

Phosphatonins – a new perspective on mineral metabolism

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ABSTRACT

The recent five years were the most prolific in scientific publications related to one of the re-emerging theme of human physiology, namely phosphate homeostasis. Classically, the phosphate absorption and excretion were thought to be mediated only by the parathyroid hormone (PTH)/vitamin D endocrine axis. Presently, apart from this traditional well-known control and feedback-loop, newly uncovered factors intervene, fine tuning the complex physiological process of renal phosphate handling and bone mineralization. The discovery of phosphatonins and Klotho gene provided new insights into the pathogenesis of several hypophosphatemic or hyperphosphatemic diseases, such as tumor induced osteomalacia, X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemia and tumoral calcinosis. Fibroblast growth factor 23 (FGF-23), secreted frizzled-related protein 4 (sFRP-4), fibroblast growth factor 7 (FGF-7) and matrix extracellular phosphoglycoprotein (MEPE) have been shown to be major phosphaturic factors. Whether and in which manner these hormones participate to the developing of secondary hyperparathyroidism, bone remodeling, and renal fibrogenesis needs to be clarified in the future. We review the current literature describing the role and mode of action of this new hormone class.

Key words: Phosphorous, calcium, renal failure, phosphatonins, vitamin D

INTRODUCTION IN PHOSPHATE HOMEOSTASIS

The calcium-phosphate balance represents the centerpiece of the skeletal growth and bone mineralization. More than a major component of hydroxyapatite, phosphorus is an important constituent of nucleic acids, bioactive signaling proteins, phosphorylated enzymes, and cell membranes phos-

pholipids. Thus, an alteration of the phosphate serum level can lead to deficient mineralization of bone, defacement of blood cell function and cell membrane integrity, and impairment of cardiovascular function (1,2).

The intestine, kidney and bone are the main mediators of phosphate homeostasis. Thus, the small intestine, predominantly the jejunum, is responsible for phosphorus absorption mediated by sodium-phosphate type IIb cotransporters (3). It also contributes partially to the elimination of phosphorus, through the feces.

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However, it is the kidney that carries out the major part of phosphate excretion and also fine-tuning of P balance. After glomerular filtration, phosphorus is reabsorbed via the type IIa and IIc sodium phosphate cotransporters (NaPi-IIa and NaPi-IIc) that are located at the apical borders of the proximal tubule cells (4). Finally, bone mineralization, including both formation and resorption, is an important component of phosphate metabolism, mediated, at least in part, by sodium-phosphate type III cotransporters (3,5).

PTH acts to decrease overall phosphate loading by its phosphaturic effect in the kidney; it also increases the synthesis of $1\alpha,25(\text{OH})_2\text{D}_3$ via stimulating the activity of the 1α -hydroxylase enzyme, in the kidney. On the other side, $1\alpha,25(\text{OH})_2\text{D}_3$ increases phosphate retention by enhancing the efficiency of phosphorus absorption in the intestine and in the kidney (2).

All studies of the last decades showed that this classical pathway is not enough to explain the complex regulation of phosphorus homeostasis, pointing to the idea that several other / new factors are also implicated in the relationship between phosphorus retention and calcitriol deficiency. Dietary phosphate intake, serum pH, dopaminergic and adrenergic activity may all contribute to the final serum Pi concentration; however a large part of this equilibrium was still not evidently explained. "Phosphatonins" are the most recent uncovered players in P homeostasis. This term was introduced to describe circulating factors responsible for the inhibition of renal phosphate reabsorption present in the serum of patients with tumor-induced osteomalacia (TIO). Phosphatonins act via cAMP-independent pathways to prevent or attenuate increased 25-hydroxyvitamin D 1α -hydroxylase activity that normally occurs in response to hypophosphatemia (2). In their first description made in 1994 by Cai et al. patients with TIO have hypophosphatemia, hyperphosphaturia, normal serum level of 25-hydroxyvitamin D ($25(\text{OH})\text{D}$) and low $1\alpha,25$ dihydroxyvitamin D ($1\alpha,25(\text{OH})_2\text{D}_3$) concentration, osteomalacia, hemangiopericytoma. This biochemical profile disappeared after removal of the tumor (6,7). Subsequently, it has been shown that hormonal factors are also implicated in some other disorders with similar or completely opposite biochemical abnormalities to those observed in TIO,

namely X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemia (ARHP), and tumoral calcinosis (8-14). Hereby, several proteins with novel hormone activity, that regulates phosphate homeostasis through a PTH-independent mechanism, have been described as phosphatonins: fibroblast growth factor-23 (FGF-23), secreted frizzled-related protein (sFRP-4), matrix extracellular phosphoglycoprotein (MEPE) and fibroblast growth factor-7 (FGF-7). □

