



Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease—A Pediatric Perspective

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Cardiovascular diseases (CVD) are a hallmark in pediatric patients with chronic kidney disease (CKD) contributing to an enhanced risk of all-cause and CV morbidity and mortality in these patients. The bone-derived phosphaturic hormone fibroblast growth factor (FGF) 23 progressively rises with declining kidney function to maintain phosphate homeostasis, with up to 1,000-fold increase in patients with kidney failure requiring dialysis. FGF23 is associated with the development of left ventricular hypertrophy (LVH) and thereby accounts to be a CVD risk factor in CKD. Experimentally, FGF23 directly induces hypertrophic growth of cardiac myocytes *in vitro* and LVH *in vivo*. Further, clinical studies in adult CKD have observed cardiotoxicity associated with FGF23. Data regarding prevalence and determinants of FGF23 excess in children with CKD are limited. This review summarizes current data and discusses whether FGF23 may be a key driver of LVH in pediatric CKD.

Keywords: fibroblast growth factor 23, left ventricular hypertrophy, children, chronic kidney disease - mineral and bone disease, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is a significant global health issue and defined as gradual loss of kidney function ultimately leading to irreversible kidney damage (1). CKD patients present a high risk for cardiovascular events. Fifty percent which remain the predominant cause of patients with CKD stage 4 and 5 develop cardiovascular diseases (CVD), which cause of death with 40% mortality rate (2). The cardiorenal syndrome (CRS) type 4 reflects the complex relationship between primary CKD and resultant CVD (3, 4). Left ventricular hypertrophy (LVH), cardiac fibrosis and vascular diseases remain the most common cardiac abnormalities in CRS 4, with 90% of adult patients with kidney failure developing LVH (5, 6). The primary causes of cardiac-associated death in these adults on haemodialysis are stroke, congestive heart failure, myocardial infarction and cardiac arrest (7, 8). Childhood CKD is also associated with amplified cardiovascular (CV) morbidity and mortality both during childhood with progressive worsening in those with childhood-onset CKD become young adults (7–9). The severity of CVDs in CKD patients is aggravated by the mineral bone disorder of CKD, called Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Thus, CKD-MBD is a CKD-specific cardiovascular risk factor and displays changes in mineral metabolism parameters including phosphate, calcium, parathyroid hormone (PTH), calcitriol

(1,25-dihydroxyvitamin D₃, or 1,25D), and fibroblast growth factor 23 (FGF23) (10). In children with CKD impaired bone architecture may result in bone pain and deformities, short stature, fractures and ectopic calcifications. In children, LVH is the commonest CV abnormality with reported prevalence between 17 and 55%, increasing prevalence with worsening GFR (11–14). As LVH and its progression are associated with adverse CV outcomes in patients with CKD (15), it remains important to understand additional risk factors. The present narrative review focusses on FGF23, a bone-derived phosphaturic hormone regulating renal phosphate homeostasis, in the development of LVH in pediatric CKD and summarizes recent clinical literature in this field.

GENERAL MECHANISMS OF CVD IN CKD

Mainly, there are two different processes involved in the development of CVD. As a response to mechanical or hemodynamic overload, a remodeling process leads to hypertrophy of the left ventricle (LV) (16). There is evidence, that LV dysfunction in children with CKD predisposes them to LVH (17). Pressure overload resulting from prolonged hypertension leads to concentric hypertrophy, whereas eccentric hypertrophy is a cause of volume overload due to e.g., aortic and mitral valve insufficiency (18). These two different mechanisms induce distinct patterns of cardiac myocyte contractile protein (sarcomere) formation. New sarcomeres are added in parallel with relative increase in the width of the myocytes during pressure-induced concentric LVH. The pronounced increase in wall thickness with only little expansion of the LV cavity is a direct effect of the myocyte growth. During eccentric hypertrophy the LV cavity together with wall thickness is increased. Here, sarcomeres are added in series producing longitudinal growth of cardiac myocytes. Importantly, when myocytes elongated only in length without an increase in diameter, the LV dilates. Both, pressure and volume overload trigger the activation of multiple signaling pathways leading to myocardial remodeling (18). In CKD patients, these mechanisms can be activated independently, since here numerous humoral factors are altered *a priori*. To make matters worse, different hemodynamic stimuli e.g., hypertension, arterial stiffness, volume expansion, and anemia can occur simultaneously in CKD, resulting in distinct alterations of LV geometry (19). Hypertrophy of the LV becomes maladaptive with decreased capillary density, arrhythmia, and myocardial fibrosis leading to myocyte death causing diastolic and systolic dysfunction. The activation of the renin–angiotensin–aldosterone system (RAAS) is also known to induce LVH (20, 21). FGF23 can stimulate RAAS directly by inhibiting renal Angiotensin Converting Enzyme 2 (ACE2), thus inhibiting its vasodilatory and hypotensive properties resulting in promotion of vasoconstrictive and inflammatory effects of angiotensin II (22–24). Vice versa, FGF23 expression may also be stimulated by RAAS activation (25). Interestingly, FGF23 blunts the protective effects of angiotensin receptor blocker (ARBs) on the kidney and mitigates the expression of anti-inflammatory genes in experimental renal failure (26). Since, hypertension

is one of the most common comorbidities in CKD patients, FGF23-mediated activation of RAAS may play an important role in hypertension in CKD.

