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## **Physiology of FGF23 and overview of genetic diseases associated with renal phosphate wasting**

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## **Abstract**

Phosphate is a cornerstone of several physiological pathways including skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling. The kidneys have a key role in phosphate homeostasis with three hormones having important functions in renal phosphate handling or intestinal absorption: parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and 1-25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). FGF23 is mainly synthesized by osteocytes; it is a direct phosphaturic factor that also inhibits 1,25(OH)<sub>2</sub>D and PTH. In addition to crucial effects on phosphate and calcium metabolism, FGF23 also has 'off-target' effects notably on the cardiovascular, immune and central nervous systems. Genetic diseases may affect the FGF23 pathway, resulting in either increased FGF23 levels leading to hypophosphatemia (such as in X-linked hypophosphatemia) or defective secretion/action of intact FGF23 inducing hyperphosphatemia (such as in familial tumoral calcinosis). The aim of this review is to provide an overview of FGF23 physiology and pathophysiology in X-linked hypophosphatemia, with a focus on FGF23-associated genetic diseases.

**Key words:** FGF23, X-linked hypophosphatemia, PHEX

## 1. Introduction

Phosphate is a key element for several physiological pathways such as skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling [1]. Phosphate is mainly stored in bone, but the kidneys have a key role in phosphate homeostasis with two hormones playing important roles in renal phosphate handling: parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Both hormones have hypophosphatemic effects by decreasing tubular phosphate reabsorption, with opposite effects on the regulation of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). A third main regulator of phosphate metabolism is 1,25(OH)<sub>2</sub>D which increases phosphate intestinal absorption and inhibits PTH synthesis. An overview of phosphate physiology, with intestinal absorption, renal excretion, and bone metabolism is provided in **Figure 1** [2].

In adults, hypophosphatemia is defined as phosphatemia below 2.5 mg/dL (0.8 mmol/L), while a level below 1 mg/dL (0.3 mmol/L) is considered severe hypophosphatemia [2]. In children, hypophosphatemia is defined based on the age-related normal range [3]. Children with hypophosphatemia from defects of tubular reabsorption of phosphate (e.g., X-linked hypophosphatemia, or proximal tubulopathy such as the De Toni Debre Fanconi syndrome or Dent disease) experience growth retardation, bone deformities and rickets [4]. In the early 2000s, overexpression of FGF23 was initially described in pediatric patients with autosomal dominant X-linked hypophosphatemia XLH [5], and it was also rapidly associated with tumor-induced osteomalacia (TIO) in adults [6], highlighting the key role of FGF23 and its regulators in phosphate physiology.

The aim of this review is to provide an up-to-date overview of FGF23 physiology and pathophysiology in XLH, with a focus on FGF23-associated genetic diseases.

## 2. FGF23 physiology

FGF23 is a 251 amino-acid protein (molecular weight = 30 kDa) with a 24 amino-acid signal peptide in the N-terminal portion; its chromosome location is 12p13 in humans. It belongs to the FGF family, in the sub-group of the 'endocrine FGFs' with FGF19 and FGF21 [7]. Although it shares a highly conserved sequence with all the FGFs, it has a unique C-terminal structure as well as a specific three-dimensional configuration (i.e., disulfide bond and  $\beta$  sheet), both accounting for its systemic action [8]. When initially described, FGF23 was thought to be cleaved by a specific metalloproteinase, namely, phosphate-regulating gene with homologies to endopeptidases on X-chromosome (PHEX), which has a known role in X-linked hypophosphatemia. These initial findings have never been reproduced and this part of FGF23 metabolism is still not fully understood [7] [8]. On the other hand, cleaved forms of FGF23 are identified, resulting from proteolytic cleavage between Arg<sup>179</sup> and Ser<sup>180</sup>, in the Arg<sup>176</sup>-X-X-Arg<sup>179</sup> region [9]. The active form of FGF23 corresponds to the full-length protein from the 25<sup>th</sup>

to the 251<sup>st</sup> amino acid. In contrast, cleavage between arginines 176 and 179 results in inactive forms of FGF23 under physiological condition [8].

