REVIEWS

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Fibroblast Growth Factor 23 – Structure, Function and Role in Kidney Diseases*

Czynnik wzrostu fibroblastów 23 – budowa, czynność i znaczenie w patogenezie chorób nerek

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Abstract

The fibroblast growth factor (FGF) family comprises a number of polypeptides which share a common homology core region. FGF-23, produced by osteoblasts and osteocytes, belongs to the FGF-19 subfamily and serves as the main phosphatonine. Two forms of circulating FGF-23 are detectable in serum: full-length FGF-23 – intact FGF-23 (iFGF-23), which is biologically active, and the inactive C-terminal FGF-23 (cFGF-23). FGF-23 with a coreceptor (Klotho protein) inhibits renal phosphate reabsorption and synthesis of calcitriol by reducing 1α-hydroxylase (CYP27B1) activity, reducing vitamin D-dependent phosphate intestinal absorption. High phosphorus intake, 1,25-dihydroxyvitamin D_3 and PTH are the main stimuli for FGF-23 secretion. Impaired FGF-23 metabolism is involved in phosphate disturbances manifesting as rickets or osteomalacia or increased tissue calcinosis. FGF-23 may be also produced by some tumors leading to hypophosphatemia. Both cFGF-23 and iFGF-23 concentrations start to increase with mild impairment of the glomerular filtration rate in stage 2 or 3 of chronic kidney disease (CKD) as a consequence of the increased FGF-23 production. It seems that enhanced FGF-23 secretion may constitute a protective mechanism against enhanced phosphate accumulation in the early stages of CKD. However, it may lead to calcitriol deficiency and escalation of secondary hyperparathyroidism. Increased FGF-23 level is supposed to be an independent factor increasing mortality of CKD patients. There is ambiguous data if FGF-23 only reflects disturbances in calcium-phosphate metabolism or if it exerts a detrimental effect itself by diminishing calcitriol synthesis, inducing cell proliferation or acting through low-affinity, Klotho-independent receptors in the heart and endothelium. So far, little evidence supports direct FGF-23 toxicity (**Adv Clin Exp Med 2012, 21, 3, 391–401**).

Key words: FGF-23, chronic kidney disease, Klotho protein.

Streszczenie

Rodzina czynnika wzrostu fibroblastów (FGF) obejmuje kilkanaście peptydów zawierających wspólny, homologiczny region. FGF-23, należący do podrodziny FGF-19, który jest wydzielany przez osteoblasty oraz osteocyty, i pełni rolę głównej fosfatoniny. W osoczu peptyd ten jest wykrywany w dwóch postaciach: o pełnej długości FGF-23 (*intact* FGF – iFGF-23), aktywnej biologicznie, oraz C-końcowych fragmentów FGF-23 (c-FGF-23). FGF-23 przy udziale koreceptora, białka Klotho, hamuje reabsorpcję zwrotną fosforanów w cewkach nerkowych oraz syntezę kalcytriolu przez hamowanie aktywności 1α-hydroksylazy (CYP27B1), zmniejszając jelitowe wchłanianie wapnia. Duża podaż fosforanów w diecie, parathormon oraz 1,25-dihydroksywitamina D_3 są głównymi bodźcami stymulującymi wydzielanie FGF-23. Nieprawidłowości metabolizmu FGF-23 prowadzą do zaburzeń gospodarki fosforanowej objawiających się krzywicą lub osteomalacją, oraz wapnieniem tkanek miękkich. FGF-23 może być także wydzielany przez komórki nowotworowe, powodując występowanie przewlekłej hipofosfatemii. Zwiększone wydzielanie FGF-23 prowadzi do wzrostu stężenia zarówno cFGF-23, jak i iFGF-23 już przy umiarkowanym upośledzeniu czynności wydalniczej nerek, w fazie 2. i 3. przewlekłej choroby nerek (p.ch.n.). Wydaje się prawdopodobne, że jest to mechanizm kompensacyjny, chroniący organizm przed kumulacją fosforanów. Zwiększenie stężenia FGF-23 przyczynia się jednak do niedoboru kalcytriolu oraz nasilenia wtórnej nadczynności przytarczyc. Przypuszcza się, że zwiększone stężenie FGF-23 może być niezależnym czynnikiem ryzyka zwiększonej śmiertelności u pacjentów z p.ch.n., dotychczas opublikowane dane są jednak niejednoznaczne. Być może stężenie FGF-23 u tych chorych odzwierciedla jedynie zaburzenia gospodarki wapniowo-fosforanowej i przez stymulację receptorów o małym powinowactwie w mięśniu sercowym i śródbłonku oraz hamowanie syntezy kalcytriolu nasila pro-