Vascular injury is promoting CVD as well. Changes in vascular tissue, leading to atherosclerotic and arteriosclerotic alterations and/or vascular calcification, are very common in CKD. Plaque and atheroma formation during atherosclerosis start with accumulation of macrophages in the vascular intima followed by aggregation of lipids, different fibers of collagen and smooth muscle cells. At the same time, calcification with the development of atherosclerotic lesions at the intima occurs causing stenosis and local closures of the artery. Circulating endothelial progenitor cells (EPCs) contribute to angiogenic processes where they are recruited to the heart vessels after injury or damage. Studies show a reduced number of EPCs with impaired function in CVD (27).

In arteriosclerosis, the process of arterial stiffening and arterial calcification results in arteries with thicker intima and media, which affects their elasticity. The increased wall thickness together with a lumen enlargement, resulting in higher systolic blood pressure and arterial stiffening, characterize the vascular remodeling processes during arteriosclerosis. The main consequences of arterial stiffening are LVH and an altered coronary perfusion (28).

Over the past decade, vascular calcification in combination with chronic inflammation have come into focus as another risk factor for CVD in CKD, driving disease progression particularly in children on chronic dialysis (29). In combination with oxidative stress, inflammation is implicated in the progression of CKD due to increased production of pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) with IL6 and TNF- α being strong inducers of vascular calcification (30). In the Modification of Diet in Renal Disease (MDRD) study and in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) higher CRP levels have been independently linked to CVD prevalence in diabetic and non-diabetic kidney disease (31, 32). Mechanistically, CRP has been shown to enhance transdifferentiation of vascular smooth muscle cells (VSMC) via an Fc fragment of IgG receptor IIa (FCGR2A)-dependent activation of oxidative stress (33). Loss of VSMCs quiescent phenotype and their transdifferentiation into osteoblastic-like cells with increased mineralized matrix secretion lead to the progression of vascular calcification (34).

The pro-inflammatory marker IL-6 is involved in the development of atherosclerotic lesions by recruiting inflammatory cells. Circulating plasma level of IL-6 were elevated in a cohort of stable haemodialysis patients enrolled in the HEMO study suggesting IL-6 to be a strong predictor of CV and all-cause mortality (35, 36). Furthermore, in a recent clinical study measuring IL-6 in patients with coronary artery calcification in CKD, IL-6 was found to be a strong and independent predictor of CV and all-cause death (37).

TNF- α is induced by inflammatory stimuli and stimulates the immune response. It was shown to be upregulated in kidney disease and LVH in patients receiving dialysis (38). Increased level of circulating TNF- α are observed in myocardial

dysfunction and fibrosis and it is thought to be involved in the development of atherosclerosis by impairing endothelial function (39). Despite these data, currently there is no therapy available for the treatment of inflammation to decrease CV calcification in those with CKD. Recently, using an experimental CKD model, Singh et al. reported that activation of FGFR4 and PLC γ /calcineurin/NFAT signaling by FGF23 in the liver stimulated an inflammatory response (40). Blockade of FGF receptor 4 (FGFR4) resulted in reduced circulating CRP levels. Since FGFR4 is expressed in a wide range of tissue, this FGFR isoform might be a promising target for clinical intervention.

CVD IN PEDIATRIC CKD

In children, LVH develops early in mild and moderate chronic renal insufficiency and exacerbates with kidney failure requiring dialysis (9, 11, 41). Children with CKD show the same risk factors that predict the development of cardiac hypertrophy as adults, although the duration of the “abnormality” is shorter. Importantly however, in contradistinction to adults, children do not have long-standing hypertension and other major co-morbidities including diabetes and smoking. Amongst modifiable risk associations for LVH in children, anemia, increasing ponderosity, hypertension and treatment with antihypertensive medications that do not target RAAS e.g., vasodilators, have been reported previously (42–44). Numerous studies have observed a correlation of increased PTH levels and the progression of LVH in children with CKD stages 2–4 with PTH having a direct effect on cardiac myocytes (45, 46). Thus, Bakkaloglu et al. show in the IPPN cohort for children with CKD an increased risk for developing LVH of over 70% (47).

