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Review Article

FGF23: A Kidney and Bone Player

Rosini Sergio[1], Rosini Stefano[2], Saviola Giannantonio[3], Casabella Andrea[4] and Molfetta Luigi[5]*

[1]*Biomaterial Reserach Center, Livorno, Italy*

[2]*Smile-Restyle, Livorno, Italy*

[3]*Istituti Clinici Scientifici Maugeri, IRCCS Castel Goffredo, Castel Goffredo, Italy*

[4]*IRCCS Policlinico S.Martino, Genoa, Italy*

[5]*University of Genoa, DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies (Italy), Genoa, Italy*

***Corresponding Author:** Molfetta Luigi, Professor, University of Genoa, DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, Genoa, Italy.

Received: August 23, 2024; **Published:** October 15, 2024

Abstract

The main function of fibroblast growth factor (FGF-23) is to regulate phosphate concentration in plasma suppressing the abundance of phosphate-transporting molecules in the apical membrane of epithelial cells which express FGFR 1, 3, and 4, in the proximal renal tubule, leading to reduced reabsorption of phosphate from the urine.

Under physiological condition FGF-23 is mainly produced by osteoblasts, osteoclasts, and osteocytes as a response to increased Vitamin D (Vit D) concentration in plasma, but also abnormal plasma concentration of phosphate, calcium, parathyroid hormone (PTH), aldosterone or iron deficiency.

Pro-inflammatory cytokines have been shown to stimulate osteoblastic/osteocytic FGF-23 secretion. FGF-23 undergoes some intra-osseous processes that stabilizes the molecule. At a physiological level FGF-target organs are those that express Klotho, like kidney, parathyroids and brain. Under pathological condition immune-cells or cardiomyocytes may also release FGF-23.

The main effect of FGF-23 is to increase kidney phosphate excretion and reduce intestinal phosphate absorption. The excess of FGF-23 along with Vit D deficiency, hypocalcemia, hyperparathyroidism, and hyperphosphatemia, lead to defective bone mineralization and extra-skeletal calcifications. FGF-23 has also been shown to interfere with some markers of bone metabolism and with bone microarchitecture in patients with osteoporosis.

Keywords: *FGF-23; Fibroblast; Phosphate Metabolism; Bone*

Introduction

Fibroblast Growth Factor-23 or FGF-23 is a glycoprotein that in humans is encoded by the FGF-23-gene. FGF23 belongs to the fibroblast growth factor family, involved in phosphate metabolism.

Its discovery came when a mutation, putatively interfering with cleavage of proteins, was identified as cause of autosomal dominant hypophosphatemic rickets (ADHRs); sometime later FGF-23 was also found in thalamic nuclei of the murine brain [1].

The main function of FGF-23 is to regulate phosphate concentration in plasma suppressing the abundance of phosphate-transporting molecules in the apical membrane of epithelial cells which express FGFR1, 3, and 4, in proximal renal tubule, leading to reduced reabsorption of phosphate from the urine [2,3].

Mouse experiments have shown that FGFR1 is probably the most important FGFR mediating the actions of FGF-23 in the kidney [4,5].

In kidney FGF-23 reduces the expression of NPT2, a type II sodium-dependent phosphate (Na/Pi) cotransporter, located in the proximal tubule with the consequence of reducing tubular reabsorption of phosphates and increasing urinary excretion.

In addition, FGF-23 suppresses the expression of the Vit D-metabolizing enzyme 1α-hydroxylase by the proximal tubular cells thereby reducing blood concentrations of 1α,25-dihydroxyvitamin D3. FGF-23 directly acts also on parathyroid gland mediating parathyroid hormone (PTH) secretion [6].

The inhibition of calcitriol synthesis and the increase of PTH prevents phosphorus overload coming from intestine absorption and bone resorption; as a consequence hypophosphatemia and the decrease of calcium concentration will act as a negative feedback control of FGF-23 production [7].

