Multiple Faces of FGF-23

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Abstract

Purpose of the review—This review examines therole of FGF-23 in mineral metabolism, innate immunity and adverse cardiovascular outcomes.

Recent findings—FGF-23, produced by osteocytes in bone, activates FGFR/α-Klotho complexes in the kidney. The resulting bone-kidney axis coordinates renal phosphate reabsorption with bone mineralization, and creates a counter-regulatory feedback loop to prevent vitamin D toxicity. FGF-23 acts to counter-regulate the effects of Vitamin D on innate immunity and cardiovascular responses. FGF-23 is ectopically expressed along with α-Klotho in activated macrophages, creating a pro-inflammatory paracrine signaling pathway that counters the anti-inflammatory actions of vitamin D. FGF-23 also inhibits ACE2 expression and increases sodium reabsorption in the kidney, leading to hypertension and left ventricular hypertrophy. Finally, FGF-23 is purported to cause adverse cardiac and impair neutrophil responses through activation of FGFRs in the absence of α-Klotho. While secreted forms of α-Klotho have FGF-23-independent effects, the possibility of α-Klotho-independent effects of FGF-23 is controversial and requires additional experimental validation.

Summary—FGF-23 participates in a bone-kidney axis regulating mineral homeostasis, proinflammatory paracrine macrophage signaling pathways, and in a bone-cardio-renal axis regulating hemodynamics that counteract the effects of Vitamin D.

Keywords

Innate immunity; vitamin D metabolism; chronic kidney disease; inflammation; hypophosphatemia; a-Klotho; renin angiotensin system

Introduction

Fibroblast growth factor 23 (FGF-23) has emerged as an important hormone in regulating mineral homeostasis in chronic kidney disease, and has been implicated in adverse cardiovascular and infectious clinical outcomes. This review outlines what we know and don't know about the mechanisms underlying FGF-23 regulation and functions.

Hormonal FGFs signal through FGFR/Klotho complexes to create novel endocrine networks

FGF-23, FGF-19, and FGF-21 belong to the subfamily of hormonal FGFs [1]. FGF-23 is a ~32 kDa protein with an N-terminal FGF-homology domain and a 71 amino acid C-terminus separated by a RXXR proprotein convertase cleavage site [2–4] that is principally produced and secreted by osteocytes and osteoblasts in bone [2, 5–8]. FGF-23's major function is to participate in a bone-kidney axis that coordinates bone mineralization with renal phosphate handling and that counteracts the actions of $1,25(OH)_2D$ [5]. Venous sinusoids of the bone marrow and thymus and in the lateral thalamic nuclei in the brain, express FGF-23, but its functions are unknown [9–12]. FGF-19 is secreted by the ileum and targets the liver to regulate bile acid biosynthesis and cholesterol metabolism; whereas, FGF-21, produced by hepatocytes in the liver, targets adipoctyes to regulate fat and energy metabolism [13, 14].

Hormonal FGF actions are imparted by a C-terminal domain that binds to α-Klotho or β-Klotho, type I membrane, ß-glycosidases that function as obligate co-receptors for FGF-23 binding to FGFRs [1]. α-Klotho (α-Kl) forms a trimeric complex with FGFRs (FGFR1c, 3c or 4, but not FGFR2) and the C-terminus of FGF-23 [15–18] to create a heparin independent FGF-23 signaling complex in kidney tubules, choroid plexus, and parathyroid glands. α-Kl can be ectopically expressed in other tissues under pathological conditions; in addition, recent studies suggest that α-Kl is much more widely expressed than originally described [19, 20]. Nevertheless, FGF-23 and α-Kl have co-dependent effects, as illustrated by *in vivo* studies showing that FGF-23$^{-/-}$ and α-Kl$^{-/-}$ mice are exact phenocopies [21, 22] and that α-Kl$^{-/-}$ mice are refractory to FGF-23 regulation of phosphate reabsorption and vitamin D metabolism [23].

The kidney is the physiologically most important tissue for FGF-23 activation of FGFRs and α-Kl binary complexes. FGF-23 targets FGFRs in the proximal of the kidney to regulate vitamin D metabolism, phosphate reabsorption and ACE2 expression and in the distal tubule to regulate sodium and calcium transport and α-Klotho expression [24]. Similarly, FGFR/β-Klotho binary complexes constitute the FGF-19 and FGF-21 receptor [23, 25].

