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CONTEMPORARY REVIEW

Clinical Potential of Targeting Fibroblast Growth Factor-23 and α Klotho in the Treatment of Uremic Cardiomyopathy

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ABSTRACT: Chronic kidney disease is highly prevalent, affecting 10% to 15% of the adult population worldwide and is associated with increased cardiovascular morbidity and mortality. As chronic kidney disease worsens, a unique cardiovascular phenotype develops characterized by heart muscle disease, increased arterial stiffness, atherosclerosis, and hypertension. Cardiovascular risk is multifaceted, but most cardiovascular deaths in patients with advanced chronic kidney disease are caused by heart failure and sudden cardiac death. While the exact drivers of these deaths are unknown, they are believed to be caused by uremic cardiomyopathy: a specific pattern of myocardial hypertrophy, fibrosis, with both diastolic and systolic dysfunction. Although the pathogenesis of uremic cardiomyopathy is likely to be multifactorial, accumulating evidence suggests increased production of fibroblast growth factor-23 and α Klotho deficiency as potential major drivers of cardiac remodeling in patients with uremic cardiomyopathy. In this article we review the increasing understanding of the physiology and clinical aspects of uremic cardiomyopathy and the rapidly increasing knowledge of the biology of both fibroblast growth factor-23 and α Klotho. Finally, we discuss how dissection of these pathological processes is aiding the development of therapeutic options, including small molecules and antibodies, directly aimed at improving the cardiovascular outcomes of patients with chronic kidney disease and end-stage renal disease.

Key Words: α Klotho ■ cardiorenal syndrome ■ FGF23 ■ fibroblast growth factor ■ growth factor ■ kidney ■ treatment

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) requiring dialysis are complex, chronic conditions with a combined prevalence of 10% to 15% of the adult population worldwide.^{1–3} Cardiovascular events and mortality increase exponentially with reduced estimated glomerular filtration rate (eGFR) independent of age, sex, and other risk factors.^{4–6} In the early stages of CKD, the risks of occlusive atheromatous disease are increased and account for the majority of cardiovascular events observed.⁷ Arterial atheroma remains an important modifiable pathophysiological process in CKD, as

evidenced by trials in early CKD showing benefit from lipid-lowering therapies in modifying the risk of atherosclerotic events.^{8–10} However, the same treatments appear much less effective in patients with advanced stages of CKD, including ESRD.^{10–12} As CKD worsens, there is a shift from atherosclerotic complications to morbidity due to heart failure and sudden cardiac death (SCD).^{7,13,14} Atrial fibrillation (AF) is also common, detected in up to 41% of patients requiring hemodialysis.¹⁴ The pathophysiological basis of these events is a unique cardiovascular phenotype consisting primarily of the development of uremic cardiomyopathy with

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ESRD	end-stage renal disease
FGF23	fibroblast growth factor 23
LV	left ventricular
LVH	left ventricular hypertrophy
SCD	sudden cardiac death

associated increased arterial stiffness and widespread atheroma.

The purpose of this article is to review the current state of the art on 2 newly postulated drivers of uremic cardiomyopathy, elevated circulating fibroblast growth factor-23 (FGF23) and reduced α Klotho, and discuss how recent insights into the pathophysiological processes has led to development of potential therapeutic options aimed at reducing the cardiovascular risk of patients with CKD/ESRD.

UREMIC CARDIOMYOPATHY

The term uremic cardiomyopathy arose in the 1980s with reports of common abnormalities in cardiac function and structure in patients with CKD/ESRD, including increased left ventricular (LV) mass and left ventricular hypertrophy (LVH); diastolic and systolic dysfunction; as well as profound myocardial fibrosis on histology.^{15–20} Uremic cardiomyopathy has been linked to conditions causing both heart failure and CKD, especially hypertension. Chronic stimulation of cardiac cells by renin, angiotensin, parathyroid hormone (PTH), cardiotonic steroids, and other uremic toxins, has also been proposed.²⁰ The severity of uremic cardiomyopathy as measured by LV mass is a powerful predictor of cardiovascular mortality probably as a result of the factors discussed below.

Increased LV Mass and Hypertrophy

Increased LV mass and LVH are common manifestations of uremic cardiomyopathy. Forty percent of patients with an eGFR <30 mL/min per 1.73 m² have LVH on echocardiography,²¹ increasing to \approx 80% in ESRD.^{22,23} In patients with CKD/ESRD, LVH is strongly associated with death; diastolic and systolic heart failure; and cardiac arrhythmias.^{22,23} However, LV mass is a continuous variable, with a graded relationship with adverse cardiovascular outcomes.^{24–28} It is also important to emphasize that cardiac structural changes occur early in the course of CKD, with a linear association between worsening renal function and a higher prevalence of LVH.^{29,30} While elevated blood pressure is an important determinant of LV mass,³¹ evidence

from both animal and human studies supports the presence of mechanisms that are independent of pressure overload and hypertension in driving cardiac hypertrophy in CKD/ESRD.^{32–36}

Diastolic and Systolic Dysfunction

Diastolic dysfunction is highly prevalent in patients with CKD, with over two thirds affected in CKD stages 2 to 4³⁰ and up to 85% in ESRD.³⁷ Diastolic dysfunction is strongly associated with increased LV mass and LVH,⁷ as well as myocardial fibrosis,^{20,38} and correlates with increased mortality.^{37,38} Furthermore, the presence of diastolic dysfunction is considered to be a major cause for the frequent presentation of hemodialysis patients with pulmonary edema or intradialytic hypotension, despite only minor changes in fluid status.^{7,38}

