REVIEW

Fibroblast growth factor 23 and its role in phosphate homeostasis

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Abstract

Phosphate homeostasis is complex and incompletely understood. The identification of different factors involved in the regulation of phosphate balance, also called phosphatonin, has largely changed our view on the regulation of phosphate homeostasis. The active role of bone has been demonstrated clearly. Currently, maintaining phosphate homeostasis is considered the result of a complex network of endocrine feedback loops between parathyroid gland, kidney, and bone. This review describes current knowledge on fibroblast growth factor 23, which is one of the best studied phosphatonin.

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Introduction

Maintaining physiological phosphate balance is of crucial biological importance not only for bone mineralization, but also for encoding of genetic material, intracellular signaling, and energy use. Up to now, in adults, PTH was thought as the main regulator of phosphate levels, notably by increasing renal phosphate excretion. However, phosphate homeostasis is complex and the classic PTH/vitamin D axis cannot explain the biochemical abnormalities observed in several hypophosphatemic diseases. The existence of other factor(s) responsible for the inhibition of renal phosphate absorption and altered vitamin D metabolism, also called phosphatonin, was suggested. The study of several renal phosphate-wasting disorders resulted in the identification of four factors with the predicted characteristics of phosphatonin, namely fibroblast growth factor 23 (FGF23), secreted frizzled related protein-4 (sFRP-4), matrix extracellular phosphoglycoprotein (MEPE), and FGF7 (1). The discovery of these phosphatonin substantially increased our insight into the regulation of phosphate homeostasis. They were shown to inhibit renal phosphate reabsorption in the proximal tubule. In addition, FGF23 and sFRP-4 also inhibit 1α-hydroxylase, leading to decreased intestinal phosphate absorption. In our review, we will focus upon FGF23.

Identification of FGF23

Recent studies on the molecular basis of several hereditary or acquired renal phosphate-wasting disorders have led to the discovery of FGF23. FGF23 was almost simultaneously identified as the causative factor for altered phosphate homeostasis by three different research groups (2–4).

FGF23 was first cloned by homology to FGF15 in mice, and the same group also cloned human FGF23 (2). FGF23 was identified as the responsible gene for autosomal dominant hypophosphatemic rickets (ADHR) (3) and tumor-induced osteomalacia (TIO) (4), which are characterized by renal phosphate wasting, decreased 1,25(OH)2vit D3 production, and rickets/osteomalacia. ADHR and TIO will be reviewed in detail later.

FGF23 molecular structure, tissue expression, and downstream signaling

FGF23 is a 32 kDa (251 amino acids) protein with an N-terminal region that contains the FGF homology domain and a specific 72-amino acid C-terminal fragment (3, 4). The FGF23 gene is located on chromosome 12p13. FGF23 is the only member of the FGF family that contains a proconvertase processing site. FGF23 is proteolytically processed between arginine 179 and serine 180 to generate smaller N-terminal and C-terminal fragments (4). The biological significance of these FGF23 fragments is not clearly defined, and they are currently considered as being inactive (5). The amino acid sequence arginine176-X-X-arginine179 just adjacent to the proteolytic processing site is recognized by furin, which is a mammalian subtilisin-like proprotein convertase involved in the processing of many precursor proteins.
Studies have shown that inhibitors of proprotein convertase could also inhibit the processing of the FGF23 protein (7, 8).

FGF23 is predominantly expressed in bone, but it is also expressed in pericyte-like cells that surround the venous sinuosoids of the bone marrow, ventrolateral thalamic nuclei, and thymus (9). The high levels of FGF23 expression in bone in comparison with other tissues suggest that circulating FGF23 is mainly derived from bone (7, 9). In bone, FGF23 is predominantly localized to osteocytes, and to a lesser extent within various cells of the osteoblast lineage. Osteocytes also express dentin matrix acidic phosphoprotein 1 (DMP1) (10), phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) (11), and MEPE (12). The osteocyte lacuno-canaliculuar system should thus be viewed as an endocrine organ regulating phosphate metabolism (13).

Studies have shown that FGF23 has the ability to interact with known receptors for other members of the FGF family (FGFRs), namely the c splice isoforms (IIIc) of FGFR1-3 and FGFR4 (14, 15). In vitro and in vivo experiments indicate FGFR1(IIIc) as the predominant receptor for mediating FGF23 actions (16, 17). Despite the ubiquitous presence of FGFRs, FGF23 downstream signaling was detected only in very restricted tissues including kidney, parathyroid gland, and pituitary gland, suggesting the existence of an essential cofactor to induce downstream signaling.