There are also circulating isoforms of α-Kl, but not β-Kl, that have FGF-23 independent functions [26]. Transmembrane α-Kl undergoes ectodomain shedding from the kidney by ADAM 10 and 17 to release a processed ~ 130 kDa α-Kl (pKL) into the circulation [27]. An alternative spliced transcript generates a ~70 kDa soluble klotho (sKl). pKl and sKl are purported to have antiaging effects through inhibition of IGF1, Wnt, and TGF-β signaling [26].

Hereditary diseases caused by FGF-23

Autosomal dominant hypophosphatemic rickets (ADHR) is caused by mutations (R176Q and R179W) in the RXXR furin-like cleavage domain of FGF23 that impairs its proteolytic inactivation [28]. In contrast, loss-of-function mutations in polypeptide *N*-acetylgalactos-aminyltransferase 3 (GalNAc-T3) that prevents O-glycosylation of Thr^{178} within the RXXR cleavage site causes tumoral calcinosis by increasing FGF-23 proteolysis. *In vitro*, PC1/3,

PC2 and PC5/6, but not furin, cleaves FGF-23 [29]. Understanding the role of posttranslational regulation of FGF-23 in health and disease requires additional study.

Transcriptional regulation of FGF-23 is clinical and pathologically most important. FGF-23 transcription in bone-derived osteoblasts and osteocytes is regulated by both local and systemic factors detail [5–7, 28, 30–32] (Figure 1).

Gene mutations that impair extracellular matrix mineralization identify local factors that regulate FGF-23 gene transcription [5, 7] (Table 1). These include inactivating mutations in phosphate regulating endopeptidase homolog, X-Linked (PHEX), dentin matrix protein 1 (DMP1), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), and family with sequence similarity 20, member c (FAM20C)[33]. Mouse genetic studies show that PHEX and DMP1 share a common pathway regulating FGF-23 gene transcription [34]. Inactivating mutations in ENPP1 deplete PPi and local concentrations of phosphate in bone [35], leading to soft tissue calcifications, impaired bone mineralization and increased FGF-23 expression. Inactivation of FAM20C also increases the expression of FGF-23 in bone. Fam20C loss directly phosphorylates FGF-23 on Ser^{180} within the FGF23 $RXXRS^{180}$, which inhibits O-glycosylation and degradation of FGF-23 [36]. Many gaps exist in our knowledge of the specific molecular pathways whereby these mutations regulate FGF-23 gene transcription, but all have in common a link between bone mineralization and FGF-23 expression [33]. Impaired mineralization and diminished uptake of phosphate in bone somehow stimulates increased FGF-23 expression and release into the circulation to regulate renal phosphate handing to match the diminished bone phosphate buffering capacity [5, 6].

Paracrine and intracrine FGFR signaling in bone regulates FGF-23, thereby linking earlier evolved FGF signaling to the later evolved hormonal FGF-23. In this regard, activating mutations in FGFRs, including mutations in FGFR1 in osteoglophonic dysplasia (OGD) and FGFR3 in Epidermal Nevus Syndrome (ENS), lead to increased FGF-23 expression [37]. Selective deletion of FGFR1 in osteocytes of *Hyp* mice reduces FGF-23 [38]. Low molecular weight (LMW, 18kDa) FGF-2 activates cell surface FGFR signaling and increases FGF-23 gene transcription via PLCγ/calcineurin/NFAT and MAPK pathways and NFAT 1 and pETS-1 binding to the FGF-23 promoter [38–40]. High molecular weight (HMW) FGF-2 isoforms elevates FGF-23 gene transcription via a cAMP-dependent integrative nuclear FGFR1 signaling (INFS) by enhancing FGFR1/CREB binding to a cycle-AMP response element (CRE) in the promoter region of FGF-23 gene [39].

FGF-23 is also the cause of tumor-induced osteomalacia (TIO) and oncogenic osteomalacia paraneoplastic syndromes. Elevated FGF-23 is observed in an adenocarcinoma with an aactivating somatic KRAS mutation (G12V), suggesting that RAS can regulate FGF-23 ectopically in non-osseous tissues. Prostate and colon cancer can also cause hypophosphatemia through ectopic production of FGF-23 [41, 42].

FGF-23 is a counter-regulatory hormone for the pleiotropic actions of Vitamin D

Circulating 1,25(OH)$_2$D is a steroid hormone produced by the kidney proximal tubule that activates VDR/RXR nuclear receptors in multiple tissues to regulate several major biological processes, including bone and mineral metabolism, inflammation and innate immune responses, and cardiovascular system dynamics [43].

