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## Non-renal related mechanisms of FGF23 pathophysiology

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### Abstract

**a) Purpose of review:** We will review non-renal related mechanisms of fibroblast growth factor 23 (FGF23) pathophysiology.

**b) Recent findings:** FGF23 production and metabolism may be affected by many bone, mineral, and kidney factors. However, it has recently been demonstrated that other factors, such as iron status, erythropoietin, and inflammation, also affect FGF23 production and metabolism. As these non-mineral factors are especially relevant in the setting of chronic kidney disease (CKD), they may represent emerging determinants of CKD-associated elevated FGF23 levels. Moreover, FGF23 itself may promote anemia and inflammation, thus contributing to the multifactorial etiologies of these CKD-associated co-morbidities.

**c) Summary:** CKD-relevant, non-mineral related, bidirectional relationships exist between FGF23 and anemia, and between FGF23 and inflammation. Iron deficiency, anemia, and inflammation affect FGF23 production and metabolism, and FGF23 itself may contribute to anemia and inflammation, highlighting complex interactions that may affect aspects of CKD pathogenesis and treatment.

### Keywords

Chronic Kidney Disease; CKD-Mineral and Bone Disorder; Fibroblast Growth Factor 23; Iron; Anemia

### Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF23) is a hormone secreted by osteocytes that physiologically functions as a homeostatic regulator of phosphate and a counterregulatory hormone to 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). FGF23 decreases expression of the kidney proximal tubule type II sodium-phosphate cotransporters (NaPi-2a and NaPi-2c), reducing urinary phosphate reabsorption [1, 2]. FGF23 also decreases expression of renal 1 $\alpha$ -hydroxylase, which converts 25(OH)D to active 1,25(OH)<sub>2</sub>D, and increases expression of

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**Conflict of Interest**

Mark Hanudel, Marciana Laster, Isidro Salusky declare no conflict of interest.

**Human and Animal Rights and Informed Consent**

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renal 24-hydroxylase, which converts 25(OH)D and 1,25(OH)<sub>2</sub>D to inactive metabolites, therefore decreasing overall renal 1,25(OH)<sub>2</sub>D production [3-5].

FGF23 is critically important in CKD-mineral bone disorder (CKD-MBD). Bone [6] and circulating [7-10] FGF23 levels increase very early in the course of CKD, representing one of the first observable biochemical abnormalities in CKD. As CKD progresses and glomerular filtration rate declines, FGF23 levels continue to increase [7-10]. Although progressively increasing FGF23 levels help to maintain normophosphatemia until late in the CKD course [7, 10], they also contribute to 1,25(OH)<sub>2</sub>D suppression, thus promoting secondary hyperparathyroidism, a hallmark of CKD-MBD.

Moreover, elevated FGF23 levels in CKD may have other, “off-target” adverse effects. *In vitro* and murine *in vivo* studies have demonstrated that FGF23 directly causes cardiac myocyte hypertrophy [11] and, in human CKD cohorts, higher circulating FGF23 levels are associated with increased left ventricular mass [11-13]. FGF23 may also promote pro-fibrotic renal transforming growth factor beta (TGF-β) signaling pathways [14, 15]. Possibly as a consequence of this, at least in part, higher FGF23 levels are associated with faster disease progression in CKD patients [16-18]. Furthermore, in the setting of CKD, elevated FGF23 levels are associated with impaired neutrophil activation [19] and infection-related hospitalization or death [20]. As will be discussed here, FGF23 also promotes anemia and systemic inflammation. Likely due to these adverse cardiovascular, renal, immune system, and hematologic effects, higher FGF23 levels in CKD are independently associated with increased mortality [17, 21].

Osteocytic FGF23 production is regulated not only transcriptionally, but also at the post-translational stage. Prior to secretion, FGF23 may be proteolytically cleaved and inactivated [22]. Regulation of FGF23 post-translational intracellular cleavage is complex, involving multiple enzymes [23, 24]. Circulating levels of bioactive, intact FGF23 are determined by the net effect of factors affecting FGF23 transcription and factors affecting FGF23 post-translational cleavage. Two FGF23 enzyme-linked immunosorbent assays (ELISA) are used to measure FGF23 in the circulation: the C-terminal ELISA captures both intact FGF23 and its cleaved C-terminal fragments, thus functioning as a surrogate measure of all FGF23 translated (“total FGF23”), and the intact ELISA captures only intact FGF23 [22]. Comparing concentrations of intact FGF23 and total (intact + cleaved) FGF23 can provide a surrogate measure of FGF23 cleavage activity. Notably, CKD seems to be a state of progressively impaired FGF23 cleavage [25]; therefore, any transcriptional stimulus in CKD may possibly result in disproportionately increased circulating levels of intact FGF23. Indeed, in end-stage renal disease patients, it has been observed that most circulating FGF23 is intact [26, 27].

