Clinical relevance of FGF-23 in chronic kidney disease

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Fibroblast growth factor (FGF)-23 is a recently discovered regulator of calcium–phosphate metabolism. Whereas other known FGFs mainly act in a paracrine manner, FGF-23 has significant systemic effects. Together with its cofactor Klotho, FGF-23 enhances renal phosphate excretion in order to maintain serum phosphate levels within the normal range. In patients with chronic kidney disease (CKD), FGF-23 levels rise in parallel with declining renal function long before a significant increase in serum phosphate concentration can be detected. However, in cross-sectional studies increased FGF-23 levels in patients with CKD were found to be associated not only with therapy-resistant secondary hyperparathyroidism but were also independently related to myocardial hypertrophy and endothelial dysfunction after adjustment for traditional markers of calcium–phosphate metabolism. Finally, in prospective studies high serum FGF-23 concentrations predicted faster disease progression in CKD patients not on dialysis, and increased mortality in patients receiving maintenance hemodialysis. FGF-23 may therefore prove to be an important therapeutic target in the management of CKD.

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Patients with chronic kidney disease (CKD) stage 5 who receive hemodialysis therapy have a more than 10-fold increased risk for cardiovascular events compared with individuals with normal kidney function.[1] In addition to classic cardiovascular risk factors (e.g., arterial hypertension, smoking, dyslipidemia, family history), disturbances in calcium–phosphate metabolism contribute to vascular calcification and higher cardiovascular mortality in CKD patients.[2,3] Disturbed calcium–phosphate metabolism was traditionally characterized by low-to-normal serum calcium, high serum phosphate, low serum 1,25-$(OH)_2$-vitamin D_3 (calcitriol), and high serum parathyroid hormone (PTH) levels.[4] Elevated serum phosphate, low calcitriol, and high PTH levels are each independently associated with future cardiovascular events and mortality in large epidemiological trials of patients with CKD stage 5.[5,6] Recent *in vitro* studies have illuminated possible mechanisms by which these factors may actively contribute to vessel damage and subsequent cardiovascular events.[7] It is therefore not surprising that preliminary data from clinical trials suggest that therapeutic interventions such as vitamin D therapy,[8–10] phosphate lowering with phosphate binders,[11] and treatment of secondary hyperparathyroidism (sHPT) with cinacalcet[12] may be vasculoprotective, even though outcome data from large randomized clinical trials are still pending.

However, the traditional pathophysiological concept of a deranged calcium–phosphate metabolism in CKD has been challenged by the recent discovery of the phosphaturic hormone, fibroblast growth factor (FGF)-23. In this article, we review available evidence on the (patho)physiological role of FGF-23 and discuss its potential clinical impact in CKD.

STRUCTURE OF FGF-23

FGFs comprise a family of polypeptides that share a common core region containing approximately 120 highly conserved amino acid residues, with variable flanking N- and C-terminal residues. The core region contains a β-trefoil structure composed of folded β-strands and loops. On the basis of phylogenetic analysis, seven known subfamilies of human FGFs have been defined.[13,14] 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, whereas FGF-19 inhibits the expression of enzyme cholesterol-7-α-hydroxylase (CYP7A1), which is the first and rate-limiting step in bile acid synthesis.[15]

FGF-21 stimulates insulin-independent glucose uptake in adipocytes and lowers triglycerides.[16] Interestingly, FGF-19, FGF-21, and FGF-23 contain a disulfide bond that is absent in most other subfamilies. This disulfide bond may stabilize their unique atypical β-trefoil structure, which differs from the common fundamental β-trefoil structure of the core homology region of other FGF subfamilies. Such a conformational change may explain why FGF-19 and FGF-23 have a low affinity for heparin,[13] and can therefore be distributed in the bloodstream throughout the body to mediate their systemic functions. In contrast, members of other FGF subfamilies bind to heparin sulfate present on the cell surface of producing cells, resulting in their capture and explaining their paracrine function.[14]

