With or without the kidney: the role of FGF23 in CKD

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The systemic balance of phosphate is maintained mainly by three organs, i.e. the intestine, kidney and bone. Several factors including parathyroid hormone (PTH) and vitamin D play a critical role in this system. Fibroblast growth factor 23 (FGF23) is a recently identified phosphatonin which also is implicated [1,2].

It has been demonstrated in several diseases that excessive activity of FGF23 resulted in hypophosphataemia, low plasma 1,25-dihydroxyvitamin D (1,25D) levels and osteomalacia [3–5]. In animals, the administration of recombinant FGF23 led to the same results [6]. Furthermore, overexpression of FGF23 led to phosphate wasting [7] and rickets, while ablation of this gene led to hyperphosphatemia and high circulating 1,25D levels [8].

Physiological role of FGF23 with a normal kidney

What are the physiological stimuli for FGF23 secretion? In normal rats, a dietary phosphate load leads to hyperphosphataemia and increased serum FGF23 levels [9]. Such an observation has also been confirmed recently in humans. It is of note that phosphate load rather than serum phosphate concentration may be most important [10].

FGF23 levels increase in response to phosphate load by as yet unknown mechanisms, which promote phosphaturia and suppresses renal 1,25D production. Thus, a significant role for FGF23 in phosphate homeostasis is suspected in physiological conditions, with the intact kidney as the target organ.

Role of FGF23 with a failing kidney

Then, what is the role of FGF23 in chronic kidney disease (CKD), when phosphate balance is often deranged? In rats made uraemic by anti-glomerular basement membrane antibody, serum FGF23 levels increased as the renal function declined, along with an increase of phosphate levels and a decrease of 1,25D levels, together with a significant increase of PTH secretion [11]. High serum FGF23 levels were also associated with a high fractional excretion of phosphate. The effects of FGF23 on 1,25D levels and fractional excretion of phosphate were abolished by treating the rats with a specific neutralizing antibody against FGF23. Enhanced PTH secretion was also suppressed by this antibody treatment. Since the increase of FGF23 preceded the decrease of 1,25D, it seems that FGF23 plays an important role in the development of secondary hyperparathyroidism in CKD.

Several papers have already been published on the serum levels of FGF23 in CKD patients [12–14]. In pre-dialysis patients, FGF23 levels were high and correlated with those of phosphate and creatinine. Nevertheless, the assay performed in these previous studies used antibodies that also detect C-terminal fragments. A new assay was developed to detect a full-length human FGF23 using two kinds of monoclonal antibodies, thus eliminating the detection of accumulating C-terminal fragments [15].

By this ‘intact’ assay, serum FGF23 levels increased along with the fall of glomerular filtration rate (GFR) [16]. As expected, serum 1,25D levels correlated negatively with serum FGF23 levels. Furthermore, maximal tubular reabsorption of phosphate (TmP/GFR) correlated negatively with serum FGF23 levels, consistent with the physiological action of FGF23 that inhibits phosphate reabsorption in the proximal tubule. In contrast, patients with advanced renal failure exhibited impaired urinary phosphate excretion, despite significantly higher FGF23 levels.

With normal renal function, FGF23, when secreted in response to phosphate load, suppresses 1α-hydroxylase activity. In turn, decreased 1,25D levels activate parathyroid function. FGF23 promotes
phosphate excretion by the kidney, which returns the serum phosphate level to normal. Since decreased serum phosphate, in turn, suppresses parathyroid function, the suppressive action on 1α-hydroxylase activity is antagonized.

In contrast, the number of viable nephrons decreases in patients with CKD. Therefore, despite high FGF23 levels, the amount of net phosphate excretion does not increase sufficiently, and serum phosphate levels remain high. Thus, high phosphate and decreased 1,25D levels further stimulate PTH secretion, leading to the development of secondary hyperparathyroidism in advanced stages of CKD.

**Role of FGF23 in the absence of a functioning kidney**

As reported recently, serum concentrations of FGF23 are extremely high in the majority of dialysis patients, even using the new intact assay. What is the role of FGF23 under these circumstances, i.e. in the absence of the major target organ, the kidney?