Under physiological condition FGF-23 is mainly produced by osteoblasts, osteoclasts, and osteocytes [8] as a response to increased Vit D concentration in plasma, but also abnormal plasma concentration of phosphate, calcium, parathyroid hormone (PTH), aldosterone or iron deficiency, in addiction pro-inflammatory cytokines have also shown to stimulate osteoblastic/osteocytic FGF-23 secretion [9-12] (Figure 1).

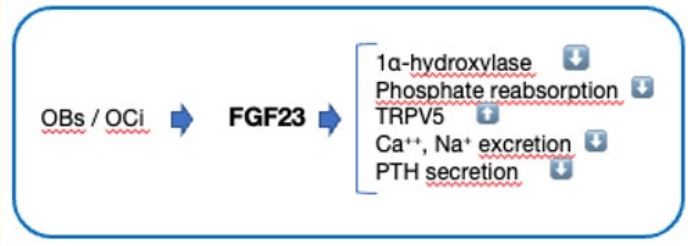

Figure 1: *Current understanding of FGF23 signaling and physiology (by animal models).*

After its transcription, which is regulated mainly by the chronic overload of phosphate, calcitriol and parathyroid hormone, FGF-23 undergoes some intra-osseous processes that stabilizes the molecule. At a physiological level, its target organs are those that express the coreceptor Klotho, like kidney, parathyroid and brain. Under pathological condition immune-cells or cardiomyocytes may also release FGF-23.

Renal actions of FGF-23

In the kidney FGF-23 acts in the proximal tubules inhibiting phosphate reuptake and expression of 1α-hydroxylase, whereas in distal tubules increase the reabsorption of calcium and sodium, this last may have influence on blood hypertension. A direct action on the heart as pro-hypertrophic factor has been reported.

The renal actions of FGF-23 require the presence of the co-receptor α-Klotho in the target cell membrane, whereas the action of FGF-23 on cardiomyocytes, bone, blood vessels, and immune cells are Klotho-independent and may depend on local concentrations.

In patients with chronic kidney disease (CKD), as the mechanisms of phosphate excretion are impaired, there is a progressive tendency for the blood phosphate concentration to increase (hyperphosphatemia). The resulting production of FGF-23 and the inhibition of active vitamin D (calcitriol) production leads to reduced absorption of calcium in the gut and reabsorption of this element from bone tissue, resulting in an overall reduction in blood calcium concentration. At the same time, FGF-23 acts on the parathyroids by reducing parathormone production and hyperplasia of the cells in a complex autoregulatory mechanism aimed at compensating for increased PTH production as a result of decreased intestinal calcium absorption. Therefore it is quite understandable that the administration of calcitriol or 1alpha-OH-D can help in promoting the expression of klotho and calcium absorption.

Under normal conditions, FGF-23 also affects serum calcium by stimulating TRPV5 expression in the apical membrane of the distal renal tubule allowing calcium reabsorption from urine.

In subjects with stable CKD stages 2-4 or under dialysis, FGF-23 expression was identified in osteocytes included in the trabecular periphery but not in osteoblasts and osteoclasts without difference between patients with CKD stages 2-4 and those treated with dialysis, with no difference in presence of normal or high bone turnover. The most prominent differences in bone FGF-23 expression were observed when comparing normal controls to subjects with any degree of CKD [13].

Soluble Klotho is dramatically decreased and FGF-23 increased in chronic kidney disease (CKD) and end-stage renal disease (ESRD). These factors have also been proposed as sensitive biomarkers for adverse renal and extrarenal outcomes in patients with CKD and ESRD.

As CKD progresses together with a loss of functional nephrons, there is an inhibition of the expression of Kloto that makes the kidney resistant to the FGF23; as a consequence, bone initiates the synthesis of FGF23 to maintain the normo-phosphatemia [14].

Several evidences indicate FGF-23 elevation as the primary pathophysiological event that lowers 1,25(OH)2D and thus increases PTH, but the primary stimulus for enhanced FGF23 secretion in early CKD is less clear. Some experimental data have proposed that decreased expression of Klotho may precede FGF-23 excess [15]. Indeed, parathyroid resistance to the inhibitory effects of FGF23 is mediated, in part, by down regulation of Klotho [16] (Figure 2).