## **2.1 Regulation of phosphate/calcium homeostasis**

FGF23 is a cornerstone of phosphate/calcium/vitamin D metabolism. An overview of this complex pathway physiology is shown in **Figure 2** [10]. Although calcium sensing by the calcium-sensing receptor (Ca-SR) is relatively well known [11], the exact mechanism for phosphate sensing by the different cells remains to be elucidated. The FGF23 protein is synthesized by osteocytes (and osteoblasts) and mainly acts as a phosphaturic factor, an inhibitor of 1,25-dihydroxyvitamin D, and a regulator of PTH synthesis and secretion [12] [13] [14], through MAPK (Erk1/2 and Akt) pathways in most tissues, as summarized in **Figure 3**. Indeed, it inhibits the expression of types IIa and IIc sodium-phosphate cotransporters (NPT2a and -2c) on the apical membrane of proximal tubular cells, thereby blocking tubular phosphate reabsorption. It also inhibits 1 $\alpha$ -hydroxylase activity and stimulates activity of the alternative enzyme, 24 hydroxylase, leading to lower circulating levels of 1,25-dihydroxyvitamin D. FGF23 is also able to increase tubular calcium reabsorption through transient receptor potential vanilloid type 5 (TRPV5) [15].

FGF23 binds with only modest affinity to the family of FGF receptors (FGFRs, mainly types 1, 3 and 4). Klotho, a single-pass transmembrane protein, can serve as a co-receptor that increases the affinity and specificity of FGF binding to FGFRs thereby allowing FGF23-mediated receptor activation [16]. Klotho/FGFR complexes are expressed in the parathyroid glands and the kidney with the highest expression of this complex found in the distal tubule whilst the main biological effects of FGF23 are in the proximal tubule [17]. This discrepancy has not been fully explained to date, but reports have also described an expression of Klotho in the proximal tubule having a direct phosphaturic effect [18]. Moreover, Klotho can also function as an enzyme modifying the sugar chains of TRPV5 in the distal tubule, preventing the internalization and inactivation of calcium channels and leading to increased calcium reabsorption [19].

## **2.2 “Off-target” effects of FGF-23**

In addition to these effects on phosphate and calcium metabolism, FGF23 also has “off-target” effects, notably on the cardiovascular, immune and central nervous systems as illustrated in **Figure 4**. The first “off-target” effect of FGF23 to be described was demonstrated on cardiomyocytes [20]. This paper was a milestone in the understanding of FGF23 physiology since it was the first time that a Klotho-independent effect of FGF23 was demonstrated, with different downstream phosphorylation pathways, mainly the calcineurin/NFAT pathway [20]. Faul et al demonstrated that high FGF23 levels were associated with left ventricular hypertrophy (LVH) in cohorts of adult patients with chronic kidney disease (CKD), and they highlighted hypertrophic and pro-fibrotic effects of FGF23 in rat cardiomyocytes [20]. Since

then, it has been demonstrated that the two MAPK and calcineurin/NFAT pathways may co-exist, for example, in the parathyroid glands: the MAPK pathway nevertheless remains the dominant pathway in this case [21].

FGF23 is also an inhibitor of monocyte 1 $\alpha$  hydroxylase, with a concomitant suppression of the antibacterial cathelicidin [22]; in line with this, clinical studies in patients on hemodialysis have confirmed a higher risk of infection with increasing FGF23 levels [23]. In the renal tubule, FGF23 stimulates sodium reabsorption thus increasing blood pressure [24]. In hippocampal cells, FGF23 enhances the number of primary neurites and the synaptic density in a FGFR-dependent manner, but it also decreases arborization, thus leading to a less complex morphology of neurons and probably explaining, at least partly, the learning and memory deficits often observed in CKD patients [25]. FGF23 may also have a role in the growth hormone axis, since therapy with recombinant human growth hormone increases FGF23 levels in the long-term, even after adjusting for age and phosphate levels [26].

Recently, novel endocrine loops have also been described, notably between FGF23 and adiponectin, with suppression of renal  $\alpha$ -Klotho, decreased bone FGF23 release and calcium renal loss by adiponectin both in mice [27], and in CKD patients [28]. There is emerging evidence for a role of adipokines in the modulation of systemic mineral homeostasis. Further research is needed to fully understand these complex loops that could be deregulated, for example, in obesity [29].