FGF-23 counters the effects of vitamin D on bone and mineral metabolism (Figure 2A)

Transgenic mouse models overexpressing FGF-23 exhibit hypophosphatemia, suppression of 1,25(OH)$_2$D, increased PTH and rickets/osteomalacia. In contrast, primary deficiency of FGF-23 results in hyperphosphatemia, elevations of 1,25(OH)$_2$D, hypercalcemia, suppression of PTH and soft tissue and vascular calcifications. 1,25(OH)$_2$D stimulates FGF-23 production in bone and FGF-23 suppresses 1,25(OH)$_2$D production by the kidney.

1,25(OH)$_2$D is by far the most important physiological regulator of FGF-23 production (Figures 1 and 2). 1,25(OH)$_2$D stimulation of FGF-23 transcription in bone has been well documented [44–47]. *In vivo* studies using vitamin D receptor (VDR) knockout mice show that the VDR is necessary for 1,25(OH)$_2$D stimulation of FGF-23 expression in osteoblasts [48], but identification of a VDRE in the FGF-23 promoter remains elusive. While a putative VDR consensus site in the proximal promoter region of mouse FGF-23 has been functionally defined [45], 1,25(OH)$_2$D may stimulate FGF-23 transcription via multiple VDREs outside of the FGF-23 proximal promoter region or indirectly stimulate FGF-23 promoter activity through induction of STAT3 and ETS1 pathways [49].

In the proximal tubule, FGF-23 inhibits sodium-dependent phosphate transport by decreasing the Npt2 transporter expression in the brush border membrane and inhibits 1,25(OH)$_2$D circulating levels, through inhibition of Cyp27b1 mediated 1,25(OH)$_2$D production and stimulation of Cyp24 mediated degradation of 1,25(OH)$_2$D.

PTH has variable actions to directly regulate FGF-23 gene transcription [50] (Figure 1 and Table 1). Activating mutations in GNAS, which encodes the signaling protein G$_s$α and PTH1R in McCune–Albright syndrome (MAS) and Jansen's metaphyseal chondrodysplasia (JMC), respectively, increase FGF-23 expression in bone[51]. FGF-23 is activated in mouse models of excess PTH [52]. Parathyroidectomy decreases circulating FGF23 in CKD patients [53]. Calcium-mediated suppression of PTH reduces serum FGF-23 levels in patients with ESRD [54]. PTH also is capable of stimulating FGF-23 indirectly through PTH-mediated increases in 1,25(OH)$_2$D [55]. However, PTH fails to stimulate FGF-23 in some cases of primary hyperparathyroidism [52, 54], in the setting of hypocalcemia and/or 1,25(OH)$_2$D deficiency [56], and after intermittent administration of PTH to mice, which leads to net increments in bone formation [57]. In several studies, PTH did not stimulate production of FGF-23 by osteoblasts *in vitro* [45]. Bone turnover, the levels of serum calcium and other co-factors likely explain these context-dependent effects of PTH on FGF-23. Indeed, PTH and its downstream effector cAMP, have limited effects to regulate FGF-23 gene transcription in osteoblast cultures. Rather, cAMP-dependent stimulation of

FGF-23 promoter activity requires the co-activation of integrative signaling pathways that may involve both nuclear FGFR1 and Nurr1, a member of the NR4A subgroup of orphan nuclear receptors [58]. Interestingly, PTH stimulates Nurr1 expression in osteoblasts prior to FGF-23 elevations and Nurr1 is essential for PTH regulation of FGF-23 gene transcription in UMR-106 osteoblasts [59–61]. VDR is known to activate Nurr1 in T-cells [62], raising the possibility that Nurr1 might also mediate the responses to $1,25(OH)_2D$ to regulate FGF-23 gene transcription [63].

Hypocalcemia is an important negative regulator of FGF-23 production. In elderly humans without CKD serum calcium concentrations, but not phosphate, are positively correlated with serum FGF-23 levels [64]. In mouse genetic models, FGF-23 expression was undetectable in the setting of hypocalcemia, in spite of elevated PTH concentrations. In addition, calcium administration increases FGF-23 levels in the *Cyp27b1* null mouse model that lacks $1,25(OH)_2D$ [56]. Extracellular calcium directly upregulates FGF-23 gene expression and promoter activity in osteoblasts *in vitro* [56, 65] (Figure 2). Calcium regulates FGF-23 through calcium channels. Nifedipine, an L-type calcium channel blocker, inhibits extracellular calcium stimulation of FGF-23 gene transcription [56] and conditional deletion of the Pkd2 (TRPP2) transient receptor potential channel in osteoblasts/osteocytes suppresses FGF-23 expression in bone [66]. Inhibition of the endoplasmic reticulum calcium release-activated calcium channel protein 1 (Orai 1) blocks FGF-23 expression in UMR106 osteoblasts [65]. NFAT transduces the effects of intracellular calcium on FGF-23 promoter activity.