The pathophysiologic regulation of FGF23 in CKD and in health remains incompletely elucidated. Mineral metabolism factors, including phosphate [28, 29], 1,25(OH)<sub>2</sub>D [28, 30], parathyroid hormone (PTH) [31, 32], calcium [33], and Klotho [34] have been shown to affect FGF23 production (Figure 1). However, as will be described here, non-mineral factors such as iron status, erythropoietin, and inflammation have been recently shown to also influence both FGF23 production and metabolism.

## Effects of iron deficiency on FGF23

Iron deficiency was first suspected as a possible determinant of FGF23 based on observations made in patients with autosomal dominant hypophosphatemic rickets (ADHR), a disease characterized by increased FGF23 levels, resultant hypophosphatemia, and osteomalacia/rickets [35]. In female ADHR patients, hypophosphatemic flares are noted to coincide with the onset of menses and following pregnancy, times when iron deficiency is common, suggesting that iron deficiency may increase FGF23 production [35]. Indeed, mice fed a low iron diet have increased FGF23 levels [35-38] and, in multiple human cohorts, inverse relationships have been observed between markers of iron status and FGF23 levels [39-44].

The mechanism by which iron deficiency may stimulate FGF23 production has been assessed in a few studies. *In vitro*, it has been demonstrated that iron chelation treatment of osteoblastic cell lines increases *Fgf23* mRNA expression in a dose-dependent fashion [35, 37]. As iron chelation stabilizes hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) protein [35, 37], it has been hypothesized that HIF1 $\alpha$  may mediate the stimulatory effects of iron deficiency on *Fgf23* transcription. Indeed, treatment of osteoblastic cell lines with an agent that activates HIF1 $\alpha$  increases *Fgf23* mRNA expression [35, 45], an effect abrogated by HIF1 $\alpha$  inhibitors [37, 45]. It has been shown that HIF1 $\alpha$  binds directly to a consensus HIF1 $\alpha$  binding site in the proximal *Fgf23* promoter to induce transcription [45]. Consistent with these observations, osteoblastic cells cultured in hypoxic conditions have increased HIF1 $\alpha$  protein expression and increased *Fgf23* mRNA expression [36]. Extended to *in vivo* models, rats housed in hypoxic conditions have increased circulating FGF23 levels [36]. Furthermore, in pediatric patients with congenital cyanotic heart disease and normal kidney function, more severe chronic hypoxemia is associated with higher plasma FGF23 concentrations [46].

Notably, iron deficiency couples increased *Fgf23* transcription with increased intracellular FGF23 post-translational cleavage, such that circulating levels of bioactive, intact FGF23 may remain near normal levels. In mice fed a low iron diet, *Fgf23* mRNA expression is increased, circulating levels of total FGF23 are increased, but increases in circulating levels of intact FGF23 are greatly attenuated [35-38], consistent with increased mRNA expression coupled with increased proteolytic cleavage. In humans with normal kidney function, total FGF23 inversely correlates with serum iron concentrations, but intact FGF23 does not [40, 43]. However, in ADHR patients, in whom a mutation at the FGF23 cleavage site renders intact FGF23 much more cleavage-resistant, both total and intact FGF23 inversely correlate with serum iron concentrations [40]. The mechanism by which iron deficiency may increase FGF23 proteolytic cleavage may in part be mediated by HIF1 $\alpha$ -mediated upregulation of furin, an enzyme that cleaves intact FGF23 [47, 48].

Importantly, CKD may represent an acquired state of impaired FGF23 cleavage [25]. As CKD progresses, total FGF23 levels increase, with a larger and larger percentage of circulating FGF23 present in its intact form [27, 26]. Therefore, in CKD, factors that increase *Fgf23* transcription may result in disproportionate increases in circulating intact FGF23. Indeed, in mouse models of CKD, iron deficiency-induced increases in *Fgf23* transcription are at least partially decoupled from increases in FGF23 cleavage, such that

iron deficiency results in a much higher percentage of circulating FGF23 that is intact in CKD vs. non-CKD states [37, 38].