Overt LV systolic dysfunction, as manifested by reduced ejection fraction, is uncommon in predialysis CKD with a reported prevalence of 8% and no association with eGFR.^{17,30} However, several studies using echocardiography have shown changes in LV deformation in early stages of CKD, indicating the presence of subnormal LV systolic function.^{39–41} In ESRD, LV systolic dysfunction is very common, with a reported prevalence 10 to 30 times greater than in the general population.^{42,43}

Myocardial Fibrosis

It has been suggested that increased interstitial myocardial fibrosis may be the unifying pathophysiological process underlying uremic cardiomyopathy.⁴⁴ In the 1990s, a postmortem study found that myocardial fibrosis was present in 91% of CKD/ESRD patients without significant flow-limiting coronary lesions. The severity of fibrosis was related to the length of time on dialysis, but independent of hypertension, blood pressure, diabetes mellitus, or anemia.¹⁵ Over a decade later, Aoki et al.¹⁶ performed endocardial biopsies in 40 ESRD patients with reduced LV ejection fraction without coronary artery disease. The predominant pathologic findings were extensive interstitial fibrosis and cardiomyocyte hypertrophy and disarray.

Studying myocardial fibrosis in CKD/ESRD has been challenging given that myocardial biopsies are not without risk, especially in multimorbid patients and therefore are not always clinically and ethically justified.^{45,46} Late gadolinium enhancement cardiac magnetic resonance imaging, a validated noninvasive method, allows in vivo quantification of myocardial fibrosis in conditions such as myocardial infarction,⁴⁷ dilated⁴⁸ and hypertrophic cardiomyopathies.⁴⁹ This technique has also been used to characterize myocardial tissue in patients with ESRD demonstrating midwall patterns of late gadolinium enhancement consistent with replacement myocardial

fibrosis not associated with large vessel coronary artery disease.¹⁷ Noncontrast myocardial native T1 relaxation time, or T1 mapping, has emerged as a novel viable technique to quantify diffuse interstitial myocardial fibrosis in CKD/ESRD⁵⁰ correlating with histological interstitial fibrosis in a number of disease states, including cardiomyopathy and valvular disease.⁵¹ Indeed, native T1 times are increased in early CKD,¹⁹ increasing with worsening CKD stages⁵² and correlates with increased LV mass.^{18,53} Native T1 mapping offers an exciting opportunity to investigate novel mechanisms of cardiac fibrosis (eg, FGF23-mediated changes), in patients with CKD and in animal models.

FIBROBLAST GROWTH FACTOR-23 AND α KLOTHO

The hormone FGF23, first discovered in 2000, is a circulating growth factor secreted by osteocytes whose main physiological role is to increase urinary phosphate excretion.^{54,55} The 4 mammalian FGF receptors (FGFR1-4) are membrane-bound receptor tyrosine kinases.^{56,57} FGFR1 is suggested to be the primary FGF23 receptor in target organs—the kidneys and parathyroid glands.^{58–61} Crystallography studies clearly demonstrate that the presence of α Klotho is required for the efficient binding of FGF23 to FGFR1.⁶² α Klotho is a cell-surface protein, mainly expressed in the kidneys and parathyroid glands.^{63–65} In addition to the membrane-associated full-length protein, the ectodomain of α Klotho can exist in a soluble form.^{66–69} In the presence of membrane-bound α Klotho or soluble α Klotho, FGF23 can activate Fibroblast Growth Factor Receptor Substrate-2 (FRS2 α)/Ras/Mitogen-Activated Protein Kinase signaling (Figure 1).^{62,70,71} Soluble α Klotho, therefore, may act as a circulating FGF23 coreceptor in cells that do not express α Klotho. Such a mechanism has been reported in osteoblasts.⁷² However, its role in the heart is yet to be fully characterized as neither cardiomyocytes nor cardiac fibroblasts express α Klotho.⁵⁵ It is possible that FGF23 might act on these cells with circulating α Klotho as a cofactor. Treatment of cardiac myofibroblasts with full-length α Klotho resulted in upregulated proliferation and ERK phosphorylation, which was suppressed by FGFR1 antagonism.⁷³ This suggests the presence of FGFR1 in cardiac myofibroblasts for which soluble Klotho acts as a circulating co-receptor, although the authors did not comment on endogenous FGFR1/FGF23 expression.

FGF23 can also exert cellular effects via α Klotho-independent mechanisms.⁷⁴ FGF23 has been shown to stimulate phospholipase C γ (PLC γ)/calcineurin/nuclear factor of activated T-cells (NFAT) via FGFR4 in cells that lack α Klotho (Figure 1).^{74–77} Such increases

in PLC γ /calcineurin/NFAT signaling appear to be important in pathological, as opposed to physiological, cardiac hypertrophy.^{78,79} Clearly further mechanistic studies are warranted to delineate mechanisms that can be targeted therapeutically in patients with elevated FGF23 levels.