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liferację komórek, przez co pośrednio przyczynia się do powikłań p.ch.n. Ostatnio pojawiły się pierwsze dowody wskazujące na bezpośrednie toksyczne działanie FGF-23 (**Adv Clin Exp Med 2012, 21, 3, 391–401**).

Słowa kluczowe: FGF-23, przewlekła choroba nerek, białko Klotho.

The prevalence of chronic kidney disease (CKD) and end-stage CKD is rising especially in elderly patients. The diagnosis and treatment of CKD is usually delayed as the clinically useful measures of early kidney impairment (stage 2 of CKD) are missing. Thus a chance to slow CKD progression to end-stage and lower cardiovascular mortality is irretrievably restricted.

The gold standard of glomerular filtration rate (GFR) determination is the measurement of inulin clearance, as inulin is neither reabsorbed nor secreted in the renal tubules and only reflects glomerular filtration. However, the measurement is cumbersome and impractical, hence, rarely used in daily clinical practice.

Therefore, the assessment of renal function is based mainly on serum creatinine concentration, and its recalculation to estimated GFR at a steady-state condition. Creatinine, a product of muscular creatine phosphate degradation, is filtered by the glomerulus but also secreted by the tubules. Its concentration depends on muscle mass and meat ingestion and thus does not precisely reflect GFR. Its tubular excretion increases with the advance of CKD leading to overestimation of GFR.

The estimation of GFR is based on equations comprising serum creatinine level: the Cockcroft and Gault (C-G), MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formulas, which are better renal function parameters than serum creatinine concentration itself. The C-G and MDRD formulas estimate GFR and employ not only serum creatinine concentration but also age, gender and race additionally in the MDRD formula. Unfortunately, even the recently implemented CKD-EPI formula has not solved the conundrum with early CKD detection.

Other formulas of GFR estimation are based on cystatin C serum concentration, a ubiquitous protein produced by all cells and freely filtered by the glomeruli, reabsorbed and degradated in the proximal tubules and without tubular excretion. Its concentration changes in some pathological situations and its use as a marker of renal function has not proved to be better than serum creatinine.

Therefore, there is still a great demand for a biochemical marker of early renal impairment. It seems that fibroblast growth factor 23 (FGF-23), a new hormone involved in calcium-phosphate homeostasis, reflecting impaired renal function in the early CKD stages, may become useful in the identification of patients with mild CKD.

Structure

The fibroblast growth factor (FGF) family comprises a number of polypeptides which share a common homology core region which contains approximately 120 amino acid residues and variable N- and C-terminal flanking residues. The core homology region constitutes a ß-trefoil structure composed of folded ß-strands and loops [1, 2]. So far seven subfamilies of human FGFs have been identified by phylogenetic analysis. The most recently identified FGF is FGF-23, which belongs to the FGF-19 subfamily [1, 2], that comprises both FGF-19 and FGF-21 [3]. FGF-23 serves as the main phosphatonine, playing an important role, as a hormone, in phosphate homeostasis [4]. FGF-23 is a 251 amino acid peptide produced by osteoblasts and osteocytes [4–6] with a 24 amino acid signal peptide and 227 residues (32 kD) forming the FGF-23 structure (residues 25–180) and C-terminal sequence (residues 181–251), unique but conservative in the FGF family [7, 8]. Enzymes responsible for FGF-23 cleavage – sutilisin-type preprotein convertase – recognize ^{179}Arg and ^{180}Ser amino acid sequences (the RXXR motif located at the boundary between the homology domain and 72-amino acid C-terminal tail) within the FGF homology region present in the N-terminal part of the FGF-23 structure [7, 9] and produce a biologically inactive peptide which comprises an inactive N-terminal (Y25 to R179) and C-terminal fragment (S180 to I251) [2].