### Effects of inflammation on FGF23

In human cohorts, positive associations between markers of inflammation and FGF23 levels have been observed [49, 50]. *In vitro*, in an osteocyte-like cell line, pro-inflammatory cytokines dose-dependently upregulate *Fgf23* mRNA expression [51]. *In vivo*, it has been demonstrated that inflammatory stimuli increase both *Fgf23* transcription and FGF23 cleavage [37]. Both acutely and chronically, in mice injected with heat-killed *Brucella abortus* or interleukin-1 $\beta$  (IL-1 $\beta$ ), bone *Fgf23* mRNA expression increases and circulating total FGF23 increases; however, circulating levels of intact FGF23 remain normal or near-normal, suggesting coupling of increased transcription with increased proteolytic cleavage [37]. Indeed, in these models, furin inhibition partially uncouples these processes, increasing circulating intact FGF23 [37]. Inflammation may directly affect FGF23 production and metabolism via HIF1 $\alpha$ -dependent mechanisms. Mice injected with *Brucella abortus* or IL-1 $\beta$  have increased bone *Hif1a* mRNA expression [37]. Moreover, HIF1 $\alpha$  inhibition attenuates inflammation-induced increases in bone *Fgf23* mRNA expression and circulating total FGF23 levels; however, despite decreases in total FGF23, circulating intact FGF23 concentrations increase, which is consistent with decreased HIF1 $\alpha$  stimulation of furin [37]. Recently, it has also been demonstrated that the interleukin-6/soluble interleukin-6 receptor complex can increase bone *Fgf23* mRNA expression independent of HIF1 $\alpha$ , acting via a STAT3 sequence in the FGF23 promoter [52].

Inflammation may also indirectly affect FGF23 via “functional” iron deficiency. Inflammation strongly induces production of hepcidin [53], a liver-derived hormone that functions to promote iron sequestration and inhibit enteral iron absorption [54]. Mice injected with exogenous hepcidin have acutely increased bone *Fgf23* mRNA expression and circulating total FGF23 levels, with normal intact FGF23 [37]. Also, the aforementioned mice injected with inflammatory stimuli had decreased serum iron concentrations [37], suggesting some component of inflammation-induced functional iron deficiency contributing to increases in *Fgf23* transcription and FGF23 cleavage [37].

### Effects of erythropoietin on FGF23

Like iron deficiency and inflammation, erythropoietin (EPO) also increases both *Fgf23* transcription and FGF23 cleavage. Importantly, EPO induces non-osseous *Fgf23* mRNA expression in the bone marrow [55-60]. Several recent murine studies have demonstrated that increased endogenous EPO levels are associated with increased FGF23. Mice with chronically high endogenous EPO levels [60], mice with phlebotomy-induced acute increases in EPO levels [56], and mice treated with hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (which pharmacologically increase endogenous EPO levels) [57] have increased marrow *Fgf23* mRNA expression, increased circulating total FGF23 levels, but attenuated increases in circulating intact FGF23 levels, suggesting (incomplete) coupling of increased *Fgf23* transcription with increased FGF23 cleavage. Similarly, exogenous EPO administration acutely increases marrow *Fgf23* mRNA expression and circulating total

FGF23 levels, with attenuated increases in circulating intact FGF23 levels [55-60]. The mechanisms by which EPO increases *Fgf23* transcription and FGF23 cleavage remain incompletely elucidated; however, the effects of EPO on FGF23 seem to be independent of iron status [55, 59, 60].

Similar to what has been observed in mice, in humans, exogenous EPO administration acutely increases circulating total FGF23 levels out of proportion to intact FGF23 [55, 59]. In humans with pre-dialysis CKD and dialysis-dependent CKD, serum EPO levels and exogenous EPO dose, respectively, are positively and independently associated with total FGF23 levels [60]. Moreover, in a cohort of 680 renal transplant recipients, serum EPO levels are associated with total FGF23, but not intact FGF23, consistent with the effects of EPO on FGF23 production and metabolism observed in the murine studies [60]. As EPO is more strongly associated with total FGF23 levels than intact FGF23 levels, suggesting a disproportionate increase in circulating FGF23 fragments, further research is needed regarding the possible physiologic and/or pathologic effects of these fragments. Nevertheless, the EPO-FGF23 association suggests another possible adverse effect potentially related to excessive EPO administration.

### Effects of FGF23 on anemia

Factors related to anemia, such as iron deficiency and increased EPO levels [61], have effects on FGF23. Conversely, FGF23 itself may have effects on erythropoiesis. *Fgf23* knockout mice have increased serum EPO concentrations and increased measures of erythropoiesis [62]. In wild type mice, the administration of recombinant intact FGF23 decreases renal *Epo* mRNA expression [59], serum EPO concentrations [62], and erythropoietic parameters [62], and the administration of an FGF23 blocking peptide increases serum EPO concentrations and some erythropoietic parameters [63]. These data suggest that FGF23 may have negative regulatory effects on erythropoiesis. Consistent with these murine studies, in a large cohort of human CKD patients, elevated circulating total FGF23 levels are independently associated with both prevalent and incident anemia [64].