FGF23, α KLOTHO, AND KIDNEY DISEASE

One of the first clinically detectable signs of CKD is an elevation in serum FGF23, probably in response to increased extracellular phosphate, although the details of the stimulus and its detection are still unclear, with levels rising steeply as kidney function worsens^{54,80} (Figure 2). Indeed, elevations are observed as early as eGFR 75 mL/min per 1.73 m², long before increased concentrations in PTH or phosphate are observed.⁸⁰ Circulating FGF23 levels are 2- to 5-fold above the normal range in early/intermediate CKD, but can reach levels of 1000-fold above normal in ESRD.^{80–82} Increased FGF23 levels are also found in heart failure^{83–88} and AF,^{89–93} and are associated with all-cause and cardiovascular mortality in patients with and without CKD.^{87,88,94–99} Ongoing research therefore explores FGF23 as both a potential biomarker¹⁰⁰ and a causative factor for cardiac mechano-electrical dysfunction. However, effective quantification of circulating FGF23 is not currently standardized. Several FGF23 assay kits utilize differing detection techniques, epitope binding regions, analytical ranges and measurement units, making direct comparisons challenging.¹⁰¹

The kidney is the principal source of circulating soluble α Klotho.^{69,102} Its levels are downregulated in the presence of albuminuria,¹⁰³ inflammation,¹⁰⁴ and with the progression of CKD. α Klotho levels start to decline in CKD stage 2 and precede the elevation of FGF23, PTH, and serum phosphate.¹⁰⁵ Low levels of circulating α Klotho are associated with increased cardiovascular events and mortality in patients with CKD/ESRD.^{106–109} It is, therefore, conceivable that some of the adverse physiological effects that have been attributed to increased FGF23 may be either caused by, or compounded by, lower α Klotho (Figure 2). These mechanistic complexities require further investigation and need to be considered when developing FGF23/ α Klotho-directed therapies.

FGF23, α KLOTHO, AND LEFT VENTRICULAR MASS/HYPERTROPHY

The heart has been shown to respond to FGF23, increasing LV mass independently of blood pressure,

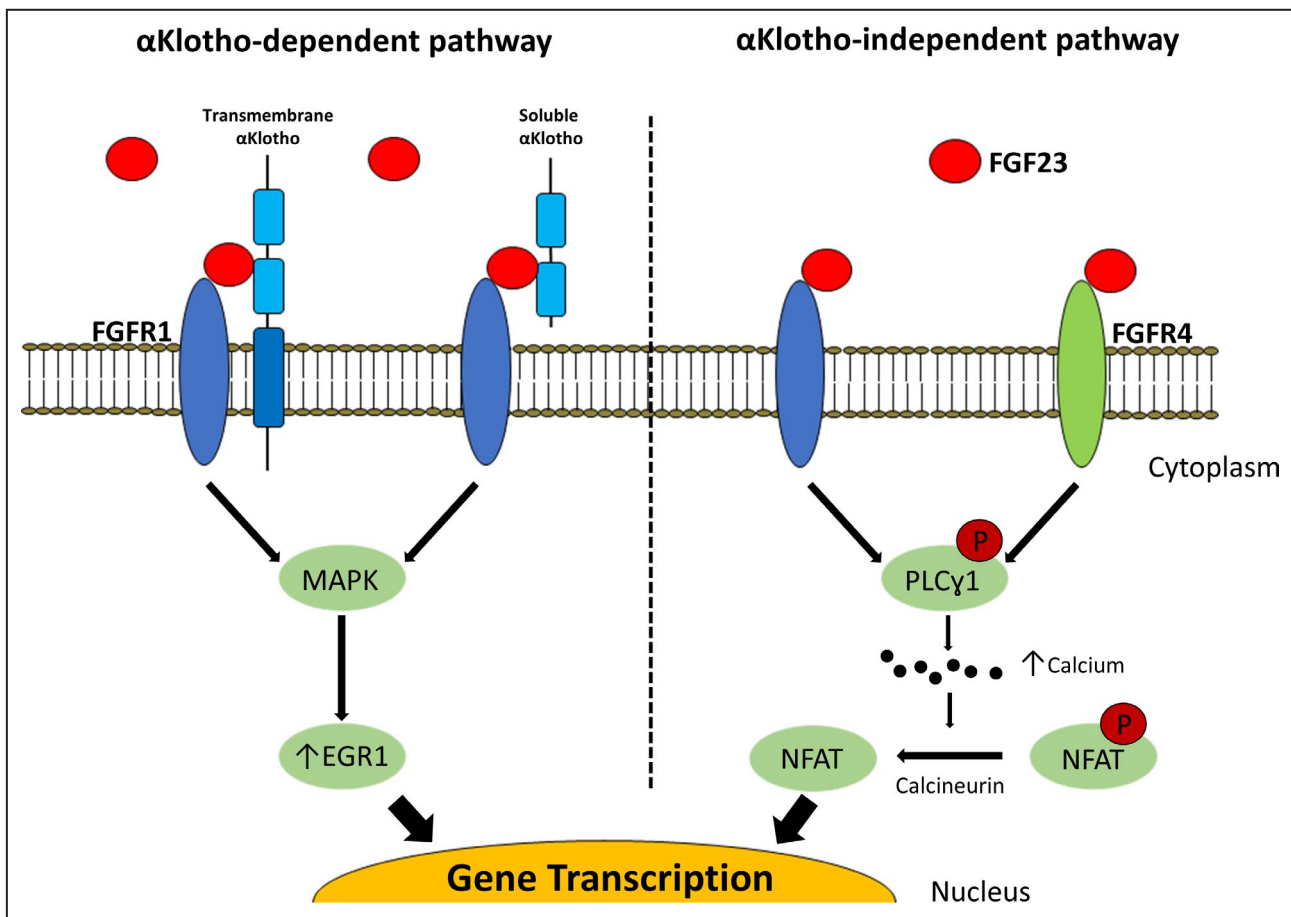


Figure 1. Potential mechanisms of fibroblast growth factor-23 (FGF23) signal transduction and signaling pathways.