Endothelial dysfunction (ED) measured by impaired endothelium-dependent flow-mediated dilation (FMD) is observed in children with advanced kidney failure, on chronic dialysis and after renal transplantation (48, 49). Nitric oxide deficiency and oxidative stress are discussed as cause and consequence of ED (50, 51). In addition, vascular abnormalities display a high prevalence in pediatric CKD. Medial vascular calcification due to its association with increased vascular stiffening and cardiac workload, poor coronary perfusion, and sudden cardiac death, is responsible for the high risk for CV mortality even in young adults with CKD and this risk may be comparable to the older people in the general population (52, 53). The association between CKD and accelerated vascular aging is evident and discussed intensively, but so far little is known about the underlying molecular mechanisms (54–56). A dysregulated calcium (Ca) and phosphate (P) metabolism accelerate vascular calcification in CKD that is promoted by the death of vascular smooth muscle cells and osteogenic differentiation (57, 58). Major physiological regulators of Ca and P metabolism are FGF23 and its co-receptor α -Klotho as well as PTH, 25-hydroxyvitamin D (25OHD) and calcitriol (59). Recently, a focus on uremic toxins has been evaluated to account for vascular calcification and fibrosis. Indoxyl sulfate (IS), a metabolite of the tryptophan metabolism that accumulates in the plasma during kidney failure, for example correlates with

congestive heart failure in patients with CKD (60). IS induces the expression of runt-related transcription factor 2 (Runx2) and osteopontin (OPN) and activates the PI3K/Akt/NF- κ B pathway, all of them participating in the differentiation of vascular smooth muscle cells (VSMCs) from a contractile to osteogenic phenotype thereby promoting vascular calcification in CKD (61–63). Furthermore, IS has pro-hypertrophic, pro-fibrotic, and pro-inflammatory properties and stimulates hypertrophy in neonatal rat cardiomyocytes and collagen synthesis in neonatal rat cardiac fibroblasts via activation of MAP kinases and NF- κ B pathways (64).

