Published in final edited form as:

Curr Opin Nephrol Hypertens. 2019 July ; 28(4): 304–310. doi:10.1097/MNH.0000000000000514.

Crosstalk between FGF23, iron, erythropoietin, and inflammation in kidney disease

Jodie L. Babitt¹, Despina Sitara^{2,3,*}

¹Division of Nephrology, Program in Membrane Biology, Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

²Department of Basic Science and Craniofacial Biology, New York University College of Dentistry, New York, NY, USA

³Department of Medicine, New York University School of Medicine, New York, NY, USA

Abstract

Purpose of review: Recent research has revealed that regulation of the bone-secreted hormone fibroblast growth factor 23 (FGF23) is not limited to classical mineral factors. Specifically, bi-directional relationships have been described between FGF23 production and anemia, iron status, and inflammation. Here, we will review the latest published articles on the crosstalk between FGF23 and the aforementioned non-classical factors.

Recent findings: It has been recently reported that erythropoietin (EPO), iron deficiency, and inflammation increase FGF23 production and metabolism. Moreover, FGF23 promotes anemia and regulates inflammatory responses. These findings are particularly important in the setting of chronic kidney disease (CKD) which is characterized by elevated FGF23 levels and several associated comorbidities.

Summary: Regulation of FGF23 is complex and involves many bone and renal factors. More recently, EPO, iron deficiency, and inflammation have been also shown to affect FGF23 transcription and cleavage. Importantly, FGF23 has emerged as a regulator of erythropoiesis, iron metabolism, and inflammation. These findings provide novel and important insights into the pathophysiologic mechanisms of CKD and may present new opportunities for therapeutic clinical interventions.

Keywords

FGF23; Iron Deficiency; Anemia; Erythropoietin; Inflammation; Chronic Kidney Disease

*Corresponding Author ds199@nyu.edu.

Authors Contact information: Despina Sitara, Ph.D., Department of Basic Science and Craniofacial Biology, New York University College of Dentistry, 345 East 24th Street, Room 902C, New York, NY10010, USA, ds199@nyu.edu, Phone: +1 212 998 9965, Fax: +1 212 995 4204

Jodie L. Babitt, M.D., Division of Nephrology, Massachusetts General Hospital - Harvard Medical School, 185 Cambridge St., CPZN 8208, Boston, MA 02114, Babitt.Jodie@mgh.harvard.edu, Phone: 617-643-3181, Fax: 617-643-3182

CONFLICTS OF INTEREST

JLB has ownership interest in Ferrumax Pharmaceuticals and has received consulting fees from Keryx Biopharmaceuticals and Disc Medicine. DS has no conflict of interest.

INTRODUCTION

FGF23 is a bone-secreted hormone that functions as a central regulator of phosphate and vitamin D homeostasis, and bone mineralization. FGF23 consists of an N-terminal FGF homology domain and a C-terminal domain which interacts with the co-receptor α -klotho that is required for efficient FGF23-FGF receptor signaling (1). An important mechanism for regulating FGF23 activity is its degradation by proteolytic cleavage, which abolishes the biological activity of the intact full-length FGF23 (iFGF23) peptide, and results in the presence of C-terminal fragments (cFGF23) in the circulation (2). Some biochemical assays that measure FGF23 detect both iFGF23 and cFGF23 (hereafter called total FGF23), whereas others detect only iFGF23. Classically described regulators of FGF23 include phosphate, calcium, vitamin D, and parathyroid hormone (PTH). The traditional actions of FGF23 are exerted in the renal proximal tubule, where it inhibits phosphate re-absorption by downregulating the type II sodium-phosphate co-transporters (NaPi-2a and NaPi-2c) (3–6). FGF23 also decreases expression of 1α -hydroxylase and increases expression of 24 -hydroxylase, causing an overall reduction in active $1,25(\text{OH})_2$ vitamin D (calcitriol) levels (7–10). In the last few years, several groups have reported new actions of FGF23 that extend beyond its phosphate- and vitamin D-regulating roles. Particularly, inflammation, iron status, and erythropoietin (EPO) have emerged as new players that are influenced by FGF23 and also participate in FGF23 regulation. This review focuses on the recent advances in understanding the role of these new players in FGF23 production, metabolism, and action.

FGF23 contributes to CKD-MBD and is associated with adverse outcomes in kidney disease

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a common complication of CKD characterized by excess FGF23, vitamin D deficiency, hypocalcemia, hyperphosphatemia, and increased parathyroid hormone (PTH), leading to bone mineralization defects and extra-skeletal calcifications (11, 12). Increased FGF23 levels represent one of the first biochemical derangements in CKD-MBD and are therefore thought to play an important causal role (13, 14). Increased FGF23 levels are also associated with accelerated kidney disease progression, greater cardiovascular risk, left ventricular hypertrophy (LVH), and mortality in CKD patients (15, 16). In addition to CKD, FGF23 is also increased and associated with adverse outcomes in acute kidney injury (AKI) (17, 18). Intriguingly, rodent studies suggest a causal role for FGF23 excess in inducing LVH (15, 16). However, a recent study demonstrated that high FGF23 was not sufficient to cause cardiovascular disease in the absence of renal impairment, suggesting that other factors, such as high phosphate levels and inflammation, play a crucial role in the effect of FGF23 excess on the heart (19)**.