Fibroblast growth factor-23 (FGF23) acts on cells that constitutively express fibroblast growth factor receptor-1 (FGFR1) and its coreceptor α Klotho. In cells that do not constitutively express α Klotho, such as cardiac myocytes and fibroblasts, circulating α Klotho is thought to perform a role similar to membrane-bound α Klotho. Circulating FGF23 can also bind to other FGFR1 and other FGFR independently of α Klotho. In cardiac myocytes, this is thought to be FGFR4 predominantly. The binding of FGF23 to an FGFR1- α Klotho complex activates MAPK (mitogen-activated protein kinase), upregulating early growth response protein-1 (EGR1), thereby modulating physiological gene expression. In the absence of α Klotho, FGF23 binding to either FGFR1 or FGFR4 activates phospholipase $\text{C}\gamma$ 1 (PLC γ 1), increasing intracellular calcium. This in turn activates calcineurin to dephosphorylate (P, in red) nuclear factor of activated T-cells (NFAT), which induces pathophysiological gene transcription.

promoting cardiac fibrosis and reducing LV systolic function in animal models.^{74,75,77,110,111} Elevations of cardiac FGFR4 and enhanced PLC γ /calcineurin/NFAT signaling have been observed in both animal models of CKD and in patients with CKD/ESRD.^{75,112–114} Several studies have shown that repetitive administration of FGF23 in wild-type mice, either intravenous or intraperitoneal, induced cardiac hypertrophy within 5 days.^{74,110,111} The signaling actions of FGF23 on the heart are still not fully characterized. However, several independent experimental approaches demonstrate the involvement of the α Klotho-independent FGFR4-PLC γ /calcineurin/NFAT signaling pathway in cardiomyocytes.^{74,75,77} On the other hand, independent studies demonstrate that α Klotho may be cardioprotective and that subnormal levels may be required for FGF23 to induce LVH.^{115–118} Although many of the studies indicate

that elevation of FGF23 and reduction in α Klotho are involved in the development of LVH, recent studies by Leifheit-Nestler and Slavic have not recapitulated these findings.^{119,120} Chronic FGF23 overexpression (via myocardial gene transfer), or genetic ablation of FGF23 or α Klotho on the background of transverse aortic constriction did not affect cardiac function or morphology.^{119,120}

FIBROBLAST GROWTH FACTOR-23, α KLOTHO, AND MYOCARDIAL FIBROSIS

Every third to fourth cell in the heart is a fibroblast. Fibroblasts produce the extracellular matrix in the heart and act as regulators of the cardiac interstitium.^{121,122} In the injured myocardium, inflammation and

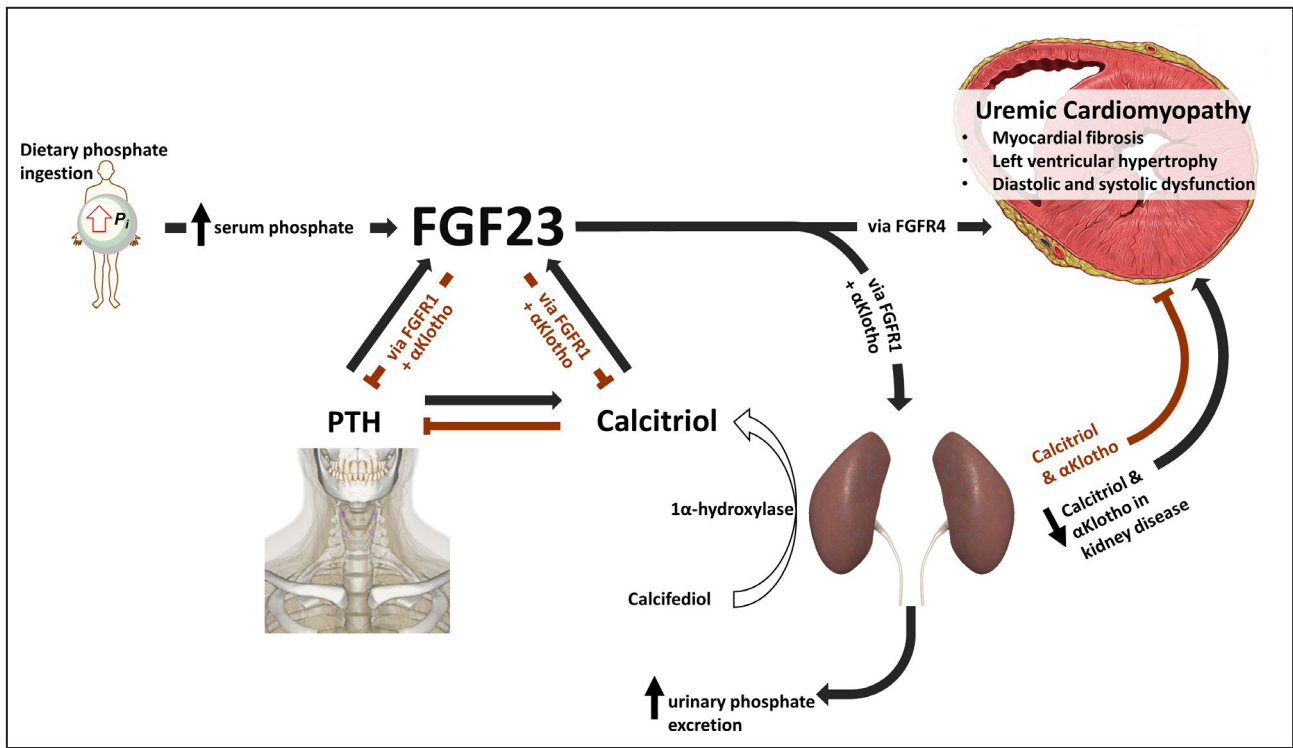


Figure 2. Dynamic interplay of fibroblast growth factor-23- α Klotho axis.