Effects of high phosphate diets on FGF-23 may be to the effects of phosphate to chelate calcium leading to stimulation of PTH and $1,25(OH)_2D$ levels. Dietary phosphate loading (i.e., 1.6 to 2% phosphate diet) in mouse models of CKD result in significant elevations in serum FGF-23 [67], but severe dietary phosphate restriction failed to lower FGF-23 in another model of CKD [68]. In humans, high dietary phosphorus increases and low dietary phosphorus decreases serum FGF-23 [46, 69, 70]; but the changes are small, and there is a delay between phosphate loading and elevations of FGF-23[70, 71]. In the setting of PTH deficiency and hypocalcemia, however, high serum phosphorus levels do not stimulate FGF-23 production in bone [56]. Hypophosphatemia caused by primary renal phosphate wasting in SLC34A1 (sodium-phosphate co-transporter 2a) knockout mice is associated with low serum FGF-23, in spite of high serum $1,25(OH)_2D$ and hypercalcemia [72, 73]. Further studies are required to understand how phosphate regulates FGF-23.

FGF-23 counter-regulator effects on vitamin D metabolism are clinically important (Figure EA). In states of vitamin D excess, FGF-23 suppress endogenous $1,25(OH)_2D$ production and increases phosphate excretion by the kidney that offsets the effects of $1,25(OH)_2D$ on the gastrointestinal tract and bone to increase influx of calcium and phosphate into the circulation, and on the parathyroid gland suppresses PTH secretion. On the other hand, in the setting of vitamin D deficiency and low calcium, FGF-23 is suppressed, which along with increments in PTH, maximizes $1,25(OH)_2D$ production, which in turn, increases gastrointestinal calcium and phosphate absorption. In this setting, elevation of FGF-23 may define a threshold for correcting vitamin D deficiency, which occurs a 25(OH)D levels of 20 ng/ml, which is lower than current levels of vitamin D sufficiency [74].

Multiple factors cause elevated FGF-23 levels in CKD. Impaired renal clearance of FGF-23 contributes as evidenced by the increase in circulating FGF-23 before elevations of FGF-23 message expression in bone or elevations in PTH, and the effect of nephrectomy and renal transplantation to respectively rapidly increase and decrease FGF-23 levels. Reductions of 25(OH)D and 1,25(OH)$_2$D were originally thought to respectively represent nutritional deficiencies and loss of renal mass; but FGF-23 mediated suppression of 1,25(OH)$_2$D production and increased degradation of vitamin D are adaptive. In this scenario, suppression of 1,25(OH)$_2$D, by reducing phosphate absorption from the gastrointestinal track and efflux from bone, protects again hyperphosphatemia. In late stages of renal failure, serum FGF-23 levels are markedly elevated and correlate with increased FGF-23 message expression in bone; and at this stage, PTH plays a role in increased FGF-23 expression, since parathyroidectomy leads to reductions in circulating FGF-23 levels. Increases in renin angiotensin and sympathetic nervous systems as well as inflammation in CKD can stimulate FGF-23 expression in bone. Reduced cleavage of FGF-23 into N- and C-terminal fragments may also be impaired in CKD.

The associations between elevated circulating FGF-23 and adverse outcomes, including increased left ventricular hypertrophy, cardiac mortality, and mortality to due to infections in chronic kidney disease, suggest that FGF-23 has effects beyond those related to mineral metabolism and highlight other functions of FGF-23 that are counter to 1,25(OH)$_2$D beneficial effects.

FGF-23 counters the effects of Vitamin D on inflammation and innate immune responses (Figure 2B)

1,25(OH)$_2$D has immunoregulatory and anti-inflammatory effects. VDR, the receptor for 1,25(OH)$_2$D is expressed in a variety of immune cells, and 1,25(OH)$_2$D ligand is produced locally by monocytes and dendritic cells that express Cp27b1. In dendritic cells, 1,25(OH)$_2$D activation of VDR inhibit the expression of IL-12, IL-23, IL-6, TNFα, INF-γ, whereas IL-10 and IL-8 expression are enhanced [75]. Moreover, vitamin D deficiency is associated with adverse outcomes linked to inflammation, whereas vitamin D administration has anti-inflammatory and pro-survival effects from infections [76, 77].

