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Simultaneous Management of Disordered Phosphate and Iron Homeostasis to Correct FGF23 and Associated Outcomes in CKD

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Abstract

Purpose of review—Hyperphosphatemia, iron deficiency and anemia are powerful stimuli of FGF23 production, and are highly prevalent complications of Chronic Kidney Disease (CKD). In this manuscript, we put in perspective the newest insights on Fibroblast Growth Factor 23 (FGF23) regulation by iron and phosphate and their effects on CKD progression and associated outcomes. We especially focus on new studies aiming to reduce FGF23 levels, and we present new data that suggest major benefits of combined corrections of iron, phosphate and FGF23 in CKD.

Recent findings—New studies show that simultaneously correcting iron deficiency and hyperphosphatemia in CKD reduces the magnitude of FGF23 increase. Promising therapies using iron based phosphate binders in CKD might mitigate cardiac and renal injury and improve survival.

Summary—New strategies to lower FGF23 have emerged, and we discuss their benefits and risks in the context of CKD. Novel clinical and pre-clinical studies highlight the effects of phosphate restriction and iron repletion on FGF23 regulation.

Keywords

iron; phosphate; anemia; chronic kidney disease; cardiovascular disease

INTRODUCTION

Chronic kidney disease (CKD) is a public health threat affecting approximately 37 million individuals in the United States (US)[1] and 750 million individuals[2] worldwide. Complex interactions between multiple biological mechanisms contribute to consequences of CKD,

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Conflicts of interest

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including disordered bone and mineral metabolism, and to associated risks of CKD progression and cardiovascular disease.

Elevated levels of the bone secreted hormone fibroblast growth factor 23 (FGF23) are a pervasive and early complication of CKD. While increased FGF23 levels help maintaining circulating phosphate in check in the early stages of the disease, FGF23 excess may contribute to kidney disease progression, cardiovascular events and death in CKD patients. This supports the rationale to design novel therapeutic strategies to lower FGF23 in CKD, but this approach requires more thorough understanding of the unknown mechanisms that cause FGF23 elevation in CKD, as well as the spectrum of disorders associated with excess FGF23.

Hyperphosphatemia contributes to higher FGF23 levels in the late stages of CKD, but does not drive the initial increase in FGF23, because increase in FGF23 occurs prior to changes in serum phosphate. Data from our group and others suggest that iron deficiency (ID) and anemia, which are common and early consequences of CKD, are novel mechanisms that stimulate FGF23 production[3–6]. In addition, hyperphosphatemia and iron deficiency can act in tandem with FGF23 to accelerate disease progression and development of negative outcomes[7–9]. Thus therapies that simultaneously reduce serum phosphate and treat iron deficiency may have a better chance of success in reducing circulating levels of FGF23 and improve clinical outcomes in CKD.

We recently showed that administration of ferric citrate, an iron based phosphate binder, to Col4a3^{KO} mouse model of progressive CKD had the potential to lower serum phosphate, correct iron deficiency and anemia and lead to a significant decrease in circulating FGF23 levels[10].

In addition, simultaneous corrections in phosphate, iron and FGF23 in CKD improved cardiac and kidney function, delayed CKD progression and resulted in prolonged lifespan[10]. This strongly suggests that combined management of iron and phosphate reduces FGF23 and is an effective therapy to improving clinical outcomes in CKD.

In this review, we will summarize recent findings highlighting the multifactorial roles of FGF23 in CKD, and the consequent multifactorial improvement that patients could benefit from FGF23 correction associated with phosphate and iron.

Physiological and pathological effects of FGF23

Under physiological conditions, FGF23 stimulates phosphaturia and reduces the efficiency of phosphate absorption in the gut by impairing production and accelerating the degradation of 1,25-dihyroxyvitamin D levels, thereby maintaining normal phosphate homeostasis[11–14]. Although in CKD elevated FGF23 maintains normal serum phosphate, this compensation is ultimately maladaptive leading to vitamin D deficiency and secondary hyperparathyroidism[14]. In addition, excess FGF23 is associated with increased risk of mortality across all stages of CKD and is independently associated with increased risk of heart failure[15]. Indeed, FGF23 has a pathogenic role in the development of left ventricular hypertrophy (LVH)[16, 17], and/or impaired cardiac function[10, 18]. These findings underscore

the necessity of understanding both FGF23 function and regulation which should lead to therapies designed to reduce FGF23 excess in CKD.