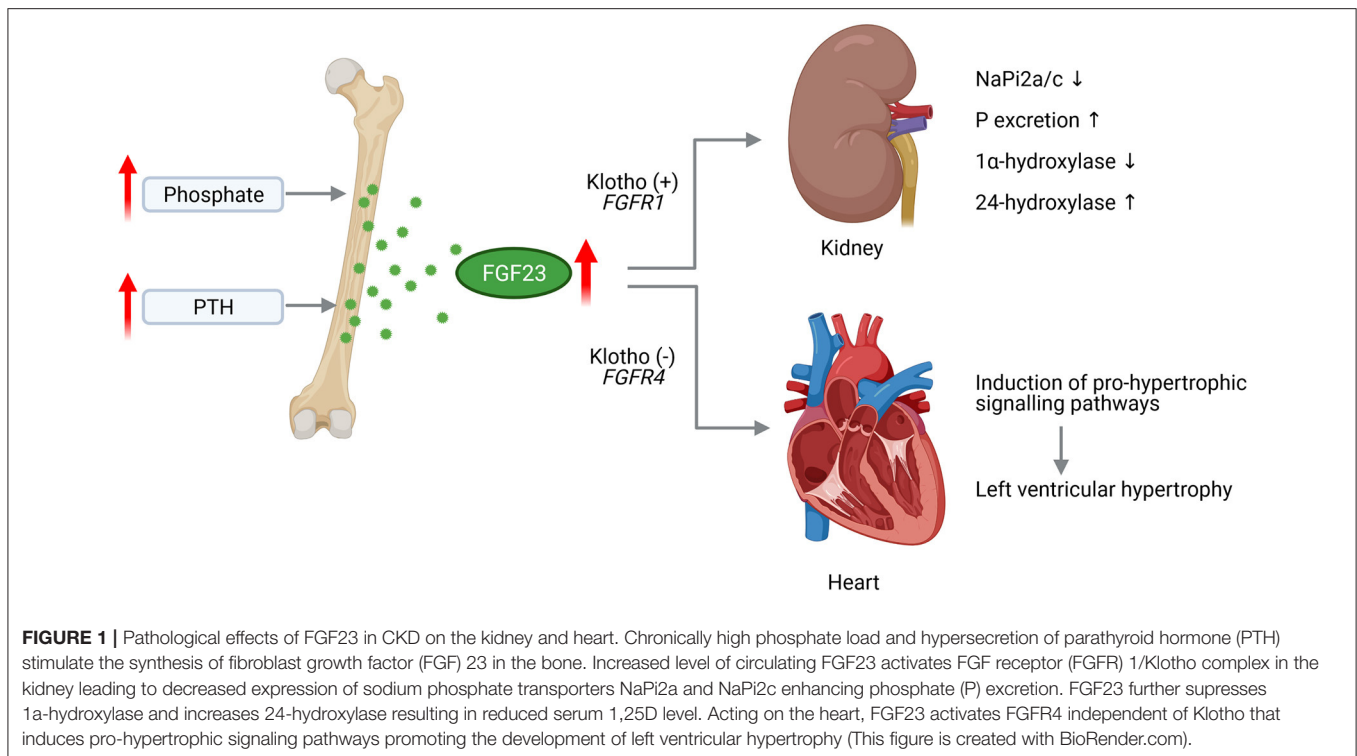
FGF23 IN CKD

FGF23 physiologically binds to the FGF receptors (FGFR) 1/ α -Klotho complex in the kidney to mediate downregulation of sodium-dependent phosphate co-transporters (NaPi2a and NaPi2c) that results in decreased tubular phosphate reabsorption and finally lower serum phosphate levels (**Figure 1**). In early stages of CKD, the increased level of FGF23 go along with unchanged level of phosphate and PTH (65, 66). The advanced progression of CKD results in phosphate retention that increases FGF23 levels further on (67, 68). At the same time, PTH levels rise and 1,25D serum concentrations decrease to diminish phosphate absorption further on (68). The decline of 1,25D due to elevated FGF23 is prolonged via suppression of renal 1 α -hydroxylase, the enzyme that catalyzes the synthesis of 1,25D from the major circulating metabolite 25OHD, as well as induction of 24-hydroxylase, the enzyme responsible for production of 24,25(OH) $_2$ D $_3$ (69). Thus, reduction of intestinal calcium absorption due to decreased 1,25D levels in conjunction with low ionized calcium leading to pronounced increase of PTH level and ultimately in secondary hyperparathyroidism.

Thus, alterations to levels of FGF23, which progressively increase together with changes in the metabolism of phosphate, calcium, PTH and/or 1,25D in worsening renal dysfunction with CKD result in CKD-MBD. This complex clinical syndrome is characterized by abnormalities in bone and mineral metabolism as well as extra-skeletal calcification resulting in fractures and bone deformities and, most prominently, in poor growth (10, 70), which all of them contribute to enhanced risk of CVD, fractures and mortality across all stages of CKD. The pathogenesis of CKD-MBD is complex, involving regulatory mechanism in bone, kidney, heart and parathyroid glands.

FGF23 AND LVH IN CKD

In early CKD, circulating FGF23 levels rise exponentially and are up-to 1,000-fold enhanced in kidney failure (65, 66). Elevated FGF23 levels are associated with all-cause and CV mortality in the general population (71, 72) as well as in CKD patients (73), LV dysfunction and atrial fibrillation (AF) in patients without CV co-morbidities (74, 75), and the development of cardiac hypertrophy (76) and fibrosis (77). Thereby, cardiac remodeling was shown to be stimulated by activation of myocardial FGFR4 although

