Review Article

Clinical Significance of FGF-23 in Patients with CKD

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FGF23 is a bone-derived hormone that plays an important role in the regulation of phosphate and 1,25-dihydroxy vitamin D metabolism. FGF23 principally acts in the kidney to induce urinary phosphate excretion and suppress 1,25-dihydroxyvitamin D synthesis in the presence of FGF receptor 1 (FGFR1) and its coreceptor Klotho. In patients with chronic kidney disease (CKD), circulating FGF23 levels are progressively increased to compensate for persistent phosphate retention, but this results in reduced renal production of 1,25-dihydroxyvitamin D and leads to hypersecretion of parathyroid hormone. Furthermore, FGF23 is associated with vascular dysfunction, atherosclerosis, and left ventricular hypertrophy. This paper summarizes the role of FGF23 in the pathogenesis of mineral, bone, and cardiovascular disorders in CKD.

1. Introduction

Patients with chronic kidney disease (CKD) are at increased risk for cardiovascular events compared with individuals with normal kidney function [1]. In addition to traditional cardiovascular risk factors, disturbances in calcium-phosphate metabolism are regarded as strong contributing factors of higher cardiovascular mortality in CKD patients [2, 3]. Indeed, elevated serum phosphate, low calcitriol, and high PTH levels represent the classical triad that leads to secondary hyperparathyroidism, each factor being independently associated with cardiovascular events and mortality in patients with CKD [4, 5].

Recently, the phosphaturic hormone, fibroblast growth factor (FGF-23), is overpoweringly entered into the traditional pathophysiological scheme of secondary hyperparathyroidism.

2. Structure of FGF-23

Seven known subfamilies of human FGFs have been defined [6, 7]. The FGF-19 subfamily is composed of three proteins—FGF-19, FGF-21, and FGF-23—which exert diverse

physiological functions. FGF-23 is a central regulator of phosphate homeostasis and calcitriol blood levels; FGF-19 inhibits the expression of enzyme cholesterol 7- α -hydroxylase (CYP7A1), which is the first and rate-limiting step in bile acid synthesis [8]; FGF-21 stimulates insulin-independent glucose uptake in adipocytes and lowers triglycerides [9]. Interestingly, FGF-19, FGF-21, and FGF-23 contain a disulfide bond that is absent in most other subfamilies. This may explain why FGF-23 can be distributed in the bloodstream to mediate its functions.

FGF-23 is a 251-amino acid protein (MW 26 kDa) synthesized and secreted by bone cells, mainly osteoblast [10]. It is composed of an amino-terminal signal peptide (residues 1–24), followed by an “FGF-like sequence” (residues 25–180) and a carboxyl-terminal extended sequence (residues 181–251) that is unique compared with other members of the FGF family [7]. The half-life of intact FGF-23 in the circulation of healthy individuals has been estimated to be 58 min [11]. FGF-23 exerts its biological effects through activation of FGF receptors (FGF-Rs); this activation is Klotho dependent as a Klotho/FGF-R complex binds to FGF-23 with higher affinity than does FGF-R or Klotho alone [12]. Klotho is a 130-kDa transmembrane β -glucuronidase capable of hydrolyzing

steroid b-glucuronides. It was named after Klotho, one of the Moirae (the fates) in Greek mythology who spun the thread of life from her distaff onto her spindle; indeed, Klotho-deficient mice manifest a syndrome resembling accelerated human aging and extensive atherosclerosis. Because FGF-23/mice show similar phenotypes to Klotho/mice, a common signaling pathway has been postulated [13, 14]. Klotho gene expression was detected in cells of the renal tubule, parathyroid, and choroid plexus. Importantly, renal Klotho expression is largely confined to the distal tubules, which is also the site for initial FGF-23 binding and signaling [15, 16]. However, renal phosphate reabsorption mainly occurs in the proximal tubules, and it is currently unknown how FGF-23 signaling in the distal tubule translates into decreased phosphate reabsorption in the proximal tubules.

3. Physiological Functions of FGF-23

Renal phosphate excretion is physiologically regulated mainly by proximal tubular cells, which express both Na/Pi Type II and Na/Pi IIc cotransporters at their apical membrane [17].

FGF-23 reduces the action of both cotransporters; in addition, it may inhibit gastrointestinal phosphate absorption by reducing intestinal Na/Pi IIb cotransporter activity in a vitamin D-dependent manner [18].