Balance of FGF23 transcription and cleavage

Circulating FGF23 levels are regulated by a balance between *Fgf23* transcription and FGF23 cleavage[4, 5]. In the circulation, FGF23 is detected as a full-length intact bioactive protein (iFGF23) and as cleaved N- and C-terminal FGF23 derived peptides. Poorly defined subtilisin-like proprotein convertases cleave FGF23[19], and GalNAc transferase 3 (GALNT3) protects newly synthesized FGF23 from cleavage, by O-glycosylation of the cleavage site[20]. FGF23 transcription and cleavage can be indirectly assessed non-invasively in vivo by using two different commercially available assays: the C-terminal FGF23 assay (cFGF23), which captures both intact FGF23 and FGF23 C-terminal peptides, and the intact FGF23 assay (iFGF23), which exclusively detects iFGF23[21]. The ratio between iFGF23 and cFGF23 can be used as a surrogate marker for FGF23 cleavage[4] and at homeostasis this ratio is approximately 40%[4, 18].

Regulation of FGF23 production

FGF23 production is regulated by local bone factors that modulate turnover and mineralization and systemic factors, such as phosphate, that control mineral metabolism[22], increase *Fgf23* transcription and lead to elevated levels of iFGF23[23, 24]. In addition to these classical factors, we and others recently discovered that iron deficiency and EPO also increase transcription of *Fgf23*[4–6, 25, 26]. In sharp contrast to classical FGF23 stimuli, in patients and animals with preserved kidney function, these novel regulators also increase FGF23 cleavage[4–6, 25, 26], leading to secretion of FGF23-derived peptides. However, in CKD, where FGF23 cleavage is impaired, iron deficiency may contribute to the rise of biologically active iFGF23 and increase the burden of the disease[4, 6, 10] (Figure 1).

Phosphate and FGF23: an old relationship

Extracellular Pi is a signaling molecule[27], but the direct effects of phosphate on FGF23 production in bone and bone cells remain unclear and are context dependent. The sodium phosphate co-transporter *Slc20a2* or *Pit2* may be the phosphate sensing mechanism in bone cells[28]. Alternatively, phosphate may regulate FGF23 production by increasing FGFR1 signaling[29], already known to increase *Fgf23* transcription[30, 31]. In these settings, phosphate may also increase FGF23 protection against proteolytic cleavage, by increasing Galnt3 expression and FGF23 O-glycosylation at the cleavage site[29]. However, suppression of *Slc20a2* increases *Fgf23* expression[28] and animals with global deletion of *Galnt3*, can still modulate *Fgf23* transcription and even FGF23 processing in response to phosphate[32]. While these mechanisms illustrate several phosphate related effects, they fail to capture the full picture of FGF23 induction by phosphate, which likely combines multiple local, bone related and distant physiological effects.

Nevertheless, phosphate loading increases FGF23 levels in both humans and animals[23, 33]. Thus, reducing phosphate levels in CKD, should lower FGF23 by addressing a root cause of its elevation. Indeed, lowering FGF23 without sacrificing normal phosphate homeostasis is imperative given that patients with elevated serum phosphate levels are at high risk of

developing end stage kidney disease (ESKD), coronary artery calcification, cardiovascular disease and mortality. FGF23 phosphaturic effects are conserved in early CKD, where increased FGF23 maintains serum phosphate levels by increasing urinary phosphate excretion[34]. In later stages of CKD, although FGF23 cannot maintain serum phosphate balance, FGF23 mitigates hyperphosphatemia, and studies showed that deletion of FGF23 or administration of anti-FGF23 antibodies to animals precipitated severe hyperphosphatemia that resulted in diffuse arterial calcification and early mortality[35, 36].