In our recent analysis of dialysis patients without hyperparathyroidism, FGF23 showed a weak but significant positive correlation with intact PTH. To our surprise, FGF23 levels showed an even better correlation with intact PTH levels 2 years after the measurement of FGF23. Further analysis using receiver operated characteristic curves revealed that the measurement of initial serum FGF23 level was a better screening test than intact PTH or calcium to discriminate patients in whom uncontrollable secondary hyperparathyroidism would develop within the subsequent 2 years [17]. In another study in dialysis patients with marked hyperparathyroidism, the pre-treatment FGF23 and intact PTH levels both significantly predicted the response to intravenous calcitriol therapy [18].

Then, what is the role of very high FGF23 levels in the development of refractory hyperparathyroidism, and where do these high levels of FGF23 come from? The first possibility is that they come from enlarged parathyroid glands. A recent report by Larsson and his associates demonstrated the development of parathyroid hyperplasia in response to FGF23 overexpression [19]. In contrast, no FGF23 mRNA expression was found in surgically removed enlarged parathyroid glands from patients with severe hyperparathyroidism [17]. In dialysis patients, serum FGF23 levels decreased slowly after surgical parathyroidectomy [20], although they did not return to normal levels. In addition, the majority of patients with primary hyperparathyroidism showed normal serum FGF23 levels, especially those with normal renal function [21]. Thus, parathyroid glands do not seem to be the origin of the very high FGF23 observed in dialysis patients. Although FGF23 expression was found in bone [17,22], other organs need to be screened as a potential source of FGF23 in renal failure.

On the other hand, the increase of FGF23 levels induced by a high phosphorus diet was abolished by parathyroidectomy in normal and uraemic rats [23]. When PTH was injected into sham-operated and parathyroidectomized rats, serum FGF23 levels increased only in sham-operated rats. Thus, although FGF23 was not produced in parathyroid glands themselves, parathyroid hyperplasia is needed to maintain high FGF23 levels in dialysis patients.

In a recent study by our group, intravenous calcitriol therapy further increased serum FGF23 levels despite suppression of PTH levels. The serum FGF23 levels at 6 months significantly correlated with the cumulative 6 month doses of calcitriol [24]. The delta increase of serum FGF23 levels during the 6 months also showed a significant positive correlation with the cumulative dose of calcitriol. In keeping with this observation, it has been reported by others that 1,25D administration increased FGF23 levels in vivo [9] and in vitro [25].

**Closed or open loop in the FGF23 system: with or without the kidney**

The regulatory system for phosphate balance involving FGF23 can be summarized as shown in Figure 1. With normal renal function, i.e. in the closed loop mode, FGF23 acts on the kidney to promote urinary phosphate excretion and to suppress 1,25D production. Serum FGF23 levels return to normal after normalization of serum phosphate levels or phosphate balance in this regulatory system. When the kidney becomes unable to excrete the phosphate load appropriately in response to FGF23, PTH secretion is progressively stimulated by low serum 1,25D as well as by high serum phosphate levels.

In contrast, the loop of the regulatory system for phosphate balance is open in the absence of the main target organ of FGF23, the kidney. In dialysis patients, FGF23 production in the bone is continuously stimulated by phosphate load, vitamin D treatment and possibly by high PTH, while the normal negative feedback loop is no longer active with respect to FGF23. This results in very high levels of serum FGF23.

**Conclusion**

Circulating FGF23 is a physiological regulator of phosphate balance. Although mechanisms of increased FGF23 levels remain to be fully elucidated, this factor turns into a potential uraemic toxin, or, in other words, a new player in the trade-off hypothesis proposed by Slatopolsky et al. more than 30 years ago to explain the pathogenesis of secondary hyperparathyroidism in CKD patients [26]. In dialysis patients, the measurement of serum FGF23 may become a promising laboratory test to predict the development of secondary hyperparathyroidism and the response to calcitriol therapy. Further studies are
needed to clarify more precisely the mechanism of the action and regulation of FGF23 under normal conditions and in CKD. In particular, the initial step of the regulatory system, i.e. sensing of phosphate load, needs to be elucidated in the near future.

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References