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The Role of Fibroblast Growth Factor-23 in Cardiorenal Syndrome

Csaba P. Kovesdy[a,b,c] and **L. Darryl Quarles**[a,b]

[a]University of Tennessee Health Science Center, Memphis, Tenn., USA

[b]Memphis VA Medical Center, Memphis, Tenn., USA

[c]Institute of Pathophysiology, Semmelweis University, Budapest, Hungary

Abstract

Abnormalities in chronic kidney disease-related bone and mineral metabolism (CKD-MBD) have emerged as novel risk factors in excess cardiovascular mortality in patients with CKD and end-stage renal disease (ESRD). The pathophysiological links between CKD-MBD and adverse cardiovascular events in this patient population are unclear. Hyperphosphatemia through induction of vascular calcifications and decreased active vitamin D production leading to activation of the renin angiotensin system (RAS) along with defects in innate immunity are purported to be the proximate cause of CKD-MBD-associated mortality in CKD. Recently, this view has been challenged by the observation that fibroblast growth factor-23 (FGF23), a newly discovered hormone produced in the bone that regulates phosphate and vitamin D metabolism by the kidney, is a strong predictor of adverse cardiovascular outcomes in patients with CKD and ESRD. Whether these associations between elevated circulating FGF23 levels and cardiovascular outcomes are causative, and if so, the mechanisms mediating the effects of FGF23 on the cardiovascular system are not clear. The principal physiological functions of FGF23 are mediated by activation of FGF receptor/α-klotho coreceptor complexes in target tissues. Elevated FGF23 has been associated with left ventricular hypertrophy (LVH), and it has been suggested that FGF23 may induce myocardial hypertrophy through a direct effect on cardiac myocytes. A direct 'off target' effect of FGF23 on LVH is controversial, however, since α-klotho (which is believed to be indispensable for the physiologic actions of FGF23) is not expressed in the myocardium. Another possibility is that FGF23's effect on the heart is mediated indirectly, via 'on target' regulation of hormonal pathways in the kidney, which include suppression of angiotensin-converting enzyme 2, Cyp27b1and α-klotho, which would be predicted to act on circulating factors known to regulate RAS, 1,25$(OH)_2$ D production and ion transport in the myocardium. Understanding of FGF23's pathophysiology and mechanisms of action responsible for its negative effects will be necessary to develop therapeutic strategies to treat CKD-MBD.

Keywords

Fibroblast growth factor-23; Chronic kidney disease; Physiology

L. Darryl Quarles, MD, University of Tennessee Health Science Center, 19 S Manassas Street, Memphis, TN 38104 (USA), dquarles@uthsc.edu.

Introduction

Patients with chronic kidney disease (CKD) and endstage renal disease (ESRD) continue to experience high morbidity and mortality, mostly as a result of extremely high rates of CV disease-associated complications [1]. Several novel risk factors have emerged to explain the excess morbidity and mortality seen in these patients including, among others, hyperphosphatemia, hypo- and hypercalcemia, hypo- and hyperparathyroidism and hyperphosphatasemia, which have been recently grouped together as CKD-related mineral and bone disorders (CKD-MBD). Recent discoveries suggest that the physiology and pathophysiology of CKD-MBD are significantly more complex, and that in addition to the well-described actions of calcium, phosphorus, vitamin D and parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23) also plays a key role in maintaining mineral and bone homeostasis, and in engendering complications related to CKD-MBD [2]. FGF23 is primarily a regulator of phosphorus and vitamin D homeostasis, with its main bone and mineral-related physiologic actions in the kidney to inhibit proximal tubule sodium phosphate cotransporter function and Cyp27b1 activity leading to phosphaturia and decreased circulating levels of $1,25(OH)_2$ vitamin D [2, 3]. In addition to its physiologic actions, FGF23 has also been shown to exert numerous other effects, which, perhaps together with its exaggerated physiologic effects, may explain why elevated FGF23 levels have been associated with a marked increase in mortality and morbidity in CKD, ESRD and kidney transplant recipients [4–6]. We will review the most recent discoveries in the physiology and pathophysiology of FGF23, discuss potential pathophysiologic links between elevated FGF23 levels and adverse cardiovascular events, and review putative therapeutic measures aimed at alleviating such adverse effects caused by FGF23.