Focusing on addressing phosphate alterations only, in order to reduce FGF23 in CKD has led however to mixed results. Reduction of the phosphate-to-protein ratio in the diet decreased serum phosphate but failed to correct FGF23 levels in ESKD patients over a short time period[37]. Nicotinamide, which inhibits the intestinal NPT2b expression *in vivo* and lowers serum phosphate levels in ESKD patients[38–42], has only led to minor reductions in FGF23 in short term studies or showed no benefits in lowering phosphate or FGF23 in larger, long term studies[43]. Several phosphate binders, such as sevelamer and lanthanum carbonate, currently used to correct hyperphosphatemia in patients with advanced CKD, also failed to effectively decrease intact FGF23 in stage 3–4 CKD patients[43–45]. Thus solely targeting phosphate has had inconsistent and limited impact in preventing FGF23 elevations and FGF23 related outcomes in CKD.

Anemia, iron and FGF23

Like phosphate, iron is a critical element in mammal physiology, mostly for the synthesis of hemoglobin, myoglobin, and iron-containing enzymes. The predominant clinical manifestation of iron deficiency is anemia and at homeostasis, a tight control of iron levels is critical to maintain normal erythropoiesis and red blood cells (RBC) function. A link between iron and FGF23 regulation was first reported in 2011[3, 5, 46]. In iron deficient patients and mice with normal kidney function, iron deficiency increased FGF23 production, but this was associated with increased proteolytic cleavage to yield FGF23 cleavage peptides[3, 5, 46]. Several studies have also shown that reduced iron leads to similar effects in culture[4, 5]. In addition to iron deficiency per se, erythropoietin (EPO) which is secreted in vivo in response to anemia, also increases FGF23 production and cleavage[25, 26], triggering a response similar to iron deficiency. However, in patients and animals harboring mutations at the FGF23 cleavage site[47], which stabilize FGF23 and cause autosomal dominant hypophosphatemic rickets (ADHR), iron deficiency increases FGF23 transcription and results in excess iFGF23 that is protected from cleavage, leading to functional consequences of hypophosphatemia, vitamin D deficiency, rickets and osteomalacia.[3, 5, 46]

FGF23 and anemia of CKD

True iron deficiency (a deficiency of total body iron) and functional iron deficiency (inadequate circulating iron despite normal or elevated body iron stores) are prevalent in CKD[48]. Anemia is also a common complication of CKD, which becomes nearly universal as CKD progresses.[49] Although anemia is of multifactorial origin, limited iron bioavailability and an insufficient production of endogenous EPO by the injured kidneys to meet the erythropoietic demands are the major drivers. Given that CKD is analogous to ADHR in that it leads to a state of impaired FGF23 cleavage[4, 50], ID, anemia or the use of EPO or EPO-

stimulating agents (ESA) to cope with the relative EPO deficiency in CKD, have the potential to increase not only total cFGF23 but also iFGF23 in CKD.

Efforts to correct iron deficiency and/or anemia have also had mixed benefits on FGF23 production in CKD, and similar to phosphate interventions, may also be context dependent. Studies of intravenous (IV) iron administration reported a large variability in FGF23 response to iron therapies[51–57]. These effects may depend on compound, dose, duration, tolerability of the compound, and comorbidities.

Something old, something new: combined effects of phosphate and iron on FGF23 production