The demonstration of strikingly similar physical and biochemical phenotypes of FGF23 knockout with KLOTHO knockout mice has led to the identification of KLOTHO as a required cofactor for FGF23-mediated receptor activation and subsequent downstream signaling (16, 18). The KLOTHO gene encodes a single-pass transmembrane protein with homology to β-glucuronidases. The transmembrane and secreted forms of KLOTHO proteins may collectively affect aging processes in mammals (19). The crucial importance of KLOTHO to mediate FGF23 downstream signaling has been demonstrated in vitro and in vivo (16, 18). The KLOTHO extracellular domain is believed to facilitate FGF23 binding to its receptor complex with much higher affinity than to FGFR alone. KLOTHO expression is also restricted to a few tissues including the distal convoluted tubules in the kidney, parathyroid gland, and the epithelium of the choroid plexus in the brain. The imperative presence of KLOTHO to induce downstream signaling likely defines the tissue specificity of FGF23 effects.

Regulating factors of circulating levels of FGF23

Both systemic and local bone-derived factors seem to regulate FGF23 expression in osteocytes (Figs 1 and 2). The systemic factors recognized hitherto as the regulators of serum FGF23 levels are 1,25(OH)2vit D3 and phosphate. In vivo studies showed a stimulatory effect of 1,25(OH)2vit D3 on circulating FGF23 levels in rodents and in humans (20–22). This effect seems to be mediated through the vitamin D receptor since vitamin D receptor-null mice did not show an increase in FGF23 levels after 1,25(OH)2vit D3 administration (20). Meanwhile, a vitamin D-responsive element was identified on the FGF23 promoter that is required for 1,25(OH)2vit D3 stimulation of FGF23 production (21). It is interesting that 1,25(OH)2vit D3 is also able to suppress PHEX mRNA levels in bone cells, and reductions in PHEX can lead to elevated FGF23 expression in osteocytes (23). Therefore, it is plausible that 1,25(OH)2vit D3 upregulates FGF23 production in part indirectly by downregulation of PHEX expression.

![Figure 1](https://www.eje-online.org)
This vitamin D-mediated increment in FGF23 production may serve as a counter regulatory hormone to enhance renal phosphate clearance in response to vitamin D-mediated increments in gastrointestinal phosphate absorption and decrements in the phospha-
turic hormone PTH (24, 25).

Circulating FGF23 levels are also influenced by both dietary phosphate and serum phosphate (20, 26). A dietary phosphate load or increased serum phosphate induces an increase in serum FGF23 level, whereas dietary phosphate deprivation or decreased serum phosphate diminishes the serum FGF23 level. Previous studies on dietary phosphate as a regulator of FGF23 showed conflicting results. Small sample size, the choice of the assay (intact versus C-terminal assay), and differences in magnitude or duration of altered phosphate intake may explain the contradictory results. The mechanism by which changes in dietary phosphate induce changes in circulating FGF23 is unclear. It has long been known that dietary phosphate intake regulates 1,25(OH)2vit D3 concentration by altering its renal production rate (25). The inhibitory effect of FGF23 on renal 1α-hydroxylase is now well established (vide infra); this suggests that the regulation of 1,25(OH)2vit D3 by dietary phosphate is mediated, at least in part, by diet-
induced changes in circulating FGF23.

Data with regard to a role for PTH in FGF23 regulation are conflicting. However, there is growing evidence that PTH may stimulate FGF23 expression and secretion by bone tissue. In the setting of primary hyperparathyroid-
ism, elevated FGF23 concentrations were observed by several groups (27, 28). In addition, Brown et al. determined FGF23 levels in a patient with Jansen’s metaphyseal chondrodysplasia (29). Jansen’s syndrome is caused by the gain of function mutations in the PTH/PTHrP receptor resulting in a constitutively active receptor. Despite hypophosphatemia and normal 1,25(OH)2vit D3 levels, FGF23 levels were markedly elevated. These data suggest a regulating (stimulating) role for PTH, or at least its receptor, in FGF23 production. Given the presence of the PTH/PTHrP receptor on bone cells, namely osteocytes and osteoblasts, and that circulating FGF23 is mainly derived from the same bone cells, persistent stimulation of the PTH/PTHrP receptor may directly induce increased FGF23 production. Of interest, the expression of constitutively active PTH/PTHrP receptor in osteogenic cells in mice has been shown to induce a cellular differentiation defect in bone resulting in a predominance of preosteoblastic cells (30). In this regard, constitutively active PTH/PTHrP receptor could also result in elevated FGF23 due to a generalized defect in altered cell maturation.