FGF-23 is a 251 amino acid protein (MW 26 kDa) synthesized and secreted by bone cells, mainly osteoblasts.[17] 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.[14] The biologically active protein can be cleaved at its RXXR motif by a subtilisin-type proprotein convertase.[18–20] The half-life of intact FGF-23 in the circulation of healthy individuals has been estimated to be 58 min.[21] Two assays for measurement of human FGF-23 are commercially available. Full-length FGF-23 levels can be determined with a sandwich enzyme-linked immunosorbent assay, in which two kinds of monoclonal antibodies detect the simultaneous presence of both the N-terminal and C-terminal portions of FGF-23. In contrast, the C-terminal assay recognizes both full-length and processed (presumably inactive) C-terminal fragments of FGF-23 (Figure 1). For the C-terminal FGF-23 assay, intra-assay variability is 5% at 52.7 and 140.0 RU/ml, whereas interassay variability is 5% at 50.9 RU/ml and 7.3% at 153.0 RU/ml, with a lower detection limit of 3.0 RU/ml. For the intact FGF-23 assay, intra-assay variability is 4.4% at 14.6 pg/ml and 2.6% at 148.0 pg/ml, whereas interassay variability is 6.1% at 15.6 pg/ml and 6.5% at 166.0 pg/ml, with a lower detection limit of 1.0 pg/ml (according to the manufacturer's specifications).

FGF-23 AND KLOTHO

Klotho is a 130-kDa transmembrane β-glucuronidase capable of hydrolyzing steroid β-glucoronides. This protein was discovered in 1997 by Kuro-o *et al.*[22] 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, as Klotho-deficient mice manifest a syndrome resembling accelerated human aging and extensive atherosclerosis. Because *FGF-23*$^{-/-}$ mice show similar phenotypes to *klotho*$^{-/-}$ mice,[23,24] a common signaling pathway has been postulated. Indeed, FGF-23 exerts its biological effects through activation of FGF receptors (FGF-Rs) in a Klotho-dependent manner, as a Klotho/FGF-R complex binds to FGF-23 with higher affinity than does FGF-R or Klotho alone.[25] *Klotho* gene expression was detected in cells of the renal tubule, parathyroid, and choroid plexus,[26] conferring FGF-23 tissue selectivity, despite the ubiquitous expression of FGF-R. Currently, it is unclear why Klotho is expressed only at these sites.

FGF-Rs consist of an extracellular domain with two or three immunoglobulin (Ig)-like ligand-binding domains, and one intracellular domain mediating tyrosine kinase activity. Four receptor tyrosine kinases are designated as high-affinity FGF-Rs (FGF-R 1–4). Alternative RNA splicing generates multiple FGF-R isoforms. In particular, this can occur in the third Ig-like domain of FGF-R 1–3, giving rise to epithelial-lineage specific 'b' and mesenchymal-lineage specific 'c'

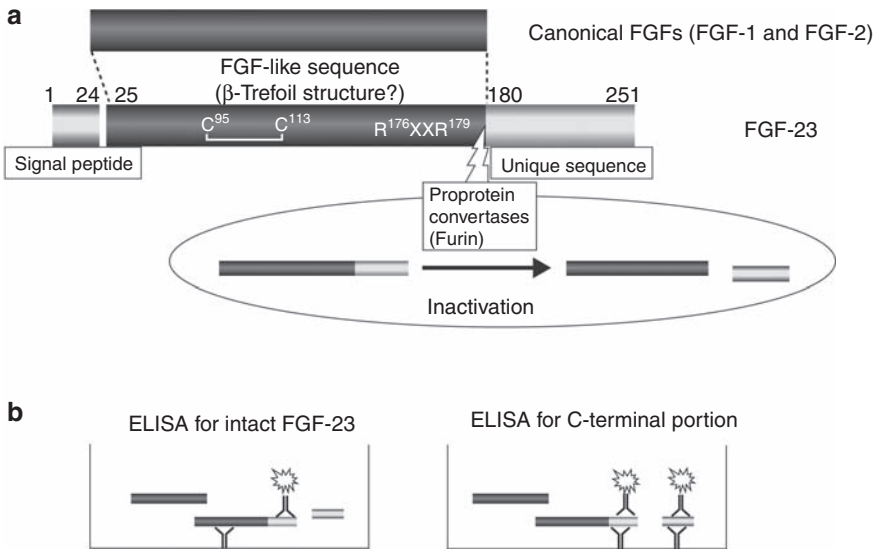


Figure 1 | Schematic structure of fibroblast growth factor (FGF)-23 and principle of FGF-23 ELISA. (**a**) Structure of FGF-23. (**b**) The intact assay detects the simultaneous presence of both the N-terminal and C-terminal portions of FGF-23. The C-terminal assay recognizes both full-length FGF-23 and processed (presumably inactive) C-terminal fragments (reproduced from Yamashita *et al.*,[14] with kind permission from Blackwell Publishing).