A link between iron metabolism and FGF23 has also been highlighted; systemic inflammation may have an impact on FGF23 levels. Indeed, FGF23 directly targets hepatocytes to promote inflammation and C-reactive protein synthesis [30]. There is an inverse association between C-terminal FGF23 and serum iron in healthy individuals, patients with X-linked hypophosphatemia and wild-type mice. Although there is also an inverse relationship between intact FGF23 and serum iron in patients with autosomal dominant hypophosphatemic rickets (ADHR, due to a mutation in the FGF23 gene leading to a resistance of FGF23 to cleavage, and thus an accumulation of the active form of the protein), this latter association was not found in healthy individuals, leading to the hypothesis that iron is involved in the cleavage of FGF23 [31]. In a cohort of 700 patients with stable renal transplants, it was shown that C-terminal FGF23 levels were higher in iron-deficient patients. Moreover, the underlying biological process driving production and cleavage of intact FGF23 (or alternatively the higher level of C-terminal FGF23 fragments) was probably an important mediator of the association between iron deficiency and mortality after transplantation [32]. The effects of iron infusions on FGF23/phosphate metabolism differ depending of the iron preparation. Specifically, ferric carboxymaltose, the currently preferred iv iron formulation, specifically induces transient hypophosphatemia via its carbohydrate moiety and not as a direct consequence of the iron infusion, probably acting via an inhibition of FGF23 degradation, as illustrated by the

discrepancies observed between decreased C-term and increased intact FGF23 levels 24 hours after infusion [33]. Older formulations such as iron sucrose avoid this specific effect. Furthermore, there are cases of osteomalacia or other complications of long-standing hypophosphatemia described in patients treated with ferric carboxymaltose, particularly those with normal kidney function.

Hypoxia and erythropoietin can stimulate FGF23 production [34] [35]; C-terminal FGF23 levels are elevated in patients with sickle cell disease and inversely correlate with hemoglobin levels [36]. Moreover, in ADHR, the human phenotype is heterogeneous, from patients who are completely unaffected to others with a delayed onset of the clinical hypophosphatemic phenotype. Notably, in a murine model of ADHR, corresponding to knock-in mice with the mutation involved in FGF23 stability, it was demonstrated that a low iron diet can induce the complete phenotype whereas mice with the mutation and a normal diet were completely normal, these results highlighting a new example of a gene/environment interaction [37].

### **2.3 FGF23 and bone**

FGF23 is regulated by systemic and local bone-derived factors involving both transcriptional and post-translational mechanisms as represented in **Figure 5**. In healthy volunteers, FGF23 synthesis was shown to be stimulated by oral phosphorus loading and inhibited by phosphate restriction [38]. In addition to phosphate, PTH, vitamin D, and calcium stimulate FGF23 synthesis whereas glycoprophosphoproteins synthesized by osteocytes, e.g., matrix extracellular phosphoglycoprotein (MEPE) and dentin matrix protein 1 (DMP1), respectively, can activate or inhibit FGF23 secretion. Both of the aforementioned proteins are strongly involved in bone mineralization, and MEPE has also been described as a phosphaturic factor in the renal tubules [39].

The specific impact of FGF23 on bone remains to be completely defined since Klotho expression has recently been shown in bone cells and chondrocytes [40]. FGF23 overexpression *in vitro* can suppress not only osteoblast differentiation but also matrix mineralization, regardless of its systemic effect on phosphate metabolism [41]. In osteoblasts, FGF23 also regulates osteopontin secretion directly by suppressing alkaline phosphatase transcription, through Klotho-independent FGFR-3 signaling [42]. Klotho is required in long bones to induce FGF23 bone secretion, with a likely autocrine feedback loop in which Klotho senses the need for FGF23 [43]. In osteoclasts, FGF23 inhibits differentiation but slightly stimulates bone resorption [44]. In addition, FGF23 acts on cartilage, suppressing chondrocyte proliferation and thereby inhibiting metatarsal growth, this being partly mediated through FGFR-3 and suppression of Indian hedgehog [45]. In teeth, ablation of FGF23 compromises the dentoalveolar complex, with ectopic matrix deposition in pulp chambers, odontoblast layer

disruption, narrowing of the periodontal ligament space and changes in cementum structure [46].