It should be emphasized that these data were obtained in the setting of parathyroid disorders. To date, it is not known whether these results may be extrapolated to normal physiology. Further studies are needed to elucidate how FGF23 is integrated in the kidney–parathyroid axis.

It is worth noting that a recent prospective study has shown that FGF23 mediates the development of hypophosphatemia after i.v. iron polymaltose adminis-
tration (31). Further studies are warranted to evaluate the mechanism whereby parenteral iron therapy influences FGF23 metabolism and to identify additional systemic factors regulating FGF23 production in order to increase our understanding of phosphate homeostasis.

Local bone-derived factors also regulate FGF23 expression (Fig. 1). Inactivating mutations in PHEX, a cell-surface endopeptidase that co-localizes with FGF23

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**Figure 2** Endocrine axis regulating phosphate homeostasis. Currently, maintenance of phosphate homeostasis is considered to be the result of a complex network of endocrinological feedback loops. Besides the classic parathyroid–kidney axis, the existence of a bone–kidney axis has been well established. Elevated phosphate and 1,25(OH)2vit D3 levels stimulate FGF23 production by bone. In turn, FGF23 inhibits renal phosphate reabsorption and diminishes 1α-hydroxylase expression in order to keep phosphate levels within the normal range. Emerging evidence also suggests an active interaction between bone and parathyroid gland. The black arrows indicate the stimulating pathways, and the dashed arrows indicate the inhibitory pathways.
in osteocytes, result in increased transcription of FGF23 and increased circulating levels (7, 9). The signaling pathway for PHEX-mediated inhibition of FGF23 expression is currently not known.

DMP1, derived from osteoblasts and osteocytes, exists as a latent protein that is cleaved into two phosphoproteins by bone morphogenetic protein 1 (BMP1) (32). The C-terminal fragment functions as a nucleator for the mineralization of extracellular matrix. Studies using the DMP1-null mouse model demonstrated that the absence of DMP1 results in increased FGF23 expression (33). The mechanisms whereby DMP1 deficiency stimulates transcription of FGF23 are yet to be identified. The ablation of FGF23 in DMP1- and PHEX-deficient mice resulted in a phenotype identical to that of FGF23-null mice, indicating the dominant role of FGF23 in regulating phosphate and 1,25(OH)2vit D3 levels (9, 33).

MEPE, expressed in osteoblasts and osteocytes, can be cleaved by cathepsin B to release a carboxy-terminal MEPE peptide containing the acidic serine–aspartate-rich motif (ASARM peptide) (34). The phosphorylated ASARM peptides potently inhibit mineralization and renal phosphate reabsorption (35, 36). In vitro studies have shown that PHex specifically binds to MEPE via the ASARM motif (35), and that the binding of MEPE inhibits PHex enzyme activities (37). PHex is the only known protease that hydrolyzes the ASARM peptide (38, 39). In vitro experiments also demonstrated that phosphorylated ASARM peptides suppress PHEx expression and increase FGF23 transcripts, which suggests a role for MEPE in the regulation of FGF23 production (35, 37). Using a murine model over-expressing MEPE in bone and kidney, David et al. have recently shown the physiological importance of ASARM–PHEx interactions in vivo (39). MEPE over-expression in mice induced a low bone mass phenotype and hyperphosphatemia. The MEPE transgenic mice exhibit a marked increase in PHEX expression. Reduced ASARM peptide levels with increased MEPE protein epitopes were observed in the bone of MEPE transgenic mice. Given the known phosphaturic effects of full-length MEPE and ASARM peptides in vivo (39, 40), these data suggest that altered MEPE protein processing in MEPE transgenic mice likely contributes to the hyperphosphatemia. In contrast, in HYP mice with inactivating mutations in PHEX, an increase in the expression of both MEPE and osteoblastic protease was noted, leading to increased production of ASARM peptides from MEPE. These ASARM peptides contribute to impaired mineralization and hypophosphatemia with links to FGF23 (36).

