Fibroblast growth factor-23 and adverse clinical outcomes in chronic kidney disease patients

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Abstract

Introduction

Fibroblast growth factor (FGF)-23 is a bone-derived phosphatonin secreted in response to oral phosphorus load. It requires Klotho for specific binding to the FGF receptor (FGFR) in classic target organs such as kidneys and parathyroid glands. Serum FGF-23 levels rise early in chronic kidney disease (CKD) and attenuate hyperphosphataemia in expense of 1,25(OH)2 vitamin D suppression, thus initiating the development of secondary hyperparathyroidism. Increased levels of FGF-23 have also been independently associated with CKD progression, mortality and cardiovascular morbidity, but the underlying mechanisms are still under investigation. However, it has been suggested that excessively high FGF-23 levels might exert off-target effects in the cardiovascular system. In agreement with the above, recent studies provided evidence that CKD is a Klotho-deficient state, which allows excessively high serum FGF-23 levels to induce left ventricular hypertrophy by Klotho-independent FGFR activation, while simultaneously attenuating its anticalcifying effects. The aim of this critical review was to discuss FGF-23 and its association with adverse clinical outcomes in patients suffering from CKD.

Conclusion

FGF-23 not only plays an important role in the development of secondary hyperparathyroidism but it is also associated with adverse clinical outcomes, including CKD progression and cardiovascular mortality and morbidity.

Introduction

Chronic kidney disease (CKD) patients are severely afflicted by high mortality and cardiovascular (CV) morbidity. This CV disease burden increases gradually as renal function declines and is dramatically high in dialysis patients. Moreover, it appears disproportionate to the high prevalence of traditional CV risk factors observed in these patients and has proven resistant to relevant risk factor modification strategies with established efficiency in the general population. Therefore, it appears crucial to identify other factors and biomarkers associated with CKD progression and CV disease, providing tools for more accurate risk stratification and more effective management of these patients.

The phosphatonin fibroblast growth factor (FGF)-23 is a key regulator of serum phosphate levels in CKD and the newly recognized initial culprit for the development of secondary hyperparathyroidism (SHPTH). Moreover, it has recently been associated with CKD progression to renal failure as well as mortality and CV morbidity across a wide spectrum of populations, including CKD patients. This critical review assesses FGF-23 and adverse clinical outcomes in CKD patients.

Discussion

FGF-23 and CKD

FGF-23 is a 251-amino acid protein with an N-terminal region containing the FGF homology domain and a 71-amino acid C-terminal domain. It was initially discovered in an attempt to elucidate the pathophysiology of conditions like X-linked hypophosphataemia, autosomal dominant and autosomal recessive hypophosphataemic rickets and tumour-induced osteomalacia, all sharing a common combination of manifestations, including hypophosphataemia, phosphaturia, osteomalacia and inappropriate low levels of 1,25(OH)2 vitamin D. FGF-23 is secreted mainly by osteocytes in response to oral phosphorus load. Its actions on classic target organs, such as the kidneys and the parathyroid glands, are mediated by its co-receptor Klotho, which allows for FGF-23–specific binding and activation of the FGF receptor (FGFR). FGF-23 principal effects include induction of phosphaturia and suppression of 1,25(OH)2 vitamin D production in the kidney, as well as inhibition of parathyroid hormone production and excretion in the parathyroid glands.

Serum FGF-23 levels progressively rise as renal function declines, reaching at initiation of dialysis up to 1,000 times higher than those encountered in healthy individuals, probably as a result of increased production due to accumulating phosphate load and/or decreased renal excretion. Suppression of 1,25(OH)2 vitamin D combined with attenuated parathormone inhibition, possibly due to reduced parathyroid Klotho expression in CKD, eventually initiates the development of SHPTH. Phosphate levels

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design; manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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are initially maintained within the normal range due to increased per nephron phosphate excretion. However, in the later stages of CKD, hyperphosphataemia ensues, as phosphate load overwhelms FGF-23–induced phosphaturia in the remaining functional nephrons.

The implication of FGF-23 in the homeostasis of 1,25(OH)\(_2\) vitamin D and phosphorus, factors associated with CKD progression, mortality and CV morbidity,\(^9\), has led to the investigation of potential associations between FGF-23 and adverse clinical outcomes in patients with CKD.

