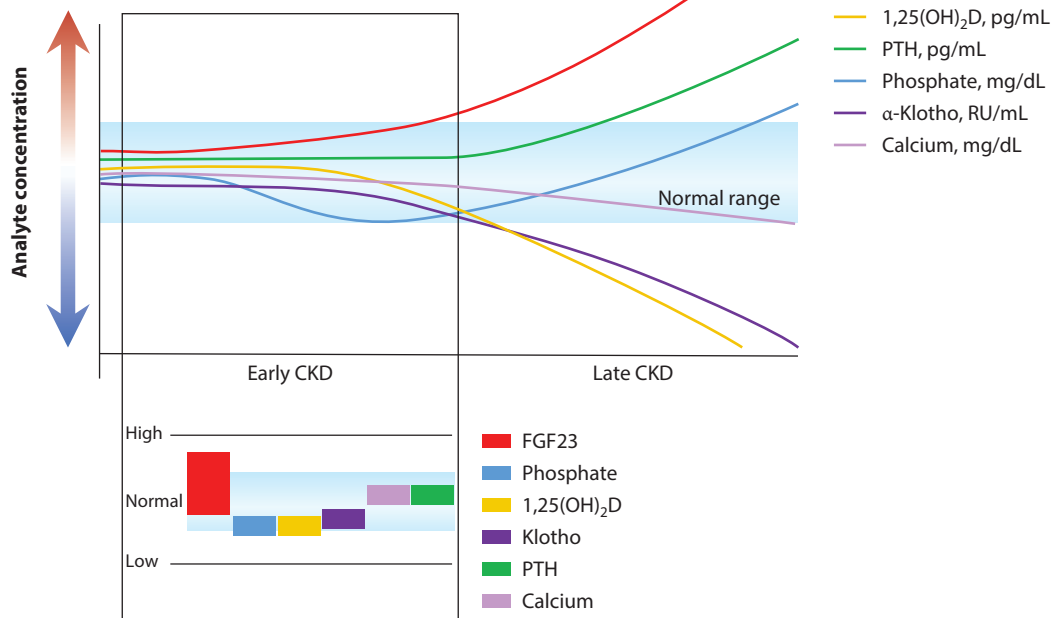
Because *Klotho* deletion causes secondary FGF23 excess due to tubular resistance to FGF23, and because Klotho expression is reduced in CKD, Klotho deficiency has been invoked as a possible primary upstream factor that drives secondary FGF23 excess in CKD (**Figure 2a**) (11). Several clinical observations argue against this hypothesis. If a primary deficiency of Klotho led to secondary increases in FGF23, patients with early CKD should manifest alterations in mineral metabolism that at least trend in the direction of those caused by Klotho deficiency, namely subtle increases in serum phosphate, calcium and 1,25-dihydroxyvitamin D. To the contrary, elevations of phosphate, calcium and 1,25-dihydroxyvitamin D are not observed in the earliest stages of CKD, and several studies reported a modest decrease in serum phosphate in early CKD when FGF23 is elevated (42). Indeed, the constellation of alterations in mineral metabolism of early human CKD trends in the direction of states of primary FGF23 excess: elevated FGF23, renal phosphate wasting, reduced serum phosphate, 1,25-dihydroxyvitamin D deficiency, subtle reductions in serum calcium, increased PTH, and likely, secondary downregulation of Klotho expression (**Figure 2b**).

Further indirect human evidence against FGF23 resistance due to Klotho deficiency in CKD comes from a randomized trial of intravenous iron that included a subgroup of patients with nondialysis-dependent CKD (37). Reduced eGFR attenuated risk of hypophosphatemia in response to ferric carboxymaltose, as expected, because the mechanism of hypophosphatemia involves FGF23-mediated renal phosphate wasting. Nevertheless, ferric carboxymaltose also reduced mean serum phosphate and 1,25-dihydroxyvitamin D levels and induced overt hypophosphatemia in a substantial number of the subgroup of patients with CKD. This demonstrates that phosphate reabsorption and 1,25-dihydroxyvitamin D production were not maximally suppressed at baseline in CKD, despite pathologically elevated FGF23, and that further FGF23 elevation was able to further suppress serum phosphate and 1,25-dihydroxyvitamin D, effects that would not be expected if Klotho deficiency caused significant tubular resistance to FGF23.

a Hypothesis: primary Klotho deficiency

- FGF23, RU/mL
- 1,25(OH)$_2$D, pg/mL
- PTH, pg/mL
- Phosphate, mg/dL
- α-Klotho, RU/mL
- Calcium, mg/dL

Normal range

Early CKD   Late CKD

High
Normal
Low

- Klotho
- Phosphate
- 1,25(OH)$_2$D
- FGF23
- PTH
- Calcium

b Hypothesis: primary FGF23 excess

- FGF23, RU/mL
- 1,25(OH)$_2$D, pg/mL
- PTH, pg/mL
- Phosphate, mg/dL
- α-Klotho, RU/mL
- Calcium, mg/dL

Normal range

Early CKD   Late CKD

High
Normal
Low

- FGF23
- Phosphate
- 1,25(OH)$_2$D
- Klotho
- PTH
- Calcium

(Caption appears on following page)

