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FGF23 and the heart

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Abstract

The prevalence of chronic kidney disease (CKD) has now reached epidemic proportions and it is very likely that it will continue to rise with the increasing prevalence of juvenile diabetes mellitus, hypertension and aging population. CKD is a risk factor for cardiovascular disease (CVD) and cardiovascular disease can lead to CKD. It is also well known that patients with CKD have a higher risk of death from CVD than of progressing to end-stage renal disease that requires renal replacement therapy. In patients with CKD, there is a higher mortality from sudden cardiac death and congestive heart failure than coronary artery disease, which is not the case in the general population. The high prevalence of congestive heart failure in CKD is due to cardiac remodeling which progresses from concentric remodeling to concentric and eccentric hypertrophy, leading to left ventricular hypertrophy with both systolic and diastolic dysfunction. Recent studies have suggested that, in patients with chronic kidney disease, common traditional risk factors for cardiovascular disease such as hypertension, hyperlipidemia and obesity may not be the main determinants of cardiovascular disease. Among the various non-traditional cardiovascular risk factors present in patients with chronic kidney disease, abnormalities of CKD related mineral and bone disorder, which includes elevated fibroblast growth factor 23 (FGF23) have been one of the most extensively studied. However, after many years of research, the debate over the exact pathways by which FGF23 may lead to increased CVD still continues. FGF23 may have both direct and indirect effects on the cardiovascular system. Better understanding of the most relevant pathophysiologic pathways for FGF23 may lead to therapeutic interventions against cardiovascular disease in patients with CKD.

Key words: FGF23, cardiovascular diseases, chronic kidney disease, fibroblast growth factor23

Introduction

Chronic kidney disease (CKD) has now reached epidemic proportions and it is estimated that more than 10% of adults in the United States—more than 20 million people—may have CKD and this is not without huge economic and health consequences [1]. Patients with CKD have increased risk of cardiovascular disease (CVD) with CKD itself being a risk factor for CVD independent of hypertension, diabetes mellitus and albuminuria [2] (full text) [3] [4]. Traditional risk factors for CVD such as hypertension, hyperlipidemia and obesity have been shown to be associated with better outcomes in CKD and ESRD patients in some studies [5] [6] (full text) [7] [8]. Non-traditional risk factors such as endothelial dysfunction, increased oxidative stress, inflammation, anemia, and CKD-mineral and bone disorders (MBD) increase as renal function declines and they have been proposed as potential explanation for the excess mortality seen in patients with CKD & ESRD [9] (full text) [10] (full text)

[11] [12] (full text) [13] (full text). CKD-MBD which is a systemic disorder of mineral and bone metabolism is associated with increased CVD & mortality. Abnormalities grouped under CKD-MBD include hyperphosphatemia, hypocalcemia, hypercalcemia, hyperparathyroidism and vitamin D deficiency [14] [15] [16] (full text) [17] (full text) [18]. A novel component among the biochemical abnormalities of CKD-MBD is elevated fibroblast growth factor-23 (FGF23), which has recently been linked to worsened outcomes independent of other abnormalities. This review will discuss the physiology of FGF23 and the pathophysiologic link between elevated FGF23 and increased cardiovascular mortality in CKD patients.

FGF23 physiology and metabolism

Fibroblast growth factors (FGF) are polypeptide growth factors with diverse biological activities including roles in angiogenesis, mitogenesis, cellular differentiation, cell migration and tissue injury repair [18]. They consist of 22 members with varied functions and four tyrosine kinase FGF receptors [19] [20] (full text). FGF are grouped into seven different subfamilies based on differences in sequence homology and phylogeny [18] and into three groups according to their mechanisms of action: the intracellular, canonical and hormone-like (endocrine) FGF [21] (full text). The hormone-like FGF which include FGF 19/21/23 acquire endocrine functions by reduced heparin-binding affinity and the presence of a carboxy terminus that permits activation of FGF receptors in the absence of heparin [22]. The reduced affinity for heparin sulfate also prevents direct interaction between endocrine FGF and FGF receptors [23] (full text). FGF23 which is part of this group requires an alternate cofactor known as α-klotho to mediate its effects through FGF receptors [23] (full text). FGF23 was discovered during the study of a group of disorders with a common phenotype that included hypophosphatemia, urinary phosphate wasting, abnormally low 1,25$(OH)_2$ vitamin D level for the degree hypophosphatemia and rickets or osteomalacia. The disorders include X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, tumor induced osteomalacia and fibrous dysplasia [24] (full text) [25].