**FGF-23 and CKD progression**

In a prospective study involving white European nondiabetic patients with CKD, who were followed-up for a median of 53 months, both serum intact FGF-23 (iFGF-23) and c-terminal FGF-23 levels (cFGF) above optimal cut-off level predicted a doubling of serum creatinine and/or the need for renal replacement therapy, independent of eGFR and proteinuria, well-established risk factors of CKD progression, and other indices of mineral metabolism, such as calcium, phosphate and parathyroid hormone.\(^7\) In a prospective study from Brazil on patients with diabetes mellitus type 2 and macroalbuminuric nephropathy, iFGF-23 was an independent predictor of the composite primary outcome defined as death, doubling of baseline serum creatinine and/or need for dialysis, even after adjustment for creatinine clearance and intact parathyroid hormone.\(^8\) In 3,879 individuals with an eGFR 20–70 ml/min/1.73 m\(^2\) enrolled in the CRIC (Chronic Renal Insufficiency Cohort), a multicentre prospective observational study, cFGF-23 levels were independently associated with increased mortality in subjects with eGFR > 30 ml/min/1.73 m\(^2\).\(^9\) However, in a cohort of 1,099 predominantly male subjects with high homocysteine levels and eGFR < 30 ml/min/1.73 m\(^2\), cFGF-23 levels were also found to be associated with initiation of chronic dialysis independent of confounders including baseline kidney function and abnormalities of mineral metabolism.\(^10\) Finally, in a recent study involving 701 older community-dwelling women, iFGF-23 independently predicted development of CKD during the 24-month follow-up after adjustment for baseline eGFR, phosphate, 1,25(OH)\(_2\) vitamin D, parathyroid hormone and other potential confounders.\(^11\)

**FGF-23 and mortality**

Initially, serum cFGF-23 levels were found to be independently associated with increased mortality during the first year of renal replacement therapy in incident haemodialysis patients.\(^12\) This finding was later replicated in prevalent haemodialysis patients,\(^13\) patients with predialysis CKD,\(^14,15\) and renal transplant recipients\(^16\) as well as in patients with known stable coronary artery disease irrespective of kidney function.\(^17\)

In a recent community study involving elderly Caucasian men, higher iFGF-23 levels, in concentrations previously regarded as pathophysiologically insignificant, were independently associated with all-cause and, even stronger, with CV mortality only in subjects with an eGFR < 60 ml/min/1.73 m\(^2\), suggesting that the clinical relevance of FGF-23 levels may be restricted to CKD patients.\(^18\) FGF-23 association with mortality in the aforementioned studies appears to be independent of traditional CV risk factors, renal function, proteinuria as well as parameters of mineral metabolism such as calcium, phosphorus and parathyroid hormone.

**FGF-23 and CV morbidity**

In agreement with the established notion that excess mortality in CKD is mainly of CV origin, FGF-23 has been directly associated with both vascular and cardiac morbidity. In haemodialysis patients, serum FGF-23 levels have been independently associated with peripheral vascular calcification assessed semiquantitatively on plain radiographs,\(^19\) with aortic calcification assessed quantitatively on CT in nondiabetics,\(^20\) and with the presence\(^21\) as well as with the progression\(^22\) of coronary artery calcification evaluated by multislice CT and quantified according to the Agatston method.

In earlier CKD stages, FGF-23 independently predicted the extent of coronary artery disease, assessed by angiography,\(^23\) and was associated with vascular dysfunction depicted on the attenuation of flow-mediated dilatation in nondiabetics without a history of CV events.\(^24\)

In community-based studies from Sweden involving elderly patients, FGF-23 levels were associated with total body atherosclerosis as determined by magnetic resonance angiography,\(^25\) endothelial dysfunction assessed by venous occlusion plethysmography and after the administration of vasoactive drug infusions, especially those with an estimated GFR > 90 ml/min/1.73 m\(^2\), and with arterial stiffness evaluated by pulse wave analysis in those with an estimated GFR < 60 ml/min/1.73 m\(^2\).

Apart from vascular changes, serum levels of FGF-23 have also been positively associated with alterations in cardiac geometry and function, as well as myocardial damage. In haemodialysis patients, FGF-23 levels were associated with the presence of left ventricular hypertrophy (LVH) and correlated with left ventricular mass index (LVM) and myocardial performance index, which is a surrogate of heart failure and increased left ventricle end-diastolic pressures.\(^26\) In predialysis, CKD FGF-23 levels were also associated with the presence and de novo development of LVH during follow-up even in normotensive patients\(^27\) and correlated with LVM, independent of eGFR and other known CV risk factors, including...
serum phosphorus levels\textsuperscript{29}. In a study involving patients with CKD stages 3 and 4, FGF-23 levels were also correlated with high-sensitivity Troponin T, an index of cardiomyocyte damage\textsuperscript{31}. Finally, the aforementioned community study from Sweden in elderly patients demonstrated a similar independent association with LVMI and LVH, which was even stronger in the group of individuals with an eGFR < 60 ml/min/1.73 m\textsuperscript{2}.

