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MOLECULAR CONTROL OF PHOSPHORUS HOMEOSTASIS (B VAN DER EERDEN, SECTION EDITOR)

Regulation of Fibroblast Growth Factor 23 by Iron, EPO, and HIF

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Abstract

Purpose of Review Fibroblast growth factor-23 (FGF23) is the key hormone produced in bone critical for phosphate homeostasis. Elevated serum phosphorus and 1,25-dihydroxyvitamin D stimulates FGF23 production to promote renal phosphate excretion and decrease 1,25-dihydroxyvitamin D synthesis, thus completing the feedback loop and suppressing FGF23. Unexpectedly, studies of common and rare heritable disorders of phosphate handling identified links between iron and FGF23 demonstrating novel regulation outside the phosphate pathway.

Recent Findings Iron deficiency combined with an FGF23 cleavage mutation was found to induce the autosomal dominant hypophosphatemic rickets phenotype. Physiological responses to iron deficiency, such as erythropoietin production as well as hypoxia inducible factor activation, have been indicated in regulating FGF23. Additionally, specific iron formulations, used to treat iron deficiency, alter post-translational processing thereby shifting FGF23 protein secretion.

Summary Molecular and clinical studies revealed that iron deficiency, through several mechanisms, alters FGF23 at the transcriptional and post-translational level. This review will focus upon the novel discoveries elucidated between iron, its regulators, and their influence on FGF23 bioactivity.

Keywords FGF-23 · Iron · Erythropoietin · Phosphate · Hypoxia-inducible factor

Introduction

Fibroblast growth factor 23 (FGF23) is a crucial bone-derived hormone for regulation of serum phosphorus. Phosphorus concentrations are maintained within a narrow physiological range through balancing intestinal absorption from dietary intake, skeletal bone storage in the form of hydroxyapatite, and renal reabsorption. Studies of human phosphate handling disorders and genetic mouse models have demonstrated that FGF23 endocrine activity coordinates the communication in this multi-organ system for stable phosphorus levels [1–5]. The kidney is the primary target for FGF23 activity as it is the crucial site for short-term serum phosphate changes. Expression of the co-receptor α-Klotho (αKl) within the distal convoluted tubule is essential for a high affinity binding event between FGF23 and FGF receptor 1 (FGFR1) [6–10] to initiate the MAP kinase signaling cascade [11]. Subsequent to FGF23 signaling, the type II sodium phosphate co-transporters Npt2a and Npt2c proteins are internalized from the apical membrane, therefore promoting phosphaturia [12]. Additionally, FGF23 alters renal 1,25-dihydroxyvitamin D (1,25D) synthesis by downregulating the anabolic enzyme 1-alpha-hydroxylase (Cyp27b1) and enhancing expression of the catabolic enzyme 24-hydroxylase (Cyp24a1) [13]. Reduced circulating levels of 1,25D decreases intestinal phosphorus absorption [1]. As a secondary effect, serum calcium is also reduced with lower serum 1,25D and consequently promotes parathyroid hormone (PTH) release to counteract the FGF23 mediated changes in renal 1,25D synthesis [14]. The overall effect of negative phosphate balance completes the feedback loop to relieve FGF23 stimulation in osteoblasts/osteocytes [15].

Positional cloning performed from patients with the Mendelian disorder of phosphate wasting in autosomal dominant hypophosphatemic rickets (ADHR) identified gain-of-function mutations within FGF23 providing a secondary

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mechanism of regulation. FGF23 protein contains a subtilisin-like proprotein convertase (SPC) proteolytic cleavage site (176RHTR/S180AE) [16, 17]. Within this site, missense mutations seen in ADHR altered R176 or R179 residues to either glutamine (Q) or tryptophan (W). In vitro characterization of the R176 mutation demonstrated preferential secretion of the 32-kDa full-length intact form of FGF23 (iFGF23) which confers biological activity. However, wild-type protein is primarily secreted as the cleaved, inactive FGF23 (cFGF23). This finding of secondary FGF23 regulation correlates with the ADHR phenotype, whereby serum iFGF23 was significantly elevated despite prevailing hypophosphatemia.