To our knowledge, the specific role of FGF23 on bone has not yet been established in conditions such as X-linked hypophosphatemia or TIO. Nevertheless, Carpenter et al showed that circulating FGF23 levels were higher in patients with X-linked hypophosphatemia than healthy controls, and moreover, increased with treatment [47].

### **3. FGF23-associated diseases in humans**

In humans, both FGF23 and Klotho expression can be modified in genetic or acquired diseases. Four groups can be distinguished: diseases with a primary excess in intact FGF23 levels (e.g., genetic X-linked hypophosphatemia and non-genetic tumor-induced osteomalacia); diseases with a primary deficiency in intact FGF23 levels or inefficient FGF23 (e.g., hyperphosphatemic tumoral calcinosis); diseases with a secondary excess in FGF23 concentration (e.g., chronic kidney disease, CKD), and diseases with a secondary deficiency in FGF23 concentration (e.g., VDR deficiency leading to vitamin D-resistant rickets) [48]. The mutations in FGF23 and most of its regulators that account for either hypophosphatemic or hyperphosphatemic disorders are summarized in **Table 1** [2].

Notably, compared to genetic diseases characterized by elevated FGF23 levels inducing hypophosphatemia, the up-regulation of FGF23 levels in CKD relies on a completely different pathophysiology, notably a counter-regulatory (and potentially beneficial) effect tending to reduce hyperphosphatemia. Therefore, the consequences of high FGF23 levels in these two different settings may be different. It is also important to highlight that FGF23 can be raised not only in primary but also secondary and tertiary hyperparathyroidism after renal transplantation [49], because of the stimulating effect of PTH on FGF23. This could further contribute to hypophosphatemia observed in these circumstances, and have different clinical consequences to those usually observed in genetic diseases characterized by a primary FGF23 excess.

### **4. Animal models of FGF23 deficiency and excess**

FGF23 knock-out mice have decreased longevity, growth retardation, skin atrophy, decreased bone density and ectopic as well as vascular calcifications [50]. In addition, they exhibit hyperphosphatemia, hypercalcemia and elevated serum 1,25(OH)<sub>2</sub>D [50]. These mice also tend to be more sensitive to insulin and are therefore at increased risk of hypoglycemia. In these animals, correcting serum phosphate levels with low phosphate diet without modifying serum calcium or 1,25(OH)<sub>2</sub>D levels, improves the phenotype and reduces mortality. Similarly, a low vitamin D diet that corrects serum calcium and 1,25(OH)<sub>2</sub>D levels without modifying serum phosphate levels improves life expectancy [51].



In contrast, mice overexpressing FGF23 develop hypophosphatemic rickets, hyperphosphaturia and hyperparathyroidism. These animals usually have normal serum calcium, circulating 1,25(OH)<sub>2</sub>D and renal function; however, they have low renal expression of some of the regulators of phosphate reabsorption, such as Klotho and Npt2a, [52].

## **5. Pathophysiology of FGF23 in X-linked hypophosphatemia**

### **5.1 Experimental studies in animals and in humans**

XLH is a dominant disorder caused by mutations in PHEX located on X-chromosome Xp22.1 [53]. PHEX encodes a cell-surface-bound protein cleavage enzyme and is predominantly expressed in osteoblasts, osteocytes, odontoblasts, muscles, teeth, lungs and ovaries [54]. The pathogenesis of XLH is yet not fully understood. The majority of XLH patients as well as Hyp mice, an orthologous animal model of XLH, have elevated FGF23 levels [55]. Excess FGF23 results in renal phosphate wasting and consequent hypophosphatemia. Loss of PHEX function is associated with reduced expression of Npt2b in cells of Hyp mouse teeth [56].