In contrast, elevations of FGF-23 are associated with enhanced inflammation in a variety of clinical settings [78–82]. FGF-23's role in adverse outcomes in CKD may be mediated by inflammatory effects and infections[83]. Administration of FGF-23 neutralizing antibody corrected the impaired leukocyte recruitment and host defense in a murine model of CKD [84]. Pro-inflammatory stimuli, such as lipopolysaccharides (LPS), increase FGF-23 expression in bone [85]. Mice injected with LPS have high levels of serum FGF-23 and increased FGF-23 release from activated dendritic cells and macrophages[81]. Furthermore, LPS/IFN-γ activation of M1 macrophages leads to ectopic expression of FGF-23 through activation of a NF-KB-dependent pathway [86]. Po-inflammatory macrophages also express FGFR1 and α-KL transcripts, thereby producing both the ligand and receptor complexes necessary for paracrine FGF-23 signaling in local inflammatory milieu [81]. Recombinant FGF-23 has direct actions to stimulate TNF-α expression in unstimulated macrophages, and to suppress Arg-1 expression in M2 alternatively activated macrophages, actions that are

counteracted by 1,25(OH)$_2$D. Interesting, 1,25(OH)$_2$D treatment of M1 macrophages, unlike its effect in osteoblasts, inhibits FGF-23 expression. Thus, FGF-23 and 1,25(OH)$_2$D function together in a paracrine manner to differentially regulate pro-inflammatory and anti-inflammatory macrophage functions *in vitro* [86].

FGF-23 counteracts the salutary effects of Vitamin D on the cardiovascular system (Figure 2C)

1,25(OH)$_2$D has important effects on the cardiovascular system in patients with normal and impaired renal function. Vitamin D deficiency is associated with hypertension and increased cardiovascular mortality, whereas treatment with vitamin D is associated with improved cardiovascular outcomes and survival in humans [76, 87, 88]. In animal models, disruption of vitamin D signaling promotes hypertension, cardiac hypertrophy, and atherosclerosis [87]. In CKD, the deficiency of 1,25(OH)$_2$D has been implicated in left ventricular hypertrophy and increased cardiovascular mortality, and treatment with calcitriol is associated with reduced mortality in retrospective observational studies [89]. The beneficial effects of vitamin D on cardiovascular system are purported to be mediated by activation of VDR in multiple tissues, leading to suppression of the RAS [90], as well as other salutary direct effects on vascular smooth muscle, endothelial cells and cardiac tissue [91, 92].

While multiple animal studies show that treatment with vitamin D improves LVH, prospective randomized trials of active vitamin D treatment to reduce the risk for cardiovascular disease have been inconclusive [93]. Interestingly, both low and high 25(OH)D levels are associated with cardiovascular mortality, producing a reverse J-shaped association between serum 25(OH)D and cardiovascular disease mortality [94]. Mortality of critically ill patients is also higher in the presence of supra-physiological levels of 25(OH)D (i.e., exceeding 100 ng/ml) [95]. Since FGF-23 is stimulated by vitamin D, could the loss of survival benefits of high dose vitamin D treatment be mediated by offsetting adverse cardiovascular effects of FGF-23?

There are several potential mechanisms underlying FGF-23 adverse effects on the cardiovascular system. One mechanism involves a possible bone-renal-cardiac axis that controls systemic hemodynamic responses through cross-talk between RAS, vitamin D and FGF-23/α-Kl signaling. FGF-23 effects on the kidney to regulate sodium reabsorption and Ang II metabolism is a component of this novel network. In this regard, FGF-23 regulates the expression of renal genes, including ACE2 and the sodium-chloride cotransporter NCC (SLC12A3) that affect blood pressure. Excess FGF-23 elevates blood pressure and causes LVH in both animal models and the clinical setting [96]. For example, in patients with XLH, elevated FGF-23 levels result in increased diastolic blood pressure and increased left ventricular mass [97]. In a mouse model, FGF-23 administration induced hypertension and LVH through stimulation of distal tubule sodium transport [96]. This response required α-Kl, involved SLC12A3, and treatment with chlorothiazide attenuated this effect. Teleologically, these unexpected hemodynamic effects of FGF-23 may represent an adaptive response to vasodilator effects of inflammation, which also stimulates FGF-23.