The ability to regulate FGF23 processing at the post-transcriptional level was identified through studying rare heritable phosphate handling disorders that led to alterations in FGF23. Tumoral calcinosis (TC) arises from loss-of-function mutations in the gene encoding GalNac-transferase 3 (*GALNT3)* [18, 19]. Patients with TC and *Galnt3*-null mice show highly elevated cFGF23 and extremely low iFGF23, demonstrating an inability to secrete full-length, bioactive protein. While FGF23 protein contains multiple motifs for GALNT3 O-glycosylation, T178 within the SPC cleavage site has been shown to protect FGF23 from degradation with presence of this modification [20]. Alternatively, promoting cleavage and inactivation of FGF23 was determined with the identification of loss-of-function mutations within Family with sequence similarity 20, member C (*FAM20C*) that gives rise to autosomal recessive hypophosphatemic rickets-type 3 (ARHR-3) [21]. Novel mutations of this gene were described in surviving Raine syndrome patients that also exhibited bowing of the long bones [22–24]. As with other rachitic phenotypes, patients with R408W *FAM20C* mutations as well as *Fam20c*-null mice show highly elevated serum iFGF23 resulting in hypophosphatemia and profound osteomalacia [25–27]. Functional studies showed that FAM20C directly targets phosphorylation of FGF23, in addition to other secreted proteins at S-X-E recognition sequences [28]. Interestingly, FAM20C mediated phosphorylation at S180, immediately following the SPC motif-inhibited GALNT3 O-glycosylation of FGF23 leading to enhanced cleavage [21]. Thus, the interplay between GALNT3 and FAM20C activity within the endoplasmic reticulum and Golgi network dictates the secreted form of FGF23. Importantly, highly elevated serum FGF23 levels have been found to induce detrimental off-target effects in tissues outside of kidney [29, 30]. Recent studies haveidentified factors regulating FGF23 not involved in the phosphate and 1,25D feedback network [31, 32]. These may contribute to the pathogenic rises in FGF23 at both the transcriptional and post-translational level. Thus, knowledge of FGF23 regulation remains incomplete and understanding the effects of these new factors may elucidate novel therapeutic targets for rare and common forms of phosphate handling disorders.

FGF23 Regulation by Iron Deficiency

Iron Deficiency as a Driver of FGF23

Similar to phosphorus, iron is an important factor for many proteins in their enzymatic reactions and critical for incorporation into hemoglobin within red blood cells for oxygen transport [33]. Iron levels are tightly controlled at both the systemic and cellular level. Iron is taken up through intestinal enterocyte active transport [34] primarily regulated by the liver enzyme hepcidin [35]. Transportation through the circulation is facilitated by iron binding to transferrin and deposition into cells through the transferrin receptor where the iron is either incorporated into proteins or stored as ferritin [35]. Iron deficiency and iron deficiency anemia can occur in numerous situations and disorders such as pregnancy [36], poor diet [37–39], inflammation [40, 41], inability to absorb iron [42, 43], and renal failure [44, 45]. The observation that iron deficiency along with the classic ADHR mutation are both critical pieces of the gene-environment interaction necessary to produce the ADHR disease phenotype provided an interesting link between iron and FGF23 [6].

Low penetrance and the observation of ADHR patients to wax and wane in their disease manifestations were found to be unique features of the ADHR phenotype [16, 46, 47]. Women carrying the ADHR mutation more frequently portrayed later onset where phenotypes correlated with pubertal menses, a state often associated with iron deficiency [46, 47]. Interconnection between FGF23 and iron was identified, whereby low serum iron levels correlated with higher serum cFGF23 in both normal controls and ADHR patients. This negative correlation remained for low serum iron and iFGF23 in ADHR patients; however, no association with iFGF23 could be observed in normal controls [48]. Testing the hypothesis of iron levels modulating FGF23 was conducted in mice containing the ADHR R176Q-*Fgf23* knock-in alleles (ADHR mice).These studies recapitulated the human data demonstrating that bone *Fgf23* mRNA and serum cFGF23 was significantly induced in all mice during iron deficiency. ADHR mice exhibited elevated iFGF23 and hypophosphatemia during iron deficiency, whereas wild-type littermate controls maintained normal serum iFGF23 and phosphorus levels [31]. Importantly, low iron status in

ADHR mice completely negated the normal feedback suppression of FGF23 from the reduced serum phosphorus. Thus, these data demonstrated that iron deficiency can enhance transcriptional activity of *Fgf23*, and that post-translational processing to cleave FGF23 is important for maintaining proper levels of serum iFGF23 and therefore phosphate balance.