isoforms.[27–29] Klotho has a high binding affinity for FGF-R 1–4, with a preference for the c-isoforms of FGF-Rs.[25] In the presence of Klotho, FGF-23 induces the phosphorylation and subsequent activation of the extracellular signal-regulated kinase (ERK), which regulates an important intracellular signal-transduction pathway.[30]

PHYSIOLOGICAL FUNCTIONS OF FGF-23

FGF-23 mediates phosphaturia

Renal phosphate excretion is physiologically regulated mainly by proximal tubular cells, which express Na/Pi Type II cotransporters at their apical membrane that control phosphate reclamation.[31] Renal phosphate reabsorption is mediated primarily through the Na/Pi IIa cotransporter,[32] whereas approximately one-third of phosphate ions are reabsorbed through the Na/Pi IIc cotransporter.[33] FGF-23 mediates its phosphaturic effect by reducing the abundance of the Na/Pi IIa cotransporter[34] (and possibly also Na/Pi IIc) in proximal tubular cells. In animal studies, transgenic mice overexpressing human or mouse FGF-23 have severe renal phosphate wasting because of suppression of renal Na/Pi cotransporter activity,[35–37] whereas FGF-23 inactivation leads to hyperphosphatemia.[24,38,39] In addition, FGF-23 may inhibit gastrointestinal phosphate absorption by reducing intestinal Na/Pi IIb cotransporter activity in a vitamin D-dependent manner.[40]

FGF-23 and PTH

Apparently, FGF-23 and PTH stimulate phosphaturia in a similar manner by reducing phosphate reclamation through Na/Pi IIa cotransporters. Nonetheless, PTH is not indispensable for FGF-23 activity, as the phosphaturic effects of FGF-23 are maintained in animals after parathyroidectomy.[37] The precise relationship between FGF-23 and PTH regulation is still under investigation. FGF-R and Klotho are expressed in parathyroid glands, suggesting that FGF-23 might regulate PTH secretion. In support of this hypothesis, *in vitro* data suggest that FGF-23 decreases PTH mRNA transcription and protein secretion in a dose-dependent manner.[41] Conversely, PTH may stimulate FGF-23 secretion by osteoblasts, as FGF-23 levels are increased in rodents with primary HPT, which may be reversed by parathyroidectomy.[42]

FGF-23 controls calcitriol blood levels

Interestingly, significantly less FGF-23 is needed to reduce calcitriol levels than that required to reduce serum phosphate levels, and calcitriol levels decrease before phosphaturia occurs.[37] In rodents, injection of recombinant FGF-23 reduces calcitriol levels within hours by decreasing renal expression of 1α-hydroxylase (CYP27B1)—the rate-limiting step in the generation of calcitriol—and increasing the expression of 24-hydroxylase (CYP24A1), which controls calcitriol degradation.[37] Consistent with this observation, marked increases in serum calcitriol levels have been reported in FGF-23-deficient mice. Hypervitaminosis D has been implicated in extensive vascular and soft tissue calcification and increased mortality in these *FGF-23*$^{-/-}$ mice.[24,38] However, recent evidence suggests that hyperphosphatemia, rather than elevated calcitriol, may be the major culprit, as normalization of serum phosphate levels prevented vascular and soft tissue calcification in *FGF-23*$^{-/-}$ mice, whereas normalization of calcitriol levels failed to do so.[39] Conversely, although FGF-23 reduces calcitriol levels, calcitriol itself stimulates FGF-23 generation by binding to a vitamin D response region in the *FGF-23* gene promoter.[43]

CLUES TO FGF-23 FUNCTION FROM HEREDITARY DISEASES OF PHOSPHATE METABOLISM

In humans, the clinical relevance of FGF-23 was first discovered in the context of hereditary diseases of phosphate metabolism, which provided further insight into the major pathways regulating serum phosphate balance. In 2000, Yamashita *et al.*[44] discovered the twenty-third FGF using homology-based PCR. FGF-23 cDNA was cloned from tumor tissue obtained from patients with tumor-induced osteomalacia.[45] This condition is characterized by inappropriately increased FGF-23 levels (i.e., a FGF-23 concentration that is too high for the concomitant level of serum phosphate) with hypophosphatemia, elevated alkaline phosphatase, severe muscular weakness, and bone pain. Tumor resection normalizes FGF-23 levels within 1 h, followed by normalization of serum phosphate levels within 6 h.[21,46] A similar phenotype is found in hereditary diseases such as autosomal dominant hypophosphatemic rachitis, X-linked hypophosphatemia, and autosomal recessive hypophosphatemic rickets, in which genetic defects lead either directly or indirectly to overstimulation of serum FGF-23 levels.[20,47–49] In contrast, hyperphosphatemia and extraosseous calcification result from inactivating mutations in the *FGF-23* gene in patients with hyperphosphatemic tumoral calcinosis,[50] and from mutations in the *GALNT3* gene that are associated with defective *O*-glycosylation and increased degradation of FGF-23 in hyperostosis–hyperphosphatemia syndrome.[51]