The phosphatonin sFRP-4 is expressed in bone, and may indirectly regulate FGF23 production through competition with DMP1 for BMP1 (41, 42).

Based on current knowledge, a hypothetical model has been proposed for the local regulation of FGF23 expression (43). Loss of PHEX or DMP1 (i.e. the common pathway) may indirectly stimulate FGF23 transcription through impaired mineralization of extracellular matrix with accumulation of the extracellular matrix of a yet unknown stimulating factor or through direct effects on osteocyte function. In this model, other phosphatonin indirectly modulate FGF23 production through the common pathway. Recent results of microarray analysis of cortical bone in HYP mice, characterized by inactivating mutations in PHEx, support this proposed model (44). In addition, FGF- and Wnt-signaling pathways were identified as the potential regulators of FGF23 production. However, the functional significance of these pathways needs to be confirmed. Currently, the proximate factors linking PHex and DMP1 to altered FGF23 expression remain unknown. In this regard, further studies on the local regulation of FGF23 production are warranted.

**Function of FGF23**

Our knowledge on the function of FGF23 has been largely derived from in vitro and in vivo studies in FGF23 transgenic and knockout models. As KLOTHO is an essential cofactor of FGF23 for receptor activation, FGF23 seems to target the kidney, parathyroid gland, and possibly the pituitary gland and choroid plexus (Fig. 2).

The kidney is the major target organ for FGF23. Two mechanisms explain the hypophosphatemic activity of FGF23. Firstly, FGF23 suppresses the expression of Na/Pi-2a and Na/Pi-2c cotransporters that mediate physiological phosphate uptake in renal proximal tubular epithelial cells. By inhibiting the Na/Pi-dependent phosphate reabsorption in the proximal tubule, FGF23 can lead to urinary phosphate wasting (45, 46). Immunofluorescent analyses following FGF23 injection in mice showed that FGF23-mediated signaling occurs within the distal convoluted tubule, whereas the downstream targets of FGF23, namely Na/Pi-2a and Na/Pi-2c cotransporters, are located within the proximal tubule (47). This raises the intriguing possibility that a yet unknown paracrine factor may be produced in the distal convoluted tubule that mediates local effects in the proximal tubule (i.e. a distal-to-proximal tubular feedback mechanism).

Moreover, FGF23 suppresses the expression of the 1α-hydroxylase (45, 46), the essential enzyme that mediates the production of the active vitamin D metabolite 1,25(OH)2vit D3. FGF23 also enhances the expression of 24-hydroxylase, an enzyme that converts 1,25(OH)2vit D3 into more hydrophilic metabolites with much less biological activity.

Studies using vitamin D receptor (VDR)-null mice have suggested that FGF23-induced changes in Na/Pi-2a and 1α-hydroxylase expression are independent of the 1,25(OH)2vit D3/VDR system (48).
However, it is currently unclear to what extent alterations in 1,25(OH)2vit D3/VDR system signaling determine the phenotypic abnormalities of disorders associated with FGF23 excess or deficiency. In vivo studies showed the ability of deletion of the VDR to rescue the phenotype of FGF23-null mice (49, 50). This suggests that the 1,25(OH)2vit D3/VDR system has an important role in mediating the phenotypic expression of FGF23 ablation.

As KLOTHO and FGFR are coexpressed in parathyroid glands, the parathyroid gland is another probable target for FGF23. Data about whether FGF23 signaling stimulates or inhibits PTH secretion are conflicting.

Both elevated serum PTH and parathyroid gland hyperplasia were observed in several studies using FGF23 transgenic mouse models (51, 52). Other authors have reported opposite findings in terms of PTH levels in mice overexpressing FGF23. Although the mice presented reduced serum phosphate and 1,25(OH)2vit D3 levels, which would be expected to increase PTH secretion, PTH levels were surprisingly decreased (53). Several agents influence the release of PTH from parathyroid glands. The calcium ion is the main regulator of parathyroid gland activity. Other known regulating factors are serum magnesium, phosphate, and 1,25(OH)2vit D3. FGF23-mediated reductions in 1,25(OH)2vit D3 production and the presence of altered calcium or magnesium levels confound the interpretation of an association of FGF23 ablation.