In addition to diet-mediated iron deficiency, blood loss from trauma, surgery, and bowel disorders can also develop iron deficiency [49, 50]. Rabadi et al. found that acute bleeding of normal mice resulted in significantly increased cFGF23 beginning at 6 h post-bleed and persisted to 48 h [51]. In a prospective cohort study, patients admitted to the intensive care unit receiving transfusions were also examined as the need for red blood cells indicated blood loss. After assessing serum of 131 patients, a significant positive association was found between cFGF23 and the number of transfusions [51]. In both cases however, there were no measurable differences in serum iFGF23 demonstrating the ability to cleave the FGF23 protein and maintain normal phosphorus levels. These results are similar to controls in the ADHR study as well as premenopausal women with anemia [52]; in that, only cFGF23 is elevated with iron deficiency. In contrast, a recent study performed in a cohort of elderly men found a significant negative correlation between iFGF23 and both serum total iron levels as well as transferrin saturation, a measure of iron binding to transferrin. Hemoglobin levels were not significantly associated with iFGF23 as only a small percentage of the subjects demonstrated anemia along with the iron deficiency [53]. Thus, aging may affect the ability of cells to sense phosphate and properly cleave FGF23 in the setting of iron deficiency.

Hypoxia Inducible Factor Transcription Factor Activity

Iron responsive proteins (IRPs) regulate many of the iron homeostasis factors, including transferrin [54]. During iron deficiency, IRPs bind secondary structures within 3′ and 5′ untranslated regions generated by highly conserved iron responsive elements (IREs) to either enhance or block translation [55, 56]. Even though IRPs have been found to target factors not involved directly in iron handling [57], examination of FGF23 has not elucidated any putative IRE consensus sites. Thus, an alternative mechanism is utilized during iron deficiency to modulate FGF23 production. One important factor for low iron and low oxygen adaptation is hypoxia-inducible factor 1 alpha (HIF1α) [58, 59]. HIF1α is constantly expressed and undergoes regulation primarily at the post-translational level. Under normoxic conditions, prolyl hydroxylase domain isoforms (PHDs) catalyze hydroxylation at specific prolines (P402, P564) within the HIF1α protein [60, 61]. Upon recognition of this modification, von Hippel-Lindau (VHL) acts as an E3 ubiquitin-ligase resulting in rapid HIF1α degradation within the proteasome [26, 62].

Under hypoxic conditions, the PHD activity and subsequent VHL degradation is inhibited, therefore allowing for HIF1α stabilization and accumulation. HIF1α subsequently translocates to the nucleus and binds DNA at conserved hypoxia responsive elements (HREs) as a heterodimer with HIF1β to activate transcription of target genes [63]. Importantly, not only is HIF1α degradation dependent upon sufficient amounts of oxygen but PHDs require iron as a co-factor for the hydroxylation enzymatic reaction [64]. Thus, it is possible for HIF activation in low iron and oxygen replete conditions [65]. Indeed, in initial studies, osteoblastic cell lines treated with the iron chelator deferoxamine (DFO) under normoxic culturing conditions showed cellular HIF1α protein accumulation corresponding with a dramatic induction of *Fgf23* mRNA expression [31]. In mice, functional iron deficiency can be induced with inflammation, a normal protective mechanism to sequester iron from pathogens [66]. Mice injected with IL-1β, to mimic a pro-inflammatory state, had significantly reduced iron levels with increases in both cFGF23 and iFGF23. Bone *Fgf23* mRNA and serum cFGF23 levels were significantly reduced when the mice were treated with a HIF1α inhibitor prior to IL-1β injections, demonstrative of HIF1α targeting transcriptional activation of *Fgf23* [67]. Interestingly, HIF1α inhibition combined with IL-1β injections increased iFGF23, suggesting that it is also involved in the secondary processing of the FGF23 protein. However, this study did not examine mRNA expression levels of the processing enzymes *Fam20c*, *Galnt3*, or *Furin* within the bone under these conditions.