On the other hand, it is not yet clear how PHEX mutations result in increased FGF23 levels. FGF23 was once thought to be a substrate of PHEX but this finding was not confirmed in later studies, as discussed above. Both hypophosphatemia and vitamin D deficiency largely explain the mineralization defect resulting in rickets and osteomalacia in pediatric and adult XLH patients respectively. In addition, it was shown that osteopontin is a substrate of PHEX, suggesting that local changes within the bone and teeth environment, specifically, a lack of complete osteopontin degradation by PHEX resulting in accumulation of mineralization-inhibiting osteopontin fragments, may also contribute to the mineralizing defect in XLH [57]. As summarized above, FGF23 is known to have various different effects on bone cells and chondrocytes, but the exact influence of increased FGF23 levels on bone metabolism in X-linked hypophosphatemia has yet to be evaluated. Interestingly, a recent paper clearly demonstrated abnormal and enlarged osteocyte lacunae in Hyp mice; treatment with either active vitamin D or FGF23 antibodies decreased osteocyte lacunar size and improved canalicular organization [58]. Lastly, since FGFRs are also present in ligaments and bone, FGF23-driven activation of FGFRs may also contribute to other complications noted in XLH patients, such as enthesopathy (calcification of tendons, ligaments, and joint capsules) and craniosynostosis [59] [60]. In Hyp mice, histological examination of the most frequently targeted fibrocartilaginous tendon insertion shows that mineralizing insertion sites are not due to bone-forming osteoblasts but rather to a significant expansion of mineralizing fibrocartilage cells expressing FGFR3 and Klotho [59]. Nonetheless, there are no data supporting a direct role of FGF23 on tendons or ligaments.

### **5.2 Clinical applications in renal phosphate wasting diseases**

Administration of anti-FGF23 neutralizing antibodies corrects hypophosphatemia and increases 1,25(OH)<sub>2</sub>D levels in Hyp mice and patients with XLH, confirming the pathogenic role of FGF23 in this disorder [61] [62]. In the future, it will be interesting to evaluate whether anti-FGF23 neutralizing antibodies may be used in non-genetic diseases with renal phosphate wasting and elevated FGF23 levels, such as TIO. On the other hand, in patients with CKD and elevated FGF23 levels as well as hyperphosphatemia, the use of anti-FGF23 neutralizing antibodies is not a therapeutic option, since a significantly higher risk of mortality has been observed in animal models of CKD receiving anti-FGF23 neutralizing antibodies [63].

## **6. Conclusion**

The management of patients with XLH remained purely symptomatic until recently, using mainly phosphate supplementation, active vitamin D analogs and native vitamin D [64]. After the demonstration of its efficacy in adults and in children [65], burosumab (a FGF23 antibody) was approved by the European Medicines Agency for children with XLH in 2018. This opens a completely new therapeutic paradigm for these patients, and the development of such a targeted therapy is the direct consequence of the dramatic advances made in our knowledge of the pathophysiology of XLH and hypophosphatemic diseases of genetic origin over the last two decades.

The description of the key role of FGF23 in the 'bone-kidney-parathyroid' axis has indeed led to a better understanding of genetic conditions associated with phosphate disorders. FGF23 is now also considered to be a systemic factor with negative effects on various systems including cardiovascular, immune, skeletal, and central nervous systems. In the future, these off-target effects should be evaluated in the setting of X-linked hypophosphatemia [66].

**Abbreviation list**

1,25 (OH)<sub>2</sub>D: 1-25 dihydroxy-vitamin D

ADHR: autosomal dominant hypophosphatemic rickets

CaSR: calcium sensing receptor

CKD: chronic kidney disease

FGF23: fibroblast growth factor

PTH: parathyroid hormone

TIO: tumor-induced osteomalacia

TRPV5: transient receptor potential vanilloid type 5

XLH: X-linked hypophosphatemia

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**Conflicts of interest**

JB has no COI to declare.

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**Table 1: FGF23 disorders and other regulators in humans**

	<b>Disease</b>	<b>Involved genes</b>
<b>Hypophosphatemia</b>	<b>Hypophosphatemic rickets (HR)</b>	Activating mutation of FGF23 <sup>***</sup> : autosomal dominant HR Inactivating mutation of PHEX <sup>***</sup> : X-linked HR Inactivating mutation of DMP1 <sup>***</sup> : autosomal recessive HR Inactivating mutation of ENPP1 <sup>***</sup> Inactivating mutation of Npt2c <sup>**</sup> Activating translocation of Klotho <sup>*/**</sup>
	<b>With hypercalciuria and/or osteopenia and/or hypercalciuria</b>	Inactivating mutation of Npt2a <sup>**</sup> Inactivating mutation of Npt2c <sup>**</sup> Inactivating mutation of NHERF1
	<b>McCune Albright / fibrous dysplasia of bone</b>	Overexpression of FGF23, somatic GNAS mutations <sup>***</sup>
	<b>Tumor-induced osteomalacia</b>	Non-genetic overexpression of FGF23, MEPE, FGF7 and/or FRP4 <sup>***</sup>
	<b>Epidermal nevus syndrome (Schimmelpenning syndrome)</b>	
<b>Hyperphosphatemia</b>	<b>Familial tumoral calcinosis</b>	Inactivating mutation of FGF23 <sup>**</sup> Inactivating mutation of Klotho <sup>***</sup> Inactivating mutation of GALNT3 <sup>**</sup>