Elevated FGF23 in early CKD: Primary FGF23 excess or secondary to Klotho deficiency? (*a*) Primary Klotho deficiency with secondary FGF23 excess hypothesis: Under this hypothesis, primary Klotho deficiency in early CKD would induce renal resistance to FGF23, which would trigger biochemical changes in mineral metabolism that trend in the direction of those observed in other genetic and acquired disorders of Klotho deficiency: secondary increases in circulating FGF23 and increases in serum phosphate, $1,25(OH)_2D$ and calcium due to reduced FGF23-Klotho-FGFR1 signaling in the kidney that would eventually result in hypercalcemia and suppressed PTH. This is not the phenotype of mineral metabolism in human CKD. (*b*) Primary FGF23 excess hypothesis: Under this hypothesis, primary increases in FGF23 in early CKD would trigger biochemical changes in mineral metabolism that trend in the direction of those observed in other genetic and acquired disorders of primary FGF23 excess: mild reduction in serum phosphate, increased fractional excretion of phosphate, and suppressed $1,25(OH)_2D$ concentrations, which eventually contribute to development of hypocalcemia and secondary hyperparathyroidism. Under this hypothesis, FGF23 excess causes secondary downregulation of Klotho directly or via reduced $1,25(OH)_2D$ or other intermediaries. This closely aligns with the phenotype of mineral metabolism in human CKD. Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

ALTERNATE MECHANISMS TO EXPLAIN FGF23 ELEVATION IN CHRONIC KIDNEY DISEASE

As CKD progresses, fragments of PTH and other peptide hormones accumulate in circulation. In contrast, the relative proportion of FGF23 fragments to full-length hormone in circulation decreases as eGFR declines, such that virtually all circulating FGF23 is full length in patients with ESRD, whereas healthy individuals tend to have a higher circulating fraction of FGF23 fragments (albeit with lower total levels) (43, 44). Furthermore, in a mouse model of progressive CKD, circulating FGF23 concentrations increased prior to measurable increases in *FGF23* transcription (45, 46). Collectively, these observations suggest that progressively downregulated or impaired FGF23 cleavage contributes to FGF23 excess that begins in early CKD.

The prototype condition of impaired FGF23 cleavage is autosomal dominant hypophosphatemic rickets (ADHR), which is caused by gain-of-function mutations in the *FGF23* cleavage recognition site that confers resistance to proteolytic cleavage (2). When ADHR-mutant *FGF23* is expressed, the lack of cleavage results in secretion of excessive full-length FGF23 that causes renal phosphate wasting and hypophosphatemia (48). Interestingly, individuals with ADHR experience a fluctuating course of FGF23 excess and hypophosphatemia, despite their germline mutations, and flares of hypophosphatemia are precipitated by iron deficiency that acts as an environmental second hit (48).

In otherwise healthy individuals, iron deficiency stimulates *FGF23* transcription but couples it to parallel increases in FGF23 cleavage (13). This results in normal iFGF23 but markedly elevated cFGF23; the lack of change in circulating concentrations of biologically active FGF23 accounts for the lack of hypophosphatemia in iron deficiency. However, in states of impaired FGF23 cleavage such as ADHR, iron deficiency leads to excess transcription of the cleavage-resistant mutant *FGF23*, resulting in secretion of full-length FGF23 that precipitates hypophosphatemia (48).

On a background of downregulated or impaired FGF23 cleavage in CKD, iron deficiency would be expected to preferentially increase iFGF23 as it does in ADHR (**Figure 1**). Indeed, chronic inflammation induced by repeated endotoxin or interleukin (IL)-1β injections in wild-type mice produced iron sequestration and markedly increased cFGF23 while iFGF23 remained stable, suggesting intact coupling of *FGF23* transcription and FGF23 cleavage (49). However, when IL-1β injections were repeated in a mouse model of CKD, both cFGF23 and iFGF23 markedly increased (49). These data indicate that FGF23 cleavage was impaired in CKD and that iron deficiency significantly increased circulating iFGF23 as observed in human CKD. It is important to emphasize that while true iron deficiency is common in CKD, it is not essential to activate this pathway. Instead, functional iron deficiency due to the inflammation of CKD is sufficient to mimic the effects of true iron deficiency in osteocytes to increase *FGF23* transcription

and thus circulating iFGF23. Further patient-oriented research is needed to test the hypothesis that inflammation-induced iron deficiency is an important upstream mechanism of the primary increases in FGF23 that begin early in the course of human CKD.

FGF23 AND COMPLICATIONS OF CHRONIC KIDNEY DISEASE

FGF23 and Mortality

Large observational studies of patients with ESRD reported that hyperphosphatemia is an independent risk factor for mortality (50). Although serum phosphate is normal in most patients with earlier-stage CKD and in individuals without CKD, higher versus lower serum phosphate within the normal range was likewise associated with increased risk of mortality (51, 52). Combined with the plausible biological mechanism that phosphate excess causes transdifferentiation of vascular smooth muscle cells into osteoblast-like cells that promote ectopic arterial calcification (53), this body of work helped to identify increased serum phosphate as a novel risk factor for mortality in patients with CKD.

The discovery of FGF23 added a new dimension to the link between phosphate and mortality. In a prospective study of patients with incident ESRD, higher FGF23 levels at their first outpatient hemodialysis treatment were associated with a dose-dependent and minimally confounded increased risk of mortality; patients in the highest FGF23 quartile had a nearly 6-fold increase in risk of death compared to those in the lowest quartile (54). The effects of FGF23 on mortality dwarfed those of serum phosphate that was measured at the same time.

In approximately 4,000 patients with CKD stages 2–4 enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study (baseline eGFR 44 mL/min/1.73 m^2), elevated FGF23 was also independently associated with increased risk for mortality (55). The magnitude of effect and strength of association were greater for FGF23 than for concomitant assessments of proteinuria, eGFR, and other markers of mineral metabolism, including serum phosphate. Repeated annual measurements of FGF23 over five years in the CRIC Study identified three longitudinal FGF23 trajectories. The majority of participants maintained stable FGF23 levels over five years, but in comparison, the smaller subpopulations with slowly or rapidly rising FGF23 were at a 4- to 15-fold higher risk of death (56). Additional studies have extended the link between FGF23 and mortality to other patient populations, including patients with CKD stages 4–5 not yet receiving dialysis, kidney transplant recipients, those with a history of cardiovascular disease, and even the general population (57–60).