HIF1α acts as a transcription factor by directly binding cis regulatory elements of target genes. In osteoblastic cells, HIF1α stabilization increased plasmid luciferase activity when cloned downstream of the mouse proximal *Fgf23* promoter [68]. Additionally, chromatin immunoprecipitation showed direct binding of HIF1α within this segment and was ablated with the use of a HIF1α inhibitor [68]. However, the exact location of the consensus HRE was not identified. In a recent study by Onal et al., a novel enhancer region 16kb upstream of the *Fgf23* transcriptional start site was identified that may mediate inflammation regulation [69••].

Interestingly, sequence annotation of the putative enhancer region identified an HRE displaying the highest matrix similarity score of all identified transcription factor binding sites. Deletion of the − 16-kb putative enhancer in mice significantly reduced bone *Fgf23* mRNA levels without affecting serum FGF23 protein [69••]. As this enhancer was originally

identified during inflammation, the enhancer knockout mice were subjected to inflammatory conditions including injections with IL-1β in a similar dose and time course to David et al. [67]. As in the previous study, IL-1β induced bone *Fgf23* mRNA and serum protein in wild-type mice, whereas deletion of the − 16-kb enhancer attenuated IL-1β induction at both bone mRNA and serum protein levels. This study did not include measurement of serum iron levels so it is unclear whether iron deficiency occurred in these animals. Additionally, the putative enhancer also contained known downstream inflammatory transcription factor binding motifs including Stat3, Stat5, and NF-κB [70]. Thus, further study is needed to fully elucidate the contribution of the HRE within this enhancer to HIF1α-mediated induction of *Fgf23* during iron deficiency (Fig. 1).

Iron Deficiency Therapeutics and Their Impact on FGF23

Erythropoietin

Erythropoietin (EPO) is a hematopoietic hormone produced primarily by the kidneys that plays a key role in the body's physiologic response to iron deficiency. It is well established that EPO production is a key downstream target of HIF regulation, specifically through HIF2α (*EPAS1*) activation [71, 72]. This hormone is crucial for stimulation of red blood cell production by signaling through the EPO receptor (EPOR) on erythroblasts and activating the canonical JAK2-STAT5 pathway [73]. Additionally, EPO works to correct iron deficiency by indirectly reducing hepcidin to promote iron store release by activating the EPO responsive factor erythroferrone (ERFE) in erythroblasts [74, 75]. Indeed, mice fed a low iron diet demonstrate normal physiological responses with increased serum EPO compared to the control diet fed mice, which correlated with elevated cFGF23 [31]. In transgenic mice that overexpress EPO, both cFGF23 and iFGF23 are significantly increased compared to normal controls [76, 77], suggesting that EPO may have a direct effect on FGF23. A novel class of compounds have recently been developed that function to inhibit the PHDs (PHi) involved in HIF degradation [78]. The subsequent stabilization and activation of HIF complex proteins after PHi administration induces endogenous EPO production. Injection of the PHi in wild-type mice induced serum EPO and cFGF23 [79] as well as iFGF23 [76]. When the mice were also administered an EPO neutralizing antibody FGF23, induction from the PHi was abrogated [79], again suggesting a direct effect of EPO on FGF23 regulation independent of HIF. Anemia is a risk factor for patients with acute kidney injury (AKI) and FGF23 is often found significantly elevated with no relation to other known factors including phosphate, PTH, or 1,25D. A mouse model of AKI demonstrated coordinating increases in both serum EPO and