Dietary phosphate (Pi) ingestion and absorption leads to osteocytes secreting fibroblast growth factor-23 (FGF23). It is not clear how osteocytes detect circulating phosphate, but the sensing of calciprotein particles (nanoparticles consisting of calcium, phosphate, and fetuin A) has been proposed as a potential mechanism. Increased FGF23 leads to increased phosphate excretion by downregulating sodium-dependent phosphate cotransporter IIa/c, via mitogen-activated protein kinase signaling, in the renal proximal tubules expressing FGF-receptor 1 (FGFR1) in an α Klotho-dependent manner. In addition, FGF23 lowers renal vitamin D hydroxylation and decreases parathyroid hormone (PTH) secretion, both actions also being α Klotho-dependent, reducing calcium entry into the circulation. In the context of reducing renal function, FGF23 production increases to compensate for reduced renal phosphate excretion, decreased activated vitamin D levels, and rising PTH secretion. High levels of circulating FGF23 have been implicated in the development of uremic cardiomyopathy through α Klotho-independent mechanisms via either the FGFR1 or, more likely, FGFR4. Circulating α Klotho may mitigate some of the pathophysiological actions of FGF23 on the myocardium. However, the kidneys are the main source of circulating α Klotho and levels decrease with reducing renal function.

mechanical stress promote activation of fibroblasts to myofibroblasts, leading to maladaptive deposition of extensively cross-linked extracellular matrix, which drives increased stiffness and impaired mechano-electrical coupling of cardiomyocytes. This loss of cardiomyocyte coupling not only leads to attenuated cardiac function, but also provides a substrate for arrhythmias.^{123–126} Although recent studies have shown that FGF23 can activate cardiac fibroblasts, neither the underlying mechanism^{127,128} nor its role in the development of cardiac fibrosis are fully defined.^{127,129} As cardiac fibroblasts do not express α Klotho,^{74,102,113,114} the alternative pathway of α Klotho-independent FGF23 signaling through FGFR4-PLC γ /calcineurin/NFAT is likely to play a role (Figure 1). Future studies are required to examine which FGF receptors are expressed in cardiac fibroblasts, whether FGF23 contributes to cardiac fibrosis, and whether these mechanisms are dependent on α Klotho.

FGF23, α KLOTHO, AND CARDIAC ARRHYTHMIAS

Patients with CKD/ESRD are at increased risk of a wide spectrum of cardiac arrhythmias, including supraventricular tachycardias, particularly AF, and potentially lethal ventricular arrhythmias.^{14,130,131} All 3 components of uremic cardiomyopathy (increased LV mass/LVH; diastolic and systolic dysfunction; and especially myocardial fibrosis) are associated with arrhythmogenesis.^{131,132} While emerging evidence from implantable loop recorder studies is beginning to implicate bradyarrhythmias as the major cause of SCD in ESRD, rather than the previously assumed tachyarrhythmias, the precise causes of SCD in ESRD are the subject of investigation.¹⁴ α Klotho has been found in sinoatrial node pacemaker cells in mice¹³³ and α Klotho-deficient animals exhibit sinoatrial node dysfunction, and higher rates of bradyarrhythmias and SCD.¹³³

FGF23 disrupts intracellular calcium cycling within the cardiomyocyte, which is an important risk factor for arrhythmogenesis.^{134–136} Administration of FGF23 to rat ventricular cardiomyocytes caused calmodulin-dependent protein kinase II-dependent aberrant intracellular calcium, resulting in *in vitro* and *in vivo* arrhythmogenicity.¹³⁷ Administration of recombinant α Klotho or a pan-FGFR blocker prevented contractile dysfunction and reduced pro-arrhythmogenic activity.¹³⁷

Large observational studies in patients with CKD or AF and in the general population have found an association between elevated FGF23 and increased risk of developing AF.^{89,138} High FGF23 and low α Klotho levels are associated with periods of AF in patients with paroxysmal or persistent AF.⁹¹ Increased expression of FGF23, FGFR4 mRNA, and FGFR4 protein in the right atrial appendages of patients with AF has been reported and positively correlate with atrial collagen fraction. Collectively these data/studies suggest that FGF23/FGFR4 may play a role in promoting AF through atrial fibrosis.¹³⁹

REVERSING OR PREVENTING UREMIC CARDIOMYOPATHY BY TARGETING THE FGF23 AND α KLOTHO AXIS

Several therapies exist that directly or indirectly target FGF23, α Klotho, and abnormalities in bone metabolism. These are reviewed below and summarized in Table.

Targeting Phosphate Levels in the Body

Studies in healthy subjects have shown that circulating FGF23 levels are associated with dietary phosphate intake levels,^{140,141} and can be further increased by acute phosphate loading.¹⁴² This can be reduced, in the short-term, by aggressive reduction of dietary phosphate absorption^{141,143–146} and restriction.¹⁴⁷ Overall, in relatively short-term studies, noncalcium-based phosphate binders lower FGF23 in patients with CKD/ESRD, whereas calcium-based binders do not.^{148–152} Calcium is thought to be a secondary stimulus for FGF23 synthesis.^{153,154} However, lowering intestinal phosphate absorption with dietary change, phosphate binders, nicotinamide,¹⁵⁵ tenapanor,^{156–158} or combination therapy¹⁵⁹ produces only modest decreases in FGF23 that do not appear to be sustained in the long term.^{150,159} Whether this is because of increased total intestinal phosphate absorption by active phosphate transport,^{160–162} high pill burden, or intolerability of the medications is unknown.