Anemia and CKD

Anemia is another common complication of CKD that often coexists with CKD-MBD (20). Two major causes of anemia in CKD are deficiency of EPO, a kidney-derived hormone responsible for stimulating red blood cell (RBC) production, and restricted supply of iron, an essential component of hemoglobin (20). Iron is provided mainly by recycling from

senescent erythrocytes, and to a lesser extent by dietary absorption (21). CKD patients are likely to develop true iron deficiency from nutritional deficits, medications that impair dietary absorption, and blood losses from hemodialysis, phlebotomy, and uremic platelets (21). They are also likely to develop functional iron deficiency caused by inflammation-mediated induction of the iron regulatory hormone hepcidin, which causes degradation of the iron exporter ferroportin to block iron release into the bloodstream from both iron recycling macrophages and dietary sources (21). CKD-associated anemia is treated by recombinant human EPO (rhEPO) or related erythropoiesis stimulating agents, and by iron supplementation (20). Recent work has shed new light on how these mediators of renal anemia and therapeutic strategies to treat anemia crosstalk with FGF23.

Iron deficiency and inflammation stimulate FGF23 production and cleavage

Iron deficiency was first discovered to regulate FGF23 when it was recognized that patients with autosomal dominant hypophosphatemic rickets (ADHR), characterized by mutations in FGF23 that impair cleavage, developed flares of hypophosphatemia that coincided with states of iron deficiency (22, 23). Numerous studies have now confirmed that iron deficiency induces FGF23 production (24). Under normal conditions, this increased production is largely balanced by increases in FGF23 cleavage, resulting in higher circulating total FGF23 with lesser or no increase in iFGF23. However, when FGF23 cleavage is impaired, this enhanced FGF23 production leads to higher circulating iFGF23 and the functional consequences of FGF23 excess. A direct effect of iron deficiency on FGF23 production was demonstrated by the ability of iron chelators to stimulate FGF23 production in isolated bone cell cultures (22, 25). Transcriptional regulation by hypoxia inducible factor (HIF)1 α has been proposed to play a mechanistic role, although the *in vivo* regulatory mechanisms are still not fully understood (22, 25).

Inflammation was similarly demonstrated to induce FGF23 production and cleavage (24). This may be, partly, an indirect effect of increased hepcidin production, thereby causing iron sequestration and functional iron deficiency (25); however, a direct effect is also suggested by the ability of inflammatory cytokines to induce FGF23 production in isolated bone cell cultures (25). The molecular mechanisms for inflammatory-mediated FGF23 induction are still not fully understood. Prior studies suggested a role for HIF1 α and NF- κ B (25, 26). More recently, IL6/soluble IL6 receptor fusion protein was reported to induce FGF23 promoter activity directly via a STAT3 response element on the FGF23 promoter (27)*. Moreover, *Il6* deletion blunted FGF23 induction in both adenine-induced CKD and folate-induced AKI mouse models, suggesting a functional role for the IL6/STAT3 pathway in inducing FGF23 in both CKD and AKI (27)*. A recent study also identified a distal enhancer 16kb upstream of the *FGF23* transcription start site that contributes to FGF23 induction by inflammation or oxalate-induced kidney injury since deletion of this enhancer in mice blunted induction of *Fgf23* expression and circulating iFGF23 by these stimuli (28).

EPO induces FGF23 production and cleavage

Recent research shows that, like iron deficiency and inflammation, EPO also increases FGF23 production and cleavage. Injection of rhEPO increased circulating total FGF23, with

lessor or no increase in iFGF23, in both humans and rodents [(29), (30)*, (31), (32), (33)**, (34)*]. Similar results were observed in mice with increased endogenous EPO levels: transgenic mice overexpressing EPO, β -thalassemia intermedia mice, phlebotomized mice, and mice treated with a HIF-proline hydroxylase (HIF-PH) inhibitor [(30)*, (32), (33)**]. Increased FGF23 in these models was not an indirect effect of EPO-induced iron deficiency because it was largely preserved when exogenous iron was co-administered and in the spontaneously iron loaded thalassemia model (29), (33)**]. Moreover, pre-treatment with neutralizing anti-EPO antibodies abolished FGF23 induction by the HIF-PH inhibitor, suggesting an EPO-dependent regulation of Fgf23 induction rather than a direct effect of modulating HIF activity (32).