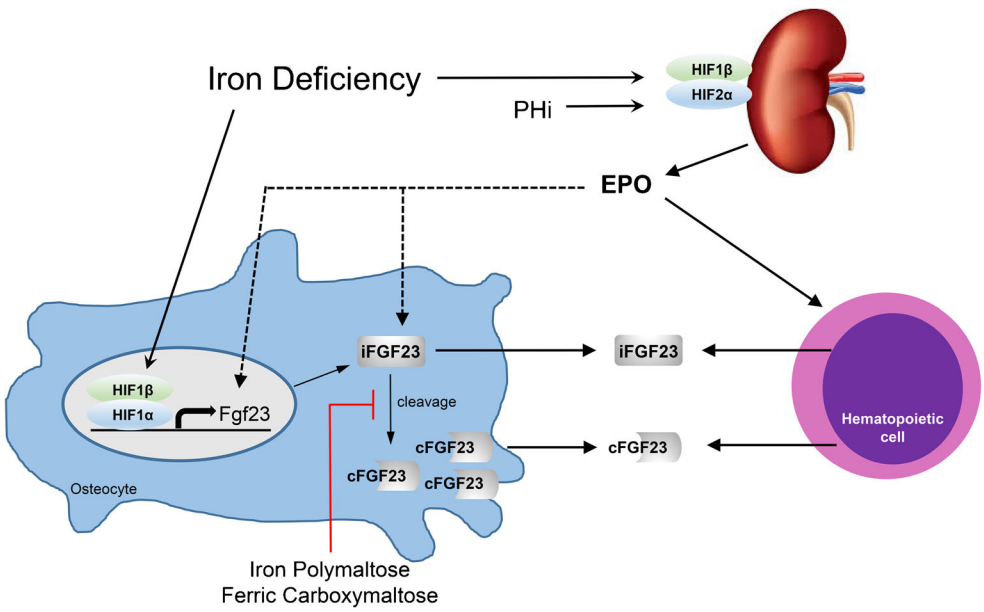

Fig. 1 Emerging evidence has demonstrated multiple aspects of iron and iron-sensing pathways altering the regulation of FGF23. Iron deficiency activates hypoxia inducible factor 1α (HIF1α) within osteoblast/osteocytes (blue cell). This transcription factor then binds to DNA hypoxia responsive elements as a heterodimer with HIF1β to activate transcription of Fgf23 mRNA. In both normal mice and humans with iron deficiency, the intact bioactive FGF23 protein (iFGF23) can be cleaved (cFGF23) prior to secretion to maintain phosphorus levels. Iron deficiency, as well as prolyl-hydroxylase inhibitors (PHi), activates HIFs within the kidney to induce renal erythropoietin (EPO) production. Within the bone, EPO activates Fgf23 at the transcriptional level in both osteoblast/osteocytes as well as in hematopoietic lineage cells which increases serum cFGF23 levels. Pharmacological doses of EPO are also found to induce release of iFGF23. Iron polymaltose and ferric carboxymaltose intravenous iron preparations appear to block cleavage of the FGF23 protein, thereby promoting release of iFGF23

cFGF23 after injury. AKI mice treated with the EPO antagonist, EMP9, resulted in a reduction of cFGF23, yet not to control levels [80]. Thus, multiple facets of iron sensing and homeostasis may be involved in regulation of FGF23.

However, these are conditions in which endogenous renal EPO production is exacerbated. It is unclear in these studies whether normal physiological levels of EPO are involved in regulating basal levels of FGF23. Additionally, while a direct effect of EPO on FGF23 production has been suggested, the factors involved in mediating transcriptional activation after EPO treatment have yet to be elucidated.