FGF23 is a 32 kDa (251 amino acids) polypeptide with an N-terminal and C-terminal region that is predominantly expressed in osteocytes and osteoblasts in the bone [26] (full text) [27] (full text). It is also produced in the venous sinusoids of the bone, ventrolateral thalamic nuclei of the brain, thymus and lymph nodes albeit in very small quantities [26] (full text) [27] (full text). The primary target for FGF23 is the FGF receptor – α- klotho complex in the distal tubule of the kidney leading to the primary physiologic actions of FGF23: inhibition of proximal tubular phosphate reabsorption via ATPase dependent Na-phosphate transporter; and suppression of circulating levels of 1,25$(OH)_2$ D through inhibition of Cyp27b1 to decrease its production and stimulation of Cyp24A1 to increase its degradation [28]. FGF23 has also been suggested to suppress parathyroid hormone (PTH) secretion [29] with the creation of a PTH-FGF23 feedback loop (increased PTH → increased FGF23→ decreased PTH) [30] (full text). FGF23 suppression of PTH remains controversial as clinically elevated PTH has been associated with elevated FGF23 though this incongruence may be explained by resistance of the parathyroid gland to FGF23 in the uremic state due to down-regulation of α-klotho [31] [32]. FGF23 also suppresses the gene transcription of α-klotho by the kidney which exists as a membrane and soluble protein [29] [33]. The effects of FGF23 on the kidney constitute a Bone-Kidney axis, in which the bone by its production of FGF23 and osteocalcin acts as an endocrine organ [34].

The main regulator of FGF23 is 1,25 $(OH)_2$D which stimulates FGF23 production thereby creating a negative feedback loop regulating 1,25 $(OH)_2$D production [35] (full text); (increased

1,25(OH)$_2$D →increased FGF23 → decreased 1,25(OH)$_2$D). Other regulators of FGF23 include bone mineralization and remodeling [36] (full text); phosphorus, calcium, leptin, estrogen and glucocorticoids [30] (full text) [37]; and iron metabolism [38]. The effect of phosphate on FGF23 remains unclear. Phosphate loading in mice increased FGF23 levels but the magnitude of the effect was small compared to the effects of 1,25(OH)$_2$D [39] and in humans, the importance of dietary phosphate in regulating FGF23 is conflicting [40] [41].

Proteolytic processing of FGF23 plays a role in its degradation and regulates its biologic activity. Intact FGF23 is cleaved between arg179 and ser180 by a furin proprotein convertase into inactive N and C-terminal fragments [42] (full text). C-terminal FGF23 may have inhibitory effects on the actions of intact FGF23. Much more work is needed to understand the roles of FGF23 degradation and inhibitory actions of the C-terminal fragment in the physiological function of FGF23 and in disease states characterized by elevated circulating FGF23 levels.

Nevertheless, the principal physiological function of FGF23 is to regulate phosphate and vitamin D metabolism. Current evidence indicates that FGF23 functions as a counter-regulatory hormone for Vitamin D and participates in a bone-kidney endocrine axis consisting of 1,25(OH)2D stimulation of FGF23 and FGF23 mediated suppression of Cyp27b1 and 1,25(OH)2D synthesis and stimulation of Cyp24 and 1,25(OH)$_2$D degradation.

FGF23 and CKD

CKD is the most common cause of chronically elevated FGF23 levels and the clinical condition in which levels are most markedly elevated [43] (full text) [44]. Physiologically FGF23's role is to regulate phosphorus and vitamin D homeostasis, but the long term effects of chronically elevated FGF23 in CKD remain less well defined. It is possible that FGF23 may be involved in both adaptive responses and cardiovascular complications related to CKD-MBD [30] (full text).

FGF23 levels increase early in the course of CKD even when the GFR is about 70-90 ml/min/1.73m^2, and before a detectable increase in serum phosphate and parathyroid hormone levels [33].

In CKD, FGF 23 levels rise as renal function declines such that patients on dialysis have levels that are 100 to 10,000 fold above the normal range for healthy controls [43] (full text) [44] [45] [46] (full text). The elevated FGF23 in patients with CKD is thought to be due to increased bone production and secretion [47] (full text). The elevated FGF23 is mostly the intact and biological active form rather than the inactive (cleaved) form [48] (full text). This could suggest decreased degradation of FGF23 in CKD patients. Elevated FGF23 in CKD is not due to decreased renal clearance [49] (full text). FGF23 elevation in CKD may initially be a compensatory response to maintain normal phosphate balance, as the capacity for renal phosphorus excretion declines [50]. Loss of α-klotho expression in CKD with resultant end-organ resistance to FGF23 may also contribute to the secondary increase in FGF23 level in CKD patients [47] (full text).