This network also involves effects of vitamin D to suppress renin and effects of angiotensin II (Ang II) to suppress renal α-Kl expression [98], as well as signaling pathways, including

effects of Ang II, the sympathetic nervous system and oxidative stress to stimulate FGF-23 production in osteoblasts in bone. FGF-23 also regulates the expression α-Klotho in the kidney. Reductions is sKl and consequent reductions in TRPC6 expression in the heart is another possible mechanism for inducing LHV in CKD [99, 100]. Consistent with this schema, angiotensin-converting enzyme inhibition has greater effects in patients with chronic systolic heart failure and elevated circulating FGF-23 levels [101]. In this proposed feed-forward bone-cardio-renal endocrine axis, Ang II, SNS and oxidative stress stimulate FGF-23 production in bone and circulating FGF-23 targets the kidney to suppress ACE2 to augment Ang II responses, to increase sodium absorption and blood pressure, to inhibit s-Kl and its circulating cardioprotective effects, and to suppresses $1,25(OH)_2D$ VDR dependent responses. Collectively these kidney effects accounting for FGF-23's adverse cardiovascular outcomes.

The second mechanism involves local effects of FGF-23 in heart disease. As noted above, FGF-23 is produced by activated macrophages and has proinflammatory effects on macrophages. In addition, macrophage infiltration of the heart has been shown to induce the ectopic expression of FGF-23 and α-Klotho the cardiomyocytes [102]. FGF-23 expression in human cardiomyocytes can be stimulated by oncostatin M (OSM) released from macrophages [103]. Thus, pro-inflammatory macrophages infiltrating the heart by reconstitute the FGF-23/α-Kl local to create a paracrine signaling pathway is responsible for LVH and cardiac fibrosis.

The third and final mechanism proposed to explain FGF-23 cardiotoxic effects and adverse infectious outcomes is a direct, α-Kl independent activation of FGFRs in cardiomyocytes and neutrophils [14, 19]. For example, FGF-23 is purported to target the heart in the absence of α-Kl through direct activation of FGFR4 FGFR4/PLC-dependent signaling [71]. FGF-23 is also purported to activate FGFR2 in the absence of α-Kl in polymorphonuclear neutrophils[84]. These "non-canonical" signaling pathways are controversial, because α-Kl is not expressed in the heart [15] and FGF-23 does not activate FGF2, even in the presence of α-Kl[15].

This provocative mechanism awaits experimental validation, however. Direct *in vivo* evidence for FGF-23 activation of FGFR4 in a model with cardiac specific deletion of FGFR4 is lacking. In addition, activation of FGFR signaling in the heart appears to be cardioprotecitive, not cardiotoxic. In this regard,FGF2 knockout mice are resistant to myocardial infarction-[25], isoproterenol- [104] and Ang II- induced cardiac hypertrophy[105], suggesting that activation of FGFR signaling is cardioprotective. Moreover, both *Fgfr1c* and β-*Klotho* are expressed in cardiomyocytes, and circulating concentrations of FGF-21 are increased in CKD [25]. *Fgf-21* knockout mice develop a dilated cardiomyopathy and exhibit increased susceptibility to isoproterenol-mediated cardiac hypertrophy, whereas activation of FGFR signaling through FGF-21 is purported to have cardioprotective effects [106]. Finally, if Klotho or another co-factor were not needed, then circulating FGFs would have generalized, overlapping, and potentially unwanted, effects. Unrestricted activation of FGFRs by hormonal FGFs would mimic gain-of-function mutations of FGFR1, FGFR3 and FGFR4, which result congenital bone diseases [107], disordered bile-acid metabolism [14], and various cancers [108, 109].

Conclusions

FGF-23 was original call "phosphatonin" to reflect its role in the regulation of serum phosphate concentrations. Unlike serum calcium, however, that activates a calcium sensing receptor (CASR) in the parathyroid gland to regulate the release of PTH in response to changes in serum calcium, changes in serum phosphate do not result in rapid changes in circulating FGF-23 [45, 110]. Rather, FGF-23 is stimulated by $1,25(OH)_2D$, regulated by other systemic and local factors to create unexpected endocrine networks that counteract the biological effects of $1,25(OH)_2D$. Thus, FGF-23 is the "yin" and vitamin D is the "yang" in complex physiological and pathological networks.

Acknowledgments

Abbreviations

FGF-23	Fibroblastic growth factor 23
1,25(OH)2D	1,25 dihydroxy -vitamin D3

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Key points

- FGF-23 is produced by bone and targets FGFR/a-Klotho binary complexes that constitute the FGF-23 receptor in physiologically relevant tissues

- FGF-23 coordinates bone mineralization with renal handling of phosphate to maintain phosphate homeostasis in response to alterations in bone remodeling.