Full-length FGF-23 – intact FGF-23 (iFGF-23) is biologically active, whereas C-terminal FGF-23 (cFGF-23) fragments are inactive and does not exert any influence on phosphate metabolism [7]. In physiological conditions, iFGF-23 is the most abundant of circulating FGF-23 peptides [10, 11], with an estimated half-life in circulation of about 58 minutes [12]. FGF-23 degradation is still not fully known [11]. The measurement of cFGF-23 comprises both iFGF-23 and C-terminal inactive FGF-23 [11].

As described above, the primary sites of FGF-23 production are bones, mainly osteoblasts and osteocytes [5] although its transcript has also been detected in other tissues: the hypothalamus, ovaries, testes, thymus, brain, choroid plexus, parathyroid glands and heart [13].

The FGF family peptides are ligands of FGF receptors (FGFR) [14, 15]. There are distinct genes encoding four FGF receptors (FGFR1 – FGFR4).

An FGF receptor consists of an intracellular domain with tyrosine kinase activity, a single transmembrane domain and an extracellular domain with up to three immunoglobulin-like structures (D1 – D3) [16, 17]. Alternative splicing of the second half of the D3 domain of FGFR1 – 3 results in a distinct ligand-binding specificity of epithelial and mesenchymal (FGFR1b – 3b and FGFR1c – 3c) receptors in different tissues [16]. Low FGF-23 binding affinity to heparin-sulfate, the consequence of structural divergence, facilitates its endocrine activity [2]. A disulfide bond, absent in other FGF subfamilies, stabilizes the unique ß-trefoil structure of the core region of the FGF-19 subfamily which is different from the fundamental trefoil structure of other FGF subfamily members. The conformational changes related to the disulfide bond lead to its low affinity to heparin sulfate, and in consequence, FGF-23 may be distributed in the bloodstream and maintain their systemic function [2]. Members of other FGF subfamilies with a high affinity to heparin sulfate are captured by the cell membrane containing heparin sulfate, limiting their influence on paracrine actions [8]. FGF-23 requires the Klotho protein as a co-receptor which stabilizes FGF-23-FGFR binding by simultaneous interaction with FGF-23 and its receptor [2, 18, 19]. Klotho surface protein with homologies to ß-glucosidases forms a tertiary complex interacting with FGF-23 and FGFR [18, 19], as there is a higher affinity of interaction between FGF-23 and the Klotho-FGF-R complex than FGFR or Klotho protein alone [19]. Klotho protein seems to be essential for FGF-23 action as Klotho, primarily described as an aging suppressor [20], is localized in target tissues of FGF-23 action (i.e. kidney, parathyroid gland, pituitary and choroid plexus in the brain) [18]. Moreover, transgenic FGF-23 null (FGF-23$^{-/-}$) and Klotho (klotho knock-out – klotho$^{-/-}$) mice represent a similar phenotype [18], regardless of high FGF-23 concentration in Klotho mice [18]. Recent studies showed that the main receptor for FGF-23 is FGFR1, while FGFR4 plays only a minor role [21]. It seems that the Klotho protein determines FGF-23 receptor selectivity and its renal action [22]. There are two forms of Klotho protein, transmembrane and soluble. FGF-23 enhances soluble Klotho form secretion. The results of a recently published study suggest that soluble Klotho protein acts as a phosphaturic agent that decreases Na/Pi IIa channel activity independently from FGF-23 [23]. Moreover, it has been shown that soluble Klotho protein concentration in urine decreases with the CKD stage. Therefore its low urinary concentration may be an early marker of CKD stage 1 or 2 [24]. In an experimental study, it was shown that Klotho protein administration in mice with a model of acute kidney injury preserves renal function by decreasing apoptosis [25]. It was also found that renin-angiotensin-aldosterone system (RAAS) activity is inversely associated with Klotho protein expression *via* the AT1 receptor activation dependent mechanism [26].