FGF-23 IN SUBJECTS WITH INTACT RENAL FUNCTION

The main physiological role of FGF-23 in healthy subjects is to regulate urinary phosphate excretion according to dietary phosphate intake and thus maintain stable serum phosphate levels. Surprisingly, large epidemiological studies have found no correlation between FGF-23 and serum phosphate levels in individuals without overt renal disease.[52,53]

Clinical trials evaluating the impact of oral phosphate intake on FGF-23 levels, renal phosphate excretion, and serum phosphate levels in healthy individuals have yielded controversial results. Most of these trials exposed healthy subjects to a period of oral phosphate loading and a subsequent period of phosphate restriction, sometimes combined with intake of oral phosphate binders. Phosphate loading generally resulted in increased renal phosphate excretion,[54–59] whereas serum phosphate levels either remained stable[54–56,58] or increased only marginally,[57] with one

notable exception.[59] During oral phosphate restriction, serum phosphate levels significantly decreased in some[55,56] but not all trials.[54,58] Interestingly, although FGF-23 levels increased by approximately 30% after phosphate loading in studies reported by Burnett *et al.*[55] and Ferrari *et al.*,[56] others found no significant increase.[54,57–59] Conversely, phosphate restriction lowered FGF-23 levels in some[54–56] but not all studies.[58]

Possible explanations for these disparate findings are 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 (with a single exception[54]). Studies reporting an increase in FGF-23 levels recruited more patients, and phosphate loading was expanded over several days.[55,56] Furthermore, only two studies[54,55] had an adequate run-in period, in which standardized diet over several days neutralized the confounding effect of the proband's usual eating habits, and only one of these trials[54] was performed under strictly controlled in-hospital conditions. To reconcile these discrepant data, it has been suggested that acute phosphate loading is rapidly answered by PTH secretion, which will augment phosphaturia within a few hours, whereas long-term phosphate loading will additionally result in FGF-23 secretion.[59,60]

Interestingly, in a very recent study, results from the PIVUS cohort suggest that FGF-23 serum levels are significantly, although weakly, associated with endothelial dysfunction among apparently healthy elderly subjects, even after adjustment for serum phosphate and 25-OH vitamin D levels.[61] In contrast, in 64 subjects who underwent coronary angiography for exclusion of coronary heart disease, FGF-23 levels did not correlate with coronary artery calcification as quantified by coronary multislice computed tomography.[53]

FGF-23 AND CKD

FGF-23 levels increase before serum phosphate in CKD

In CKD, circulating FGF-23 levels gradually increase with declining renal function (Figure 2).[62] Although the increase in FGF-23 is most pronounced in patients with advanced CKD, it may begin at a very early stage, as shown in the MrOS study.[52] Among apparently healthy elderly subjects with cystatin-based estimated glomerular filtration rate >60 ml/min, a significant (although weak) correlation between FGF-23 levels and estimated glomerular filtration rate was found. Similarly, in cross-sectional trials of CKD patients, the increase in FGF-23 starts with modestly impaired estimated glomerular filtration rate, when serum phosphate levels are still within the normal range (Kidney Disease Outcomes Quality Initiative (KDOQI) stages 2–3),[58,62,63] whereas FGF-23 levels increase by more than 100-fold in advanced CKD (KDOQI stage 5) compared with healthy controls.[58]

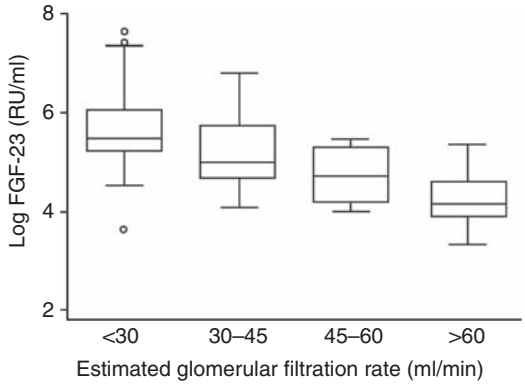


Figure 2 | Fibroblast growth factor (FGF)-23 levels rise with declining renal function in nondialysis chronic kidney disease patients. Note that FGF-23 levels are depicted on a logarithmic scale (reproduced from Gutiérrez *et al.*[62] with kind permission from the American Society of Nephrology).