The finding across multiple prospective cohort studies of dose-dependency, large magnitude effects and minimal confounding, including by eGFR, proteinuria, phosphate, and PTH, raised the possibility that FGF23 might be contributing directly to increased risk of mortality. A recent meta-analysis confirmed the strong associations of increased FGF23 with increased risk of mortality across diverse populations, but it questioned causality on the basis of similar effect estimates when comparing upper versus lower categories of FGF23 within individual populations from non-CKD through ESRD (61). Limitations of the meta-analysis include its noteworthy omission of certain studies with results that run counter to the main claim of the analysis, including the original report in patients with ESRD and the FGF23 trajectory study, each of which had far larger effect estimates than studies that were included. Nevertheless, definitively confirming or refuting causality will require interventional studies that compare clinical outcomes in patients randomized to FGF23-lowering treatments versus inactive comparators.

FGF23 and Cardiovascular Disease Events

Cardiovascular disease is pervasive in the CKD population, and event rates increase as eGFR declines (62). Multiple prospective studies across the spectrum of CKD severity reported increased

risk of cardiovascular disease events in association with elevated FGF23, but the results were highly variable for specific types of events, including myocardial infarction, stroke, peripheral vascular disease, heart failure, and atrial fibrillation (**Figure 3**) (60, 63–66). Among the specific cardiovascular outcomes, FGF23 excess is most consistently and strongly associated with incident and recurrent heart failure and atrial fibrillation. For example, in the nearly 4,000 participants with CKD stages 2–4 in the CRIC Study, higher FGF23 was independently associated with graded risk of heart failure but not atherosclerotic events even after adjustment for kidney function and traditional cardiovascular risk factors (67). Elevated FGF23 levels were also independently associated with increased risk of atrial fibrillation, which was partially mediated by increased left ventricular mass index but not reduced ejection fraction, suggesting an intermediate mechanism involving diastolic dysfunction (66). These data comport with other studies of CKD and non-CKD patients that reported that elevated FGF23 associated most strongly with risk of heart failure and atrial fibrillation compared to other event types (58, 59, 68, 69).

FGF23 and Intermediate Measures of Cardiovascular Disease: Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is a ubiquitous complication of CKD that increases risks of heart failure, atrial fibrillation, ventricular arrhythmia, and sudden cardiac death (70). In observational studies, higher FGF23 independently associates with higher left ventricular mass index and higher prevalence of LVH (**Figure 3**) (71, 72). In a prospective study of more than 3,000 CRIC participants with echocardiograms at baseline and three years later, higher FGF23 was independently associated with higher left ventricular mass index and higher prevalence and incidence of concentric and eccentric LVH (70).

As a potential underlying mechanism of the link between FGF23 and LVH, exogenous FGF23 can induce hypertrophic growth of cardiac myocytes and disrupt their normal calcium cycling (70, 73, 74). The prohypertrophic effects of FGF23 are mediated by its binding to FGFR4 on cardiac myocytes, which activates the calcineurin-NFAT signaling pathway (75). This effect is blocked by a global FGFR small-molecule inhibitor, but not by *Klotho* deletion, supporting an FGFR4-dependent, Klotho-independent mechanism (70).

Recent work suggests that cardiac tissues might produce and secrete FGF23 in response to ischemia, pressure overload, and acute decompensated heart failure, and that locally produced FGF23 can stimulate profibrotic factors that promote pathogenic cardiac remodeling (76–79). Further studies are needed to define the human relevance of ectopic FGF23 production and its local effects in the heart and other tissues (80).

Klotho deficiency has also been implicated in the pathogenesis of LVH. However, because in vivo models of *Klotho* deletion manifest FGF23 excess and vice versa, disentangling the individual effects of each is a challenge that remains unresolved (81, 82). Nevertheless, because both FGF23 excess and Klotho deficiency are consequences of CKD, these data suggest that disordered phosphate homoeostasis might contribute causally to cardiovascular disease and death via direct cardiac injury that culminates in LVH, heart failure with preserved ejection fraction, and atrial fibrillation.

FGF23 and Intermediate Measures of Cardiovascular Disease: Arterial Calcification