- FGF-23 counteracts the effects of Vitamin D on mineral metabolism, innate immunity and cardiovascular responses.

- The association between FGF-23 and adverse outcomes may be due to a-Klotho-dependent effects of circulating FGF-23 on the kidney to regulate blood pressure or to ectopic expression of FGF-23 in macrophages and diseased tissues to enhance inflammation and tissue fibrosis.
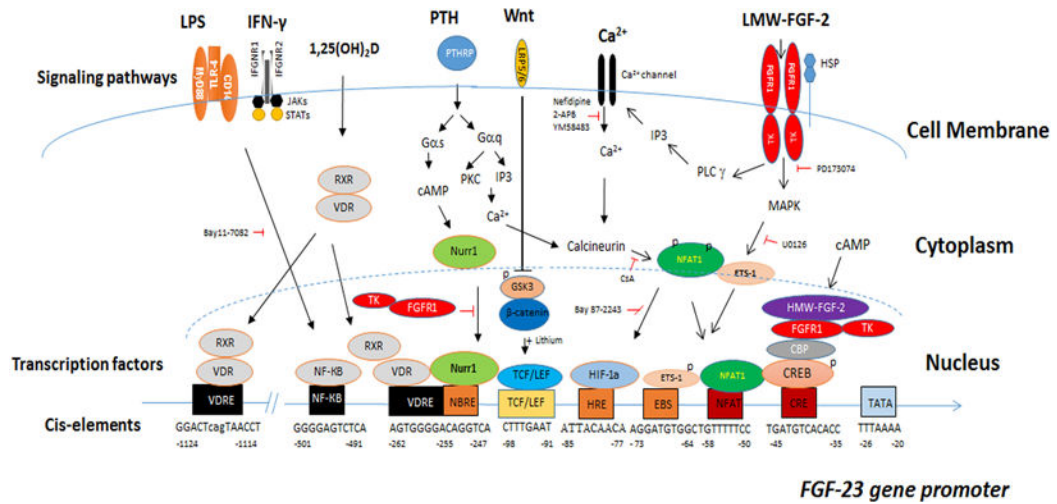
Figure 1. Integrative model of systemic and local factors and signaling pathways that directly regulate FGF-23 gene transcription

Diverse receptors, including G-protein receptors, nuclear calcium channels, receptor tyrosine kinases, toll-like and cytokine receptors, have the capacity to activate FGF-23 gene transcription through both distinct and overlapping pathways. This diversity permits FGF-23 to participate in regulation by calcitrophic hormones involved in mineral metabolism, cytokine pathways involved in regulating innate immune responses, and oxidative stress, sympathetic nervous system and renin angiontensin system activation that lead to adverse cardiovascular outcomes.
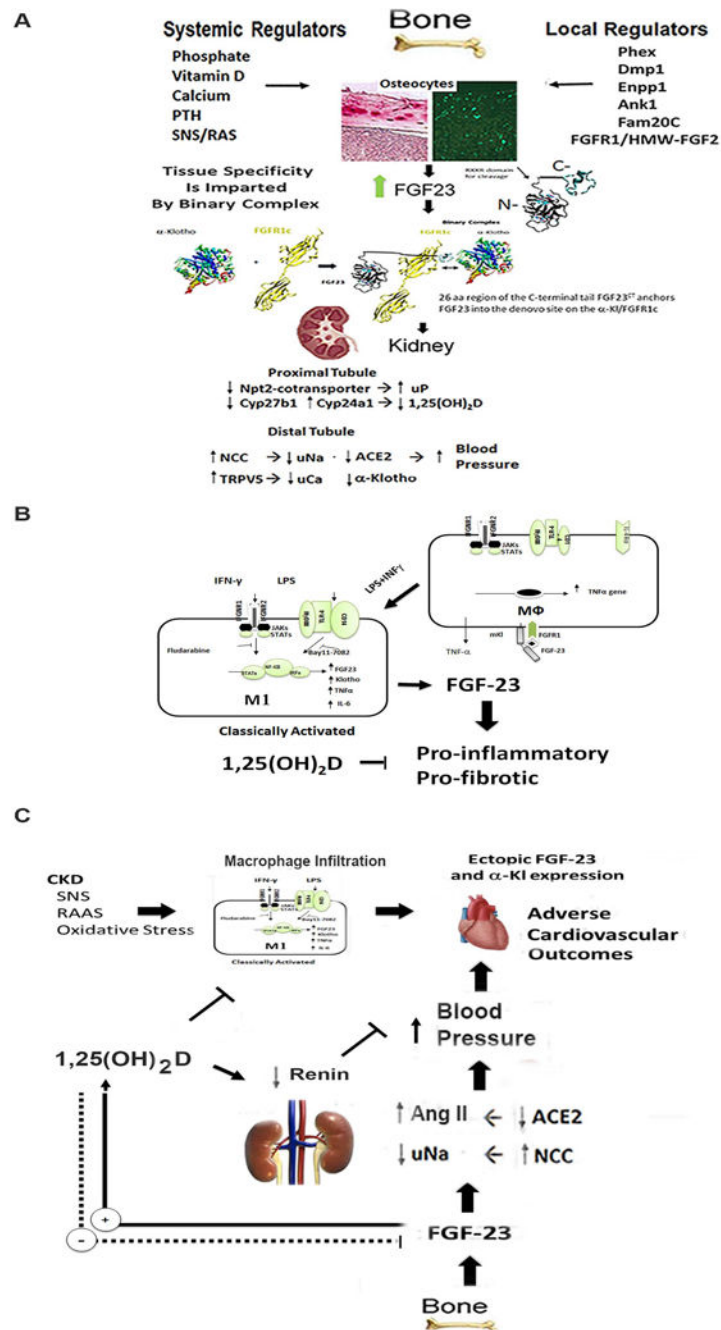
Figure 2. FGF-23 and Vitamin D exhibit counter-regulator effects