Interestingly, two in vitro studies that used parathyroid cells in culture showed that FGF23 acts directly on the parathyroid gland to activate the MAPK pathway and decrease PTH secretion (54, 55). These in vitro models provide a good system to study the inhibitory effect of FGF23 on the parathyroid gland as exposure to other humoral factors known to act on the parathyroid gland can be easily controlled. However, the physiological relevance and specificity of these findings need to be confirmed in vivo.

FGF23 might also target the pituitary gland and choroid plexus, which are sites of FGFR1c and KLOTHO expression. The function of FGF23 on these sites remains speculative. The Na/Pi cotransporter and KLOTHO expressed in the choroid plexus might regulate cerebrospinal fluid phosphate levels.

FGF23 and its role in disorders associated with altered phosphate homeostasis

As mentioned previously, the study of the renal phosphate-wasting disorders ADHR and TIO resulted in the identification of FGF23. Since the discovery of FGF23, the molecular mechanisms in several disorders with altered phosphate metabolism have been elucidated (Table 1).

ADHR is a rare disorder characterized by hypophosphatemia due to renal phosphate wasting, reduced 1,25(OH)2vit D3 levels, and rickets/osteomalacia. Using a positional cloning approach, FGF23 was identified as the causative factor of ADHR (3). ADHR results from activating mutations in the FGF23 gene located within three nucleotides between residues 176 and 179 in the proprotein convertase cleavage site. These mutations prevent proteolytic cleavage of the FGF23 protein to presumably inactive fragments, with the net result being an enhanced biological activity of FGF23 (56).

Table 1 Genetic disorders associated with altered phosphate homeostasis related to inappropriate fibroblast growth factor 23 (FGF23) levels.

<table>
<thead>
<tr>
<th>Hypophosphatemic disorders</th>
<th>Mutated gene</th>
<th>Mechanism</th>
<th>FGF23 level</th>
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<tbody>
<tr>
<td>Autosomal dominant hypophosphatemic rickets</td>
<td>FGF23</td>
<td>Resistance to proteolytic cleavage</td>
<td>↑*</td>
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<tr>
<td>X-linked hypophosphatemic rickets</td>
<td>PHEX</td>
<td>Increased FGF23 expression</td>
<td>↑*</td>
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<tr>
<td>Autosomal recessive hypophosphatemic rickets</td>
<td>DMP1</td>
<td>Increased FGF23 expression</td>
<td>↑</td>
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<tr>
<td>Hypophosphatemic rickets and hyperparathyroidism</td>
<td>α-KLOTHO</td>
<td>Direct or indirect effects of increased plasma KLOTHO level</td>
<td>↑</td>
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<tr>
<td>McCune–Albright syndrome/ polyostotic fibrous dysplasia</td>
<td>GNAS1</td>
<td>Increased production of FGF23 by fibrous bone cells</td>
<td>↑</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Hereditary familial tumoral calcinosis</td>
<td>GALNT3</td>
<td>Defect in glycosylation, facilitating</td>
<td>C terminal ↓</td>
</tr>
<tr>
<td>FGF23 degradation</td>
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<tr>
<td></td>
<td></td>
<td>Failure to secrete intact FGF23</td>
<td>C terminal ↑</td>
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<tr>
<td></td>
<td></td>
<td>Resistance to FGF23</td>
<td>C terminal ↑</td>
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DMP1, dentin matrix protein 1; FGF23, fibroblast growth factor 23; GALNT3, UDP-N-acetyl-α-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3; GNAS1, guanine nucleotide-binding protein, α-stimulating gene; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome.

*FGF23 levels are elevated in many, but not in all patients.
X-linked hypophosphatemic rickets/osteomalacia (XLH) is an X-linked dominant disorder of isolated phosphate wasting. XLH is the most common form of inherited rickets. Patients with XLH present laboratory findings that are similar to those presented by patients with ADHR. XLH is caused by inactivating mutations in the PHEX gene encoding a zinc-dependent endopeptidase (57). Several mutations have been identified using positional cloning experiments. Circulating FGF23 levels are elevated in many, but not all, patients with XLH (58–60). Serum phosphate concentrations are negatively correlated with circulating FGF23 levels in patients with XLH, suggesting that elevated FGF23 contributes to hypophosphatemia in this disorder (59). The precise function of PHEX is not yet elucidated. Initially, it was presumed that the endopeptidase PHEX is responsible for the degradation of FGF23, and that decreased degradation of FGF23 by mutated PHEX accounts for excessive amounts of circulating peptide. However, the data regarding FGF23 as a substrate for PHEX are conflicting. Several studies failed to demonstrate PHEX-dependent cleavage of intact FGF23 (7, 8). Instead, several groups reported of enhanced expression of FGF23 and overproduction by bone cells in the mouse homologue of XLH (7, 9). As discussed previously, the current theory is that PHEX somehow inhibits FGF23 expression in bone, but the exact mechanism is still unclear.