Action

Three proteins of the FGF-19 subfamily, FGF-19, FGF-21 and FGF-23, exert diverse physiological functions. FGF-19 inhibits the expression of cholesterol-7-α-hydroxylase (CYP7A1), the first and rate-limiting step in bile acid synthesis [27]. FGF-21 lowers triglyceride concentration and stimulates insulin independent glucose uptake by adipocytes [28].

FGF-23 acts as a phosphatonin, inhibiting renal phosphate reabsorption by reducing the abundance of sodium-dependent phosphate cotransporters (Na/Pi IIa and Na/Pi IIc) in the apical brush border membrane in kidney proximal tubules [21, 29]. Renal phosphate reabsorption is mainly mediated by the IIa cotransporter, while approximately one third is reabsorbed through the IIc cotransporter [30]. Klotho protein is also expressed in the distal tubule [31] but phosphate reabsorption does not take place there [32]. The exact intracellular pathway of FGFR-Klotho complex stimulation leading to inhibition of phosphate reabsorption and vitamin D_3 hydroxylation still remains unknown.

FGF-23 also inhibits the Na/Pi IIb cotransporter localized in the gastrointestinal tract and reduces vitamin D-dependent phosphate absorption [33]. FGF-23 decreases calcitriol synthesis [7, 34] by reducing 1α-hydroxylase (CYP27B1) activity – a rate-limiting step in calcitriol synthesis – and increasing the alternative pathway of vitamin D metabolism by enhancing 24-hydroxylase expression (CYP24A1) [7].

The expression of FGF-23 has been detected in other organs, such as the testes, ovaries and brain (pituitary and choroid plexus). It is unknown if Klotho protein is co-expressed in other organs with FGF-23 expression and what the effects of FGF-23 stimulation in these organs are [35].

Regulation

The main stimuli for FGF-23 secretion are as follows: high phosphorus intake, 1,25-dihydroxyvitamin D_3 and PTH directly or indirectly by enhancing calcitriol synthesis [4, 36]. It seems that non-dietary increase of serum phosphate is a weaker stimulus for FGF-23 secretion [37, 38].

Both FGF-23 and PTH stimulate phosphaturia in a similar manner but the exact mechanism of interaction between FGF-23 and PTH is still unknown. Accumulation of serum phosphate in patients with hypoparathyroidism and normal kidney function proves that FGF-23 alone, even in increased concentration, is unable to maintain phosphaturia at a sufficient level [39]. However, in a single study, in animals after parathyreidectomy, an independent phosphaturic effect of FGF-23 was demonstrated [7].

Some authors suggest that FGF-23 regulates phosphorus balance rather than the phosphorus level itself. However, the increased level of FGF-23 in hypoparathyroid subjects seems to be a compensatory response to hyperphosphataemia [39] and negates this theory.

FGFRs and Klotho protein are co-expressed in the parathyroid glands and may regulate PTH secretion. *In vitro,* it has been shown that PTH transcription decreases in parathyroid glands after FGF-23 injection in a dose-dependent manner [40]. On the other hand, PTH may stimulate FGF-23 secretion by osteoblasts with primary hyperparathyroidism at least in rodents [41], probably enhancing phosphate wasting.

The data concerning the role of FGF-23 in bone mineralization is conflicting [42, 43]. Moreover, no precise mechanism of FGF-23 secretion by osteocyte cells has been detected.