New emerging iron-based phosphate binders for the simultaneous management of hyperphosphatemia, iron deficiency and anemia in CKD might achieve a better control of FGF23 in CKD. One such a compound is ferric citrate (FC), which is commercialized in the United States as Auryxia (Akebia Biopharmaceuticals, Boston, MA, USA), and is effective in correcting hyperphosphatemia and iron deficiency in CKD[10, 58]. By targeting these independent mechanisms of FGF23 production, FC treatment reduced both cFGF23 and iFGF23 levels in two different experiments in Col4a3^{KO} mice with CKD[10]. Our studies also suggest that reducing FGF23, in addition to correcting iron and phosphate balance, might be more beneficial to correct anemia. Indeed, FGF23 is also a risk factor for CKD patients to develop anemia[59] and FGF23 excess could explain the relative EPO deficiency seen in patients with CKD[60]. Given FGF23 pro-inflammatory effects[61], which accentuate functional iron deficiency in CKD[62], reducing FGF23 might also lead to better management of iron stores, thus breaking a potential feed-forward loop of FGF23 stimulation. Consistent with these hypotheses, we found that, animals fed a 5% FC enriched diet, showed lower inflammatory markers and increased circulating EPO[10].

Cardiovascular impact of ferric citrate treatment in CKD

As terminally differentiated cells, cardiac myocytes' primary response to stress is hypertrophy. Initially adaptive, chronic myocardial stress leads to pathological left ventricular hypertrophy, which is the major CKD-related CVD event, a key mechanism of heart failure and ultimately death[63, 64]. Hyperphosphatemia has long been recognized as a risk factor for CVD in patients with ESKD and earlier stages of CKD[8, 65], however, more recently, FGF23 has emerged as the major molecular mechanism linking phosphate to increased CVD risk[16, 17].

FGF23 induces hypertrophic growth of cardiac myocytes in vitro and LVH in rodents[16, 17] suggesting that FGF23 represents a novel therapeutic target for attenuating LVH and heart failure in CKD[18, 66]. Consistent with these observations, CKD mice treated with FC which resulted in reduced FGF23 also show a net improvement in cardiac function[10], but corrections of phosphate and iron may also contribute to this improvement. Indeed, hyperphosphatemia alone, independently of FGF23, results in arterial calcification and early mortality[67]. Conversely, iron deficiency and anemia contribute to the development of cardiovascular outcomes[68–70]. Thus, whether the cardiovascular benefits of FC treatment are partially mediated by the increase in circulating iron, correction of anemia or reduced

phosphate requires further study. Nonetheless animal studies show that FGF23 reduction in CKD, consistently leads to improvement of heart disease[10, 66]. The pro-hypertrophic effects of FGF23 on cardiac myocytes are mediated by FGFR4/PLCγ/calcineurin/NFAT signaling[16, 17], and our studies suggest that activation of Ras/mitogen-activated protein kinase (MAPK) by FGF23 might lead to development of systolic dysfunction in mice[10]. A pathological FGF23 signaling through FGFR3, the highly expressed FGFR3 isoform in CKD mice[18, 71], might be responsible for the onset and progression of systolic dysfunction. These effects are also potentiated by phosphate, given that administration of phosphate to mice rapidly induces cardiac MAPK activity and increases FGFR3 expression[10]. Thus FGF23 and phosphate reduction following FC treatment attenuates CKD associated systolic dysfunction[10]. It is also probable that increased iron and correction of anemia might also play a role in the improvement of cardiac function[72, 73] (Figure 2) but additional studies are needed to confirm these effects.

Clinical perspectives: a silver bullet for CKD progression?

Despite current therapies, CKD patients remain at high risk for progression toward ESKD, and alternative renoprotective treatments that prevent further kidney function decline or reverse the course of the disease are needed. Most interestingly, FC treatment of mice with early CKD also resulted in marked improvement of kidney morphology and function, but had no effect on CKD progression when treatment was initiated later in the course of CKD[10]. Hyperphosphatemia[74, 75] and excess FGF23[76, 77] have long been recognized as risk factors for CKD progression. FGF23 is an independent predictor of progression of kidney disease in both adults and children with CKD[78, 79], but several animal studies show that decrease of FGF23 in CKD has no immediate benefit[66] or further reduces kidney function in rodents[35]. In contrast, phosphate restriction in several experimental models[80–82] reduces markers of tubular injury and fibrosis, slowing the progression of the renal damage and delaying the appearance of ESKD. Thus, by aggravating hyperphosphatemia, reduced FGF23 might accentuate the onset and severity of CKD, and higher FGF23 might have a renoprotective effect in CKD[35]. However, alternative mechanisms may explain the underlying association between FGF23 levels and CKD progression. FGF23 may promote renal sodium absorption[83] and suppression of angiotensin-converting enzyme 2 (ACE2)[61], increasing blood pressure and the risk of faster CKD progression[84]. Finally, FGF23 also increases the total kidney phosphate burden, by increasing phosphaturia, which may also predict kidney disease progression[85]. Thus, this further emphasizes the need of simultaneous phosphate and FGF23 control, in early CKD, in order to slow CKD progression.