Targeting Vitamin D

There is strong experimental data supporting vitamin D as a potential treatment for FGF23-mediated uremic cardiomyopathy. Calcitriol, the synthetic analogue of

vitamin D₃, blocks FGF23-induced activation of FGFR4 and cardiomyocyte growth.¹¹⁴ Increases in FGF23 expression, FGFR4-induced calcineurin/NFAT signaling, and LVH in 5/6 nephrectomized rats are reduced by calcitriol.¹¹⁴ Vitamin D also increases α Klotho expression.^{163,164} Observational studies demonstrate a survival advantage of vitamin D therapy in patients with CKD/ESRD despite raising calcium and phosphate levels.^{165,166} However, in a randomized, placebo-controlled study in patients with CKD stages 4 to 5, paricalcitol (activated vitamin D₂ analogue) treatment did not reduce LV mass.¹⁶⁷ Taken together, these data suggest combining vitamin D receptor activation with FGF23/FGFR4 signaling blockade could have beneficial synergistic actions on uremic cardiomyopathy.

Targeting Parathyroid Hormone

In patients on dialysis, the clinically available allosteric modulators (calcimimetics) of the calcium-sensing receptor, cinacalcet and etelcalcetide, are used to treat hyperparathyroidism and consistently lower circulating FGF23.^{168–172} In secondary analyses of the large and well-designed EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) trial, a >30% reduction in FGF23 in patients randomized to cinacalcet was associated with a reduction in cardiovascular mortality, SCD, and admissions for heart failure. The findings were amplified in those with a >50% reduction in FGF23.⁸⁷

In CKD patients not requiring dialysis, randomized-controlled trials of cinacalcet have reported significant reductions in FGF23, but also poor suppression of PTH as well as high rates of hypocalcemia and hyperphosphatemia.^{173,174} These actions are thought to negate many of the clinical benefits of calcimimetics and these agents are not licensed for use in patients with non-end-stage CKD. Nevertheless, cinacalcet remains a promising therapeutic option for the treatment of uremic cardiomyopathy in ESRD.

Other Indirect Targets

Intensified dialysis treatment,¹⁷⁵ renal transplantation,¹⁷⁶ reduced inflammation,^{147,177,178} and treatment of iron deficiency^{152,178–180} all reduce circulating FGF23 levels. Angiotensin-receptor antagonists,¹⁸¹ statins,¹⁸² peroxisome proliferator-activated receptor gamma agonists,¹⁸³ and exercise^{184,185} all increase α Klotho expression. The clear indications for these treatments remain and may well continue to give further insights into the pathophysiology of FGF23, but it is unlikely that these interventions will be used to directly target FGF23 and α Klotho.

DIRECTLY TARGETING FGF23

The mechanism(s) regulating FGF23 synthesis are poorly understood and no “phosphate-sensor” has

Table. Potential Therapies for Reversing or Preventing Uremic Cardiomyopathy by Targeting the Fibroblast Growth Factor-23 and αKlotho Axis

Treatment	Study	Species	CKD Status	Outcome
Targeting phosphate				
Dietary phosphate restriction	Burnett et al ¹⁴¹	Human	No renal impairment	Reduction in serum FGF23
	Antoniucci et al ¹⁴³	Human	No renal impairment	
	Moe et al ¹⁴⁴	Human	CKD Stage 3B to 4	
	Di Iorio et al ¹⁴⁵	Human	CKD Stage 3A to 4	
	Sigrist et al ¹⁴⁶	Human	No CKD & Stage 3A to 4	
	Rodriguez-Ortiz et al ¹⁴⁷	Rat	5/6 Nx	
Calcium-sparing phosphate binders (eg, sevelamer)	Oliveira et al ¹⁴⁸	Human	CKD Stage 3A to 4	
	Block et al ¹⁴⁹	Human	CKD Stage 3B to 4	
	Chue et al ¹⁵⁰	Human	CKD Stage 3	
	Rodelo-Haad et al ¹⁵¹	Human	ESRD on HD	
	Sprague et al ¹⁵²	Human	ESRD on HD/PD	
Nicotinamide	Shahbazian et al ¹⁵⁵	Human	ESRD on HD	
Tenapanor	Block et al ¹⁵⁷	Human	ESRD on HD	
	Labonte et al ¹⁵⁶	Rat	5/6 Nx	
Combination therapy with lanthanum and nicotinamide	Ix et al ¹⁵⁹	Human	CKD Stage 3B to 4	No sustained reduction in serum FGF23
Targeting Vitamin D				
Calcitriol	Leifheit-Nestler et al ¹¹⁴	Rat	5/6 Nx	Reduction in LVH, cardiac FGF23 & FGFR4 expression, and NFAT/calcineurin activation
	Leifheit-Nestler et al ¹¹⁴	Rat (NRVM)	n/a	In vitro reduction in FGF23-induced cardiomyocyte hypertrophy
Calcitriol & paricalcitol	Lau et al ¹⁶³	Mice	Partial renal ablation, phosphate loaded	Increase in serum αKlotho. No effect on renal/parathyroid αKlotho expression
Paricalcitol	Ritter et al ¹⁶⁴	Rat	5/6 Nx	Preservation of renal αKlotho, and increase in parathyroid αKlotho expression in uremia
Targeting parathyroid hormone				
Cinacalcet	Moe et al ¹⁶⁷	Human	ESRD on HD	Reduction in serum FGF23, cardiovascular death, SCD, and heart failure
	Charytan et al ¹⁷³	Human	CKD Stage 3A to 4	Reduction in FGF23 and PTH
	Chonchol et al ¹⁷⁴	Human	CKD Stage 3A to 4	Reduction in FGF23 and PTH; increase in hypocalcemia
Other indirect targets				
Intensified (daily) hemodialysis	Zaritsky et al ¹⁷⁵	Human	ESRD on HD	Reduction in FGF23 vs conventional hemodialysis
Renal transplantation	Barros et al ¹⁷⁶	Human	ESRD (½ on HD)	Reduction in FGF23 and phosphate
Treatment of iron deficiency (eg, ferric citrate)	Block et al ^{179,180}	Human	CKD Stage 3A to 5	Reduction in serum FGF23
Inhibition of inflammation (eg, NFκB inhibitor)	Rodriguez-Ortiz et al ¹⁴⁷	Rat	No renal impairment	Attenuation of LPS-induced FGF23 elevation
ATII receptor blockade	Yoon et al ¹⁸¹	Mice	CsA-induced renal injury	Increase in renal αKlotho expression
Statins (eg, atorvastatin, pitavastatin)	Narumiya et al ¹⁸²	Mouse (IMCD3)	n/a	In vitro upregulation of αKlotho mRNA expression
PPARγ agonist (eg, pioglitazone)	Yang et al ¹⁸³	Rat	No renal impairment	Increase in renal αKlotho expression
Exercise	Matsubara et al ¹⁸⁴	Human	No renal impairment	Increase in serum/plasma αKlotho
	Tan et al ¹⁸⁵			