Finally, it should be stressed that other phosphaturic mechanisms than PTH and FGF-23 may participate in the regulation of phosphate metabolism and urinary phosphorus excretion [44, 45].

The Role of FGF-23 in Pathology

FGF-23 is involved in such phosphate metabolism diseases as autosomal recessive and dominant hypophosphatemic rickets (ARHR and ADHR, respectively). In ADHR, familial hypophosphatemic rickets/osteomalacia, there is no response to physiological doses of vitamin D. It is caused by a variety of missense mutations of the FGF-23 gene destroying the RXXR motif by replacement of ^{176}Arg or ^{179}Arg with other amino acids followed by cleavage resistance [46]. However, the enhanced action of FGF-23 seems not to be a satisfactory explanation of the pathogenesis of AHR. Comparable level of FGF-23 in hypophosphatemic and control subjects suggests the derangement of FGF-23 production in the disease [47].

In ARHR patients, mutations in dentin matrix protein 1 (DMP-1) expressed in osteocytes and odontoblasts have been identified [48], accompanied by a high level of FGF-23. However, it still remains unclear how DMP-1 derangement enhances the production of FGF-23.

Similarly, FGF-23 overexpression has already been shown in X-linked hypophosphatemic rickets/osteomalacia (XLH) [10]. Deletion of a 3' region of phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), whose expression was detected in osteocytes, osteoblasts and odontoblasts, is known as a causal factor of XLH [49]. The function of PHEX protein in cells is still not clear and its influence on FGF-23 production has not been clarified.

In patients with rickets/osteomalacia associated with McCune-Albright syndrome and fibrous dysplasia, characterized by replacement of the medullar cavity with fibrous, chondral and osseous tissues, increased circulatory levels of FGF-23 were observed [50]. Mutations of the guanine nucleotide binding protein, alpha stimulating 1 gene (GNAS1) have been demonstrated, but the pathway of enhancing FGF-23 production is unknown too.

FGF-23 is abundantly expressed in cells of phosphaturic mesenchymal tumors, mixed connective tissue variant (PMTMCT) which leads to an increased concentration of plasma FGF-23 [51]. The removal of tumors resulted in normalization of FGF-23 and phosphate levels.

Mutations of GALNT3, Klotho and FGF-23 have been implicated in the etiology of hyperphosphatemic syndromes with ectopic calcifications [52, 53, 54]. FGF-23 and GALNT3 genes mutations between ^{179}Arg and ^{180}Ser amino acid residues resulting in enhanced FGF-23 cleavage and a decreased level of the intact, active form of FGF-23 [52, 53]. GALNT3 missense mutations affect FGF-23 glycosylation, making it less resistant to degradation [52, 53]. Finally, Klotho mutations result in decreased production of Klotho protein and lower sensitivity to stimulation of target tissues by FGF-23 [54].

FGF-23 and Physiological Kidney Function

Although the main physiological role of FGF-23 is to maintain a stable phosphate serum level, no correlation between FGF-23 and serum phosphate concentration in subjects with normal kidney function has been observed [55, 56].

The results of the studies evaluating the impact of oral phosphate load have usually demonstrated increased renal phosphate excretion [11, 57–61] with stable [11, 57–59] or only slight increases [60] of serum phosphate concentration and elevated FGF-23 level. In line with these findings,

Table 1. Inherited and acquired fibroblast growth factor 23 (FGF-23) related hypophosphatemic diseases

Tabela 1. Wrodzone i nabyte choroby przebiegające z hipofosfatemią zależne od zaburzeń czynnika wzrostu fibroblastów 23 (FGF-23)