Chronically elevated FGF23 may be involved in more complex and ultimately deleterious processes beyond short term regulation of phosphorus and vitamin D metabolism, as suggested by the fact thatelevated FGF23 levels are associated with increased mortality and morbidity in CKD patients, ESRD patients on dialysis and post-renal transplant patients [46] (full text) [51] (full text) [52] (full text) [53] [54] (full text) [55] (full text) [56] (full text). In CKD patients with elevated FGF23, the level of FGF23 correlates with their risk of mor-

tality with patients in the highest quartile having the worst outcome [52] (full text) [54] (full text).

FGF23 and CVD: Mechanisms of action

The high CVD event rates and mortality associated with elevated FGF23 levels may be due to various effects on the cardiovascular system, including left ventricular hypertrophy, arterial stiffness, vascular calcifications, endothelial dysfunction and increased levels of inflammatory markers [57] [58] (full text) [59] (full text) [60] (full text) [61] [62]. With the bone recognized as an endocrine organ, a direct effect on the cardiovascular system by bone-derived hormones could be construed as the "Osteo-cardiac syndrome". Additional indirect effects through the action of FGF23 on the kidney will create the "Osteo-reno-cardiac syndrome".

LVH

Left ventricular hypertrophy is one of the most common cardiovascular disorders in ESRD patients on dialysis and an independent risk factor for cardiovascular death in this group [48] (full text) [63] [64] (full text) [65]. FGF23 has been associated with left ventricular hypertrophy [58] (full text) [66] [67] (full text) [68] [69] (full text). However whether this suggests a direct causative effect or an indirect effect on the heart is still a subject of debate. Faul et al showed in a murine experiment that FGF23 mediated left ventricular hypertrophy through direct activation of FGF receptors [57]. This action was klotho independent because klotho, the primary co-receptor for FGF23 is not expressed in myocardial cells. However, in another murine study done by Agarwal et al, klotho deficient mice did not have left ventricular hypertrophy in contrast to 1-α hydroxylase deficient mice [70] (full text). Other studies have also questioned the direct effects of FGF23 on the myocardium [71] (full text) [72] [73]. At this time it remains unclear whether the discrepant results of these studies are due to different experimental circumstances, and if FGF23 could indeed have a direct effect on cardiomyocytes.

1,25 $(OH)_2$ D

1,25$(OH)_2$ D is produced predominantly in the kidney by the action of 1-α-hydroxylase on 25-hydroxyvitamin D. Various extra-renal tissues including most cardiovascular and inflammatory cells express Cyp27b1 enabling local synthesis of 1,25 $(OH)_2$D [74] (full text). The target cell synthesis of 1,25 $(OH)_2$D is particularly important in the non-skeletal actions of vitamin D [75]. FGF23 has been shown to suppress 1-α- hydroxylase activity at extra-renal sites [76]. The resultant effect of this in CKD patients with markedly elevated FGF23 is decreased levels of 1,25$(OH)_2$D and loss of its hormonal, autocrine and paracrine functions.

1,25 $(OH)_2$D exerts its actions through vitamin D receptors (VDR) which is found among others in all major cardiovascular cell types like vascular smooth muscle cells, endothelial cells, and cardiac myocytes [77] [78] (full text) [79]. All these cells play a role in the development of CVD in CKD patients. 1,25$(OH)_2$D deficiency may lead to maladaptive cardiac remodeling due to progressive myocyte hypertrophy and interstitial fibrosis (80). A murine study showed that left ventricular hypertrophy developed in 1-α-hydroxylase deficient mice [70] (full text). VDR is also expressed by many immune cells including dendritic cells, macrophages, monocytes and activated T-cells [81]. In the immune system, 1,25$(OH)_2$D serves as an immune modulator leading to decreased inflammatory cell proliferation and decreased release of interleukins and tumor necrosis factor which are known risk factors for CVD in CKD patients [82]. Deficiency of 1,25$(OH)_2$D may lead to an increased inflam-

matory state as is the case in CKD with increased CVD risk. Murine gene deletion studies have shown that 1,25$(OH)_2$D is involved in the regulation of the renin-angiotensin system (RAS) [80]. In its deficiency, there is marked increase in the expression of renin which leads to increased angiotensin II production resulting in hypertension and cardiac hypertrophy [83] (full text) [84]. Under normal physiologic circumstances, FGF23 regulates 1,25$(OH)_2$D level and prevents ill-effects of excess vitamin D such as vascular calcification. However, under pathologic circumstance where FGF23 are not adaptive any more (but rather maladaptive), like in ESRD, it is possible that extremely elevated levels of FGF23 could over-suppress 1,25$(OH)_2$D production and thus lead to poor cardiovascular outcomes.