THE ROLE OF PHOSPHATONINS IN NORMAL KIDNEY

Phosphatonins induce renal phosphate loss by decreasing renal sodium-dependent phosphate transport, inhibit 25-hydroxyvitamin D 1α -hydroxylase activity (Figure 1). At bone level they interfere with mineralization, and are likely to be substrates for PHEX (candidate gene for XLH), and therefore regulate multiple aspects of mineral metabolism. FGF-23, sFRP-4, MEPE and FGF-7 inhibit sodium-dependent phosphate transport in cultured renal epithelia and inhibit renal tubular phosphate reabsorption in vivo, and variably alter vitamin D metabolism (15).

Fibroblast growth factor-23 (FGF-23): FGF-23 is the most studied phosphatonin. It is a phosphate-regulating peptidic hormone that is primarily expressed in osteocytes and osteoblasts in the bone and in the endothelial cells that line the venous sinusoids of bone marrow and the thymus (5, 16-18). Possibly the rate of cleavage of FGF-23 by PHEX protease that results in its inactivation determines at least in part the blood level of fibroblast growth factor 23. Although, there are some papers which showed that the serum concentrations of FGF-23 are not influenced by short-term or long-term dietary phosphorus intake (20-22), most data indicate that dietary phosphate load is the main stimulating factor of FGF-23 secretion (21, 23). Besides, Ferrari et al. asserted that phosphate load rather than serum phosphate concentration lead to increased level of FGF-23 (23). While current data that suggest a direct regulation of FGF-23 by plasma phosphate concentrations are still debatable, serum levels and expression of FGF-23 are certainly increased following $1\alpha, 25(\text{OH})_2 \text{D}_3$ treatment (5).

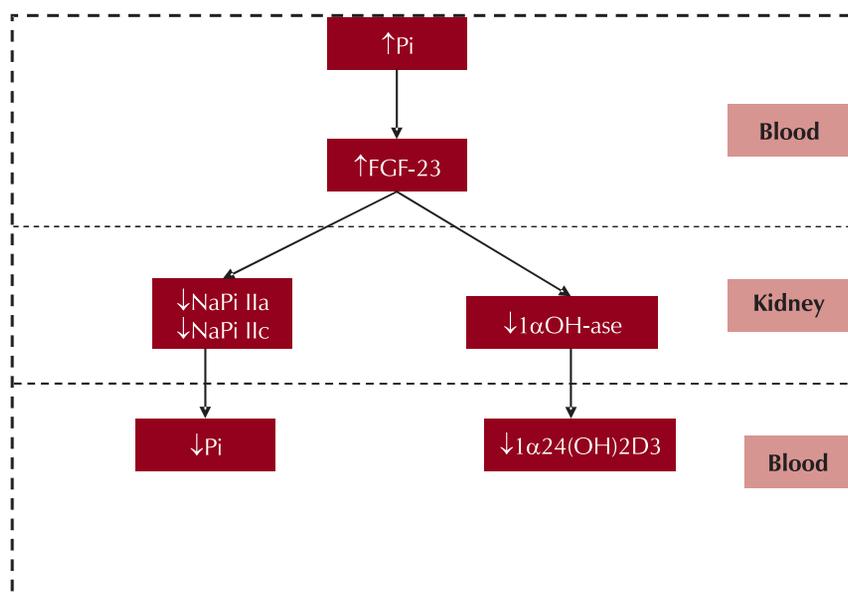


FIGURE 1. Biological effects of FGF-23

Legend. Pi – serum ionic phosphorus level, FGF-23 – fibroblast grow factor 23, NaPi IIa – phosphate sodium-dependent cotransporter IIa, NaPi IIc – phosphate sodium-dependent cotransporter IIc, 1αOH-ase – 25-hydroxyvitamin D 1α-hydroxylase, 1α24(OH)2D3 – 1α,25 dihydroxyvitamin D