*FGF: fibroblast growth factor*

*PHEX: phosphate-regulating gene with homologies to endopeptidases on the X chromosome*

*DMP1: Dentin matrix protein 1*

*ENPP1 : ecto-nucleotide pyrophosphatase / phosphodiesterase 1*

*Npt2a: type IIa sodium-phosphate cotransporter (SLC34A1)*

*Npt2c: type IIc sodium-phosphate cotransporter (SLC34A3)*

*NHERF1: Na(+)/H(+) exchange regulatory cofactor NHE-RF1 (SLC9A3R1)*

*MEPE: matrix extracellular phosphoglycoprotein*

*FRP4: frizzled related protein 4*



*GALNT3: UDP-N-acetyl- $\alpha$ -D-galactosamine:polypeptide N-acetylgalactosaminyltransferase3*

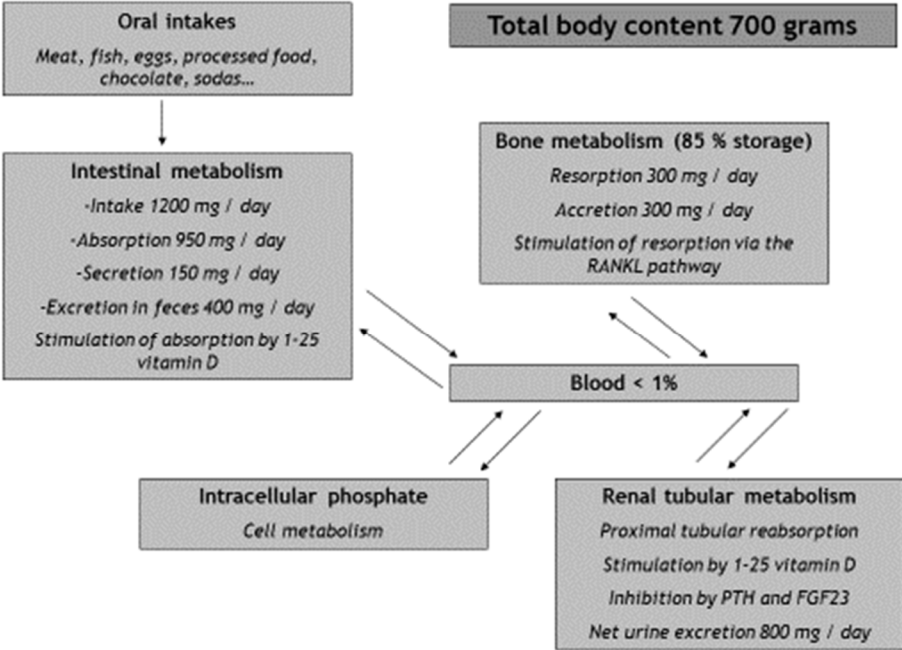
*\* with associated hyperparathyroidism*

*\*\* disease associated with a low FGF23 serum level*

*\*\*\* disease associated with a high FGF23 serum level*

*In some diseases that are usually considered differential diagnoses, some patients may nevertheless present with hypophosphatemia. These orphan diseases should be ruled out when the diagnosis is not clear, for example, Raine syndrome (mutations in *Fam20c* or *DMP4*) also known as osteosclerotic bone dysplasia, osteoglophonic dysplasia (mutations in *FGFR1*), and Jansen metaphyseal chondrodysplasia (mutations in *PTH-R1*).*