Pathophysiologic background

The pathophysiologic mechanisms underlying the associations between FGF-23 and adverse outcomes are still under investigation. The argument that FGF-23 is merely a marker of reduced renal function, of accumulated phosphate toxicity or a surrogate for vitamin D deficiency and hyperparathyroidism, all associated with mortality and CV morbidity, is contradicted by the fact that the associations between FGF-23 and adverse outcomes appear independent of the aforementioned potential confounders\textsuperscript{18}. Thus it appears reasonable to conclude that FGF-23 is actively involved in the pathogenesis of CV damage in uraemia, although the exact mechanisms are not yet fully elucidated. Increased FGF-23 levels in CKD might exhibit direct CV toxicity or reflect a protective response against injury, potentially ineffective by uraemia-related resistance. Finally, a differential effect in cardiac and vascular tissue might derive from site-specific variability in FGFR and Klotho expression and FGF-23 interaction\textsuperscript{30,33}.

The lack of Klotho expression on cardiomyocytes appeared to question the direct effect of FGF-23 on the heart implied by the observed association between elevated FGF-23 levels and LVH. However, a recent comprehensive study combining human and experimental data provided solid evidence of a Klotho-independent, FGFR-mediated LVH induction by excessively high FGF-23 levels, as observed in CKD\textsuperscript{30}. Using in vitro and in vivo animal experiments, the above study demonstrated that FGF-23 causes cardiac hypertrophy by activating the calcineurin-NFAT signalling cascade after binding to the FGFR, without the requirement of Klotho acting as a co-receptor. Furthermore in an animal model of CKD that is characterized by elevated FGF-23 levels, severe hypertension and LVH, cardiac hypertrophy was prevented by FGFR blockade, independent of blood pressure\textsuperscript{30}. Thus, it was suggested that Klotho-independent cardiotoxicity may be facilitated through low-affinity FGF-23 binding with the FGFR as a result of prolonged high serum FGF-23 concentrations, as observed in CKD, where reduced Klotho expression in the kidneys, parathyroid glands and other tissues might further potentiate FGF-23 binding to FGFR in nonclassical target organs\textsuperscript{34}. Alternatively, higher affinity binding to cardiac-specific FGFRs, such as FGFR-4, which is able to bind FGF-23 in the absence of Klotho, might explain the hypertrophic effect of FGF-23, although further studies on the subject are obviously needed\textsuperscript{34}.

The positive association of FGF-23 with arteriosclerotic vascular changes, such as arterial stiffness and calcification, appears to contradict experimental findings, such as extensive vascular and soft-tissue calcification in FGF-23 knockout mice, and in-vitro inhibition of osteoblast mineralization, which suggest a protective role of FGF-23 on the vasculature\textsuperscript{33}. A recent study, which investigated arterial wall Klotho expression in health and uraemia, provided valuable information in elucidating this discrepancy. The above study demonstrated for the first time that uraemia is a state of vascular Klotho, FGFR-1 and FGFR-3 deficiency, mediating FGF-23 resistance and potentiating the development of calcification. Furthermore, vitamin D receptor activation restored Klotho expression and rendered the vascular smooth muscle cells responsive to FGF-23 anticalcifying effects\textsuperscript{33}. Thus it appears that in CKD reduced GFR and accumulating phosphate load in combination with the reduced Klotho expression on the kidneys, parathyroids and vasculature restrict the effects of FGF-23 on phosphaturia, parathormone suppression and inhibition of calcification, while allowing excessive FGF-23 to exert Klotho-independent cardio-toxicity (Figure 1).

Clinical implications

The elucidation of the pathogenetic mechanisms underlying the FGF-23 associations with adverse outcomes bears potential for clinical applications. In earlier CKD stages, FGF-23 levels might reflect accumulating phosphate toxicity before the development of overt hyperphosphataemia, offering guidance for interventions involving oral phosphate restriction or binding\textsuperscript{34,35}. In more advanced CKD stages, targeting FGF-23 directly, for example with neutralizing antibodies, might confer some cardioprotection by attenuating LVH, but could potentially enhance extraosseous calcification by replicating the FGF-23 null phenotype\textsuperscript{16}. On the other hand, strategies to restore Klotho expression in the vascular wall or in the parathyroids might enable FGF-23 to inhibit calcification and hyperparathyroidism. Certainly more evidence from experimental and clinical trials is required before relevant novel therapeutic strategies would be available, which hopefully should result in improved clinical outcomes.

Conclusion

FGF-23 is gradually gaining importance in our understanding of CKD progression and the associated cardiovascular morbidity. Besides its role as the initial effector of secondary hyperparathyroidism, FGF-23 is emerging as a novel marker and possibly a mediator of cardiovascular

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Critical review

Figure 1: Putative mechanisms of FGF-23-related adverse outcomes in CKD. Decreased Klotho expression inhibits response of target organs to FGF-23, leading to SHPTH, phosphate retention and vascular calcification, further increasing FGF-23 levels, leading to Klotho-independent induction of left ventricular hypertrophy (LVH).

Abbreviations list
FGF, fibroblast growth factor; FGFR, FGF receptor; CKD, chronic kidney disease; CV, cardiovascular; SHPTH, secondary hyperparathyroidism; iFGF, intact FGF; cFGF, c-terminal FGF; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index

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