Physiologic Regulation of FGF23, and Its Actions under Normal Circumstances

FGF23 is a 32-kDa protein produced in the osteoblasts and osteocytes in bone. FGF23 belongs to the FGF19 subfamily of secreted FGFs. Members of this subfamily due to a unique C-terminus are different from those of the other six subfamilies of paracrine and autocrine FGFs. FGF23 and other FGF19 family members are unable to bind heparan sulfate glycosaminoglycans, which would otherwise capture them in the extracellular matrix. As a result, FGF23 is released in the circulation and acts in an endocrine manner as a circulating hormone [7]. Crucially, the weak heparin-binding ability of FGF23 reduces its affinity for FGF receptors; rather, FGF23 and other circulating FGFs have a unique C-terminus, which interacts with α-klotho, a cofactor that is necessary for FGF23's interaction with and activation of FGF receptors [8]. The expression of α-klotho is limited to certain tissues, most notably to the kidney proximal and distal convoluted tubule [9], the choroid plexus in the brain, and in the parathyroid and pituitary glands, and to a lesser extent in the sinoatrial cells of the heart, placenta, skeletal muscle, urinary bladder, aorta, pancreas, testis, ovary and colon. Some studies have reported expression of α-klotho in human vascular smooth muscle cells, but this finding is controversial [10].

The primary target for FGF23 is the FGF receptor-α-klotho complex in the kidney leading to the primary physiologic actions of FGF23 to inhibit proximal tubular phosphate reabsorption via Na-dependent phosphate transporters, and suppress circulating $1,25(OH)_2$ vitamin D levels, in part by inhibiting Cyp27b1 (1α hydroxylase), and in part by activating Cyp24 (24-hydroxylase) [3]. Another physiologic effect of FGF23 contributing to the bone-kidney endocrine axis includes the suppression of PTH secretion, as shown by in vivo and in vitro studies [11]. However, this effect remains controversial, as clinically elevated FGF23 levels have been associated with higher, not lower PTH levels, and with refractory secondary hyperparathyroidism [12]. This incongruence may be explained by resistance to FGF23 effects on the parathyroid gland in uremia, perhaps due to downregulation of klotho [13]. In addition to its effects on phosphorus, vitamin D and PTH, FGF23 also suppresses klotho gene transcription in the kidney. Besides being an essential cofactor of FGF23, α-klotho is also released in the circulation, and has various metabolic effects which could thus result in further indirect effects of FGF23 on other organ systems [3]. The role of α-klotho in mediating FGF23 effects is also supported by the identical phenotype of α-klotho$^{-/-}$ and Fgf23$^{-/-}$ mice, both of which are characterized by hyperphosphatemia and elevated $1,25(OH)_2$ D levels. The extrarenal effects of FGF23 on tissues that express α-klotho is uncertain since the increased mortality observed in α-klotho$^{-/-}$ and Fgf23$^{-/-}$ mice is corrected by either phosphate restriction or inhibition of vitamin D receptor activation [14].

The main regulator of FGF23 is $1,25(OH)_2$ vitamin D, which stimulates FGF23 production, thereby creating a endocrine feedback loop regulating $1,25(OH)_2$ vitamin D production [15]. The role of other regulators remains controversial. Stimulation of FGF23 production by PTH was suggested [16], but could not be confirmed by all studies [17]. Recent studies suggest that bone mineralization and remodeling may have a direct effect on FGF23 production through complex mechanisms involving activation of FGF receptors in bone by putative paracrine factors [18]. FGF23 is also regulated by leptin, estrogen and glucocorticoids [2]. Interestingly, serum phosphorus level does not appear to have either an immediate or major effect on FGF23 production. Studies that examined the effects of oral phosphate intake on FGF23 have described either no effect [19], or described changes in FGF23 production in response to alterations in dietary phosphate intake after a lag time of up to 1 week [20], suggesting that phosphate may affect FGF23 indirectly as an additional component integral of bone mineralization. Degradation of FGF23 happens via cleavage into N and C terminal inactive fragments by enzymes that have not yet been identified [21]. Cleavage of intact FGF23 abrogates its effects by removing the binding site to the FGFR-klotho complex. Direct competitive inhibitory effects of the C-terminal peptide fragment have also been proposed, but the physiological significance is unclear [7]. Mutations of the RXXR cleavage sites underlie autosomal dominant forms of hereditary hypophosphatemia. The potential role of FGF23 degradation in acquired diseases of excess FGF23 is not well understood. FGF23 also requires O-glycosylation for secretion and processing [22].