### Effects of FGF23 on inflammation

Inflammation is a stimulus of FGF23 production, and FGF23 itself may be pro-inflammatory. A recent study showed that three different high FGF23 murine models (wild type mice administered recombinant intact FGF23,  $\alpha$ -klotho null mice, and wild type mice fed a high phosphate diet) had increased hepatic C-reactive protein (CRP) and interleukin-6 (IL-6) mRNA expression and increased serum CRP levels [65]. These pro-inflammatory changes were ameliorated in FGF receptor 4 (FGFR4) knockout mice [65], suggesting that FGF23 may directly stimulate hepatic secretion of inflammatory cytokines via FGFR4 binding and activation. Lastly, in a rat model of CKD (5/6 nephrectomy), administration of an isoform-specific FGFR4 blocking antibody decreases hepatic and serum CRP [65], suggesting that FGF23 may represent a pro-inflammatory factor in the setting of CKD.

## Summary

FGF23 is an important hormone centrally related to CKD-MBD pathophysiology. FGF23 regulation is complex, as FGF23 is regulated at both the transcriptional and post-translational stages, and FGF23 may be affected by many bone, mineral, and kidney factors. Interestingly, several recent studies have demonstrated that non-mineral factors, such as iron status, erythropoietin, and inflammation, also affect FGF23 production and metabolism. Specifically, iron deficiency, erythropoietin, and inflammation have been shown to concurrently increase FGF23 transcription and FGF23 post-translational cleavage, as evidenced by the observations that these stimuli induce increases in circulating total (C-terminal) FGF23 levels out of proportion to intact FGF23 levels. The degree to which increased post-translational cleavage offsets increased transcription determines, in part, how much intact FGF23 is secreted. Further research is needed regarding the mechanisms by which these factors increase FGF23 transcription; how FGF23 post-translational cleavage is regulated; and what the physiologic and/or pathologic implications are of elevated FGF23 fragment concentrations.

As these non-mineral factors are especially relevant in the setting of CKD, they may represent emerging determinants of CKD-associated elevated FGF23 levels. However, relationships between anemia/inflammation and FGF23 may be bidirectional in nature. Anemia-related factors and inflammation can affect FGF23 production and metabolism, and FGF23 itself may contribute to anemia and inflammation. These associations underscore the complex interrelationships among aspects of CKD-related anemia, CKD-MBD, and their respective treatment modalities. How these interrelationships affect clinical outcomes in CKD patients requires further study.

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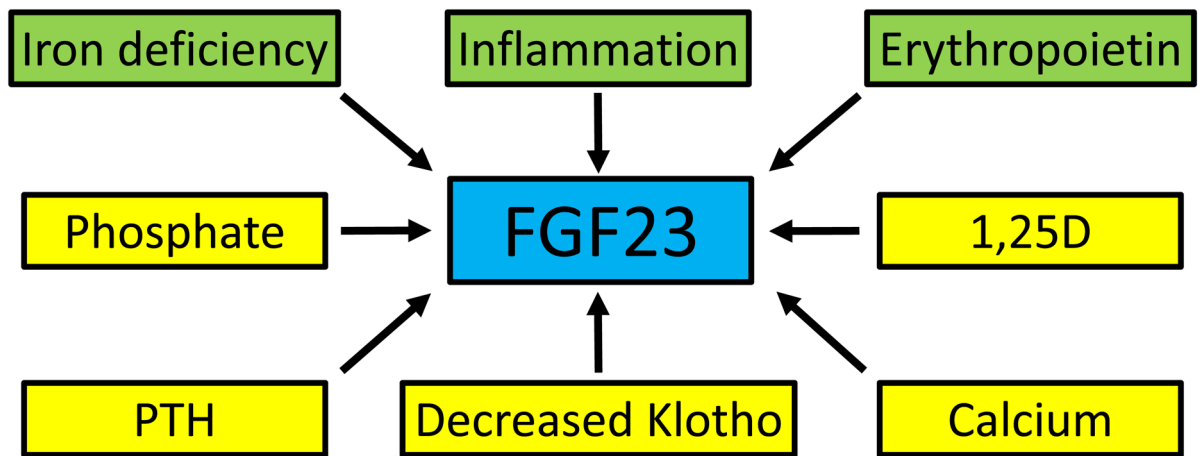
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# Stimuli of FGF23 Production



**Figure 1:**

Mineral and non-mineral factors involved in FGF23 regulation include phosphate, 1,25-dihydroxyvitamin D, parathyroid hormone, calcium, Klotho, iron, inflammation, and erythropoietin.