A) Bone-Kidney Endocrine Axis. FGF-23 produced in bone regulates FGFR/α-Klotho complexes in the kidney to inhibit phosphate reabsorption and lower circulating $1,25(OH)_2D$ through suppression of *Cyp27b1* synthetic and activation of *Cyp24a1* degradative pathways. FGF-23 also suppresses ACE2 and increases distal tubule sodium reabsorption, leading to increased blood pressure. FGF-23 also regulates the expression of α-Klotho, which is released into the circulation by ectodomain shedding and acts as a hormone with FGF-23 independent effects. $1,25(OH)_2D$ stimulates systemic release of FGF-23 from bone that in turn suppresses $1,25(OH)_2D$ release from the kidney to create a negative feedback loop. A

positive feedback cardiovascular loop is theoretically created by Ang II and SNS stimulation of FGF-23 expression by bone and effects of circulating FGF-23 to decrease ACE2 and increase renal sodium reabsorption. B) FGF-23 and α-Klotho are also expressed in activated macrophages, which creates a pro-inflammatory paracrine FGF-23 signaling pathway. FGF-23 expression in macrophages and stimulation of TNF-α may offset the anti-inflammatory effects of vitamin D on the innate immune response. In macrophages, $1,25(OH)_2D$ may suppress FGF-23 expression. C) A model of FGF-23 cardiotoxicity derived from FGF-23 effects on the kidney and/or the ectopic expression of FGF-23/α-Klotho in infiltrating macrophages. Stimulation of FGF-23 release into the circulation by RAS, SNS, or oxidative stress or local production of FGF-23 in macrophages could attenuate the beneficial effects of Vitamin D on the cardiovascular and innate immune responses.

Table 1

Mutations causing increased FGF-23 gene transcription in bone.

Disorder	Inactivating Mutations						Activating Mutations			
	ARHR1	ARHR2	XLH	RNS ARHR3	OGD	None	ENS	MAS	HR/HPT	JMC
OMIM#	241520	613312	30780	259775	166250		*134934 163200 *164790	174899	612089	168468
Mutated Gene	DMP1	ENPP1	PHEX	FAM20C	FGFR1	FGF2-HMW	FGFR3 HRAS NRAS	GNAS1	α-Kl	PTH/PTHR

Abbreviations: ARHR1, autosomal recessive hypophosphatemic rickets 1; ARHR2, autosomal dominant hypophosphatemic rickets 2; HR/HPT, hypophosphatemic rickets and hyperparathyroidism; FGF2-HMW, high-molecular weight FGF2; JMC, Jansen metaphyseal chondrodysplasia; MAS, McCune–Albright syndrome; OGD, osteoglophonic dysplasis; Tg, transgene; XLH, X-linked hypophosphatemic rickets; RNS, Raine's Syndrome; ENS, Epidermal Nevi Syndrome. PTH, Parathyroid Hormone; PTHR, Parathyroid hormone receptor; DMP1, dentin matrix protein 1; ENPP1, Ectonucleotide Pyrophosphatase/Phosphodiesterase 1.