There are new data concerning the FGF-23 mechanism of action. FGF-23 binds to and activates its FGF receptors that belong to type 1 transmembrane phosphotyrosine kinase receptors to obtain a biological response in its target tissues (23,24). Recently, it was showed that FGF-23 also requires Klotho, as an obligatory co-factor for receptor activation which acts to convert FGFR1c to a receptor specific for FGF-23 (23-25). Animal experimental studies advocate the co-receptor role of klotho by expressing the same phenotype in both klotho-deficient mice and FGF-23 null mice (26). Klotho is a single-pass membrane protein which has structural homologies with β-glucosidases (26-28). A circulating and cerebrospinal fluid form of klotho was described, that derives from the cleavage of the membrane-bound form of the protein (28,29). The kidney, reproductive tissues and brain are several tissues that display klotho (30).

Elevated FGF-23 level promotes phosphaturia and suppresses calcitriol production. FGF-23 acts by decreasing mRNA and protein levels of the NaPi-IIa and NaPi-IIc cotransporters, and therefore leads to renal phosphate loss. Likewise, FGF23 decreases mRNA for 25-hydroxyvitamin D 1α-hydroxylase suppressing calcitriol production (31).

There are still more unanswered questions concerning the production, metabolism and function of this peptide. Among these, one derives from the observation that high levels of FGF-23 were reported in malignancies associated with humoral hypercalcemia and not only in tumor-induced osteomalacia. Furthermore, elevated concentrations of FGF-23 were found in the serum of patients with malignancies not associated with phosphaturia. The proposed explanation consists in the possibility of a very high FGF-23 concentration present before the occurrence of hypophosphatemia or in the presence of yet another factor formed in excessive amounts that are able to cause hypophosphatemia in TIO (2).

At this moment, most data related to these newly described hormones are available for fibroblast grow factor 23. The limited informations related to the other peptides known as phosphatonins are derived more from animal experimental studies, rather than human observations. The major drawback reside in the unavailability of a robust assay able to distinguish modified forms such as proteolytic fragments derived from the intact molecule of these proteins (2).

Secreted frizzled-related protein (sFRP-4): sFRP-4 reduces renal phosphate reabsorption

by lessen sodium phosphate transporters in renal proximal tubules and inhibits formation of $1\alpha,25(\text{OH})_2\text{D}_3$ in vivo and therefore co-acting with FGF-23 (32).

Fibroblast growth factor-7 (FGF-7): FGF-7 inhibits sodium-dependent phosphate transport in opossum kidney cells, proximal tubular-like epithelial cells that own sodium-phosphate cotransporters NaPi-IIa and NaPi-IIc. Carpenter et al. observed that anti-FGF-7 antibodies attenuate the phosphate transport inhibition induced by FGF-7 (33). In addition, the Shaiks et al. study has recently shown that FGF-7 is phosphaturic in vivo (34).

Matrix extracellular phosphoglycoprotein (MEPE): MEPE increases the fractional excretion of phosphate and therefore leads to hypophosphatemia in vivo (35). In addition, it was also showed that MEPE inhibits bone mineralization in vitro. This assumption is sustained by the animal model in which MEPE null mice have increased bone mineralization. Another outstanding matter is the fact that MEPE does not inhibit $1\alpha, 25(\text{OH})_2\text{D}_3$ formation (5). □

THE ROLE OF PHOSPHATONINS IN CHRONIC KIDNEY DISEASE

The nephrological community has been enthusiastic by the discovery of phosphatonins that could help to understand the complex relationship between phosphorus retention and calcitriol deficiency (23).

In the setting of chronic kidney disease (CKD) the serum phosphate concentrations increase due to the kidney incapacity to excrete the phosphorus load in response to FGF-23. Thus, increased serum phosphate levels and low serum $1\alpha,25(\text{OH})_2\text{D}_3$ levels stimulate PTH secretion leading to secondary hyperparathyroidism.