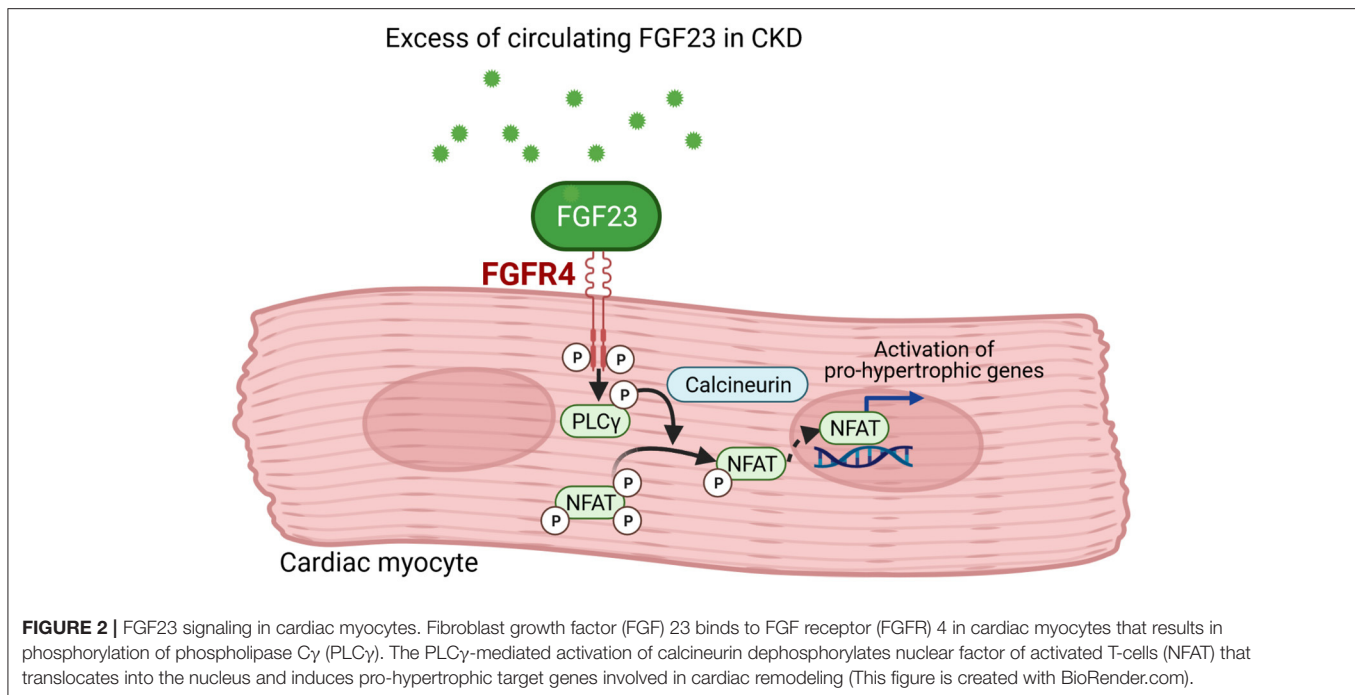


independent of α -Klotho (**Figure 1**) (78, 79). Higher FGF23 levels were further observed in stable ischaemic cardiomyopathy (72) and heart failure (HF) with reduced ejection fraction (HFREF) (80–82).

The role of FGF23 in the development of LVH in children with CKD was investigated intensively since the last decade. Thereby it was shown that FGF23 level are markedly increased in haemodialysis patients with prevalent concentric LVH (66, 83), while in a study cohort of 83 children with non-dialysis stages 3–5 CKD no significant relationship between circulating FGF23 and LVH was observed (84). However, the Chronic Kidney Disease in Children (CKiD) study enrolled children with mild-to-moderate pre-dialysis CKD, respectively, concluded that a high plasma FGF23 concentration above 170 RU/ml together with estimated GFR \geq 45 ml/min per 1.73 m² is associated with a higher prevalence of LVH (85, 86). Importantly, these studies differ in methods and number of enrolled children. Sinha et al. measured serum intact FGF23 in 83 children, whereas Portale et al. and Mitsnefes et al. measured C-terminal FGF23 plasma level in 419 and 587 children, respectively. This is controversial, since on the one hand intact FGF23 level are varying with a diurnal rhythm and have a high intraindividual variation (87). Furthermore, carefully handling is needed when processing K2-EDTA plasma, otherwise intact FGF23 will be unstable (88). On the other hand, intact FGF23 may reflect the biological relevance more than C-terminal FGF23 does (89). There is evidence, that the active full-length form is counter-regulated by the C-terminal fragments (90). Also, it was shown that the effect of dietary phosphate restriction on FGF23 has a greater impact on intact FGF23 than on the C-terminal form (91). The situation is complicated

further by the fact that the four commercially available FGF23 assays are not validated for clinical use and are not standardized (92, 93).

Mechanistically, it was shown that FGF23 directly induces hypertrophic growth of cardiac myocytes *in vitro* and cardiac hypertrophy *in vivo* that was abolished by inhibition of phospholipase C γ (PLC γ) or calcineurin, but not by the use of MAP kinase, PI3 kinase or Akt inhibitors. Also, the use of PD173074 to block all FGFRs reduced LV mass and the cardiac expression of genes associated with LVH (94). A few years later, FGFR4 was identified to be the main effector of FGF23 signaling in the heart (78) leading to the conclusion that cardiac hypertrophy induced by FGF23 is mediated by the FGFR4/PLC γ /calcineurin pathway that activate nuclear factor of activated T-cells (NFAT) and consequently pro-hypertrophic NFAT target genes (**Figure 2**). A second mode of action for FGF23's pro-hypertrophic properties could be the direct regulation of the sodium-chloride channel NCC in distal renal tubules by FGF23 rendering it to be a sodium-conserving hormone (95). A connection of FGF23, cardiac hypertrophy and the local RAAS in the heart is also discussed. In 5/6 nephrectomised rats as experimental model of uraemia, an increase in size of myocyte as well as enhanced cardiac fibrosis together with induction of cardiac *Fgf23* and RAAS-associated gene expression was overserved (23). Paricalcitol mediated downregulation of RAAS and NFAT, respectively, together with diminished FGF23 level could thus attenuate cardiac hypertrophy (96, 97). In a retrospective case-control study in 24 pediatric CKD patients with kidney failure the relevance of FGF23 on cardiac fibrosis was evaluated (98). Increased