In mice, the increase in plasma total FGF23 coincided with increases in *Fgf23* mRNA, suggesting that EPO induces FGF23 production. Interestingly, bone marrow was a major tissue where EPO induced *Fgf23* mRNA [(29), (30)*, (31), (32), (33)**, (34)*], particularly in erythroid lineage cells [(30)*, (31), (34)*]. However, bone *Fgf23* mRNA was not increased in 2 studies that utilized lower EPO doses [(30)*, (34)*]. At higher EPO doses, *Fgf23* mRNA was also induced in bone [(29), (32), (33)**] and other hematopoietic progenitor cell subsets [(29), (34)*]. A functional role for bone marrow in EPO-mediated FGF23 induction was supported by the blunting of FGF23 induction after bone marrow ablation (29).

Analogous to iron deficiency and inflammation, EPO administration led to greater increases in intact FGF23 in a mouse model of CKD where FGF23 cleavage is reduced (29). However, the percentage of iFGF23 relative to total FGF23 was still reduced in CKD, suggesting that FGF23 cleavage was stimulated by EPO in CKD (33)**]. How EPO stimulates FGF23 cleavage remains uncertain, but mice with increased endogenous EPO production due to phlebotomy or chronically elevated EPO levels, did exhibit reduced bone and bone marrow levels of N-acetylgalactosaminyltransferase 3 (Galnt3), which inhibits FGF23 proteolysis by glycosylating its cleavage site [(33)**, (34)*]. However, GALNT3 downregulation was not observed acutely after EPO injection [(33)**, (34)*].

Recent studies suggest that EPO may also play a pathogenic role in FGF23 induction in AKI (31). Septic AKI induced by cecal ligation and puncture in mice was associated with increased endogenous EPO production, bone marrow *Fgf23* mRNA, and circulating intact and C-terminal FGF23 levels. Importantly, pharmacologic blockade of the EPO receptor partially prevented the increase in iFGF23 and cFGF23 (31). Plasma EPO levels were also positively associated with circulating iFGF23 and cFGF23 levels in septic patients, and both EPO and FGF23 (intact and C-terminal) levels were higher in patients who developed AKI compared with those who did not (31). However, the relevance of EPO-induced FGF23 in AKI and the molecular mechanisms driving it, need further investigation.

FGF23 as a regulator of inflammatory responses

Recent studies suggest that not only FGF23 is regulated by EPO, iron status, and inflammation, but also FGF23 may promote anemia, iron deficiency, and systemic inflammation, especially in the setting of CKD. Singh *et al* showed that high FGF23 levels

in mice (by injection with recombinant FGF23, a high phosphate diet, or α -klotho knockout) led to increased hepatic and serum levels of C-reactive protein (CRP) and IL6 (35). Importantly, these inflammatory increases were ameliorated in *Fgfr4* knockout mice, and after treatment with an FGFR4 blocking antibody in rats with CKD induced by 5/6 nephrectomy (35). These studies suggest that FGF23 may directly stimulate secretion of pro-inflammatory cytokines via FGFR4 binding and activation. Recently, it was reported that inhibition of FGF23 signaling ameliorated inflammation in a CKD mouse model, and improved renal dysfunction, reduced renal inflammation and prevented renal fibrosis, in a mouse model of diabetic nephropathy, suggesting that blocking FGF23 activity could be used as a therapeutic target to attenuate inflammation [(36)**, (37)].

Although bone is the major source of FGF23 production, it was also reported that FGF23 is produced by M1 pro-inflammatory macrophages, suggesting that FGF23 may act locally to mediate inflammatory responses (38). The same study showed that recombinant FGF23 (rFGF23) promoted TNF α expression in RAW264.7 M0-type macrophages and peritoneal macrophages. Moreover, peritoneal macrophages from Hyp mice, which have increased endogenous FGF23 production, exhibited higher basal TNF α expression and an exaggerated TNF α response to LPS/IFN- γ treatment (38). This effect of FGF23 may be due to its inhibitory effect on local production of calcitriol by M2 macrophages, which counteracts the pro-inflammatory effects of FGF23 and stimulates anti-inflammatory responses (38). A different study demonstrated that FGF23 directly inhibits neutrophil activation and recruitment in CKD by interfering with integrin expression and thus negatively impacts host defense (39). In line with these data, treatment of healthy leukocytes with FGF23 *in vitro* resulted in significantly lower expression of CD11b both in resting and activated cells compared with untreated cells, suggesting that FGF23 impairs neutrophil recruitment ability (40).

FGF23 as a regulator of iron homeostasis and erythropoiesis

FGF23 also has a functional impact on erythropoiesis. *Fgf23* deletion in mice increased renal Epo expression, circulating EPO levels, hemoglobin, RBC number, bone marrow erythroid progenitors and hematopoietic stem cells (HSCs), whereas administration of rFGF23 resulted in the opposite effects in wild-type mice (41). The effects of *Fgf23* deletion on erythropoiesis were independent of vitamin D, and they were also detected in fetal livers, suggesting that they are not the result of altered bone marrow niche alone (41). Importantly, inhibition of FGF23 signaling using an FGF23 blocking peptide rescued anemia and iron deficiency in a mouse model of CKD by increasing EPO and other erythropoietic parameters (hemoglobin, RBC number, and bone marrow erythroid progenitors), decreasing erythroid cell apoptosis, and driving HSCs toward the erythroid lineage (36)**. Moreover, inhibition of FGF23 signaling significantly increased serum iron and ferritin levels and attenuated inflammation (36)**. These data suggest that high FGF23 levels negatively affect erythropoiesis, whereas loss/inhibition of FGF23 stimulates erythropoiesis.