Correction of anemia and iron deficiency could also have an impact CKD progression[86], but the renoprotective effects are more subtle[87] and disputed, compared to the impact on cardiovascular disease. While reduced oxygen delivery could further impair kidney function, correction of anemia does not profoundly impact the rate of CKD progression[88]. However, it is unknown if the lack of robust and reproducible benefits on renal function, are due to the either lack of effects of increased hemoglobin (Hb) or adverse effects of high dose ESAs[89, 90]. Similarly, iron supplementation shows lack of effects on kidney function of either oral or IV iron administration in CKD[91, 92], despite increased levels of kidney injury markers observed in infants and children with IDA[93, 94] which are corrected by iron therapy.

Nevertheless, increase in transferrin saturation following treatment of CKD mice with FC might have an important impact in slowing kidney disease progression[10]. Thus, combined reductions of phosphate, FGF23 and correction of anemia and iron balance (Figure 2) might explain why FC treatment resulted in lower rates of death or the progression to dialysis, lower rates of hospitalization, and fewer hospital days in a single-center pilot study of patients with advanced CKD[95]. Additional large multi-center clinical trials are needed to confirm these exciting preliminary findings.

CONCLUSION

CKD is a public health epidemic requiring the development of new ways to prevent and treat CKD progression and associated CVD, which is critical for reducing the overwhelming mortality in affected patients. Comprehensive investigative efforts in clinical and basic research established that reductions of FGF23, a mediator of CVD in CKD, combined with correction of hyperphosphatemia and iron deficiency may provide a potential therapeutic approach to delay CKD progression, improve cardiac function and ultimately increase lifespan in CKD. Although further studies are required to determine the individual mechanisms of end-organ injury inflicted by exposure to FGF23, phosphate and iron, including dose and duration, the functional effects of these findings can serve as the foundation for novel scalable multifactorial therapeutic strategies to be tested in future studies aimed at improving outcomes in patients with CKD.

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KEY POINTS

1. Greater long-term exposure to elevated FGF23 levels leads to increased risks of cardiovascular disease and death in CKD.
2. Hyperphosphatemia, iron deficiency and anemia in CKD contribute to excess circulating FGF23, development of cardiac disease and premature death.
3. Corrections of disordered phosphate and iron metabolism in CKD dramatically reduce FGF23 levels.
4. Simultaneous corrections of hyperphosphatemia, iron, anemia and FGF23 result in marked improvement in kidney and cardiac function and result in prolonged lifespan in animal models of CKD.