Increased FGF-23 secretion in CKD

Previously, it was hypothesized that increased FGF-23 levels in CKD result primarily from decreased renal clearance.[58] However, this is inconsistent with the observation that there is no increase in the accumulation of degraded FGF-23 in advanced CKD. These data instead favor a mechanism involving increased FGF-23 secretion as the cause of elevated FGF-23 levels.[64] Instead of decreased renal clearance, an end-organ resistance to the phosphaturic stimulus of FGF-23 may exist because of a deficiency of the necessary Klotho cofactor. Similarly, Koh *et al.*[65] reported significantly reduced Klotho mRNA expression in kidney biopsy specimens of CKD patients. Moreover, higher FGF-23 levels in CKD may reflect a physiological compensation to stabilize serum phosphate levels as the number of intact nephrons declines. As a result, FGF-23 increases urinary phosphate excretion and decreases gastrointestinal phosphate absorption directly and through inhibition of 1α-hydroxylase and reduction of circulating calcitriol levels indirectly. Oversecretion of FGF-23 allows the body to maintain phosphate levels within a 'physiological' range ($\sim$2.5 to 4.5 mg/dl) until very advanced CKD stages. Supporting this idea, the SEEK study[4] reported normal phosphate levels in most patients suffering from CKD stages 1–4, with an increase in phosphate levels not occurring until CKD stage 5 when phosphaturic capacity is exhausted.

A new understanding of sHPT

Upregulation of FGF-23 in patients with CKD inhibits renal 1α-hydroxylase and results in early calcitriol deficiency, which may initiate the development of sHPT. Indeed, in the SEEK trial,[4] a significant prevalence of calcitriol deficiency in the very early stages of CKD was reported, starting from CKD stage 2. Results of the NephroTest study[66] revealed that with declining renal function, HPT is the first CKD-related metabolic complication, occurring long before the onset of anemia, acidosis, hyperkalemia, or hyperphosphatemia.

These findings challenge our pathophysiological understanding of sHPT, which has traditionally been considered to result from a loss of renal function with a reduction in renal 1α-hydroxylase, producing low serum calcitriol levels and subsequent oversecretion of PTH. This hypothesis does not

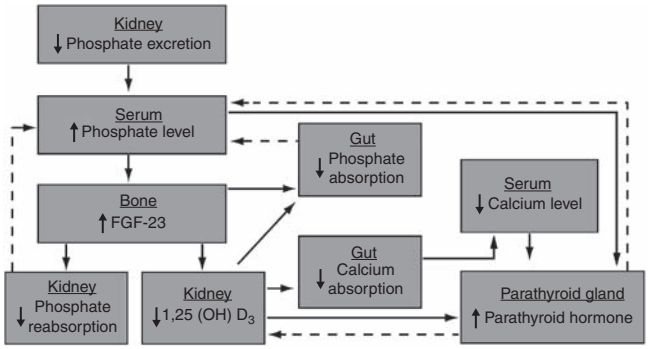
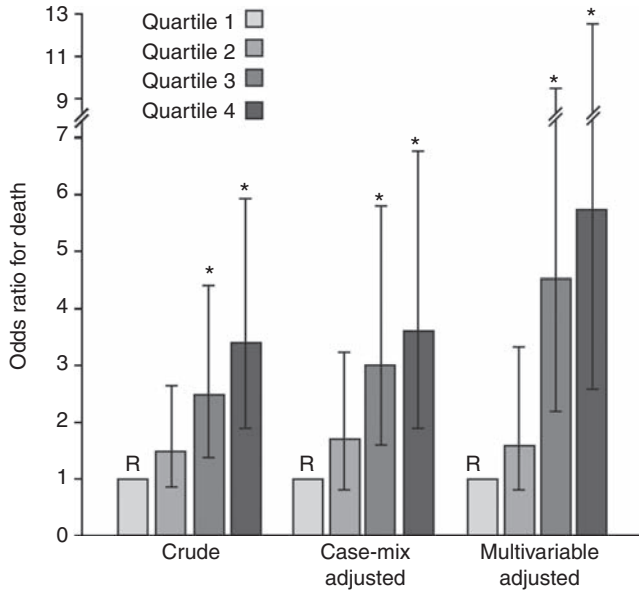