Along with LVH, arterial calcification is the other most common and morbid intermediate phenotype of cardiovascular disease in CKD (83). Although some observational studies suggested a link
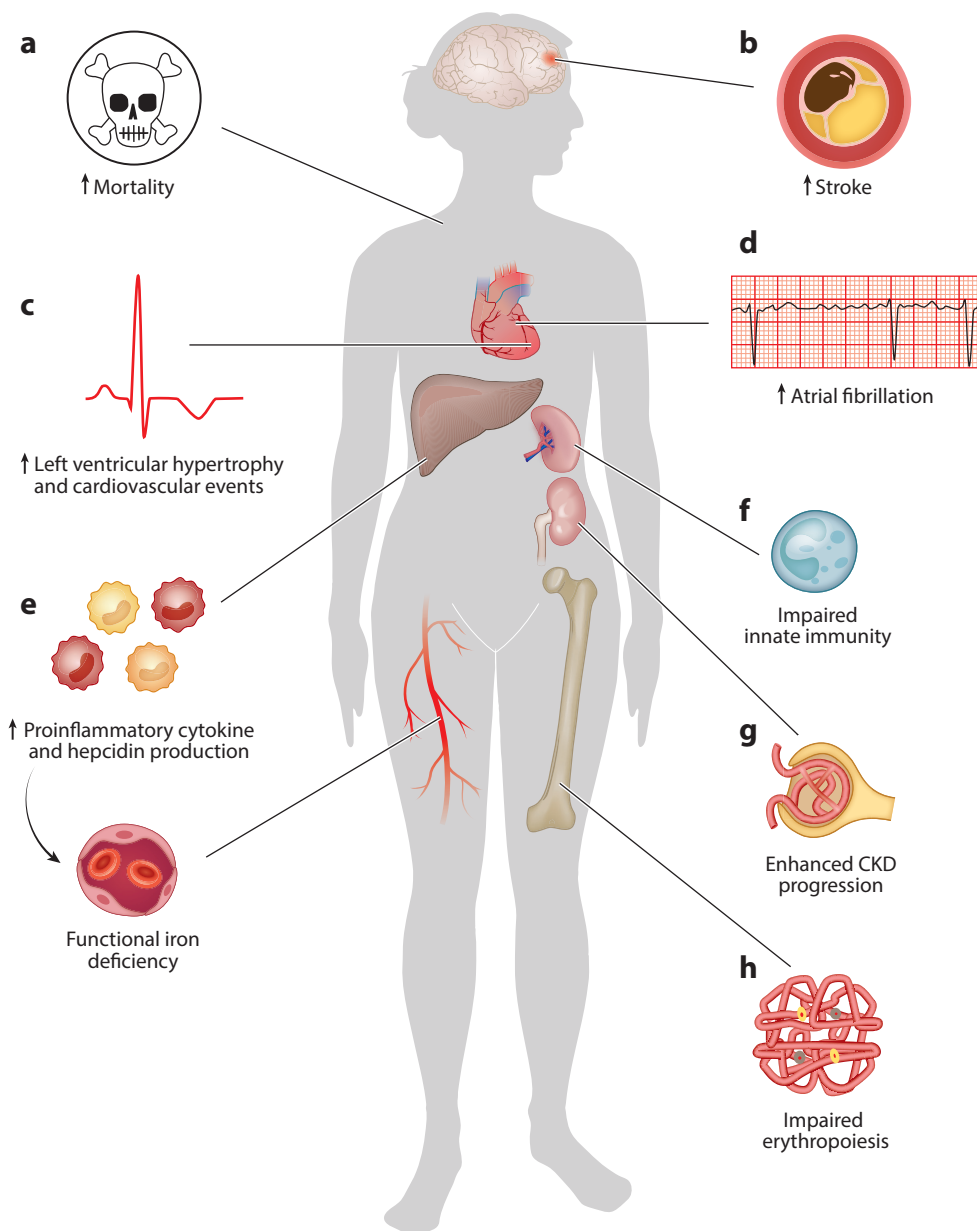
Figure 3

Complications of chronic kidney disease (CKD) associated with elevated fibroblast growth factor 23 (FGF23). Secondary elevation of FGF23 in CKD is associated with (*a*) increased mortality, (*b*) cerebrovascular events such as stroke, (*c*) left ventricular hypertrophy and heart failure, (*d*) atrial fibrillation, (*e*) proinflammatory cytokine and hepcidin production leading to functional iron deficiency, (*f*) impaired innate immunity, (*g*) accelerated CKD progression, and (*h*) impaired erythropoiesis.

between higher FGF23 levels and vascular calcification, others reported no association, and laboratory studies also failed to consistently demonstrate direct effects of FGF23 (84–90). Conversely, elevated serum phosphate is a well-established, independent risk factor for vascular calcification that induces osteogenic transformation of vascular smooth muscle cells with ectopic calcification (53). In the largest study of FGF23, phosphate, and arterial calcification in patients with CKD, higher serum phosphate was independently associated with increased prevalence and severity of coronary artery calcifications, independent of kidney function, traditional cardiovascular risk factors, and FGF23, which was not associated with coronary calcification (88). Furthermore, vascular calcification is not described in transgenic animals that overexpress FGF23, whereas genetic deletions of *FGF23* or *Klotho* that result in hyperphosphatemia cause severe vascular calcification (17, 39, 91). These data support a role for phosphate, but not FGF23, in the pathogenesis of vascular calcification. Further studies are needed to better characterize whether the anticalcification effects attributed to Klotho are mediated by direct effects on vascular tissues or indirectly by changes in serum phosphate or other factors (92, 93).

FGF23 and Chronic Kidney Disease Progression

Prospective observational studies suggest that elevated FGF23 is associated with progression of CKD to ESRD, independent of traditional risk factors, including decreased eGFR and proteinuria (**Figure 3**) (55, 94–96). Some studies went further and reported associations of elevated FGF23 with incident CKD, whereas others found no association (96, 97). These studies should be interpreted with caution because FGF23 is associated with eGFR, and baseline eGFR is such a potent risk factor for ESRD, unlike other outcomes such as mortality and cardiovascular disease. In this setting, traditional approaches to multivariable modeling may not adequately adjust for the effects of kidney function, especially longitudinally over time (98). More sophisticated analytic strategies that account for longitudinal time-varying changes in both FGF23 and eGFR and their interrelationships, such as marginal structural models modeling, could help further establish whether the effects of FGF23 are truly independent of kidney function. Ultimately, however, even this approach may be insufficient, and randomized trials of FGF23-lowering treatments may be the only way to precisely parse effects on CKD progression that are attributable to FGF23.