Associations between FGF23, anemia, and EPO in CKD patients

Previous studies reported significant associations between circulating FGF23 levels and both iron deficiency and inflammation in humans (24). Recent studies have expanded these findings to report significant associations between FGF23 levels, anemia, and EPO levels in CKD patients. A prospective cohort study of 3869 patients with non-dialysis CKD reported that higher levels of circulating total FGF23 were significantly associated with prevalent anemia, the decline in hemoglobin over time, and the risk of incident anemia (42)*. These associations remained significant even after adjusting for CRP, as a marker of inflammation, and RBC mean cell volume and iron supplementation, as markers of iron deficiency; however, more direct iron status markers were not reported (42)*. Another prospective longitudinal study of 2,089 Korean patients reported a positive association between log-transformed total FGF23 levels and prevalent anemia as well as risk of incident anemia (43). Log-transformed total FGF23 was also inversely associated with serum iron and transferrin saturation and positively associated with hepcidin in this study; however, the associations between total FGF23 and anemia persisted even after adjustment for these and other potential confounding parameters, including ferritin and CRP (43). Although neither of these studies reported EPO levels, another publication reported that EPO levels were positively associated with log total FGF23 levels in a small cohort of non-dialysis CKD patients, and rhEPO dose was positively associated with log total FGF23 levels in a small cohort of hemodialysis patients (33)**. These associations remained significant even after adjusting for serum transferrin saturation, ferritin, hemoglobin, and CRP (33)**. In a cohort of 680 kidney transplant recipients, both EPO levels and anemia were independently associated with total FGF23 levels, even after multivariable adjustment including ferritin and CRP (33)**. Limitations of these studies are that iron, inflammation, EPO, and hemoglobin levels have interdependent effects, making it difficult to fully adjust for their potential confounding effects on each other. Moreover, these associational studies are not able to demonstrate causality.

Effects of iron supplementation on FGF23 levels and mineral metabolism in clinical trials

A recent substudy of a large randomized controlled, which compared the safety and efficacy of ferric carboxymaltose versus ferumoxytol to treat iron deficiency, investigated the impact of these two different intravenous (IV) iron preparations on FGF23 levels and mineral metabolites [(44)**, (45)]. Total FGF23, but not iFGF23, levels were elevated at baseline in these patients and were independently associated with lower serum ferritin and hemoglobin (44)**. In the subgroup of patients with CKD, iFGF23 levels were higher than in patients without CKD, whereas total FGF23 levels were similar, consistent with reduced cleavage in CKD and a potential contributory role for iron deficiency in CKD-associated FGF23 excess (44)**. Importantly, both intravenous iron preparations reduced total FGF23 levels concomitant with improvements in serum iron parameters and hemoglobin [(44)**, (45)].

Notably, only ferric carboxymaltose significantly induced circulating iFGF23 levels, which was associated with renal phosphate wasting, reduced serum calcitriol and calcium,

increased parathyroid hormone and hypophosphatemia (44)**. Hypophosphatemia occurred in 50.8% of the ferric carboxymaltose group, with 10% of patients having severe hypophosphatemia and 30% having persistent hypophosphatemia 4 weeks after the last dose, compared with 0.9% of the ferumoxytol group (44)**. Iron-induced hypophosphatemia was previously reported in case reports dating back to 1982 as well as smaller retrospective and pilot studies, in some cases associated with serious musculoskeletal complications (46–51). These complications have been observed with only a subset of IV iron preparations, mainly ferric carboxymaltose, iron polymaltose, and saccharated iron oxide, suggesting it is not a class effect of all IV iron, but may be a consequence of the carbohydrate shell associated with certain preparations [(44)**, (46), (48)]. Although the specific mechanisms are unknown, these data suggest that the culprit IV iron preparations uncouple FGF23 production and cleavage, leading to inhibition of FGF23 cleavage relative to production and the biological consequences of excess iFGF23. The risks of hypophosphatemia are attenuated in CKD patients due to their reduced ability to excrete urinary phosphate [(44)**, (46), (48)].