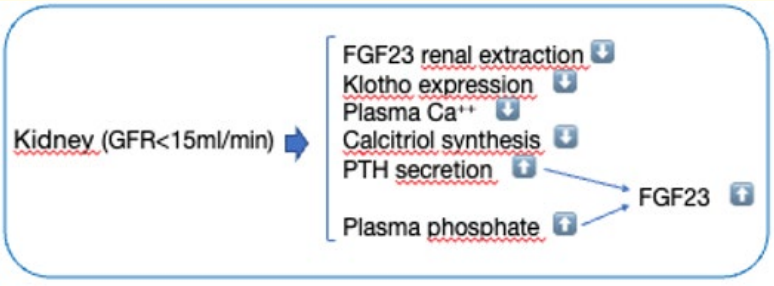

Figure 2: *Some analytical aspects during a severe kidney insufficiency.*

It has been observed that in the early CKD a reduction of the phosphatemia is associated with already elevated FGF-23 levels suggesting that perhaps renal injury itself may be an initial stimulus for FGF23 secretion by causing increased production of a factor that stimulates FGF-23 secretion or decreased expression of a tonic inhibitor. However, in CKD, there are high levels of both FGF-23 and PTH and now we know that there is a decrease in parathyroid gland Klotho and FGFR1 mRNA and protein levels in advanced experimental CKD. These changes may contribute to the resistance of the parathyroid to the high levels of FGF-23 in CKD.

We need to notice that not all of the CKD patients have elevated FGF-23 levels and there is also a significant variability across the spectrum of estimated glomerular filtration rate (eGFR). Some of this heterogeneity may be due to unknown physiologic or genetic factors, but some data show that also a lower income could be associated with higher FGF-23 independent of eGFR suggesting the importance of environmental factors [17,18].

A decline in renal function leads initially to phosphate retention, elevated parathyroid hormone (PTH) levels, and low 1,25-dihydroxy Vit D; however, serum phosphate levels are often maintained within the normal laboratory range until relatively late in the course of CKD.

Beside being associated with kidney disease, hyperphosphatemia is implicated in substantial cardiovascular morbidity and mortality as well as independently linked with calcification of the coronary arteries and aorta, pathologies also influenced by the increase of PTH.

Recently FGF23 has been verified to be also a stimulus for a systemic inflammation which is present in chronic kidney disease and deemed to promote vascular calcification (VC) in CKD patients. The factors involved, IL-1, IL-6 TNFα may proceed the vascular calcification. This finding demonstrates the contribution of FGF-23 to the chronic inflammatory status of CKD. It also highlights the role of FGF23 in the vessel inflammation that precedes arterial calcification [19].

Kidney-specific damage-associated molecular patterns (DAMPs) including crystals and uromodulin released by renal tubular damage trigger innate immunity by activating Toll-like receptors, purinergic receptors, or the NLRP3 inflammasome [20].

Bone effects

In addition to direct renal effects, FGF-23 exerts both directly and indirectly effects on bone metabolism. Besides kidney, parathyroid glands express Klotho endogenously and thus is identified as a target organ of FGF-23 [21]. In parathyroid, FGF23 suppresses production and secretion of parathyroid hormone (PTH), whereas PTH reciprocally induces FGF-23 expression [22].

Klotho also has a role over PTH production directly and indirectly through modulation of plasma levels of active Vit D, Pi, and FGF23. In addition, membrane Klotho may have a direct effect on PTH production and release [23].

Membrane Klotho is expressed in the parathyroid gland with FGFR1 and FGFR3 suggesting that the parathyroid gland is a target organ of FGF23 and that Klotho is a prerequisite for FGF23 action.

More information also comes from studies on tumor-induced osteomalacia (TIO) which have shown different results regarding the concentration of FGF23. TIO is predominantly caused by tumors that ectopically secrete FGF23, a primary regulator of phosphate and Vit D homeostasis; the induced chronic hypophosphatemia and compromised Vit D activation, results in osteomalacia. Elevated FGF23 may also affect expression of osteopontin, alkaline phosphatase (ALP) and the renal calcium channel transient receptor potential vanilloid 5 (TRPV5) [24,25] leading to defective bone mineralisation.