FGF23 and Anemia

Anemia is another common complication of CKD that increases in frequency and severity as eGFR declines (99). Historically, anemia of CKD has been understood as a consequence of (*a*) inflammation-mediated impairments in gut absorption of iron, (*b*) inflammation-mediated sequestration of iron in the reticuloendothelial system, (*c*) overt iron deficiency, (*d*) relative erythropoietin deficiency, and (*e*) bone marrow suppression by uremia (100).

Recent studies suggest that elevated FGF23 may be an additional factor that exacerbates anemia in CKD (**Figure 3**). In the CRIC Study, higher levels of baseline FGF23 were significantly associated with prevalent anemia, a decline in hemoglobin over 4 years, and the development of incident anemia, independent of eGFR, inflammatory markers, and other mineral metabolism markers (101). Animal models suggest potential underlying mechanisms. Injection of recombinant human FGF23 or dietary phosphate loading to induce endogenous FGF23 production significantly reduced renal erythropoietin mRNA production, levels of circulating erythropoietin, and hematopoietic stem cell enrichment in the spleen, bone marrow, and peripheral blood (102). Conversely, early hematopoietic progenitors increased in number and proliferative capacity following *Fgf23* ablation, suggesting negative regulatory effects of FGF23 on erythropoiesis (103).

FGF23 may also indirectly impair erythropoiesis by augmenting inflammation that exacerbates functional iron deficiency. In the CRIC Study, higher FGF23 was strongly associated with increased levels of inflammatory markers (104), and in animal studies, FGF23 directly stimulated hepatocyte production of proinflammatory cytokines via an FGFR4-dependent, Klotho-independent mechanism (105).

FGF23 and Infection

After cardiovascular disease, infection is the second most common life-threatening complication of CKD, accounting for approximately 20% of annual mortality in patients with ESRD (106). In a prospective study of nearly 1,400 participants in the HEMO study, higher FGF23 strongly associated with the composite end point of infectious hospitalization or infectious death, independent of dialysis vintage or baseline markers of inflammation (107). In vivo modeling of chemokine-activated neutrophils suggests that circulating FGF23 inhibits neutrophil adhesion and transendothelial migration via FGFR2 activation (108). Downregulation of FGFR2 abrogated the effects of FGF23 on myelocyte chemotaxis, but inhibition of Klotho did not block the effects, suggesting an FGF23-FGFR2-dependent, Klotho-independent mechanism (**Figure 3**) (108, 109).

In addition to effects on neutrophils, FGF23 may contribute to increased infectious risk by impairing innate immune functions of monocytes, which produce the antibacterial cathelicidin in a process that relies on monocyte expression of *CYP27B1* to support autocrine 1,25-dihydroxyvitamin D production and signaling (110). In vitro studies of mononuclear cells collected from healthy donors' peripheral blood and from peritoneal dialysate effluent from patients with ESRD demonstrated that exposure to exogenous FGF23 resulted in downregulation of *CYP271B* expression, leading to attenuated intracrine 1,25-dihydroxyvitamin D production and suppressed cathelicidin production (111).

SECONDARY FGF23 EXCESS IN OTHER CLINICAL SETTINGS

Heart Failure

Besides CKD, heart failure appears to be the second most common cause of secondary FGF23 excess. Prospective studies demonstrate that FGF23 rises during heart failure exacerbations, associates with disease severity, and predicts risk of heart failure–related death and likelihood of therapeutic response to certain heart failure treatments (**Figure 3**) (112–115). Whether FGF23 elevation in heart failure represents an effect of heart failure itself independent of CKD or is a consequence of subclinical reductions in renal perfusion that stimulate FGF23 production through the same pathways as in early CKD is unknown. It is also currently unknown if FGF23 excess is solely a biomarker or contributes mechanistically to adverse outcomes in patients with heart failure.

Acute Kidney Injury

Acute kidney injury (AKI) is associated with significant morbidity and mortality (116). No effective pharmacologic interventions exist, and timely diagnosis is delayed by lack of sufficiently sensitivity biomarkers of early kidney injury. Recent studies explored FGF23 as a potential prognostic and diagnostic biomarker in patients at risk for AKI. In folic acid–induced AKI in mice, FGF23 levels increased significantly within 1 h of injury and by 18-fold at 24 h (117). The results were unchanged when AKI was induced in mice with osteocyte-specific PTH receptor deletion, global deletion of PTH or the VDR, and dietary phosphate restriction. This suggests an intrinsic effect

of AKI to raise FGF23 independently and likely upstream of other mineral metabolites, although Klotho was not measured.

Prospective cohort studies of critically ill patients confirm these findings. In patients undergoing elective cardiac surgery in whom the onset of kidney injury can be more precisely pinpointed than in other causes of critical illness, FGF23 levels rose 15-fold in the first 24 h postoperatively before significant decrements in renal function were detected (118). Among the mineral metabolites, elevated FGF23, but not simultaneously measured calcium, phosphate, PTH or vitamin D, independently associated with increased risk for development of AKI and death in patients with critical illness of diverse causes (118, 119). These data suggest that FGF23 could serve as a novel biomarker of early AKI across a spectrum of renal insults. Beyond a biomarker, determining whether FGF23 excess contributes to the adverse outcomes of AKI will require additional study.

THERAPEUTIC APPROACHES TO LOWERING FGF23

Given the potential mechanistic links between FGF23 excess and adverse clinical outcomes in CKD, multiple different therapeutic strategies to lower FGF23 are under investigation (**Figure 4**).

Direct Targeting of FGF23: Burosomab

The monoclonal antibody, burosomab, was approved by the US Food and Drug Administration (FDA) to block FGF23 in X-linked hypophosphatemia (XLH). By preventing FGF23 from binding FGFRs, burosomab attenuates phosphate wasting and improves skeletal health in XLH (120).