collagen type I and III together with enhanced expression of pro-fibrotic growth factors and components of RAAS were observed, leading to the conclusion that FGF23 is induced by activated RAAS thereby promoting cardiac fibrosis. *In vitro*, FGF23-induced hypertrophic growth of isolated neonatal rat ventricular myocytes (NRVM) could be reversed by incubation with cyclosporine A, losartan and spironolactone (25). Furthermore, FGF23-mediated induction of TGF- β and CTGF in neonatal cardiac fibroblasts (NRCF) could be suppressed by losartan and spironolactone. Thus, leading to the conclusion that beside FGFR4/PLC γ /calcineurin signaling pathway, FGF23 promotes cardiac hypertrophy and fibrosis via activation of intra-cardiac RAAS.

During LVH, cardiac *Fgf23* expression is higher in cardiomyocyte-specific calcineurin A transgenic mice with normal *Fgf23* mRNA levels in bone (99). This phenomenon was also observed in an animal model as well as in humans with myocardial infarction (100, 101), indicating that an intra-cardiac synthesis of FGF23 may trigger a pathological cardiac phenotype in a paracrine manner. The latter is in line with a study in myocardial autopsy samples of pediatric patients with kidney failure showing in association of high cardiac FGF23 expression with LVH (79). Moreover, Leifheit-Nestler and Grabner et al. postulate in addition to FGF23 that the upregulation of FGFR4 in the myocardium of uremic rats further contributes to the development of LVH (102). Paradoxically, different mouse models of X-linked hypophosphatemia (XLH) as well as patients with XLH develop no cardiac hypertrophy although presenting high FGF23 level (103–105). The different clinical phenotype of XLH with its low serum phosphate and calcium level, normal renal function and no signs of atherosclerosis could

be an explanation for those findings. Interestingly, a recent study in mice showed that a conditional deletion of *Fgf23* in late osteoblast/osteocyte (*Fgf23^{fl/fl}/Dmp1-Cre⁺*) followed by inducing CKD using an adenine-containing diet did not prevent hyperparathyroidism. Rather increased phosphate level as well as more pronounced cardiac hypertrophy were observed compared to uremic controls leading the authors to the conclusion that elevated FGF23 level in CKD may have a protective role to maintain cardiac homeostasis (106). Taken together, both the latter study and the studies in XLH conclude that phosphate may be a key mineral for FGF23 to exert its cardiotoxicity. However, further studies need to investigate the relationship between high FGF23 levels and altered phosphate homeostasis.

Cardiac hypertrophy is often accompanied by myocardial fibrosis, an excessive proliferation of fibroblast resulting in stiffening of cardiac tissue thereby giving resistance to pressure overload, but also stimulating diastolic dysfunction. FGF23 was recently discovered to be involved in the development of cardiac fibrosis. In a rat model of cardiac hypertrophy by pulmonary artery banding, FGF23 expression was highly upregulated in cardiac myocytes. Myocytes then secreted FGF23 to promote the activation of fibroblasts together with TGF- β 1 and to transform fibroblasts into myofibroblasts via FGFR1 (107). Finally, FGF23 levels correlated with fibrosis in heart failure patients with preserved ejection fraction (HFpEF) (108). However, the expression of cardiac FGF23 did not correlate with the amount of cardiac fibrosis in pediatric patients with kidney failure (95). Thus, the impact of FGF23 on the development of cardiac fibrosis has to be investigated in future studies in more detail.