Some investigation in rat calvarial cells *in vitro* have shown that over expression of FGF23 inhibits bone mineralization independent of its systemic effects on phosphate homeostasis but due to elevated expression of osteopontin (OPN), a well-known inhibitor of bone mineralization [26]. Although the pleiotropic action of FGF23 is rather complex there is evidence for a negative influence on bone mineralization [27].

As already reported, FGF23 has been verified to be also a stimulus for a systemic inflammation which is present in chronic kidney disease and deemed to promote vascular calcification (VC) in CKD patients. The factors involved, IL-1, IL-6, TNFα may proceed the

vascular calcification. This finding demonstrates the contribution of FGF23 to the chronic inflammatory status of CKD. In a clinical study of Mendoza [28] elevated FGF23 was independently associated with higher serum levels of CRP, IL-6 and TNFα, and greater probability of severe inflammation.

It has been also shown that inflammation increases FGF23 transcription in osteocytes [29], indicating a causative interconnection between inflammation and FGF23 production. In a study in mice it was observed that FGF23 stimulates hepatic production of inflammatory cytokines through an α-klotho-independent signaling pathway, similar to the described mechanism of FGF23-induced signaling in cardiac myocytes. It has been postulated that FGF23's direct actions on hepatocytes might contribute to systemic inflammation in CKD and further elevations of FGF23 production [30].

The progressively increasing concentration, of toxic substances due to the impaired renal function leads to an alteration of the immuno system and especially monocytes.

This immuno-activation contributes to systemic inflammation via increased synthesis of pro-inflammatory cytokines similar to the chronic low-grade state of systemic inflammation that is associated with an aging immune system.

In addition to being associated with a mineralization defect, FGF23 has also been shown to interfere with some markers of bone metabolism and with bone microarchitecture in patients with osteoporosis.

In a cross-sectional study the associations between c-FGF23 levels with laboratory markers of bone metabolism and bone microarchitecture in 82 patients with osteoporosis was examined. Bone microarchitecture was evaluated by HR-pQCT at distal radius and tibia. The data showed that high FGF23 levels are associated with impaired trabecular bone, but not with cortical bone microarchitecture also after adjusting for all confounding variables [31].

Although the reported study showed some experimental shortcomings the finding suggests a direct role of FGF23 in the degree of bone mineralization and microarchitecture [32].

It is therefore established that FGF23 intervenes in the regulation not only of the metabolism of phosphorus and Vit D, but can also play a direct role on the trabecular structure and on the degree of bone mineralization extending its role from the CKD to the bone disease.

Discussion and Conclusion

Fibroblast growth factor 23 (FGF23) is a phosphotropic hormone secreted by osteoblasts osteocytes into the systemic circulation and acts in the kidney, parathyroid, heart, bone and possibly other organs.

FGF23 has been shown to be a critical phosphaturic hormone which, along with parathyroid hormone (PTH), regulates phosphate recycling and synthesis of calcitriol in kidneys. Canonical FGF23 signalling requires the obligatory co-receptor alpha klotho, a transmembrane protein.

The main effect of FGF23 is to increase kidney phosphate excretion and reduce intestinal phosphate absorption, thereby lowering serum phosphate levels. Inadequate FGF23 production results in hyperphosphatemia and ectopic calcifications, as seen in hyperphosphatemic familial tumoral calcinosis. Conversely, excess FGF23 causes hypophosphatemia, leading to defects in skeletal metabolism. Serum FGF23 levels are also markedly elevated in patients with chronic kidney disease (CKD) and acute kidney injury (AKI). Although the

induction of FGF23 in CKD may have a physiologic role to limit hyperphosphatemia, it also contributes to mineral and bone disorders. The excess of FGF23 along with vitamin D deficiency, hypocalcemia, hyperparathyroidism, and hyperphosphatemia, lead to defective bone mineralization and extra-skeletal calcifications.

The excess of FGF23 is also associated with several other diseases including a risk of cardiac hypertrophy, cardiovascular events, kidney disease progression and mortality.

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Volume 15 Issue 11 November 2024