The hypothesis that true or functional iron deficiency may contribute to FGF23 excess in CKD has led to recent studies testing whether iron supplementation has a therapeutic effect to lower FGF23 levels in CKD patients (52–57). Several studies have focused on oral iron-based phosphate binders, such as ferric citrate, that have the dual effect to reduce dietary phosphate absorption and treat iron deficiency. A recent randomized phase-3 trial in non-dialysis CKD patients with iron deficiency demonstrated that ferric citrate treatment for 16 weeks increased serum iron parameters and hemoglobin compared with placebo (53). This was associated with a significant reduction in serum phosphate as well as iFGF23 and total FGF23 levels (53). Since both hyperphosphatemia and iron deficiency may contribute to FGF23 excess in CKD, a subsequent *post hoc* analysis used statistical methods to explore whether the decrease in FGF23 by ferric citrate was driven by phosphate lowering or increased transferrin saturation (52). This study concluded that reductions in total FGF23 were partially mediated by increased transferrin saturation, whereas reductions in iFGF23 were partially mediated by decreased serum phosphate (52).

Another prospective open-label study of 60 hemodialysis patients receiving either lanthanum carbonate or switching from lanthanum carbonate to ferric citrate showed that the ferric citrate group had greater increases in iron parameters compared with the lanthanum group and only the ferric citrate group had significant increases in hemoglobin levels, and reductions in ESA dose (56). Notably, iFGF23 levels were significantly reduced in the ferric citrate group compared to the lanthanum group, despite the fact that serum phosphate, calcium, and PTH were unchanged in either group, suggesting that the decrease in FGF23 was not driven by phosphate, but most likely it was due to reversal of iron deficiency. A complicating factor is that the lanthanum group received significantly more IV iron in the form of saccharated ferric oxide (56), which could at least partially account for the higher iFGF23 levels in this group.

CONCLUSION

Recent studies have revealed that iron status, inflammation, and EPO regulate FGF23 production and cleavage. Moreover, these relationships are bi-directional as FGF23 itself affects erythropoiesis and regulates inflammatory responses (Figure 1). These findings provide novel and important insights into the pathophysiologic mechanisms of CKD and may present new therapeutic opportunities. Further research is needed to fully understand how FGF23 expression and cleavage are affected by these factors and what are the physiological and pathological implications of the associations between FGF23 and EPO-iron status –inflammation in the clinical outcomes and treatment modalities associated with CKD.

ACKNOWLEDGEMENTS

FINANCIAL SUPPORT AND SPONSORSHIP

JLB is supported by NIH grant R01-DK087727 and R01-DK102815. DS is supported by CDMRP grant W81XWH-16-1-0598.

REFERENCES

Papers of particular interest, published recently, have been highlighted as:

- Of major importance
- Of importance

1. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, and Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature* 2006;444(7120):770–4. [PubMed: 17086194]
2. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, and Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A* 2001;98(11):6500–5. [PubMed: 11344269]
3. Gattineni J, Bates C, Twombly K, Dwarakanath V, Robinson ML, Goetz R, Mohammadi M, and Baum M. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. *Am J Physiol Renal Physiol* 2009;297(2):F282–91. [PubMed: 19515808]
4. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, and Yamashita T. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest* 2004;113(4):561–8. [PubMed: 14966565]
5. Sitara D, Kim S, Razzaque MS, Bergwitz C, Taguchi T, Schuler C, Erben RG, and Lanske B. Genetic evidence of serum phosphate-independent functions of FGF-23 on bone. *PLoS Genet* 2008;4(8):e1000154. [PubMed: 18688277]
6. Sitara D, Razzaque MS, Hesse M, Yoganathan S, Taguchi T, Erben RG, Juppner H, and Lanske B. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. *Matrix Biol* 2004;23(7):421–32. [PubMed: 15579309]
7. Christakos S, Dhawan P, Verstuyf A, Verlinden L, and Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol Rev* 2016;96(1):365–408. [PubMed: 26681795]
8. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, and Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 2004;19(3):429–35. [PubMed: 15040831]