**Figure 1: Overview of phosphate physiology in adults**

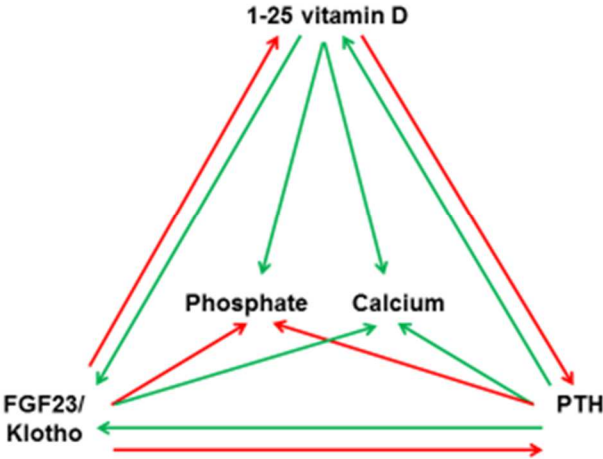


*PTH: parathyroid hormone*

*FGF23: Fibroblast Growth Factor 23*

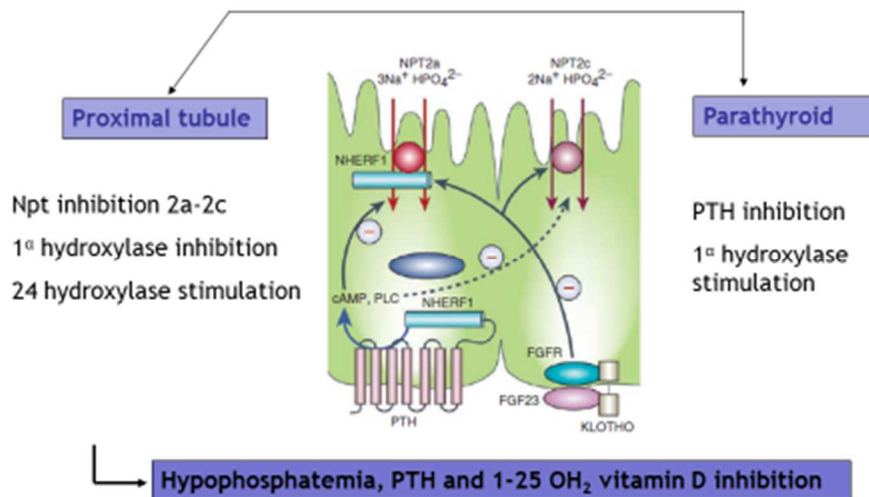
*RANKL: Receptor Activator for Nuclear Factor κB Ligand*

Figure 2: Overview of phosphate/calcium metabolism, adapted from (2)



Green lines corresponding to a positive effect  
Red lines corresponding to an inhibitory effect  
FGF23: fibroblast growth factor 23  
PTH: parathyroid hormone

**Figure 3: The ‘classical’ effects of FGF23 on phosphate and calcium metabolism, adapted from (10)**



(-) corresponding to an inhibitory effect

FGF23: fibroblast growth factor 23

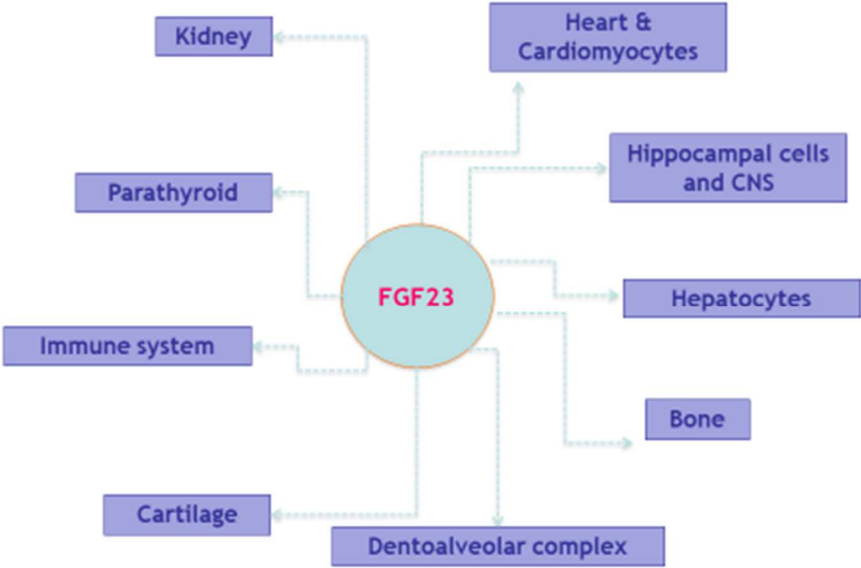
FGFR: fibroblast growth factor receptor

PTH: parathyroid hormone

Npt 2: type II sodium-phosphate cotransporters (types a and c)