Disease (Choroba)	Gene mutation (Mutacja genu)	Clinical manifestation (Manifestacja kliniczna)	Reference (Piśmiennictwo)
Autosomal dominant hypophosphatemic rickets (ADHR)	missense mutations of FGF-23	hypophosphatemic rickets/osteomalacia, resistance to vitamin D	[47]
Autosomal recessive hypophosphatemic rickets (ARHR)	dentin matrix protein 1 (DMP-1)	hypophosphatemic rickets/osteomalacia, resistance to vitamin D	[48]
X-linked hypophosphatemic rickets/osteomalacia	phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX)	hypophosphatemic rickets/osteomalacia, resistance to vitamin D	[49]
McCune-Albright syndrome	guanine nucleotide binding protein, alpha stimulating 1 (GNAS 1), somatic mosaicism	hypophosphatemic rickets/osteomalacia; fibrous dysplasia	[50]
Phosphaturic mesenchymal tumors, mixed connective tissue variant (PMTMCT)	acquired disease – enhanced expression of FGF-23	hypophosphatemic rickets/osteomalacia	[51]

Table 2. Inherited fibroblast growth factor 23 (FGF-23) related hyperphosphatemic diseases

Tabela 2. Wrodzone choroby przebiegające z hiperfosfatemią zależne od zaburzeń czynnika wzrostu fibroblastów 23 (FGF-23)

Gene mutation (Mutacja genu)	Clinical manifestation (Manifestacja kliniczna)	Reference (Piśmiennictwo)
GALNT3 and FGF-23 gene mutations	hyperphosphatemic calcinosis	[52, 53]
GALNT3 gene mutation	hyperphosphatemic calcinosis	[52]
Klotho gene	hyperphosphatemic calcinosis, FGF-23 resistance	[54]

GALNT3 – gene encoding polypeptide N-acetylgalactosaminyltransferase 3.
GALNT3 – gen kodujący poplipeptyd transferazy N-acetylogalaktozaminy 3.

phosphate restriction was followed by a FGF-23 concentration decrease [57–59]. Some discrepant results might be the consequences of a different time of phosphate loading – from three [11, 57, 60, 61] to several days [58, 59], a non-adequate run-in period in most studies [11, 59–61] that emphasized the effect of previous eating habits.

Both PTH and FGF-23 are responsible for increased phosphate excretion after oral phosphate load. PTH enhances phosphaturia just a few hours after oral intake, while the increase of FGF-23 takes place after longer oral phosphate loading [61, 62].

FGF-23 in the Pathogenesis of Chronic Kidney Disease

FGF-23 concentrations start to increase with mild impairment of the glomerular filtration rate in stage 2 or 3 of chronic kidney disease (CKD), before the increase of serum phosphate is detectable [11, 63–65], and gradually rise along with the advance of CKD, [62] reaching levels 1000 times higher than in healthy subjects [11]. In the more advance stages of CKD, the FGF-23 increase is parallel to those of phosphate, Ca x P and PTH [11, 22, 29, 32, 63, 65, 66].

There are strong correlations between concentrations of intact and c-terminal FGF-23. The increased concentrations of FGF mostly reflect phosphate accumulation in CKD patients [65].

Increased concentrations of FGF-23 precede a decrease in circulating distal tubule and calcitriol and an increase in phosphate which suggest a significant role of FGF-23 in phosphorus homeostasis in CKD before secondary hyperparathyroidism develops [64, 67]. Overproduction of both FGF-23 and PTH allow the maintenance of the physiological level of phosphorus even in advanced CKD stages [68].

FGF-23 concentrations increase independently with mild decrements in GFR and microalbuminuria in patients with cardiovascular disease [69]. It suggests that FGF-23 is one of the earliest detectable biochemical markers of glomerular filtration rate impairment [69]. cFGF-23 concentration increases clearly with GFR levels, approximately < 90 ml/min/1.73m^2, independently from age, gender, race, blood pressure, presence of diabetes and body mass index [69].

It is still not clear why the level of FGF-23 increases in the early stages of CKD. It has been hypothesized that it results from the decreased renal FGF-23 clearance [11], however no increase in FGF-23 metabolites has been detected [66], suggesting an increase in FGF-23 production [66].