Soluble Klotho

Klotho protein exists in two forms, membrane klotho and soluble or secreted klotho. Membrane klotho is bound to the cell membrane and functions as a co-receptor for FGF23. Soluble klotho functions as a humoral factor with enzymatic activity [85] (full text) [86]. Soluble klotho is the circulating form of klotho produced from increased gene transcription of the alternatively spliced secreted isoform or from ectodomain shedding of membrane extracellular domain of full length klotho [30] (full text). Soluble klotho protects the heart against stress induced cardiac hypertrophy and remodeling by down regulation of TRPC6 channels [87]. Klotho-deficient mice have been shown to develop pathologic cardiac hypertrophy and remodeling in response to stress [87]. In CKD patients, with the progressive decline in glomerular filtration rate, serum levels of soluble α-Klotho and 1,25$(OH)_2$D decrease as serum levels of FGF23 increase [88] [89] [90] (full text). It has been suggested that elevated FGF23 causes the down-regulation of soluble α-klotho [33] and this could represent another indirect effect of FGF23 on the heart. Other effects of soluble klotho includes its phosphaturic effect independent of FGF23 by modulation of the sodium phosphate cotransporter [91] (full text); it increases calcium reabsorption in the kidney and reduces calciuria by internalization of the cell-surface calcium channel TRPV5 [92] (full text); it functions as an anti-aging gene by suppression of tyrosine phosphorylation of insulin and insulin-like growth factor1 leading to downregulation of IGF1 signaling [93] (full text) and finally it also functions as an inhibitor of vascular calcification [94] (full text).

Renin-Angiotensin System (RAS)

The RAS is a central regulator of cardiovascular and renal function and it plays a role in various cardiovascular and renal diseases [95]. Angiotensin II through its interactions with the AT_1 receptor has been shown to increase fibroblast proliferation, and myocyte hypertrophy leading to myocardial fibrosis and remodeling **[96]** [96] [97] (full text) [98]. It is also pro-inflammatory and stimulates generation of reactive oxygen species, inflammatory cytokines and adhesion molecules [99] [100] (full text) which are known risk factors for cardiovascular disease in CKD patients. Angiotensin-converting enzyme 2 (ACE2) which is highly expressed in the kidney and heart prevents cardiac remodeling and hypertrophy by converting angiotensin II to the inactive angiotensin 1-7 **[101]** [101] (full text). FGF23 suppresses angiotensin-converting enzyme 2 (ACE2) expressions in the kidney which can lead to activation of the renin angiotensin system [102] (full text). Therefore, another potential mechanism of action for FGF23 could be increased activation of the renin angiotensin system with increased production of angiotensin II leading to LVH and a pro-inflammatory state, with subsequent increase in cardiovascular mortality.

Renal Sodium Handling

FGF23 has been shown to regulate sodium retention and excretion in the distal renal tubules in a recent article published by Andrukhova et al [103] (full text). In their murine exper-

iment, absorption of sodium in the distal tubules was reduced in mouse models of FGF23 and α-klotho deficiency. Conversely, mice injected with recombinant FGF23 or those with elevated endogenous FGF23 had increased sodium absorption in the distal tubules. This effect was mediated by the ability of FGF23 to increase the membrane abundance of sodium chloride co-transporter(NCC) in the distal tubules. The increased renal sodium retention and volume expansion led to hypertension and left ventricular hypertrophy (LVH). The NCC inhibitor chlorothiazide was shown to prevent this effect when it was given with recombinant FGF23.

Inflammation and oxidative stress

Another mechanism linking FGF23 to CVD is its effect on markers of inflammation and oxidative stress. A murine experiment showed that FGF23 increases the production of inflammatory markers such as lipocalin-2, transforming growth factor-β and tumor necrosis factor [102] (full text). In observational studies, FGF23 level has been shown to correlate with different markers of inflammation and oxidative stress like interleukin-6, C-reactive protein, tumor necrosis factor-α, advanced oxidation protein products and advanced glycation end products in CKD patients [60] (full text) [104] (full text). Inflammatory markers which are one of the risk factors for cardiovascular disease in CKD patients have been associated with increased CKD progression [105], atherosclerosis [106] (full text), arterial calcification [107] and increased cardiovascular mortality [108] [109].