Autosomal recessive hypophosphatemic rickets/osteomalacia (ARHR) is caused by inactivating mutations in the DMP1 gene (located on chromosome 4q21) (61). The clinical phenotype of ARHR patients is similar to that of ADHR and XLH patients. Loss of DMP1 causes impaired osteocyte differentiation and increased production of FGF23 (62). The high circulating levels of FGF23 are responsible for phosphaturia and aberrant vitamin D metabolism.

One report described a patient with hypophosphatemic rickets and hyperparathyroidism (HRH) (63). The primary genetic abnormality is a translocation (t(9,13)(q21.13;q13.1)) that results in elevated levels of circulating α-KLOTHO. Renal phosphate wasting, altered vitamin D metabolism, and rickets/osteomalacia are the prominent features. However, HRH differs from the renal phosphate-wasting disorders described above by the presence of hyperparathyroidism as a predominant feature. In HRH, FGF23 levels are inappropriately high, and the mechanism whereby excess KLOTHO is linked to increased FGF23 levels is not clear. α-KLOTHO could potentially bind and prevent the degradation of FGF23, and target bone to increase FGF23 production, or increased FGF23 concentrations could be part of a negative feedback loop in response to hyperparathyroidism induced by the increased α-KLOTHO levels.

McCune–Albright syndrome (also called polyostotic fibrous dysplasia) results from postzygotic mutations in the GNAS1 gene. GNAS1 encodes the α-subunit of the heterotrimeric stimulatory G-protein (Gsα), which is inappropriately activated by the mutations. A mutation early during development, affecting many tissues, results in McCune–Albright syndrome, whereas a mutation arising in bone induces only monostotic or polyostotic fibrous dysplasia. Clinical characteristics of McCune–Albright syndrome are variable and depend on the tissue location of the mutation. They include polyostotic fibrous dysplasia, skin hyperpigmentation, and endocrinological abnormalities such as precocious puberty, thyrotoxicosis, pituitary gigantism, and Cushing’s syndrome.

Approximately, 50% of these patients have renal phosphate wasting, disturbed vitamin D metabolism, and osteomalacia. A recent study implicates FGF23 as the key mediator of the associated renal phosphate-wasting syndrome (64). It was shown that FGF23 levels were significantly elevated in fibrous dysplasia patients, and that the circulating FGF23 levels, as well as the degree of phosphate wasting, were correlated with bone disease burden. The mechanism for the increase in circulating FGF23 in fibrous dysplasia is unknown.

The constitutively active Gsα may increase FGF23 expression directly via the cyclic AMP/protein kinase A pathway or indirectly by a generalized defect in altered cell maturation.

Pathophysiological similarities between Jansen’s metaphyseal chondrodysplasia and McCune–Albright syndrome are evident (29). Both diseases are characterized by a constitutively active G-protein-coupled receptor pathway (i.e. common mechanism). Increasing knowledge on these disorders suggests the existence of a common mechanism inducing the increased FGF23 expression in these rare metabolic bone diseases and perhaps also in the more general setting of hyperparathyroidism.

TIO, also referred to as oncogenic osteomalacia, is a paraneoplastic syndrome with a clinical and biochemical phenotype similar to that of ADHR. These clinical and biochemical findings resolve rapidly and completely if the entire tumor (which is most often of mesenchymal origin) is removed surgically. FGF23 has been identified as a causative factor of TIO, in which the tumors express the mRNA and protein for FGF23 abundantly (4, 58, 60, 65). However, FGF23 concentrations are not elevated in all patients with TIO. Three other phosphaturic peptides have so far been isolated from phosphate-wasting tumors associated with TIO, namely sFRP-4, MEPE, and FGF7 (1).

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare autosomal recessive disorder characterized by hyperphosphatemia secondary to increased renal tubular phosphate reabsorption, increased or inappropriately normal 1,25(OH)2vit D3 levels, and severe ectopic calcifications in soft tissues. At present, mutations in three genes have been identified as the cause of HFTC.