9. Sitara D, Razzaque MS, St-Arnaud R, Huang W, Taguchi T, Erben RG, and Lanske B. Genetic ablation of vitamin D activation pathway reverses biochemical and skeletal anomalies in Fgf-23-null animals. *Am J Pathol* 2006;169(6):2161–70. [PubMed: 17148678]
10. Razzaque MS, Sitara D, Taguchi T, St-Arnaud R, and Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J* 2006;20(6):720–2. [PubMed: 16436465]
11. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69(11):1945–53. [PubMed: 16641930]
12. Seifert ME, and Hruska KA. The Kidney-Vascular-Bone Axis in the Chronic Kidney Disease-Mineral Bone Disorder. *Transplantation* 2016;100(3):497–505. [PubMed: 26356179]
13. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011;79(12):1370–8. [PubMed: 21389978]
14. Hasegawa H, Nagano N, Urakawa I, Yamazaki Y, Iijima K, Fujita T, Yamashita T, Fukumoto S, and Shimada T. Direct evidence for a causative role of FGF23 in the abnormal renal phosphate handling and vitamin D metabolism in rats with early-stage chronic kidney disease. *Kidney Int* 2010;78(10):975–80. [PubMed: 20844473]
15. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011;121(11):4393–408. [PubMed: 21985788]
16. Grabner A, Schramm K, Silswal N, Hendrix M, Yanucil C, Czaya B, Singh S, Wolf M, Hermann S, Stypmann J, et al. FGF23/FGFR4-mediated left ventricular hypertrophy is reversible. *Sci Rep* 2017;7(1):1993. [PubMed: 28512310]
17. Leaf DE, Jacob KA, Srivastava A, Chen ME, Christov M, Juppner H, Sabbisetti VS, Martin A, Wolf M, and Waikar SS. Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness. *J Am Soc Nephrol* 2017;28(6):1877–85. [PubMed: 28028134]
18. Leaf DE, Siew ED, Eisenga MF, Singh K, Mc Causland FR, Srivastava A, Ikizler TA, Ware LB, Ginde AA, Kellum JA, et al. Fibroblast Growth Factor 23 Associates with Death in Critically Ill Patients. *Clin J Am Soc Nephrol* 2018;13(4):531–41. [PubMed: 29519954]
- 19*. Pastor-Arroyo EM, Gehring N, Krudewig C, Costantino S, Bettoni C, Knopfel T, Sabrautski S, Lorenz-Depiereux B, Pastor J, Strom TM, et al. The elevation of circulating fibroblast growth factor 23 without kidney disease does not increase cardiovascular disease risk. *Kidney Int* 2018;94(1):49–59. [PubMed: 29735309] This study shows that high circulating FGF23 levels are not sufficient to cause cardiovascular disease in the absence of renal impairment and normal/high phosphate levels.
20. Fishbane S, and Spinowitz B. Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. *Am J Kidney Dis* 2018;71(3):423–35. [PubMed: 29336855]
21. Dev S, and Babitt JL. Overview of iron metabolism in health and disease. *Hemodial Int* 2017;21 Suppl 1(S6–S20. [PubMed: 28296010]
22. Farrow EG, Yu X, Summers LJ, Davis SI, Fleet JC, Allen MR, Robling AG, Stayrook KR, Jideonwo V, Magers MJ, et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. *Proc Natl Acad Sci U S A* 2011;108(46):E1146–55. [PubMed: 22006328]
23. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, and Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. *J Clin Endocrinol Metab* 2011;96(11):3541–9. [PubMed: 21880793]
24. Hanudel MR, Laster M, and Salusky IB. Non-renal-Related Mechanisms of FGF23 Pathophysiology. *Curr Osteoporos Rep* 2018;16(6):724–9. [PubMed: 30353318]
25. David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, Zumbrennen-Bullough KB, Sun CC, Lin HY, Babitt JL, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int* 2016;89(1):135–46. [PubMed: 26535997]