Figure 3 | Serum phosphate regulation and evolution of secondary hyperparathyroidism. With progressing chronic kidney disease, renal phosphate excretion is impaired, resulting in increased serum phosphate levels and subsequent elevation of fibroblast growth factor (FGF)-23 secretion from osteoblasts. High FGF-23 levels augment phosphate excretion and decrease circulating calcitriol levels, leading to increased parathyroid hormone levels resulting in secondary hyperparathyroidism. Dashed lines indicate counter-regulatory pathways.



	Crude	Case-mix adjusted	Multivariable adjusted
Quartile 1	Reference	Reference	Reference
Quartile 2	1.5 (0.9–2.7)	1.7 (0.8–3.2)	1.6 (0.8–3.3)
Quartile 3	2.5 (1.4–4.4)	3.0 (1.6–5.8)	4.5 (2.2–9.4)
Quartile 4	3.4 (1.9–5.9)	3.6 (1.9–6.9)	5.7 (2.6–12.6)

Figure 4 | Crude, case-mix-adjusted and multivariate adjusted odds ratio for 1-year mortality according to C-terminal fibroblast growth factor (FGF)-23 quartiles in 400 incident dialysis patients. R, reference group (reproduced from Gutiérrez *et al.*,[71] with kind permission from the Massachusetts Medical Society).

explain why early decline in renal function, for example, in CKD stage 2/3, should result in a substantial reduction of 1α-hydroxylase, whereas secretion of erythropoietin remains unaffected. Further uncertainty arises from results of animal studies showing that 1α-hydroxylase mRNA expression is not significantly decreased in CKD,[67] and that this enzyme is also expressed in extrarenal tissues, potentially providing additional sources of calcitriol.[68] Hence, a novel understanding of sHPT and hypovitaminosis D emerges, in which incipient kidney disease results in oversecretion of FGF-23. Subsequent control of serum phosphate levels occurs at the cost of a decrease in calcitriol levels, which is more pronounced than would be expected from the amount of nephron loss. Calcitriol deficiency induces PTH secretion and thus sHPT both directly and indirectly (through reduced gastrointestinal calcium absorption and subsequent hypocalcemia) (Figure 3).

Among dialysis patients, the level of FGF-23 may identify patients at risk for future therapy-resistant sHPT,[69] and may help to predict the efficacy of calcitriol treatment in these patients.[70]

FGF-23 as a prognostic factor in CKD

Interest in FGF-23 increased tremendously after publication of two prospective cohort studies in which FGF-23 was identified as a risk factor predicting worse outcome in CKD patients. The ArMORR study revealed that high FGF-23 levels in patients starting hemodialysis were an independent predictor of 1-year mortality after adjustment for serum phosphate levels.[71] In a multivariable adjusted model, subjects in the highest quartile of FGF-23 levels had nearly a sixfold increase in risk as compared with subjects in the lowest quartile (Figure 4). Thus, FGF-23 was a much stronger predictor of mortality than serum phosphate levels.

In the MMKD trial,[63] 227 patients suffering from nondiabetic CKD stages 1–4 were prospectively followed up for a median of 53 months to assess the progression of renal disease. Among various parameters of calcium–phosphate metabolism, FGF-23 levels were a significant independent predictor of CKD progression (Figure 5), defined as doubling of serum creatinine and/or terminal renal failure. Again, FGF-23 levels were a better outcome predictor than were serum phosphate levels; in Cox regression analysis, phosphate levels lost their predictive value after adjusting for FGF-23.

The first clinical data linking high FGF-23 levels to end-organ damage in CKD were presented at the American Society of Nephrology Renal Week in 2008, when Gutiérrez *et al.*[72] reported an association between left ventricular hypertrophy and high FGF-23 levels. This remained significant in a multivariate regression analysis that included, among other factors, estimated glomerular filtration rate and phosphate levels as independent variables.