Biallelic inactivating mutations in genes encoding UDP-N-acetyl-α-d-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) (66–68) or FGF23 (69, 70) result in HFTC. GALNT3 is a...
Golgi-associated enzyme that initiates O-glycosylation of mature polypeptides. This O-glycosylation appears to prevent cleavage of the intact FGF23 protein within the cell, by either modifying the protein structure or interfering with the protein convertases to access the processing site of FGF23. An in vitro study confirmed that this O-glycosylation is required for the secretion of full-length FGF23 (71). Missense mutations in FGF23 have been shown to result in failure to secrete the intact protein, which seems to be retained in the Golgi complex, whereas the C-terminal fragment is secreted. Patients with HFTC due to inactivating mutations in the GALNT3 gene or FGF23 gene have low circulatory levels of intact FGF23, but exhibit high circulatory levels of the processed C-terminal FGF23 fragment.

A missense mutation in the KLOTHO gene may also be the causative factor in HFTC (72). The mutation diminishes the ability of KLOTHO to function as a cofactor necessary for FGF23 signaling through FGF receptors, and thereby impairs FGF23 bioactivity. In contrast to the reduced levels of intact FGF23 in HFTC secondary to mutations in GALNT3 or FGF23 genes, the intact FGF23 levels are increased in HFTC due to a mutation in the KLOTHO gene.

**FGF23 and chronic renal insufficiency**

Circulating levels of FGF23 are markedly increased in patients with chronic kidney disease (CKD) (73). Using the ‘intact’ assay that only detects full-length (active) FGF23, FGF23 levels were shown to increase as the renal function declines (74). The causative factors for increased FGF23 levels in progressive CKD are not clear. The accumulation of full-length FGF23 appears to be relevant because FGF23 may be cleared by the kidneys (75). However, many other factors are known to regulate the production rate of FGF23, so it is unlikely that increased FGF23 levels in CKD are just a reflection of decreased renal clearance (74).

The functional role of elevated circulatory FGF23 levels in different stages of CKD is not well understood. In CKD stages 3 and 4, increased FGF23 might contribute to the adaptive increase in fractional excretion of phosphate as renal function declines to maintain serum phosphate levels within the physiological range (76). In contrast, in patients with more advanced renal failure (exhibiting an important decrease in the number of functional nephrons), the amount of net phosphate excretion does not increase sufficiently, despite high FGF23, and serum phosphate levels remain high.

The increased FGF23 levels in patients with mild renal insufficiency, in whom the potential ability to synthesize 1,25(OH)2vit D3 is preserved, seem to have a causative role in the decrease in serum 1,25(OH)2vit D3 concentrations (76). Although direct effects of FGF23 on PTH secretion remain speculative (see above), FGF23 might indirectly contribute to the development of secondary hyperparathyroidism associated with renal insufficiency by decreasing 1,25(OH)2vit D3 synthesis. In dialysis patients, serum FGF23 level was shown to be a predictive factor for future secondary hyperparathyroidism refractory to calcitriol therapy (77, 78). This supports a potential direct involvement of FGF23 in the progression of secondary hyperparathyroidism.

Hyperphosphatemia and 1,25(OH)2vit D3 deficiency are associated with increased mortality in end-stage renal disease (79, 80). A prospective study involving patients starting hemodialysis showed that increased FGF23 levels are associated with mortality independently of established risk factors (81). Thus, FGF23 may represent a sensitive prognostic marker especially in patients with early kidney disease, in whom FGF23 levels are increased long before hyperphosphatemia appears (76). It may also be a useful tool to guide the clinician in his/her decision to initiate certain therapeutic modalities to manage phosphate balance.

**Conclusion**

Classically, phosphate homeostasis was considered the result of an active interaction between kidney and parathyroid gland with bone viewed as a target for hormones. Since the discovery of FGF23 and other phosphatonin, which are mainly produced in bone, our view on the role of bone has largely changed. Bone should be considered as a bona fide endocrine organ. Bone has an active role in controlling phosphate metabolism by increasing phosphaturia mediated by secreted phosphatonin, and it also actively interacts with other endocrine organs. The existence of a bone–kidney axis with reciprocal regulation of FGF23 production by bone and 1,25(OH)2vit D3 by kidney has been well established. Emerging evidence also suggests an active interaction between bone and parathyroid gland.

**Declaration of interest**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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