Management of Elevated FGF23

Strategies to completely abolish the effects of FGF23 seem to follow the idiomatic expression "Throw out the baby with the bath water". In a murine experiment done by Shalhoub et al, neutralization of the effect of FGF23 with monoclonal FGF23 antibody in rats with CKD led to the development of hyperphosphatemia, aortic calcification and increased mortality though the rats had resolution of secondary hyperparathyroidism, increased vitamin D levels, increased serum calcium and normalization of bone structure and turnover rate [72]. This is consistent with the finding in FGF23-null mice in a different study [110]. In another murine experiment on XLH and ARHR phenotype mice, the use of pharmacological inhibition of FGFRs counteracted the pathological FGF23 signaling with the correction of hypophosphatemia, hypocalcemia, enhanced bone growth, increased mineralization and normalization of bone turnover. There was however no report of increased mortality in the mice used for this study [111] (full text) [112] [113]. This will suggest that the increased mortality seen in the previous study is related to the level of FGF23 blockade as shown in the experiment by Shalhoub et al. In this study, animals in the high dose FGF23 monoclonal antibody group had a higher mortality and aortic calcification score than those in the low dose group [72]. These finding suggests that FGF23 is a physiologic hormone with many beneficial effects with the potential to become pathologic at higher levels and completely abrogating its effects will lead to increased morbidity and mortality.

Dietary phosphate restriction combined with a phosphate binder has been shown to lower FGF23 level in CKD patients when taken over a long period of time [114] [115] (full text) [116] (full text) [117]. A similar effect was not seen when this was done over a 2 week period [118] (full text). Moe et al showed that the protein source of the phosphorus is also important in a study done comparing meat based diet with vegetarian diet [119] (full text). Compared to patients on meat based diet, patients on vegetarian diet had lower serum phosphate levels and significantly decreased FGF23 levels despite equivalent protein and phosphorus intake in both groups.

Some medications used in the treatment of CKD MBD have been shown to decrease the levels of FGF23. In a study on hemodialysis patients, those randomized to sevelamer and calcium carbonate had lower serum phosphate and FGF23 levels compared to those on calcium carbonate alone [120]. Another study on CKD 4 [121] and CKD 3-4 [122] (full text) patients showed a greater decrease in FGF23 level with sevelamer compared to calcium acetate that is independent of the decrease in serum phosphate. The patients in these studies however had baseline FGF23 levels that were either normal or only modestly elevated. Treatment with lanthanum for 4 weeks in a small study done on 18 patients with CKD 3, led to a decrease in serum FGF23 levels [123] (full text). On the contrary, treatment with lanthanum over a 2 weeks period did not result in any significant decrease in FGF23 levels [118] (full text). These findings suggest the need for a more robust randomized trial to evaluate the effects of calcium based and non-calcium based phosphate binders in CKD and ESRD patients with significantly elevated FGF23 levels and also their effect on cardiovascular mortality.

Finally, cinacalcet used in the treatment of secondary hyperparathyroidism has been shown to lower FGF23 level in hemodialysis patients [124] (full text) [125] (full text) [126] (full text) while calcitriol as will be expected has been shown to increase FGF23 level [126] (full text) [127] [128] (full text). In a randomized study done by Cozzolino et al on patients with CKD5 on hemodialysis, paricalcitol reduced circulating bone turnover markers and iPTH levels more than cinacalcet but increased FGF23 levels compared to cinacalcet. However the effect on mortality in these two groups was not reported [129].

Conclusion

FGF23 is more than just a phosphaturic hormone and it has emerged as an important risk factor for cardiovascular morbidity and mortality in pre-dialysis CKD patients, CKD patients on dialysis and post renal transplant patients. Effects of FGF23 on the cardiovascular system could be due to a direct "off target" effect (osteo-cardiac syndrome) and an indirect effect through its actions on the kidney to decrease the level of 1,25 $(OH)_2D$, decrease the expression of soluble klotho and activate the renin angiotensin system (osteo-renocardiac syndrome). For the time being FGF23 could serve as a marker of increased risk of adverse outcomes in various populations with kidney disease. More studies are needed to determine if lowering of FGF23 by yet-to-be-determined means could be used as a therapeutic intervention in CKD and ESRD.

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