The Role of FGF23 in CKD: Adaptation versus Maladaptation

FGF23 levels increase very early in the course of CKD, possibly representing the earliest manifestation of disordered bone-mineral metabolism [23, 24]. In response to the decrease in glomerular filtration rate in CKD, a typical constellation of gradually worsening elevated

FGF23, PTH and phosphorus, and lower serum $1,25(OH)_2$ vitamin D levels ensues [23, 25]. Of all these abnormalities, increases in FGF23 appear to display by far the greatest severity, with levels that can be up to 1,000-fold higher than normal in patients with ESRD. The primary stimuli for elevations of serum FGF23 levels in CKD are not clear. Excessive stimulation of FGF23 production and secretion by yet to be defined factors arising from the diseased kidney (possibly reflecting end-organ resistance to FGF23) and/or uremic effects on bone mineralization and the phosphate buffering capacity of bone play important roles in the early increased circulating levels of FGF23 in CKD. In spite of some evidence suggesting decreased degradation of FGF23 in CKD [26], there are no abnormalities of FGF23 clearance in animal models of CKD. Loss of α-klotho expression and end-organ resistance to FGF23 can also lead to secondary increments in circulating FGF23 levels and might also contribute to increases in FGF23 in CKD. In more advanced CKD, elevated PTH also plays a role in the increased circulating FGF23 levels, as evidenced by the reductions in circulating FGF23 following parathyroidectomy [27]. Treatment with active vitamin D analogues also contributes to increased circulating FGF23 concentrations in CKD [28]. Phosphate plays an unexpectedly minor role in regulating FGF23, as noted above. Indeed, recent studies show that a 900-mg phosphate diet plus use of a phosphate binder reduce FGF23 levels by 35%, whereas neither phosphate restriction nor binder alone significantly lowers circulating FGF23 concentrations [29]. Animal studies support the idea that increases in FGF23 levels are an adaptive mechanism aimed at trying to maintain neutral phosphate balance in the setting of declining filtration (i.e. enhanced phosphate excretion and reduced $1,25(OH)_2$ D production and consequent reduced gastrointestinal calcium and phosphate absorption). In this regard, either ablation of FGF23 or use of FGF23 blocking antibodies worsens hyperphosphatemia and decreases survival in animal models of CKD [30].

On the other hand, the chronic and extreme elevation in FGF23 levels observed in advanced CKD or ESRD may be maladaptive. Underscoring the clinical relevance of elevated FGF23 are numerous observational studies that have shown a significant association between elevated FGF23 levels and mortality in patients with ESRD, with non-dialysis-dependent CKD and with kidney transplants [4–6, 31–33], independent of other abnormalities that typically correlate with elevated FGF23 levels, such as hyperphosphatemia or secondary hyperparathyroidism. The higher mortality associated with elevated FGF23 may be induced by effects on the cardiovascular system, as suggested by numerous other observational studies linking elevated FGF23 to cardiovascular events [34], vascular calcification [35], left ventricular hypertrophy (LVH) [36–38], arterial stiffness and endothelial dysfunction [37], and increased levels of inflammatory markers [39].

At present, it is not clear whether elevated FGF23 and these associations represent causation (fig. 1) or whether FGF23 is a secondary marker of some other abnormality resulting from CKD. Moreover, not all studies have found an association between FGF23 and outcomes. For example, in a prospective cohort of patients with CKD from Japan, elevated intact FGF23 concentrations predicted incident cardiovascular events before starting dialysis, but did not predict events after initiation of dialysis treatment [40]. Resolving the uncertainties regarding FGF23 as a cardiovascular risk factor would be advanced by understanding the mechanism, whereby FGF23 might exert its untoward effects.