FGF-23 in renal transplant recipients

After successful kidney transplantation, excessive FGF-23 secretion temporarily persists, even in the case of primary graft function.[73,74] Three months after successful transplantation, FGF-23 levels are higher than in glomerular filtration rate-matched controls, but this inappropriate 'hyperphosphatoninism' diminishes within the first 12 months after transplantation.[75] Oversecretion of FGF-23, rather than

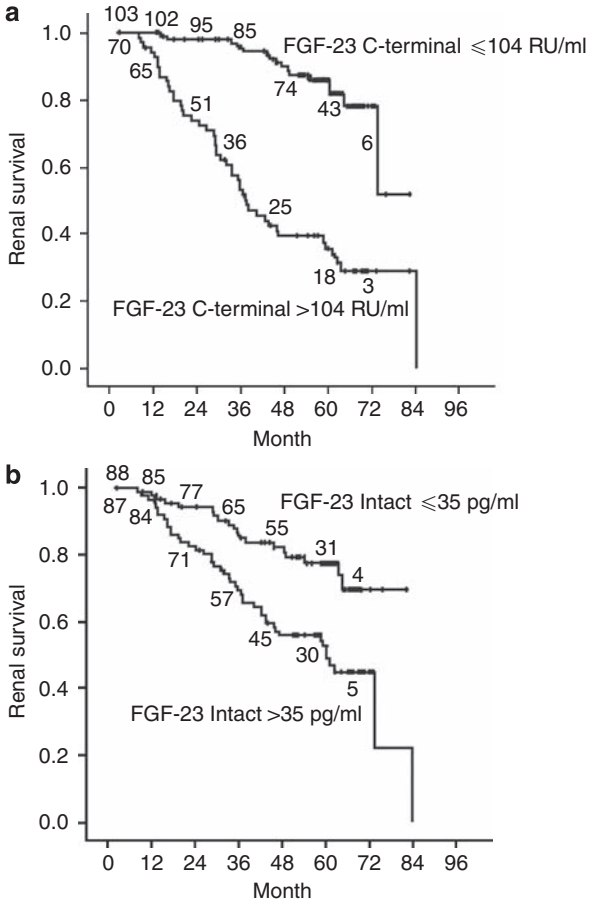


Figure 5 | Impact of fibroblast growth factor (FGF)-23 on renal survival. Kaplan–Meier survival curves for renal end points (doubling of serum creatinine and/or terminal renal failure) in nondiabetic chronic kidney disease patients, stratified by optimal cutoff values (**a**) 104 RU/ml for C-terminal FGF-23 and (**b**) 35 pg/ml for intact FGF-23 (reproduced from Fliser *et al.*,[63] with kind permission from the American Society of Nephrology).

persistent HPT or the effect of specific immunosuppressive drugs such as calcineurin inhibitors, is considered to be the primary pathogenic factor for hypophosphatemia during the early posttransplant period in many patients,[73] even though the phosphaturic effect of PTH may still dominate in allograft recipients with severe HPT.[76] In addition, inappropriately high FGF-23 levels (i.e., a FGF-23 concentration that is too high for the concomitant level of serum phosphate) result in low serum calcitriol levels, despite excellent allograft function and the stimulatory effects of hypophosphatemia and HPT.[73,74]

The pathophysiological background of this hyperphosphatoninism has not yet been elucidated. Pretransplant levels of FGF-23 are the main predictor of FGF-23 levels at 3 months after transplantation (followed by low calcitriol levels and high calcium and PTH levels).[74,75] Thus, autonomous secretion of FGF-23 by osteoblasts, provisionally termed tertiary hyperphosphatoninism,[73,74] has been postulated, resulting from resistance to inhibitory stimuli because of longstanding excessive FGF-23 stimulation. Interestingly, FGF-23 levels at 12 months after transplantation are only weakly associated with pretransplant levels but more strongly correlate with allograft function.

Taken together, the current evidence suggests that the impact of FGF-23 may exceed its role in regulating phosphate excretion and serum vitamin D levels. Data from current clinical trials suggest that high FGF-23 levels are associated with endothelial dysfunction among apparently healthy subjects in the general population,[61] with myocardial hypertrophy in CKD patients,[72] with progressive loss of kidney function in nondialysis CKD patients,[63] and with mortality in CKD patients receiving hemodialysis.[71]

FGF-23—MORE THAN AN INNOCENT BYSTANDER

The question arises as to whether FGF-23 is merely an 'innocent bystander' that reflects a disturbed calcium–phosphate metabolism, if it exerts its undesirable effects indirectly by lowering vitamin D levels, or has some untoward effects independent of its role in phosphate and vitamin D regulation.