In another study [70], reduced Klotho protein expression in the kidneys was observed, which may result in organ resistance to FGF-23 action. Additionally, it seems that FGF-23 downregulates the expression of Klotho protein which accounts for a rising resistance to FGF-23 and its compensatory increase, as well as stimulating PTH secretion and inhibiting 1,25-$(OH)_2D_3$ synthesis in CKD [71]. All these hypotheses assume that the increase in FGF-23 in CKD is a compensatory mechanism of phosphate retention along with nephron loss, resulting in increased single nephron phosphate urinary excretion and diminished calcitriol-dependent intestinal phosphate absorption.

Another hypothesis comprises enhanced FGF-23 production in bones by a kidney-driven, unknown stimuli in the course of CKD.

Even if FGF-23 enhanced secretion is a protective mechanism against hyperphosphatemia, it may lead to calcitriol deficiency and escalation of secondary hyperparathyroidism. It should be stressed that both calcitriol deficiency and hyperphosphatemia are independent risk factors of cardiovascular mortality in dialysis CKD patients [72, 73]. It has also been shown that the FGF-23 level is independently associated with increased mortality in CKD patients [74]. Nearly 6 times higher mortality has been observed in the quartile of patients with the highest FGF-23 concentration when compared to the lowest quartile [74]. Moreover, it has been proved that FGF-23 concentration was a better predictor of mortality than hyperphosphataemia in hemodialysis [74] and in predialysis patients [75]. Higher FGF-23 concentration maintains a predictive value even in subjects with a serum phosphate level lower than 5.5 mg/dl, suggesting that a high FGF-23 level itself may constitute an indication of intensification of phosphorus binder therapy despite phosphataemia within the recommended range.

In another observational study, FGF-23 was associated with increased risk of death and predicted the development of end-stage renal failure among patient with eGFR between 30 and 44 ml/min/1.73m^2 in a population of patients with CKD stages 2–4 [19].

It should be noted that FGF-23 concentration seems to be a better predictor of CKD progression (time to doubling of serum creatinine) than calcitriol, calcium or phosphate levels are [65]. This is also true in patients with diabetic nephropathy and macroalbuminuria [76]. Moreover, an association between FGF-23 levels and left ventricular hypertrophy in predialysis CKD patients [77], on dialysis [78] and without renal dysfunction has been revealed [79]. Finally, higher FGF-23 levels were associated with vascular reactivity impairment due to endothelial dysfunction in subjects with normal kidney function and with arterial stiffness in subjects with CKD [80]. This data is raising a hypothesis of FGF-23 toxicity.

Increased concentration of FGF-23 was observed in patients after kidney transplantation even with normal graft function [81]. FGF-23 levels are higher in kidney transplant recipients than in GFR-matched controls [82] three months after transplantation and they tend to decline within one year after transplantation [82]. It seems that an inappropriately high FGF-23 level is partially responsible for a lower serum phosphate level during the early period after transplantation [81] due to suppression of calcitriol synthesis and stimulation of parathyroid overactivity [74–81]. It is hypothesized that higher FGF-23 concentrations are caused by autonomous FGF-23 secretion, resistant to inhibitory stimuli, by osteoblasts, related to its excessive production prior to transplantations [81]. It has been shown that the FGF-23 level before transplantation predicts its concentration 3 months posttransplant [82] and the occurrence of hypophosphatemia in a 12-month follow-up [83]. It has been shown that, a year after kidney transplantation, FGF-23 level is related to glomerular filtration rate [82], and predicts the risk of kidney graft deterioration in the follow-up [84].

The FGF-23 and Vitamin D Paradox

Treating predialysis and hemodialysis CKD patients with vitamin D, although beneficial (longer survival) [73], may increase FGF-23 concentration, as calcitriol is a well-known stimulus of FGF-23 secretion. As high FGF-23 levels are associated with higher mortality in CKD patients, some doubt may arise if this is the correct treatment.