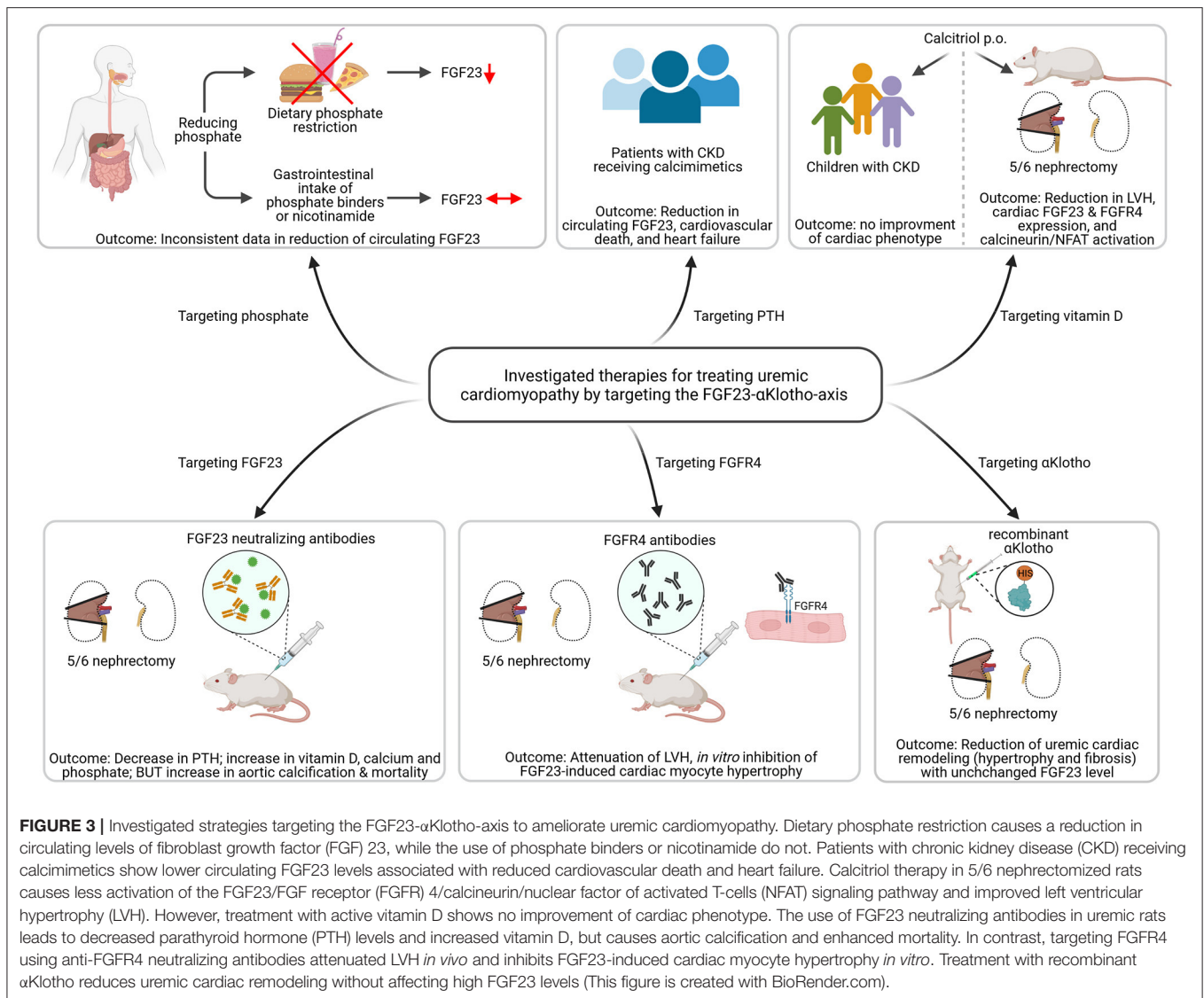


FIGURE 3 | Investigated strategies targeting the FGF23- α Klotho-axis to ameliorate uremic cardiomyopathy. Dietary phosphate restriction causes a reduction in circulating levels of fibroblast growth factor (FGF) 23, while the use of phosphate binders or nicotinamide do not. Patients with chronic kidney disease (CKD) receiving calcimimetics show lower circulating FGF23 levels associated with reduced cardiovascular death and heart failure. Calcitriol therapy in 5/6 nephrectomized rats causes less activation of the FGF23/FGF receptor (FGFR) 4/calcineurin/nuclear factor of activated T-cells (NFAT) signaling pathway and improved left ventricular hypertrophy (LVH). However, treatment with active vitamin D shows no improvement of cardiac phenotype. The use of FGF23 neutralizing antibodies in uremic rats leads to decreased parathyroid hormone (PTH) levels and increased vitamin D, but causes aortic calcification and enhanced mortality. In contrast, targeting FGFR4 using anti-FGFR4 neutralizing antibodies attenuated LVH *in vivo* and inhibits FGF23-induced cardiac myocyte hypertrophy *in vitro*. Treatment with recombinant α Klotho reduces uremic cardiac remodeling (hypertrophy and fibrosis) with unchanged FGF23 level.

THERAPEUTIC APPROACHES TO REDUCE FGF23'S CV COMORBIDITIES

The aim of any therapeutic approach in pediatric CKD is to delay the progression of kidney failure and to improve CVD outcomes. FGF23 is associated with adverse CV outcome in CKD-MBD and it is thought to be a promising biomarker and a target for future therapeutic approaches. One of the most important studies that directly targeted FGF23 by using anti-FGF23 antibodies failed to improve the CV outcome in uremic rats and even increased mortality due to high phosphate-mediated vascular calcifications (Figure 3) (109). Whether therapeutic use of anti-FGF23 antibodies in dialysis patients, relieved of chronic phosphate load by dialysis, is more effective in reducing cardiac remodeling remains an open question.