Theoretically, burosomab could also be used to mitigate deleterious effects of FGF23 excess in CKD. However, nonselectively blocking FGF23 in states of secondary FGF23 excess, such as CKD, would severely exacerbate hyperphosphatemia and increase endogenous 1,25-dihydroxyvitamin D, which would increase risk of hypercalcemia, as confirmed in FGF23-deficient mice and rats treated with anti-FGF23 antibodies (35, 121). Worsened hyperphosphatemia, accompanied by hypercalcemia, would likely exacerbate arterial calcification in CKD that could accelerate mortality, as observed in rats with CKD (121). Thus, any cardiovascular, immune, or hematological benefits of globally blocking FGF23 in CKD would likely be offset by other toxicities.

A case could be made to consider burosomab in oligoanuric ESRD, in which lack of renal phosphate excretion would make it less likely for FGF23 antibodies to exacerbate hyperphosphatemia. Nevertheless, it is still possible that reversal of FGF23-mediated suppression of 1,25-dihydroxyvitamin D concentrations would increase risk of hypercalcemia and perhaps hyperphosphatemia by increasing gut absorption of both minerals.

Targeting Dietary Phosphate

Because dietary phosphate absorption is a major stimulus of FGF23 production, approaches that reduce the amount of absorbed phosphate in need of FGF23-mediated disposal are attractive therapeutically because they would be expected to lower FGF23 without raising serum phosphate.

Targeting dietary phosphate: dietary phosphate restriction. In healthy individuals, dietary phosphate restriction lowers FGF23 and serum phosphate (20). However, pilot studies in patients with CKD stages 3–4 yielded mixed results; positive effects were observed only with the most restrictive diets (750 mg/day), longer duration of exposure (>2 weeks), or the addition of phosphate binders (122–124). Conversely, increasing dietary phosphate beyond 1,500 mg/day was sufficient to increase FGF23 in small studies of patients with CKD (122, 125).
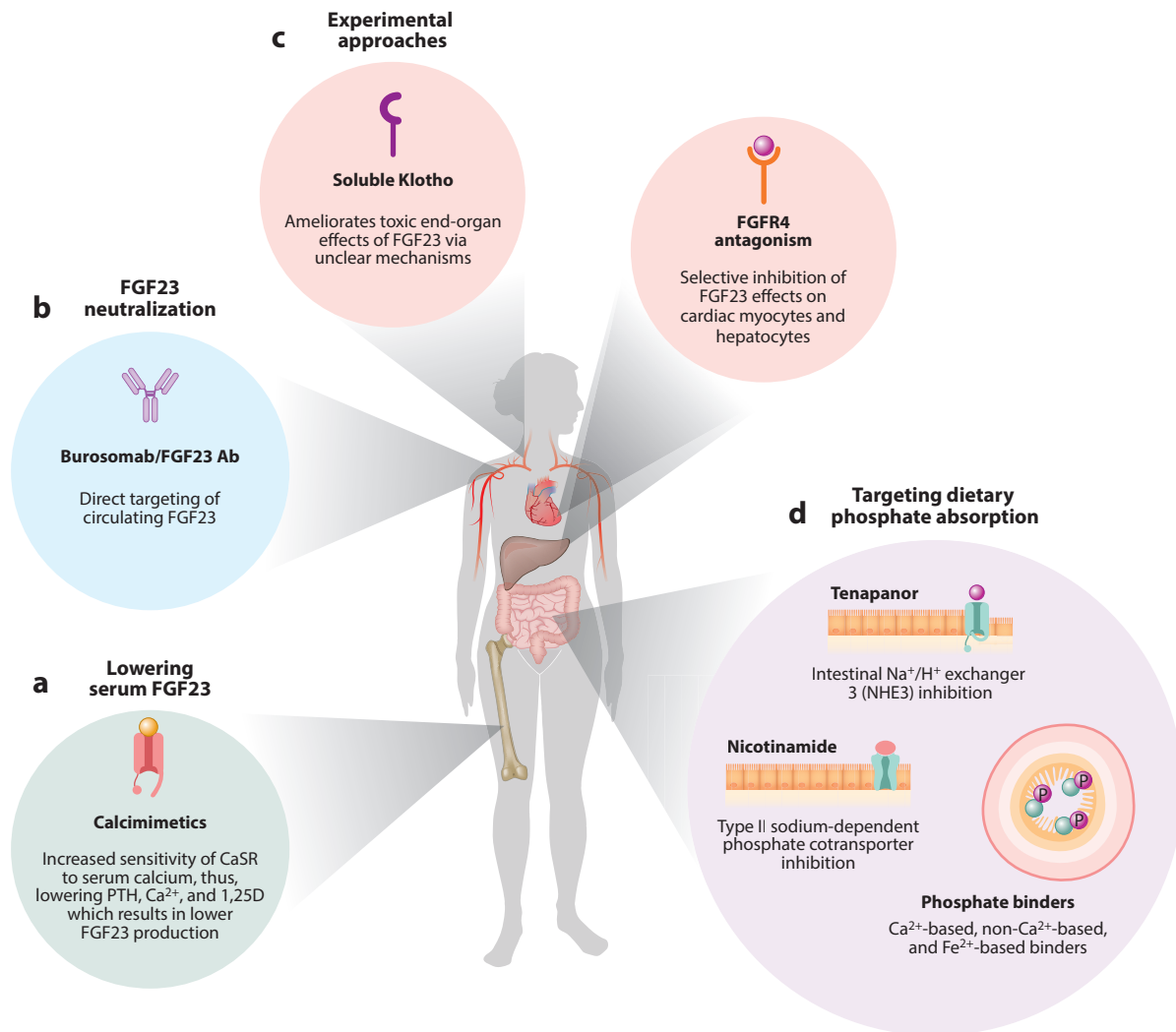
Figure 4