(Continued)

Table. Continued

Treatment	Study	Species	CKD Status	Outcome
Directly targeting FGF23				
FGF23 neutralizing antibodies	Hasegawa et al ¹⁸⁹	Rat	Anti-GBM nephritis	Decrease in PTH; increase in vitamin D, calcium and phosphate
	Shalhoub et al ¹⁸⁸	Rat	5/6 Nx	In addition to above, increase in mortality & aortic calcification
FGFR antagonists				
FGFR4 antibody	Grabner et al ¹⁷⁵	Rat	5/6 Nx	Attenuation of LVH
		Rat (NRVM)	n/a	In vitro inhibition of FGF23-induced cardiac myocyte hypertrophy
Pan-FGFR antibody	Faul et al ⁷⁴	Rat	5/6 Nx	Attenuation of LVH
		Rat (NRVM)	n/a	In vitro inhibition of FGF23-induced cardiac myocyte hypertrophy
	Di Marco et al ¹⁹¹	Rat	5/6 Nx	Reduction in LV mass and fibrosis; improvement in ejection fraction
	Yanochko et al ¹⁹²	Rat	No renal impairment	Cardiac toxicity, hyperphosphatemia and ectopic calcification
Sodium-phosphate co-transporter PiT2 knockout	Bon et al ¹⁸⁷	Mice	No renal impairment	PiT2 regulates FGF23 synthesis; potential target for therapeutics
Directly targeting α Klotho				
Intravenous α Klotho transgene	Xie et al ¹⁹⁸	Mice	5/6 Nx±heterozygous Klotho	Attenuation of cardiac hypertrophy and fibrosis
Recombinant α Klotho	Hu et al ¹⁹⁶	Mice	Uni-nephrectomy + contralateral IR injury	Preservation of cardiac function, reduced hypertrophy and fibrosis; attenuation of renal fibrosis
	Yang et al ¹¹⁸	Mice	5/6 Nx	Inhibition of LVH and reduction in myocardial reactive oxygen species production
	Yu et al ²⁰⁰	Mice	No renal impairment	Attenuation of angiotensin II-induced cardiac hypertrophy, fibrosis, and dysfunction
	Suassuna et al ¹⁹⁹	Rat	5/6 Nx	Reduction of uremic cardiac remodeling (hypertrophy and fibrosis)
	Yang et al ¹¹⁸	Rat (NRVM)	n/a	In vitro inhibition of uremic toxin-induced (indoxyl sulphate) myocyte hypertrophy
Small molecule α Klotho modulators	King et al ²⁰¹	Human (HEK293)	n/a	In vitro elevation of α Klotho protein expression

5/6 Nx indicates 5/6 nephrectomized; anti-GBM, anti-glomerular basement membrane; ATII, angiotensin II; CKD, chronic kidney disease; CM, cardiomyocyte; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FGF23, fibroblast growth factor-23; FGFR, fibroblast growth factor receptor; HD, hemodialysis; HEK293, human embryonic kidney 293 cells; IR, ischemia-reperfusion; LPS, lipopolysaccharide; LV, left ventricle; LVH, left ventricular hypertrophy; n/a, not applicable; NFAT, nuclear factor of activated T-cells; NRVM, neonatal rat ventricular myocytes; PD, peritoneal dialysis; PPAR γ , peroxisome proliferator-activated receptor γ ; PTH, parathyroid hormone; and SCD, sudden cardiac death.

yet been found in mammals.^{186,187} Animal data have recently suggested that sodium-phosphate cotransporter PiT2 found in bone might regulate phosphate-dependent FGF23 synthesis and that targeting PiT2 could potentially reduce FGF23 synthesis.¹⁸⁷ The development of novel small molecules against PiT2 or the yet-to-be characterized PiT2-FGF23 pathway would give a proof of principle approach in animals for blocking FGF23 synthesis.