The principal physiological stimuli for increased FGF-23 expression both *in vitro* and *in vivo* are 1,25(OH)₂D₃ and high dietary phosphate intake [19–22]. Persistent hyperphosphataemia is an effective trigger for FGF-23, while rapid changes in serum phosphate concentrations may not induce an acute increment in serum FGF-23 levels [23]. It is therefore possible that FGF-23 responds to the net phosphate balance rather than to the serum phosphate level, but experimental data supporting this hypothesis are scarce.

4. FGF-23, PTH, and Calcitriol

FGF-23, PTH, and calcitriol may influence each other in opposite manner. FGF-R and Klotho are expressed in parathyroid glands; FGF-23 might decrease PTH mRNA transcription [24]. FGF-23 activity is not dependent on PTH, as the phosphaturic effects of FGF-23 are maintained in animals after parathyroidectomy [25]. Conversely, PTH may stimulate FGF-23 secretion by osteoblast, as FGF-23 levels are increased in rodents with primary HPT, which may be reversed by parathyroidectomy [26]. In rodents, injection of recombinant FGF-23 reduces calcitriol levels within hours by decreasing renal expression of 1 α -hydroxylase (CYP27B1) and increasing the expression of 24-hydroxylase (CYP24A1), which controls calcitriol degradation [25]. Conversely, calcitriol itself stimulates FGF-23 generation by binding to a vitamin D response region in the FGF-23 gene promoter [27].

5. FGF-23 in Subjects with Intact Renal Function

The main physiological role of FGF-23 in healthy subjects is to regulate urinary phosphate excretion to maintain stable serum phosphate levels. However, no correlation between FGF-23 and serum phosphate levels has been found in individuals without overt renal disease [28, 29]. Possible explanation for this finding is that most studies which found no significant change in FGF-23 levels were smaller, and phosphate loading was restricted to a maximum of 3 days [21].

6. FGF-23 in Subjects with CKD

In CKD, circulating FGF-23 levels gradually increase with declining renal function such that by the time patients reach end-stage renal disease, FGF23 levels can be up to 1000-fold above the normal range [30]. The increase in FGF-23 begins at a very early stage of CKD as a physiological compensation to stabilize serum phosphate levels as the number of intact nephrons declines [28, 30–32]. In contrast, it was hypothesized that increased FGF-23 levels in CKD result primarily from decreased renal clearance [31]. However, there is no increase in the accumulation of degraded FGF-23 in advanced CKD. It is also likely that FGF-23 levels depend on an increased secretion due to an end-organ resistance to the phosphaturic stimulus of FGF-23 because of a deficiency of the necessary Klotho cofactor [33, 34]. Other potential explanations for the early rise in FGF-23 could be the release of unidentified FGF-23 stimulatory factors or loss of a negative feedback factor(s) that normally suppress FGF-23, by the failing kidney.

7. FGF-23, Mortality, and Cardiovascular End Points

Since alterations in mineral metabolism are associated with increased cardiovascular risk in CKD, it is plausible that FGF-23 is directly involved in it. Indeed, in patients starting hemodialysis, higher FGF-23 levels were strongly associated with increased risk of 1-year mortality both in crude- and multivariate-adjusted models, with the highest FGF-23 quartile reaching a nearly 6-fold higher risk than the lowest [35]. In addition, in this population, FGF-23 was stronger predictor of mortality than the serum phosphate level. Importantly, FGF23 did not associate to mortality in patients within the highest quartile of serum phosphate (>1.77 mmol/L), suggesting that the prognostic value of FGF23 is blunted in the presence of severe hyperphosphatemia.

The role of FGF-23 on cardiovascular or renal end points but not on mortality has been evaluated in patients with CKD not on dialysis. In 227 diabetic patients with CKD stages 1–4, the progression of renal disease was assessed [32]. It was found that FGF-23 but not serum phosphate levels was significant independent predictor of CKD progression, defined as doubling of serum creatinine and/or terminal renal failure. In a cross-sectional study, a large cohort of