Therapeutic approaches (*clockwise*) to lowering fibroblast growth factor 23 (FGF23). (*a*) Calcimimetics lower FGF23, perhaps via reductions in parathyroid hormone (PTH), calcium, and 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], but exact mechanisms are unclear. (*b*) Circulating FGF23 can be directly neutralized by the commercially available monoclonal anti-FGF23 antibody burosomab. (*c*) Soluble Klotho is an experimental approach that appears to attenuate multiple end-organ effects of elevated FGF23 via unclear mechanisms. In the future, perhaps cardiotoxic and proinflammatory hepatic effects of FGF23-FGFR4 signaling will be able to be blocked by small molecule inhibitors of FGFR4 acting in the heart and liver. (*d*) Dietary phosphate restriction, use of phosphate binders, nicotinamide, and tenapanor can each decrease enteric phosphate absorption and thus, FGF23 production.

Altering the dietary phosphate profile to less bioavailable sources is an alternative approach to lower net phosphate absorption without altering the absolute amount of dietary phosphate (126). High phosphate bioavailability food sources include animal and dairy products, from which phosphate is readily absorbed, and processed foods that are often loaded with easily absorbed phosphate salts that are major components of additives used by the food industry to enhance taste, shelf life, and appearance of products while reducing their cost (127). In contrast, plant-based diets

have lower phosphate bioavailability due to much of the phosphate being found in phytate (127). Absorption of phytate-based phosphate requires the cleavage enzyme, phytase, that is not encoded in the human genome.

As a proof-of-concept for the therapeutic potential of altering the phosphate bioavailability profile of the diet, serum phosphate and FGF23 significantly decreased in uremic rats fed a plant-based versus a casein-based diet (128). In a study of patients with CKD stages 3–4, switching from a meat-based diet to a plant-based diet with identical total phosphate contents decreased FGF23 by approximately ∼30% in parallel with decreases in serum phosphate and urinary phosphate, indicating less phosphate absorption (129). While it is possible that the lower acid loads of the plant-based diets contribute to FGF23 reduction, as suggested by in vitro data (130), these studies suggest that dietary phosphate restriction and modifying the dietary phosphate composition from higher to lower bioavailable sources are tenable routes to reduced FGF23 in CKD. However, given the difficulty of long-term adherence to restrictive or modified diets and the ubiquity of phosphate additives in the Western food supply, dietary interventions likely need to be combined with pharmacological approaches to achieve sustained FGF23 reduction.

Targeting dietary phosphate: phosphate binders. Phosphate binders reduce gastrointestinal phosphate absorption and are the cornerstone of management of hyperphosphatemia in patients with ESRD. Several trials investigated the therapeutic potential of administering phosphate binders to patients with nondialysis-dependent CKD and normal serum phosphate in an effort to lower FGF23. The main findings were that noncalcium-based phosphate binders, including sevelamer and lanthanum, lower FGF23 more than placebo, sometimes statistically significantly, but usually only modestly and often nonsignificantly (131–135). Calcium-based phosphate binders fared worse, sometimes raising rather than lowering FGF23, likely because calcium loading is an independent stimulus of FGF23 that offsets the FGF23-lowering effects of calcium-mediated phosphate binding (131). Limitations of these trials were their relatively small sample size, short durations, and selection of patients with only modestly elevated FGF23 at baseline, who were likely on stable FGF23 trajectories that were resistant to reduction.

Sucroferric oxyhydroxide and ferric citrate are newer iron-based phosphate binders. Despite differences in their relative amounts of systemic iron absorption, both preparations demonstrated FGF23-lowering effects (136–138). Whereas the theoretical benefit of leveraging two different mechanisms—both phosphate binding and iron repletion—to lower FGF23 suggests that iron-based binders might be the most potent FGF23-lowering binders, head-to-head studies with other phosphate binders are needed to test this hypothesis.

Targeting dietary phosphate: nicotinamide. Nicotinamide is a derivative of niacin that inhibits intestinal NPT2b (134). Whereas passive paracellular transport is the major pathway for phosphate absorption across the intestine, animal studies of NPT2b deletion overlaid on CKD with and without use of phosphate binders suggest that NPT2b becomes more important to net phosphate absorption in the setting of phosphate binder use in CKD (139). Preliminary studies in humans suggested that nicotinamide could reduce phosphate absorption and perhaps FGF23 (140, 141). Based on these results, the CKD Optimal Management with BInders and NicotinamidE (COMBINE) trial tested whether treatment of 200 patients with CKD stages 3–4 for one year with lanthanum carbonate versus placebo and nicotinamide versus placebo could safely, effectively, and tolerably lower serum phosphate and FGF23 (134). There was no significant difference across the four parallel groups in either of the coprimary end points, phosphate or FGF23, indicating no synergistic effects of coadministering binders with nicotinamide. Upon further analysis, nicotinamide had no effect, whereas the phosphate binder induced significantly lower FGF23, although

the effect was modest relative to the high pill burden and frequent side effects that challenged adherence (134).