Several studies target dietary phosphate restriction to lower FGF23 levels (Figure 3). Thereby, dietary phosphate restriction

in healthy participants resulted in decreased intact FGF23 level, whereas phosphate-enriched diets increased intact FGF23 (110). The same findings were observed in studies of CKD and phosphate-restricted vs. phosphate-enriched diets (111, 112). However, it was further reported that C-terminal FGF23 was not changed regardless of the dietary phosphate content (113, 114). A recently published randomized clinical trial in stage 3b/4 CKD patients, the CKD Optimal Management with BInders and NicotinamidE (COMBINE) study, hypothesized that lowering phosphate level in early CKD prevents rising level of FGF23 and with that FGF23-associated morbidity and mortality (Figure 3). However, a 12 months therapy with lanthanum carbonate and/or nicotinamide failed to lower serum phosphate and FGF23 levels (115). The same was observed in other studies (116–118). Calcimimetics turned out to be more effective in lowering FGF23 and with that lowering mortality and CVD events significantly in patients with kidney failure (Figure 3) (119). However, further studies need to confirm the promising beneficial use of

calcimimetics on cardiac function in the future and to elucidate the exact molecular mechanisms of its possible cardioprotection.

Further studies included the treatment of Vitamin D deficiency in 5/6 nephrectomized rats with calcitriol that reduced the expression of FGF23 and FGFR4 in the heart inactivating calcineurin/NFAT signaling and thereby reduced the development of LVH (102). However, active vitamin D treatment failed to improve LVH in pediatric CKD patients (Figure 3) (120). Targeting FGFR4 with neutralizing antibodies attenuated LVH in animal models of CKD or high phosphate load by reducing cardiac remodeling without affecting FGF23 level (78). However, clinical studies on the therapeutic benefit of anti-FGFR4 antibodies in LVH are still pending. Treatment of uremic cardiomyopathy in rodents with recombinant α Klotho ameliorated LVH and fibrosis independent of high FGF23 synthesis (Figure 3), but again, clinical studies are lacking to prove the positive effects of Klotho therapy on the CV system (121).

Currently, FGF23 concentrations are not routinely measured in patients. One reason is the absence of reliable immunoassays for measurement of FGF23, which are validated for clinical use (93, 122). Another reason is the reduced stability of biologically active intact FGF23 when blood processing is delayed (123), thus making it difficult to apply its use in routine clinical work. It remains questionable if FGF23 is a good predictor for progression of CKD. So far, only one study in adults with CKD has shown a benefit of adding FGF23 to existing prediction models for CKD progression (124), whereas all other studies have thus far failed to show any advantage in risk prediction for CKD onset when including FGF23 (125–127). Nevertheless, for the prediction of all-cause mortality in CKD patients, FGF23 seems to be a better prognostic marker (125, 128). Regarding CV outcomes, studies remain inconsistent. Alderson et al. point toward FGF23 to be a good predictor of CV events in pre-dialysis patients (128). Besides, Emrich et al. suggest that inclusion of NT-proBNP into the prediction model eliminates the association between FGF23 level and CV outcome (129). However, there is evidence that measured FGF23 levels can nevertheless predict the accessibility

of patients to certain therapeutic approaches as shown for the treatment of patients with e.g., stable ischemic heart disease with angiotensin-converting enzyme inhibitor (130).

Experimental and clinical data reviewed here suggest it remains reasonable to consider that reducing elevated level of FGF23 is potentially a promising therapeutic pathway for reducing CVD in CKD in adult and children. Randomized clinical trials targeting the pathophysiology of FGF23-induced CVD are needed to help clarify the impact of FGF23 on LVH in CKD.

CONCLUSION

In summary, the scientific community gained a lot of knowledge about the regulation and effects of FGF23. Although FGF23 mainly regulates phosphate homeostasis, in adults as well as in pediatric CKD the levels of FGF23 are markedly increased with progressing kidney failure and high FGF23 levels are strongly associated with left ventricular hypertrophy. However, a direct link to other CKD associated CV abnormalities needs to be proven in pediatric patients. In fact, CV events e.g., cardiac arrest and arrhythmia, are the leading cause of death in children with CKD and a dysregulated FGF23 metabolism may additionally have detrimental effects on the cardiovascular system. Regardless, many findings are contradictory and large prospective clinical studies are needed to elucidate the exact pathological mechanisms of FGF23 induced CVDs in pediatric CKD.

AUTHOR CONTRIBUTIONS

AG performed literature research, drafted the manuscript, and designed the figures. MS critically discussed content of review and all revisions of the manuscript. DH critically discussed the content of the review and revised the manuscript. ML-N critically discussed the content of the review and revised the manuscript and the figures. All authors contributed to the article and approved the submitted version.

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