Mechanisms of Action Responsible for the Association of FGF23 with Adverse Outcomes

As detailed above, it is possible and even likely that the main mechanisms responsible for the adverse effects attributed to elevated FGF23 are cardiovascular in nature (fig. 1). The various other biochemical abnormalities that elevated FGF23 correlates with (such as hyperphosphatemia, hyperparathyroidism and hypovitaminosis D) have themselves been linked to adverse cardiovascular events, and hence it is possible that the associations of FGF23 with similar events are a reflection of these other underlying mechanisms, and FGF23 is merely a surrogate marker of CKD-MBD in general. In particular, high FGF23 levels may be a measure of primary loss of α-klotho functions, which itself has hormonal functions. Alternatively, FGF23, which suppresses α-klotho expression in the kidney, might result in decreased release of secreted klotho into the circulation. Circulating klotho has been shown to downregulate TRPC6 channels in the heart leading to a cardioprotective effect [41], as well as act as an antagonist for the Wnt/b-catenin pathway [9]. An increase in these pathways due to FG23-mediated reductions in circulating klotho could lead to LVH in CKD.

Notwithstanding the plausibility of this argument, it is possible that FGF23, itself, may have separate actions independent of CKD-MBD, and that these actions may be instrumental in engendering adverse cardiovascular effects. First, observational studies have suggested that the associations of FGF23 with adverse events are independent of other biochemical abnormalities characteristic of CKD-MBD (vide supra). Second, the degree of increase in FGF23 levels in ESRD overshadows that of any other component of CKD-MBD, making it less likely that FGF23 is merely a surrogate marker of the latter, and more likely that it could have various unrelated effects. Third, more recently studies have shown associations between higher FGF23 and mortality even in patients with normal kidney function [34], in whom the typical constellation of abnormal bone-mineral metabolism seen in CKD and ESRD is not present. Finally, recent discoveries regarding novel physiologic and pathophysiologic actions of FGF23 indicate that this molecule may have effects that have direct or indirect cardiovascular actions that are distinctly different from its effects on bone-mineral metabolism.

The renin-angiotensin system (RAS) plays a central role in increased cardiovascular morbidity and mortality through various effects such as worsened hypertension, baroreceptor dysfunction, sympathetic activation, diabetic nephropathy, progression of atherosclerosis, endothelial dysfunction, the inhibition of the fibrinolytic system and LVH [42]. Recently, a study examining the effects of FGF23 on the stimulation and suppression of various genes has indicated that FGF23 stimulates the RAS by suppressing angiotensin-converting enzyme-2 (ACE2) expression in the kidneys, independent of other abnormalities typical of bone-mineral disorders [43]. Activation of the RAS could thus be a potential link explaining the association of FGF23 with adverse outcomes such as LVH. That CKD-MBD might play a role in RAS-mediated mechanisms was also suggested by a recent secondary analysis of the Ramipril Efficacy in Nephropathy trial, showing that the renoprotective effects of ACE inhibitor therapy were only present in individuals with lower serum phosphorus levels [44].

This study did not examine FGF23 levels; hence, it is unclear if elevated FGF23 levels might have played a role in the observed effect modification by serum phosphorus.

A second possible mechanism directly linking FGF23 to adverse cardiovascular events is its putative effect on inflammation. Experimental data suggest that FGF23 increases production of inflammatory markers such as lipocalin-2, transforming growth factor-β and tumor necrosis factor-α [43]. Elevated FGF23 levels have also been associated with inflammatory markers in an observational study [39]. The exact pathways involved in the putative effects of FGF23 on inflammation are yet to be clarified.

Most recently, an intriguing hypothesis has been promoted, suggesting that not only could FGF23 have effects outside of its main CKD-MBD effects, but also that these effects could occur through direct actions of FGF23 on organs that do not express α-klotho. A number of experiments performed by a single group of investigators suggested that FGF23 could induce LVH in vitro and in experimental animals [38]. Cardiac myocytes do not express klotho; hence, these results directly challenge the physiologic paradigm that FGF23's effects on the FGF receptor are weak without the concomitant presence of α-klotho, even at high concentrations of FGF23 [8]. It remains to be confirmed whether or not such off-target effects by FGF23 are possible at concentrations as high as those seen in ESRD, but studies linking elevated FGF23 to LVH in patients with normal kidney function suggest that such effects may not simply be a result of extreme elevations in serum FGF23 levels.