26. Ito N, Wijenayaka AR, Prideaux M, Kogawa M, Ormsby RT, Evdokiou A, Bonewald LF, Findlay DM, and Atkins GJ. Regulation of FGF23 expression in IDG-SW3 osteocytes and human bone by pro-inflammatory stimuli. *Mol Cell Endocrinol* 2015;399(208–18). [PubMed: 25458698]
- 27*. Durlacher-Betzer K, Hassan A, Levi R, Axelrod J, Silver J, and Naveh-Manly T. Interleukin-6 contributes to the increase in fibroblast growth factor 23 expression in acute and chronic kidney disease. *Kidney Int* 2018;94(2):315–25. [PubMed: 29861060] This study shows that deletion of IL-6 prevents elevation of FGF23 in both acute and chronic kidney disease.
28. Onal M, Carlson AH, Thostenson JD, Benkusky NA, Meyer MB, Lee SM, and Pike JW. A Novel Distal Enhancer Mediates Inflammation-, PTH-, and Early Onset Murine Kidney Disease-Induced Expression of the Mouse *Fgf23* Gene. *JBM R Plus* 2018;2(1):32–47. [PubMed: 29527594]
29. Clinkenbeard EL, Hanudel MR, Stayrook KR, Appaiah HN, Farrow EG, Cass TA, Summers LJ, Ip CS, Hum JM, Thomas JC, et al. Erythropoietin stimulates murine and human fibroblast growth factor-23, revealing novel roles for bone and bone marrow. *Haematologica* 2017;102(11):e427–e30. [PubMed: 28818868]
- 30*. Rabadi S, Udo I, Leaf DE, Waikar SS, and Christov M. Acute blood loss stimulates fibroblast growth factor 23 production. *Am J Physiol Renal Physiol* 2018;314(1):F132–F9. [PubMed: 28877877] This study demonstrates a role of EPO as a stimulator of FGF23 by showing that FGF23 production is rapidly increased after acute blood loss and this increase is mediated by EPO.
31. Toro L, Barrientos V, Leon P, Rojas M, Gonzalez M, Gonzalez-Ibanez A, Illanes S, Sugikawa K, Abarzua N, Bascunan C, et al. Erythropoietin induces bone marrow and plasma fibroblast growth factor 23 during acute kidney injury. *Kidney Int* 2018;93(5):1131–41. [PubMed: 29395333]
32. Flamme I, Ellinghaus P, Urrego D, and Kruger T. FGF23 expression in rodents is directly induced via erythropoietin after inhibition of hypoxia inducible factor proline hydroxylase. *PLoS One* 2017;12(10):e0186979. [PubMed: 29073196]
- 33**. Hanudel MR, Eisenga MF, Rappaport M, Chua K, Qiao B, Jung G, Gabayan V, Gales B, Ramos G, de Jong MA, et al. Effects of erythropoietin on fibroblast growth factor 23 in mice and humans. *Nephrol Dial Transplant* 2018. This study shows that FGF23 production and cleavage are increased in mice with high endogenous EPO or in mice with CKD treated with rEPO and the source of *Fgf23* production is the bone marrow. Similar results were obtained from human subjects with CKD or after kidney transplantation.
- 34*. Daryadel A, Bettoni C, Haider T, Imenez Silva PH, Schnitzbauer U, Pastor-Arroyo EM, Wenger RH, Gassmann M, and Wagner CA. Erythropoietin stimulates fibroblast growth factor 23 (FGF23) in mice and men. *Pflugers Arch* 2018;470(10):1569–82. [PubMed: 29961920] This study shows that recombinant EPO increases both iFGF23 and cFGF23 as well as *Fgf23* expression in bone and bone marrow erythroid progenitor cells in mice but increases only cFGF23 in human subjects.
35. Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, Czaja MJ, Bartz R, Abraham R, Di Marco GS, et al. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. *Kidney Int* 2016;90(5):985–96. [PubMed: 27457912]
- 36**. Agoro R, Montagna A, Goetz R, Aligbe O, Singh G, Coe LM, Mohammadi M, Rivella S, and Sitara D. Inhibition of fibroblast growth factor 23 (FGF23) signaling rescues renal anemia. *FASEB J* 2018;32(7):3752–64. [PubMed: 29481308] This study shows that inhibition of FGF23 signaling rescues renal anemia by stimulating erythropoiesis and decreasing erythroid cell apoptosis, and ameliorates iron deficiency by attenuating inflammation.
37. Zhang X, Guo K, Xia F, Zhao X, Huang Z, and Niu J. FGF23(C-tail) improves diabetic nephropathy by attenuating renal fibrosis and inflammation. *BMC Biotechnol* 2018;18(1):33. [PubMed: 29843712]
38. Han X, Li L, Yang J, King G, Xiao Z, and Quarles LD. Counter-regulatory paracrine actions of FGF-23 and 1,25(OH)₂D in macrophages. *FEBS Lett* 2016;590(1):53–67. [PubMed: 26762170]
39. Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstadt HJ, Meersch M, Unruh M, and Zarbock A. FGF23 signaling impairs neutrophil recruitment and host defense during CKD. *J Clin Invest* 2016;126(3):962–74. [PubMed: 26878171]