Iron deficiency and iron deficiency-induced anemia is a frequent co-morbidity arising in chronic kidney disease [81] with the incidence and prevalence of the diagnosis increasing as renal function declines [82]. Iron deficiency during renal failure is multifaceted, but is frequently due to reduced EPO synthesis [83]. Therefore, replacement therapy with recombinant EPO is a primary avenue for correcting iron deficiency and anemia in this patient population. However, the effect of these therapies on FGF23 was previously unknown. Acute injections of pharmacological doses of recombinant EPO into wild-type mice significantly increased not only cFGF23 [51] but also iFGF23 [76, 84••]. The mouse renal failure model of juvenile cystic kidney disease (Jck mice) was also treated with EPO in a similar manner. Serum levels of iFGF23 increased in all of the animals that received EPO. However, Jck mice treated with EPO further stimulated the induction of iFGF23 potentially due to effects of the underlying renal failure. To ensure that EPO did not cause a local iron deficit and subsequent HIF activation, EPO was co-administered with iron. Regardless of iron administration, EPO induced iFGF23 to a similar extent [84••]. In an adenine diet-induced model of chronic renal failure, EPO injections elicited a significant induction of cFGF23 but not iFGF23 [77]. These different observations may be due to the stage of renal failure in the mice at the time of injection and/or the EPO doses used in the two studies. In either case, EPO treatment was also found to induce bone *Fgf23* mRNA. EPOR is well characterized within hematopoietic cells. However, whether EPOR is expressed on osteoblasts and osteocytes remains controversial [85]. Marrow ablation prior to EPO injections abolished the known EPO response of erythroferrone induction. Interestingly, cFGF23 was reduced following marrow ablation combined with EPO injections compared to the EPO injections alone. However, the levels were still above that of saline-injected control mice. Additionally, *Fgf23* mRNA expression from the femur shaft was elevated with EPO injection and unaffected by marrow ablation [84••]. In contrast, other studies found EPO or epoetin alfa injections were unable to stimulate cortical bone production of *Fgf23* mRNA [51, 76]. Taken together, these data suggested that EPO directly affected expression of *Fgf23* mRNA and that marrow cells may contribute to circulating levels of FGF23. Immunostaining bone marrow after EPO injection highlighted co-localized expression of FGF23 with markers for erythroid, myeloid, and dendritic cells [76]. Flow cytometry of marrow cells demonstrated that the hematopoietic precursors designated as lineage$^-$ c-kit$^+$Sca-1$^+$ (LSK) cells significantly express *Fgf23* mRNA after EPO administration [80, 84••]. Many of these studies have focused on the acute effects of EPO but CKD patients are maintained on EPO replacement therapy for prolonged durations to correct hematocrit and hemoglobin levels. Thus, future studies are needed to elucidate the chronic effects of EPO on FGF23 especially in the setting of renal failure.

Iron Supplementation

In light of the iron deficiency results from ADHR patients and ADHR mutant mice, iron repletion was tested as a therapeutic option to correct the elevated iFGF23 driving hypophosphatemia [48]. In ADHR mice, replacement of the low iron diet with an iron-repleted diet reversed the disease phenotype. Serum levels of iFGF23 of the ADHR mice returned to wild-type levels and serum phosphorus was restored to normal [86]. A patient with an R176Q FGF23 mutation exhibited late onset of the disease and when treated with intravenous iron II sulfate, rather than the standard phosphorus and 1,25D regimen, all disease-associated endocrine disturbances were rescued [87]. Serum phosphorus and 1,25D levels improved with normalization of serum FGF23. These data initiated a clinical trial for treating ADHR with iron supplementation beyond therapy using FGF23 stimulating factors. Whereas this iron preparation was able to reduce the pathogenic elevation of iFGF23, hypophosphatemia has been noted to occur with iron supplementation for other pathologies [88]. Two major categories exist for iron formulations including oral iron and intravenous iron. Oral iron has been a longstanding supplementation for the treatment of iron deficiency and anemia [89]. These preparations are extremely cost-effective, but due to the requirement of intestinal absorption, they are found to induce adverse side effects including nausea, vomiting, and diarrhea resulting in non-adherence. Intravenous (IV) iron preparations are chosen to circumvent gastrointestinal side effects and increase efficacy in correcting iron deficiency as measured by transferrin saturation or hemoglobin. This is especially important in late stage CKD patients as well as patients diagnosed with Crohn's disease or inflammatory bowel disease when the intestinal absorption of iron is inhibited. Iron preparations for infusion are complexed with carbohydrate ligands to reduce unregulated release of labile iron known to cause oxidative stress [90]. Iron polymaltose was introduced in 1978 and is widely approved for the treatment of anemia. Hypophosphatemia and osteomalacia have been reported in multiple cases where patients harboring blood loss conditions were treated for their iron deficiency