Serum FGF-23 levels concordantly increase with the fall of glomerular filtration rate (GFR). Of note, the same parallelism between FGF-23 concentration and kidney function was observed in studies that applied both previous assay that used antibodies that also detected C-terminal fragments of FGF-23 (biologically inactive) and also the newer assay, which was able to detect the full-length human FGF-23, by employment of two types of monoclonal antibodies (36-40). In patients with chronic kidney disease, serum FGF-23 levels are increased in response to elevated plasma phosphate, but

also probably secondary to reduced clearance of this phosphatonin. Serum FGF-23 concentrations increase along with the decline of kidney function, even before the development of hyperphosphatemia (36,40,41).

The presumed physiological role for FGF-23 is promoting phosphaturia and suppressing renal calcitriol production in response to phosphorus retention. Fukagawa and Kazama's explain secondary hyperparathyroidism via FGF-23 high serum concentrations which act to prevent hyperphosphatemia at the expense of low calcitriol (23,42). Therefore, in CKD patients serum FGF-23 levels correlate negatively with $1\alpha, 25(\text{OH})_2\text{D}_3$ concentrations, and also with maximal tubular reabsorption of phosphate (TmP/GFR). In patients with advanced renal failure renal phosphate excretion is impaired, despite significantly higher FGF23 levels. This is explained by a significant reduction of the viable nephron mass that leads to an insufficient net phosphate excretion concomitantly with a decrease in a kidney production of $1\alpha, 25(\text{OH})_2\text{D}_3$. Thus, persistently high plasma phosphate concentrations along with low calcitriol levels continuously stimulate PTH secretion resulting in the development of secondary hyperparathyroidism (42).

Dialysis patients exhibit higher serum FGF-23 levels comparatively with mild or moderate CKD patients. FGF-23 production in patients on renal replacement therapy is continuously stimulated by phosphate load, calcitriol (analogue) treatment and possibly by high PTH concentration (42,43).

Since plasma FGF-23 concentrations present a positive correlation with serum phosphate levels and intact PTH levels, Nakanishi et al revealed that the measurement of the initial serum FGF-23 level could be a better screening test than intact PTH or calcium for developing secondary hyperparathyroidism within the subsequent two years (44). Admittedly that calcitriol and its analogues are the mainstays for the prevention and treatment of secondary hyperparathyroidism in dialysis patients (45), another Japanese group studied the efficiency of intravenous calcitriol therapy in patients diagnosed with secondary hyperparathyroidism. They observed that elevated plasma FGF-23 concentration is associated with resistance to treatment, and thus concluded that serum FGF-23 levels could be an additional predictor for calcitriol therapy resistance (46).

Equally, recent papers reported that calcitriol administration increased serum FGF-23 levels, despite suppression of PTH levels (47-49). Sato et al. hypothesized a possible interrelation between abnormal PTH secretion and FGF23 regulation consistent with his observation that total parathyroidectomy leads to piecemeal decreasing of elevated circulating fibroblast growth factor 23 (50).

Accordingly to all these observation we can hypothesize for an important role of the newly uncovered FGF-23 hormone in renal bone disease. Actually, very recent data show no correlation between FGF-23 and bone mass or bone remodeling markers (51). Future studies are needing to confirm this unexpected finding.

More thought-provoking are data from Fliser et al. assigning to FGF-23 a role in progression of kidney damage resulted from the observed correlation between increased FGF-23 concentrations and the progression of chronic renal

failure in patients with mild-to-moderate chronic renal disease. Since many other variables such as the CaxP product, parathyroid hormone, and vitamin D usage correlate with progression, it is debatable if FGF-23 has a role in renal fibrogenesis (52). □

Conclusion

Phosphatonins, one of the most exciting finding of the recent years, unravel some riddles touching the physiopathology of phosphate abnormalities associated disorders. Although it has been appointed their ability to induce phosphaturia and inhibit calcitriol production, there are still more inconsistencies and gaps in the insight into metabolism and function of these new hormones. Additionally, they seem to be involved in many aspects of cronic kidney disease, such as secondary hyperparatiroidism, calcitriol therapy resistance, renal fibrogenesis. Therefore, further heuristic studies must to establish the firm role of phosphatonins in chronic kidney disease and its capability to grow into therapeutical target. □

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