Targeting dietary phosphate: tenapanor. Tenapanor is a nonabsorbable oral inhibitor of sodium-hydrogen exchanger 3 (NHE3) that acts as a topical therapy in the gastrointestinal lumen. It is under development for treatment of irritable bowel syndrome with constipation and for hyperphosphatemia in ESRD. Tenapanor treats constipation by reducing gut absorption of sodium that increases stool electrolytes and water. The mechanism of treatment of hyperphosphatemia is more interesting. By blocking NHE3-dependent sodium absorption, tenapanor prevents proton secretion by enterocytes. The resultant decrease in intracellular pH reduces the permeability of the tight junctions that connect neighboring enterocytes (142). This results in less paracellular phosphate absorption, reduced serum phosphate, and significant FGF23 reductions (142). The primacy of the paracellular pathway for enteric phosphate absorption over the active transport pathway via NPT2b is supported by the more potent effects of tenapanor to lower serum phosphate and FGF23 than nicotinamide and by the lack of a phosphate phenotype in human syndromes of NPT2b deletion (143). Tenapanor holds significant promise as a novel therapy for ESRD given its modest pill burden (2 small tablets swallowed per day) and outsized phosphate- and FGF23-lowering effects relative to phosphate binders. While tenapanor demonstrated cardiac benefits in preclinical animal models of CKD (144), further human studies are needed to define the long-term tolerability of tenapanor, its potential to improve clinical outcomes in ESRD, and its potential application to lower FGF23 in patients with normal serum phosphate and nondialysis-dependent CKD.

Calcimimetics

The calcimimetics cinacalcet and etelcalcetide are FDA-approved treatments for secondary hyperparathyroidism in ESRD. Animal and human studies demonstrate that calcimimetics lower FGF23 in both CKD and ESRD despite differential effects on serum phosphate. In animal models and patients with nondialysis-dependent CKD, cinacalcet decreases PTH, 1,25-dihydroxyvitamin D, and FGF23, triggering hypocalcemia and hyperphosphatemia (145, 146). In patients with ESRD who do not rely on urinary phosphate excretion to maintain their serum phosphate, calcimimetics lower rather than raise serum phosphate, demonstrating that the effects of calcimimetics on FGF23 are independent of serum phosphate (147). Although the exact mechanisms are unknown, calcimimetics could theoretically lower FGF23 via reductions in PTH, calcium, and 1,25-dihydroxyvitamin D, even though the FGF23-lowering effects of cinacalcet and etelcalcetide occur independently of changes in PTH (148–150).

Among the calcimimetics, etelcalcetide demonstrated superior potency to cinacalcet, reducing FGF23 by approximately 50% regardless of whether or not vitamin D or dialysate calcium was simultaneously increased for treatment of concomitant hypocalcemia (150). Based on this far larger magnitude of FGF23 reduction than any other known therapy and on data suggesting that the magnitude of FGF23 lowering induced by cinacalcet influenced risk of adverse cardiovascular outcomes in the randomized Evaluation of Cinacalcet HCL Therapy to Lower Cardiovascular Events (EVOLVE) trial, it is tantalizing to consider whether a repeat of the EVOLVE trial (REVOLVE perhaps?) using etelcalcetide would push the near significant EVOLVE results across the "$p = 0.05$" finish line (151, 152). Unfortunately, conducting such a complex trial using an already approved agent would invoke all the same limitations related to drop-ins and drop-outs that undermined the original EVOLVE trial (153).

Experimental Approaches

In addition to burosomab, FGFR antagonists are being developed for treatment of XLH and related disorders of primary excess (154). Although global FGFR antagonists would be subject to the same limitations as anti-FGF23 antibodies, selective inhibition of FGFR4 could theoretically block the effects of FGF23 on cardiac myocytes and hepatocytes without interfering with phosphate homeostasis that is more dependent on FGF23 activating FGFR1-Klotho complexes.

Correction of Klotho deficiency in CKD with exogenous Klotho is another therapeutic approach under development. In preclinical models, exogenous soluble Klotho attenuated renal remodeling following ischemia-reperfusion injury, attenuated vascular calcification and LVH, and prolonged lifespan (155, 156). Among the poorly understood possible mechanisms underlying the putative benefits of Klotho, exogenous soluble Klotho may bind FGF23 in circulation and could theoretically attenuate its deleterious effects by shunting FGF23 signaling toward healthy Klotho-dependent pathways rather than the toxic Klotho-independent pathways that may predominate in advanced CKD when Klotho expression is downregulated (157).

Kidney Transplantation

Kidney transplantation is the definitive treatment for FGF23 excess due to CKD. Although the early posttransplant period is often marked by FGF23-mediated hypophosphatemia that is enabled by the capacity of the allograft to respond to the markedly elevated FGF23 levels of ESRD, posttransplant hypophosphatemia is often asymptomatic and self-limited (158). By three months posttransplant, FGF23 levels have typically normalized and are perhaps lower than expected (159). The latter may relate to tertiary hyperparathyroidism, which is much slower to resolve, and can maintain some degree of renal phosphate wasting that reduces total body phosphate and is somehow sensed and leads to appropriate downregulation of FGF23. Whether reduced FGF23 contributes to the markedly improved long-term clinical outcomes experienced by kidney transplant recipients is impossible to determine given the vast and simultaneous benefits of transplantation on nutrition, blood pressure, hematopoiesis, functional status, cardiovascular health, and multiple other systems and complications of uremia.

CONCLUSION

In a short time since the discovery of FGF23 as the cause of rare disorders of hypophosphatemic rickets, research into FGF23 biology in health and in CKD has helped usher in new paradigms of normal and disordered mineral metabolism and new opportunities for targeted interventions. While much has been learned, new questions abound about mechanisms of FGF23 regulation and effects in CKD and, most importantly, whether interventions that successfully target FGF23 can meaningfully improve clinical outcomes in patients living with and suffering from CKD.

DISCLOSURE STATEMENT

ACKNOWLEDGMENTS

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