40. Wallquist C, Mansouri L, Norrback M, Hylander B, Jacobson SH, Larsson TE, and Lundahl J. Associations of Fibroblast Growth Factor 23 with Markers of Inflammation and Leukocyte Transmigration in Chronic Kidney Disease. *Nephron* 2018;138(4):287–95. [PubMed: 29301137]
41. Coe LM, Madathil SV, Casu C, Lanske B, Rivella S, and Sitara D. FGF-23 is a negative regulator of prenatal and postnatal erythropoiesis. *J Biol Chem* 2014;289(14):9795–810. [PubMed: 24509850]
- 42*. Mehta R, Cai X, Hodakowski A, Lee J, Leonard M, Ricardo A, Chen J, Hamm L, Sondheimer J, Dobre M, et al. Fibroblast Growth Factor 23 and Anemia in the Chronic Renal Insufficiency Cohort Study. *Clin J Am Soc Nephrol* 2017;12(11):1795–803. [PubMed: 28784656] This study shows that elevated FGF23 is associated with prevalent anemia, the change in hemoglobin over time, and the development of anemia in CKD patients.
43. Nam KH, Kim H, An SY, Lee M, Cha MU, Park JT, Yoo TH, Lee KB, Kim YH, Sung SA, et al. Circulating Fibroblast Growth Factor-23 Levels are Associated with an Increased Risk of Anemia Development in Patients with Nondialysis Chronic Kidney Disease. *Sci Rep* 2018;8(1):7294. [PubMed: 29740119]
- 44**. Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, and Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight* 2018;3(23). This study shows that intravenous iron therapy (ferric carboxymaltose) rapidly increases biologically active FGF23 resulting in hypophosphatemia, calcitriol deficiency, and secondary hyperparathyroidism.
45. Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M, Kaper RF, Chertow GM, and Krop JS. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. *Am J Hematol* 2018;93(5):683–90. [PubMed: 29417614]
46. Zoller H, Schaefer B, and Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens* 2017;26(4):266–75. [PubMed: 28399017]
47. Bartko J, Roschger P, Zandieh S, Brehm A, Zwerina J, and Klaushofer K. Hypophosphatemia, Severe Bone Pain, Gait Disturbance, and Fatigue Fractures After Iron Substitution in Inflammatory Bowel Disease: A Case Report. *J Bone Miner Res* 2018;33(3):534–9. [PubMed: 29068481]
48. Huang LL, Lee D, Troster SM, Kent AB, Roberts MA, Macdougall IC, and McMahon LP. A controlled study of the effects of ferric carboxymaltose on bone and haematinic biomarkers in chronic kidney disease and pregnancy. *Nephrol Dial Transplant* 2018;33(9):1628–35. [PubMed: 29165637]
49. Klein K, Asaad S, Econs M, and Rubin JE. Severe FGF23-based hypophosphatemic osteomalacia due to ferric carboxymaltose administration. *BMJ Case Rep* 2018;2018(
50. Muras-Szwedziak K, and Nowicki M. Associations Between Intravenous Iron, Inflammation and FGF23 in Non-Dialysis Patients with Chronic Kidney Disease Stages 3–5. *Kidney Blood Press Res* 2018;43(1):143–51. [PubMed: 29444509]
51. Urbina T, Belkhir R, Rossi G, Carbonnel F, Pavy S, Collins M, Mariette X, and Seror R. Iron Supplementation-Induced Phosphaturic Osteomalacia: FGF23 is the Culprit. *J Bone Miner Res* 2018;33(3):540–2. [PubMed: 29281120]
52. Block GA, Pergola PE, Fishbane S, Martins JG, LeWinter RD, Uhlig K, Neylan JF, and Chertow GM. Effect of ferric citrate on serum phosphate and fibroblast growth factor 23 among patients with nondialysis-dependent chronic kidney disease: path analyses. *Nephrol Dial Transplant* 2018.
53. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K, and Chertow GM. Effects of Ferric Citrate in Patients with Nondialysis-Dependent CKD and Iron Deficiency Anemia. *J Am Soc Nephrol* 2017;28(6):1851–8. [PubMed: 28082519]
54. Fukao W, Hasuike Y, Yamakawa T, Toyoda K, Aichi M, Masachika S, Kantou M, Takahishi SI, Iwasaki T, Yahiro M, et al. Oral Versus Intravenous Iron Supplementation for the Treatment of Iron Deficiency Anemia in Patients on Maintenance Hemodialysis-Effect on Fibroblast Growth Factor-23 Metabolism. *J Ren Nutr* 2018;28(4):270–7. [PubMed: 29703633]
55. Iguchi A, Yamamoto S, Yamazaki M, Tasaki K, Suzuki Y, Kazama JJ, and Narita I. Effect of ferric citrate hydrate on FGF23 and PTH levels in patients with non-dialysis-dependent chronic kidney disease with normophosphatemia and iron deficiency. *Clin Exp Nephrol* 2018;22(4):789–96. [PubMed: 29181658]

56. Maruyama N, Otsuki T, Yoshida Y, Nagura C, Kitai M, Shibahara N, Tomita H, Maruyama T, and Abe M. Ferric Citrate Decreases Fibroblast Growth Factor 23 and Improves Erythropoietin Responsiveness in Hemodialysis Patients. *Am J Nephrol* 2018;47(6):406–14. [PubMed: 29874654]
57. Shima H, Miya K, Okada K, Minakuchi J, and Kawashima S. Sucroferric oxyhydroxide decreases serum phosphorus level and fibroblast growth factor 23 and improves renal anemia in hemodialysis patients. *BMC Res Notes* 2018;11(1):363. [PubMed: 29884226]

KEY POINTS

- Inflammation and iron deficiency stimulate FGF23 production and cleavage and the IL6/STAT3 pathway contributes to inflammation-mediated FGF23 transcription.
- EPO directly increases FGF23 production and cleavage and bone marrow plays a functional role in EPO-mediated FGF23 induction.
- Prospective studies of CKD patients show that high levels of circulating total FGF23 are significantly associated with prevalent anemia, decline in hemoglobin, and the risk of incident anemia, regardless of inflammation and iron status.
- Intravenous iron supplementation reduces total FGF23 levels concomitant with improvements in serum iron parameters and hemoglobin; however, certain iron preparations induce intact FGF23, phosphate wasting, hypophosphatemia, and serious musculoskeletal complications.
- FGF23 regulates inflammatory responses, iron status, and erythropoiesis, and blocking FGF23 activity rescues anemia and iron deficiency, attenuates inflammation, improves renal dysfunction, and prevents renal fibrosis in mice with renal impairment, suggesting a potential new therapeutic strategy.

Figure 1. Traditional and non-traditional regulators of FGF23.

Overview of the pleiotropic actions of FGF23 and the interactions between organs and hormones involved in the regulation of FGF23. Red lines: inhibition, Blue arrows lines: stimulation.