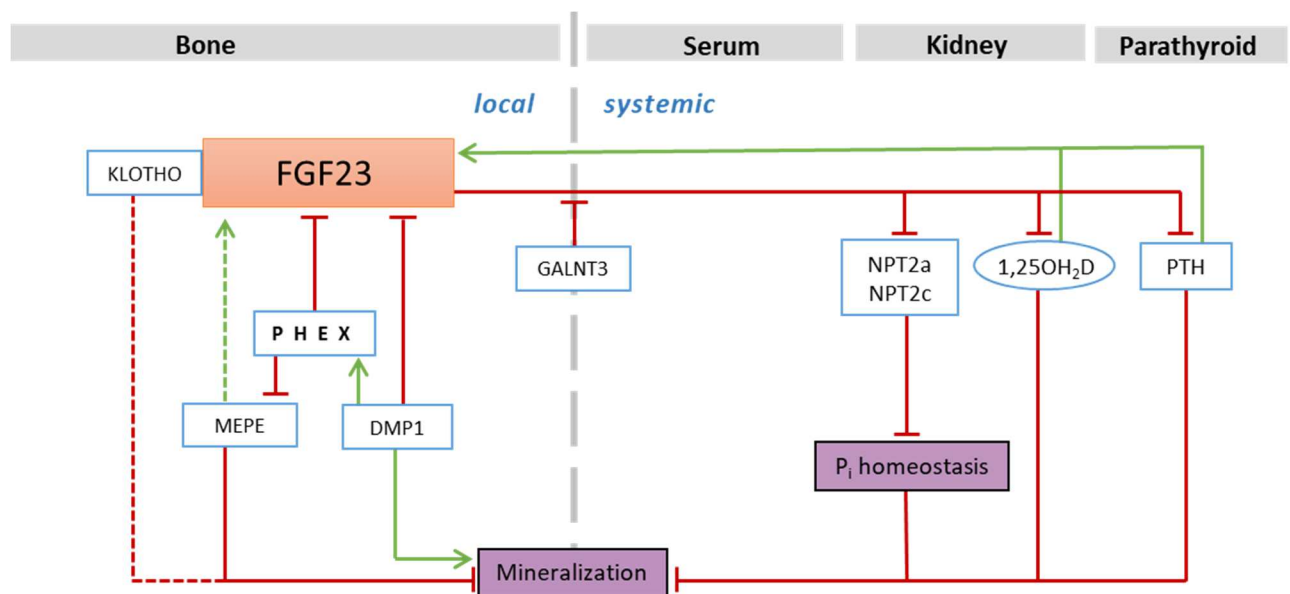
NHERF1: Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor

**Figure 4: Off-targets effects of FGF23**



*Complex regulations between FGF23 and all these systems have been described; for more details, see the text. Briefly, FGF23 is associated with left ventricular hypertrophy, synaptic modifications (arborization), synthesis of inflammatory markers in the liver, modifications of bone homeostasis (mineralization in osteoblasts and differentiation/resorption in osteoclast), impaired immunity in monocytes and homeostasis of phosphate/calcium metabolism.*

**Figure 5: Putative local/systemic function and regulation of FGF23 in normal mineralization, adapted from (62)**



Green indicates a stimulatory effect; red indicates an inhibitory effect. PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; DMP1, dentin matrix acidic phosphoprotein-1; FGF23, Fibroblast Growth Factor 23; MEPE, matrix extracellular phosphoglycoprotein; NPT2a and NPT2c, type IIa and IIc sodium-phosphate co-transporters; 1,25OH<sub>2</sub>D, 1,25-dihydroxyvitamin D; PTH, Parathyroid hormone; GALNT3, : UDP-N-acetyl- $\alpha$ -D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3; P<sub>i</sub>, phosphate