Treatment of Elevated FGF23

Determining whether FGF23 has direct or indirect effects on the cardiovascular system, and whether its effects are through CKD-MBD or independent of it, are crucial in devising therapeutic strategies aimed at alleviating its adverse cardiovascular effects. Such interventions could on the one hand involve correction of CKD-MBD related biochemical abnormalities such as hyperphosphatemia, hyperparathyroidism, or especially hypovitaminosis D. Since there are to date no clinical trials that examined the effects of any kind of intervention aimed at correcting bone-mineral abnormalities on hard clinical end points in CKD or ESRD, it is unclear to what extent such interventions could be applied towards lowering FGF23 and result in improved clinical outcomes. Nevertheless, the administration of various medications used to treat bonemineral abnormalities has been shown to significantly affect FGF23 levels. Prolonged administration of sevelamer and lanthanum carbonate, two non-calcium-containing phosphate binders, has significantly lowered FGF23 levels [45–47]. Interestingly, calcium-containing binders did not seem to have a similar effect on FGF23 [45, 48], suggesting that the effects of phosphate binders may not be solely mediated by their effects on serum phosphorus, but that other effects (e.g. such as bone turnover) may also play a role. Supporting this hypothesis was another study showing that short-term administration of lanthanum carbonate had no effect on FGF23 levels in spite of significantly decreasing urine phosphorus levels [19].

Treatments used for secondary hyperparathyroidism have also been shown to affect FGF23 levels. Administration of active vitamin D leads to the stimulation of FGF23 production and higher FGF23 levels [49], whereas the administration of cinacalcet has been shown to

decrease FGF23 levels [49, 50]. Whether or not these divergent effects of the two classes of agents on FGF23 levels are clinically relevant or not, is unclear. Active vitamin D use has been consistently associated with lower mortality in observational studies of CKD and ESRD, but there are no clinical trials to corroborate their beneficial effects. A potential explanation for how active vitamin D could lead to higher FGF23 levels, yet still remain clinically beneficial, is via FGF23 exerting its negative effects through the lowering of $1,25(OH)_2$ D levels. This would also require that the pharmacological activation of vitamin D receptor beneficial functions would negate the putative negative effects of elevated FGF23. Further investigation of this hypothesis is needed. If elevated FGF23 levels are toxic, the biochemical profile associated with cinacalcet hydrochloride, which does not increase serum calcium, phosphate or FGF23, should portend more favorable outcomes compared to active vitamin D. A recent clinical trial comparing a cinacalcet-based strategy with an active vitamin D-based strategy, however, did not show a significant reduction in cardiovascular mortality [51].

Nevertheless, if FGF23 has actions on the cardiovascular system mediated by activation of RAS through suppression of ACE2 or stimulation of inflammation, then there are additional possibilities for the treatment of the adverse effects of excess FGF23. These could include inhibitors of the RAS (such as ACE inhibitors, angiotensin receptor blockers, or aldosterone receptor blockers), or various pharmacologic or other interventions aimed at decreasing inflammation. These intriguing possibilities will have to be examined in future studies. Since FGF23 may also have a direct effect on the myocardium (vide supra), preventing such an effect may require interventions using agents that can directly block the effects of FGF23 on target organs. Such agents have been shown in experimental studies to reverse the skeletal and biochemical abnormalities of excess FGF23 in experimental settings of X-linked hypophosphatemic rickets [52, 53] and CKD [30]. However, this intervention also resulted in the development of hyperphosphatemia, a significant increase in aortic calcification and increased mortality. These findings may mean that FGF23 in fact represents an essential regulatory mechanism, and completely abolishing it may be deleterious. Whether or not the use of interventions that selectively block only certain subtypes of the FGF receptor, or that only block FGF23 partially, could prove beneficial, remains to be seen.

Conclusions

FGF23 has emerged as a novel and powerful risk factor of mortality and cardiovascular events in patients with CKD and ESRD. FGF23 has been implicated in numerous physiologic processes that are independent from its main role as a regulator of bone-mineral homeostasis, and that may explain its strong association with mortality and other adverse outcomes independent of CKD-MBD. Clarification of FGF23's physiologic and pathophysiologic pathways is paramount for the development of new therapeutic paradigms aimed at improving outcomes in patients with CKD and ESRD.