men and women in CKD stage 2 with a mean eGFR of 73 mL/min/1.73 m² was evaluated. In this cohort, that represented a valuable model of healthy individuals and early CKD, it was observed that higher FGF-23 was linked to several dynamic measurements of vascular function, including arterial stiffness measured by pulse wave velocity and endothelial dysfunction measured by an invasive forearm technique [36] in both crude- and multivariate-adjusted models. A subgroup of this population underwent a novel technique named whole-body magnetic resonance imaging angiography, which provides information about the degree of arterial stenosis as a surrogate marker of atherosclerosis in all major vascular territories. Higher FGF-23 level was associated with higher atherosclerosis score [37]. It is important to underline that FGF-23 in some studies has been linked to peripheral vascular calcification and/or coronary artery calcification score, whereas other reports have failed to show such an association [29, 38–41]. On this regard, it has been speculated that FGF-23 could function as a local inhibitor of vascular calcification; FGF-23 inhibits calcification in vascular smooth muscle cells in vitro; this inhibitory effect is strengthened in an inflamed setting, which is often present in CKD patients [42]. Given the osteogenic transformation of vascular smooth muscle cells that occurs in atherosclerotic plaques, it is possible that FGF-23 may be locally expressed in the cardiovascular system. But the presence of FGF-23 in the heart or aorta has not been demonstrated yet [43]. It is currently thought that, at least in early CKD, FGF-23 indirectly contributes to decreased vascular calcification through maintaining a normal serum phosphate level. Finally, the relation between FGF-23 and left ventricular hypertrophy has been evaluated, that is another strong cardiovascular risk factor in CKD. This issue is clinically relevant because other members of the FGF family have been implicated in the pathogenesis of myocardial hypertrophy. Serum FGF-23 was positively associated with left ventricular mass index and increased risk of having left ventricular hypertrophy. In particular, these associations were found in the highest FGF-23 tertile (>48 pg/mL) and were strengthened when restricted to subjects with eGFR <60 mL/min/1.73 m² [35]. It is worth noticing that the associations between FGF-23, vascular dysfunction, atherosclerosis, and left ventricular hypertrophy were all progressively strengthened in patients with a lower eGFR despite normal phosphate levels. This finding supports the hypothesis that FGF-23 may reveal information about phosphate-related toxicity that cannot be obtained by measurements of serum phosphate.

8. Open Questions

The mechanism by which FGF-23 increases cardiovascular events and mortality is still unclear. Thus, it is debated whether FGF-23 is merely a marker of disturbed calcium-phosphate metabolism, or it exerts its undesirable effects by lowering vitamin D levels. Indeed, the correlation of FGF-23 levels with serum phosphate in CKD patients [31, 32, 44, 45] and the association of hyperphosphatemia with adverse outcome in these patients [4, 5, 46–52] may suggest that

negative effects of FGF-23 on survival are the mirror of the negative effects of serum phosphorus. Alternatively, FGF-23 may influence outcomes by inducing hypovitaminosis D suppressing 1 α -hydroxylase with subsequent reduction in calcitriol secretion. Vitamin D deficiency is a nontraditional cardiovascular risk factor in CKD [53–55]. However, available data seem to exclude an ancillary role for FGF-23 as mirror of serum phosphorus because adverse effects associated with high FGF-23 levels remained statistically significant after adjustment for phosphate, calcium, and PTH levels [32]. On the same way, adverse effects associated with high FGF-23 levels remained statistically significant after adjustment for vitamin D levels [35, 36]. In addition, FGF-23 has recently been shown to antagonize some effects of vitamin D in vitro; in a cell culture model, vitamin D induced cell apoptosis, whereas FGF-23 and Klotho induced cell proliferation [56]. Therefore, some hypotheses have been proposed. It has been hypothesized that FGF-23 at very high serum concentrations (as observed in CKD patients) may exert certain nonspecific and presumably adverse effects through low-affinity, Klotho-independent binding to FGF-R, for example, on endothelial cells [57].

9. Conclusion

FGF-23 is a regulator of calcium-phosphate metabolism. In clinical trials, elevated FGF-23 levels were independently associated with faster progression of CKD, therapy-resistant secondary hyperparathyroidism, left ventricular hypertrophy, and increased cardiovascular mortality in dialysis patients. However, FGF-23 is not just a marker of the derangements of calcium-phosphate metabolism in CKD, but rather a relevant factor responsible for the inception of secondary hyperparathyroidism and for cardiovascular morbidity and mortality. Thus, FGF-23 could represent a promising therapeutic target that might improve the fatal prognosis of patients with CKD.

Disclosure

The authors declare that the content of this paper has not been published elsewhere and is not currently under consideration by another journal published by SAGE-Hindawi or any other publisher. The paper's publication has been approved by all the other coauthors.

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