It seems that vitamin D is a weaker stimulus for FGF-23 secretion in patients with advanced CKD than in healthy controls. The authors still do not know if vitamin D analogs, characterized by a lower hypercalcaemic and hyperphosphataemic effect, stimulate FGF-23 secretion.

Finally, despite the fact that hyperphosphatemia is associated with increased mortality in CKD patients, vitamin D therapy proved to be beneficial regardless of the increase in serum phosphate levels [73, 74]. Perhaps the beneficial effects of vitamin D therapy overcome the postulated detrimental effects of FGF-23 [85].

Is FGF-23 Only a Bystander?

It still remains to be established if serum FGF-23 concentration reflects only disturbances in calcium-phosphate metabolism or if it may exert detrimental effects itself, in patients with CKD. As FGF-23 concentration reflects phosphorus accumulation in CKD patients [11, 64, 65] and hyperphosphataemia increases significantly the cardiovascular risk [72, 73], the predictive value of high FGF-23 levels may be indirect. It should be noted that FGF-23 diminishes synthesis of calcitriol and that it may increase mortality [86] and explain the harmful effect of FGF-23 in CKD patients.

However, phosphate accumulation and calcitriol deficiency seems not to fully explain the detrimental effect of high FGF-23 levels in CKD patients. Even after adjustment for the disturbances of calcium-phosphate metabolism [65] and vitamin D [74, 80], high FGF-23 levels were still associated with worse outcome in CKD patients.

Perhaps the potential direct FGF-23 toxicity in CKD patients may be related to deregulation of the cell circle. In experimental studies, both FGF-23 and Klotho protein induce cell proliferation [87], while vitamin D exerts a proapoptotic effect. Moreover, extremely high concentrations of FGF-23 may act through low-affinity, Klotho-independent FGFR in organs other than kidneys, such as the heart and endothelium [88]. However, no unusual cardiovascular complication has been reported in patients with syndromes with primary high FGF-23 concentrations.

A recently published study showed left ventricle hypertrophy (LVH) development after intravenous and intramyocardial application of FGF-23 in mice. Furthermore, a FGF-R blocker attenuated the negative effects of FGF-23. Of interest, in Klotho-deficient mice with FGF-23 coreceptor deficiency and higher FGF-23 levels, the development of LVH was also observed [89]. This suggests that FGF-23 may act by Klotho-independent, low-affinity FGF receptors (FGFR4). The data described above may partially explain the cardiovascular toxicity in CKD patients. It should be emphasized that in a large cohort of hemodialysis patients, an association between circulating FGF-23 levels and LVH was found [89].

FGF-23 potentially may also have vascular toxicity. It has been shown that FGF-23 level is a predictor of carotid intima-media thickness and artery calcification in hemodialysis patients [90, 91].

The authors are uncertain whether FGF-23 should become the new therapeutic target in CKD patients. So far, no specific pharmacologic agent for FGF-23 lowering therapy is available. However, oral phosphate binder use results in a reduction of FGF-23 concentrations both in animals [67] and humans [92]. Furthermore, a study assessing the influence of phosphate binders on mortality in patients with CKD on hemodialysis proved to have a beneficial effect not only in patients with overt hyperphosphataemia, but also in those with phosphate concentrations within the recommended range [69]. It still remains unknown if the effect may be the result of a reduction in FGF-23 concentration in addition to improvement of calcium-phosphate metabolism [69].

The authors concluded that FGF-23 is a regulator of calcium-phosphate metabolism. It seems that it may be the early biochemical marker of glomerular filtration rate deterioration in the course of CKD. FGF-23 concentrations predict a worsening of CKD, left ventricular hypertrophy and mortality in hemodialysis patients. It seems that its higher levels in normophosphatemic patients may emerge after intensive phosphate binder use. Direct FGF-23 toxicity on the cardiovascular system has recently been proven. Thus FGF-23-lowering therapy is a potential new therapeutic target in CKD patients.

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