Indiscriminate FGF23 neutralization with monoclonal antibodies has been shown to worsen hyperphosphatemia, and increase vascular calcification and mortality in rat models of CKD.^{188,189} Use of anti-FGF23 monoclonal antibodies such as burosumab,

currently approved for the treatment of x-linked hypophosphatemia, causes severe side effects in patients with CKD by decreasing phosphaturia.¹⁹⁰ Analogous to the use of calcimimetics, total blockade of FGF23 may theoretically be of benefit in ESRD. From a clinical therapeutic and drug development perspective, the ideal target would be the FGFR responsible for the adverse cardiac effects of FGF23 and not FGFR1, which is critical for maintaining normal phosphate levels. Indiscriminate blockade of FGFRs, although shown to be effective at preventing the development of,¹⁹¹ and reversing LVH in rodents,⁷⁴ results in cardiac toxicity, hyperphosphatemia, and ectopic calcium deposition.¹⁹² Targeting cardiac FGFR4, especially

its α Klotho-independent activation of downstream signaling pathways, represents an exciting possibility. Indeed, FGFR4-blocking antibodies have been shown to inhibit FGF23-induced hypertrophy of isolated rat cardiomyocytes in vitro, and attenuated LVH in a 5/6 nephrectomy rat model of CKD.⁷⁵ Currently, very little is known about the specific FGFRs mediating the actions of FGF23 in nonmyocyte cardiac cells including fibroblasts, or whether blocking FGFR4 prevents or reverses cardiac fibrosis.¹²⁸ Several anti-FGF small molecule tyrosine kinase inhibitors and related compounds, monoclonal antibodies, and FGFR-analogues currently in development are mainly for use in oncology.¹⁹³ Development of these agents specifically for the treatment of uremic cardiomyopathy is, therefore, a real possibility.

DIRECTLY TARGETING α KLOTHO

In animal studies, administration of α Klotho protein has been shown to be effective in protecting against progression of CKD.^{194–197} Intravenous administration of a transgene-encoding soluble α Klotho reduces LVH in α Klotho-deficient mice.¹⁹⁸ Recombinant α Klotho also attenuates cardiac remodeling, fibrosis,^{195,199} reactive oxygen species production, and LVH¹¹⁷ induced by CKD in mice. In another study, α Klotho improved cardiac function and reduced hypertrophy and fibrosis in a mouse model of hypertension, although decreasing FGF23 expression.²⁰⁰ However, it remains unclear whether α Klotho is cardioprotective in the absence of increased FGF23.

Elevated FGF23 and decreased circulating α Klotho are observed in both aging and in CKD,^{116,197,198} leading to speculation that both CKD and the age-related decline in this and other physiological functions are caused in part by increased FGF23 and decreased α Klotho.⁵⁵ If true, this would assume soluble α Klotho acts as an inhibitor of α Klotho-independent actions of FGF23. Potential mechanisms include inhibiting FGF23/FGFR4 signaling by either binding first to FGFR4 or via an initial interaction with FGF23 (decoy receptor). An alternative mechanism involves FGF23 and FGFR4 forming a complex in the presence of soluble α Klotho but activating FRS2 α /Ras/mitogen-activated protein kinase rather than PLC γ /calcineurin/NFAT signaling (Figure 1).⁵⁵ Therefore, development of α Klotho-mimetics, through the development of protein–protein inhibitors, provides another potential therapeutic option. Trials of such agents to prevent progression of CKD are expected to start in the next couple of years.

To date, small molecule α Klotho modulators have been identified from a high-throughput screen of 150 000 compounds with those showing most

promise being α Klotho transcription activators. Furthermore, extracellular signal-regulated kinase phosphorylation in FGFR-transfected cells increased, demonstrating an effect on FGF23 signaling.²⁰¹ The recently discovered crystal structure of α Klotho:FGF23:FGFR1 in a 1:1:1 relationship has provided new insight into this dynamic interplay of factors and may reveal new therapeutic options.⁶² Although clearly at an early stage of exploration, the identification of new small molecules demonstrates the potential of drugs acting via α Klotho.

CONCLUSIONS

While patients with early stages of CKD are at increased risk of atherosclerotic complications, later stages of kidney disease are associated with heart failure and sudden death caused by uremic cardiomyopathy. Significant progress has been made over the past 2 decades in our understanding of, and ability to study the pathological basis of uremic cardiomyopathy using native T1 mapping. There are clear clinical data illustrating an association of increased FGF23 and reduced α Klotho with uremic cardiomyopathy in patients with CKD, and in heart failure and AF in subjects without known CKD. However, whether FGF23 has a truly causal relationship in uremic cardiomyopathy remains controversial. Characterization of the receptors and molecular pathways by which FGF23 might mediate LVH, cardiac fibrosis, and arrhythmias will help to identify therapeutic targets. Further work is required to identify the interplay between FGF23, cardiomyocytes and fibroblasts, and the effects of these interactions on the subsequent cardiac remodeling to reveal the molecular and cellular targets of FGF23 and α Klotho. Improved understanding is likely to enable the development of novel therapeutic interventions capable of effectively reducing the excess cardiovascular risk associated with CKD/ESRD, and perhaps even the risk of AF and heart failure in patients without CKD.

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