anemia with long-term iron polymaltose infusions [91]. While in both cases bone pain was associated with iron infusions, one patient sustained minimal trauma fractures due to persisting osteomalacia. Renal phosphate wasting was found secondary to increased iFGF23 and cessation of iron allowed for iFGF23 levels, and therefore serum phosphorus concentrations to return to normal. Ferric carboxymaltose (FCM) came on the market to replace iron polymaltose as it was well tolerated at higher doses and harbored less adverse events [92]. Hypophosphatemia was observed in a transient fashion when FCM was used to treat anemic premenopausal women [52]. In this initial study, cFGF23 was measured prior to treatment and was significantly elevated compared to controls owing to the effect of iron deficiency on *FGF23* expression. Interestingly, immediately after FCM infusion cFGF23 levels decreased with a coordinating dramatic increase in serum iFGF23 leading to hypophosphatemia [52]. Iron dextran, also a high molecular weight-infused preparation, showed a similar reduction in cFGF23 in response to FCM with no change in iFGF23. Many other case reports have emerged in different patient populations receiving FCM that have exhibited hypophosphatemia due to significant elevations of iFGF23 [93–96]. These studies demonstrated that specific carboxyhydrate ligands reduce the ability to cleave iFGF23 into its inactivated fragments.

Treating functional iron deficiency and anemia in CKD is important as it is linked to increased morbidity and mortality in these patients [97–99]. This could be potentially mediated through FGF23 as iron deficiency and anemia can induce *Fgf23* expression, and FGF23 has been linked to mortality through cardiovascular events in CKD [29, 100]. In a prospective randomized study, CKD patients with iron-deficiency anemia were treated with either oral iron (50 mg sodium ferrous citrate daily) or IV iron (40 mg of saccharated ferric oxide weekly) for 10 weeks. Serum cFGF23 levels were reduced in both groups, whereas only IV iron increased serum iFGF23 levels [101], suggesting oral preparations as preferential for iron supplementation to avoid further increases in iFGF23. This study was performed on CKD patients undergoing maintenance hemodialysis, and many of the patients received EPO or EPO-stimulating agents throughout the study. Thus, it is unclear whether EPO harbored effects on the ratio of iFGF23 to cFGF23. Besides iron deficiency, it is important to note that CKD is a multi-faceted disease state that has effects on additional factors known to induce FGF23. Among these changes is dysregulation of phosphate homeostasis that leads to elevated serum phosphorus due to a lack of excretion. To combat this loss of regulation, phosphate binders have been developed. The first iteration of calcium-containing phosphate binders was cost-effective. However, they increased the risk of hypercalcemia and vascular calcification. Sevelamer is a calcium-free phosphate binder, reducing the risk of hypercalcemia, yet its efficacy for reducing phosphorus is suboptimal and fails to significantly reduce FGF23 [102]. Iron-based phosphate binders have emerged as a new class in the form of sucroferric oxyhydroxide and ferric citrate. In comparison to sevelamer, sucroferric oxyhydroxide demonstrated an ability to lower serum phosphorus to a greater extent [103] and also modestly improved iron parameters [104] due to its low iron release. Importantly, CKD patients on hemodialysis treated with sucroferric oxyhydroxide also showed a significant reduction in serum FGF23. Ferric citrate acts similarly in that the efficacy in reducing serum phosphorus is superior to sevelamer [105] and also significantly improves iron parameters as measured by ferritin and transferrin saturation [106]. In hemodialysis CKD patients, ferric citrate improved serum iron and hemoglobin, which was also associated with a reduction in serum FGF23 [107]. In contrast, treatment with ferric citrate in non-dialysis CKD patients had a modest reduction in serum FGF23 that did not reach significance. However, the study utilized a small sample size, which likely did not have enough power to demonstrate significant effects [108]. It is therefore possible that simultaneously reduced serum phosphorus and iron deficiency correction provides the most beneficial reduction in iFGF23. Nevertheless, it is difficult with this compound to tease out the effects of each component independently on iFGF23 levels.

Conclusion

In summary, dovetailed mouse and human studies involving iron and iron-sensing pathways have elucidated novel aspects of FGF23 regulation. Iron deficiency, through HIF1α and EPO, independently activate *Fgf23* mRNA expression as well as iFGF23 depending upon the context, including presence of ADHR mutation and status of renal function. These laboratory findings have therefore provided evidence for important considerations in the clinical application of iron supplementation. The evolutionary aspect of intertwined iron and phosphate homeostasis remains unclear. However, recent studies have established a strong foundation to interrogate these mechanistic questions further and eventually optimize therapeutic regimens.

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Compliance with Ethical Standards

Conflict of Interest Jonathan A. Wheeler and Erica L. Clinkenbeard each declare no potential conflicts of interest.

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