Indeed, the correlation of FGF-23 levels with serum phosphate in CKD patients[58,62,63,77] and the association of hyperphosphatemia with adverse outcome in these patients[5,6,78–84] may partly explain why subjects with high FGF-23 levels are at increased risk for prevalent and incident cardiovascular events. In addition, given the suppression of 1α-hydroxylase by FGF-23 and subsequent reduction in calcitriol secretion, and the large body of evidence for vitamin D deficiency as a nontraditional cardiovascular risk factor in CKD,[85–87] increased FGF-23 levels may indirectly cause harm by inducing hypovitaminosis D.

Nevertheless, evidence emerges that FGF-23 is far more than just an innocent bystander or an inducer of hypovitaminosis D. First, adverse effects associated with high FGF-23 levels remained statistically significant after adjustment for phosphate, calcium, and PTH levels in the MMKD study,[63] and after additional adjustment for vitamin D levels in the PIVUS[61] and ArMORR studies.[71] Second, 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.[88] Finally, 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.[89]

In light of the high cardiovascular morbidity of CKD patients, as well as the failure of traditional therapeutic concepts (e.g., cholesterol-lowering[90] or angiotensin-converting enzyme inhibitor therapy[91]) and of nontraditional approaches (e.g., normalization of hemoglobin levels,[92] increasing dialysis dose,[93] and use of high-flux dialyzer[93]), the option of pharmacological lowering of high circulating FGF-23 levels appears as a ray of hope lighting a presently too dark sky.

POSSIBLE PROGNOSTIC IMPACT OF PHOSPHATE BINDERS

Although drugs that can directly reduce inappropriately high FGF-23 levels in CKD patients do not seem forthcoming in the near future, serum FGF-23 levels can indirectly be lowered by use of phosphate binders. Results from animal studies[94] and preliminary human data[77,95] suggest that lowering of phosphate levels by intake of phosphate binders will substantially reduce serum FGF-23 levels. In this context, recent data from the ArMORR trial are of uttermost importance. In this prospective observational study, treatment with phosphate binders was associated with a reduced 1-year mortality among incident hemodialysis patients.[11] Although the prognostic impact of phosphate binder therapy on patient outcome has—astonishingly—never been assessed before in an adequately designed prospective trial, at first glance, the study results are hardly surprising and confirm the harmful impact of hyperphosphatemia on survival in CKD patients, which had been previously well established.[5,6,78–84] However, statistical analysis of the ArMORR trial revealed some puzzling details. First, the benefit of phosphate lowering is not limited to patients with overt hyperphosphatemia, as those with physiological phosphate levels (3.7–4.5 mg/dl) significantly benefit from phosphate reduction. Second, the survival benefit of therapy with phosphate binders was only marginally attenuated when adjusted for follow-up phosphate levels. Thus, data from the ArMORR trial suggest a benefit of phosphate binder therapy beyond reduction of serum phosphate levels. It is tempting to hypothesize that some of this additional benefit may result from a reduction in FGF-23 levels induced by phosphate binders.[11] Data from large intervention trials comparing the effect from various phosphate binders on FGF-23 levels are not yet available.

As FGF-23 levels have been measured in this study cohort,[71] we eagerly await future data from the ArMORR study group to test the hypothesis that mortality reduction by phosphate binders is predicted by pretreated FGF-23 levels and/or treatment-induced reduction of FGF-23. Once these additional data are available, a randomized controlled trial should be designed to evaluate whether phosphate binder therapy can reduce cardiovascular morbidity in CKD patients with elevated FGF-23 levels. According to current KDOQI guidelines, this patient population has no 'conventional' indication for phosphate-lowering therapy, that is, serum phosphate levels are within the normal range. At the same time, it will be necessary to elucidate at the cellular level the mechanisms by which seemingly adequate increases in FGF-23 change to become detrimental.

CONCLUSION

FGF-23 is a recently discovered regulator of calcium–phosphate metabolism. In clinical trials, elevated FGF-23 levels were independently associated with faster progression of CKD, therapy-resistant sHPT, left ventricular hypertrophy, and increased cardiovascular mortality in dialysis patients. However, FGF-23 is not just an innocent bystander, reflecting unfavorable derangements of calcium–phosphate metabolism (e.g., increased serum phosphate levels) in CKD, but rather a pathophysiologically relevant factor. Thus, FGF-23 could represent a promising therapeutic target that might improve the fatal prognosis of patients with CKD.

DISCLOSURE

Dr Seiler has nothing to disclose. Dr Heine and Dr Fliser have been speakers for Shire.

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