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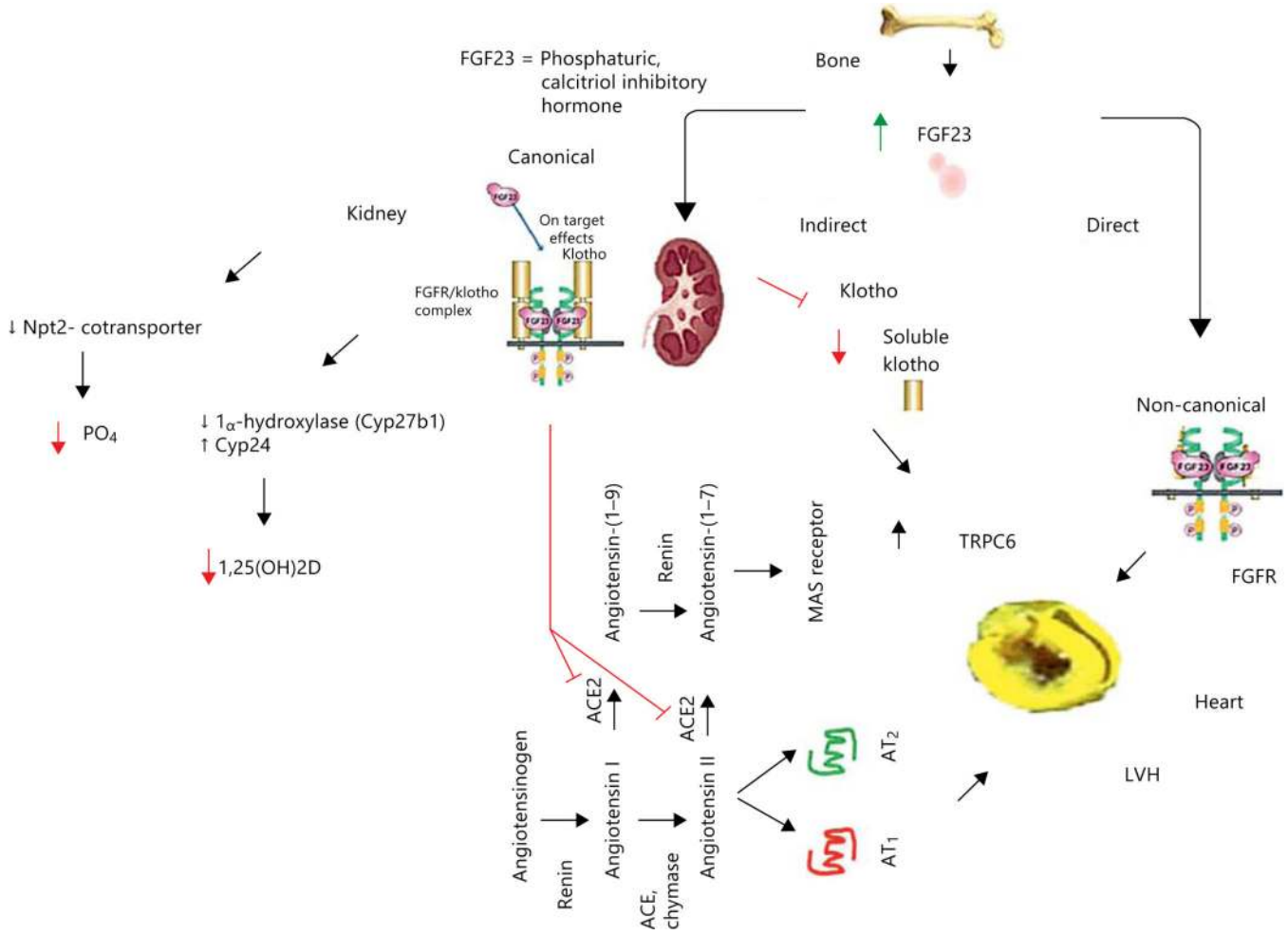

Fig. 1.

Mechanisms of FGF23 actions on the kidney and heart. FGF23 released from osteoblast/osteocytes in bone into the circulation targets transmembrane FGFR/α-klotho complexes in renal tubules (canonical pathway). This results in the suppression of sodium-phosphate cotransporters leading to phosphaturia, inhibition of Cyp27b1 and increase in Cyp24 leading to reductions in $1,25(OH)_2$ D production, inhibition of ACE2 expression, theoretically leading to activation of the RAS and suppression of α-klotho and possible inhibition of soluble secreted klotho. Both activation of RAS and suppression of secreted klotho could lead to LVH by activation of angiotensin receptors and upregulation of the calcium channel TRPC6 in the heart, respectively. Alternatively, FGF23 has been purported to directly stimulate FGF receptors in the heart leading to LVH.