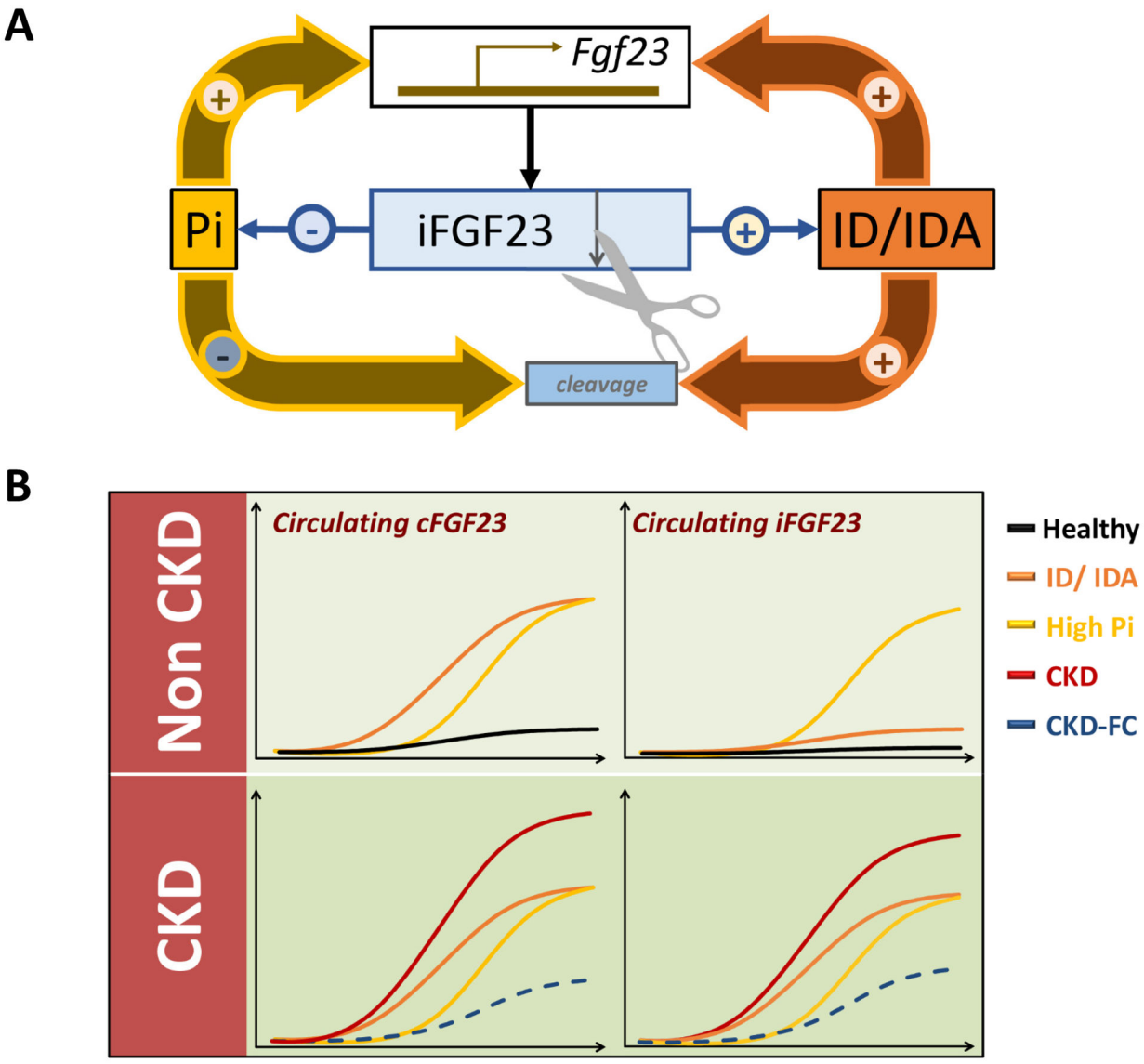

Figure 1: FGF23 regulation by phosphate and iron.

(A) Increased phosphate (Pi), iron deficiency (ID) and iron deficiency anemia (IDA) increase transcription of *Fgf23* resulting in increased production of intact FGF23 (iFGF23). Phosphate increases stabilization of iFGF23 and minimizes its cleavage, while ID and IDA increase FGF23 cleavage. (B) In consequence, in animals and patients without impaired kidney function, increased phosphate levels trigger an increase in total FGF23, assessed by cFGF23, and iFGF23 levels. In contrast, iron deficiency and anemia lead to an increase in cFGF23 but only mild elevations of iFGF23. In CKD, where FGF23 cleavage is reduced, hyperphosphatemia, iron deficiency and anemia increased circulating levels of both total cFGF23 and iFGF23. Administration of ferric citrate (FC), which decreases intestinal phosphate absorption, increases circulating iron and corrects anemia, results in reductions of both total and intact FGF23.

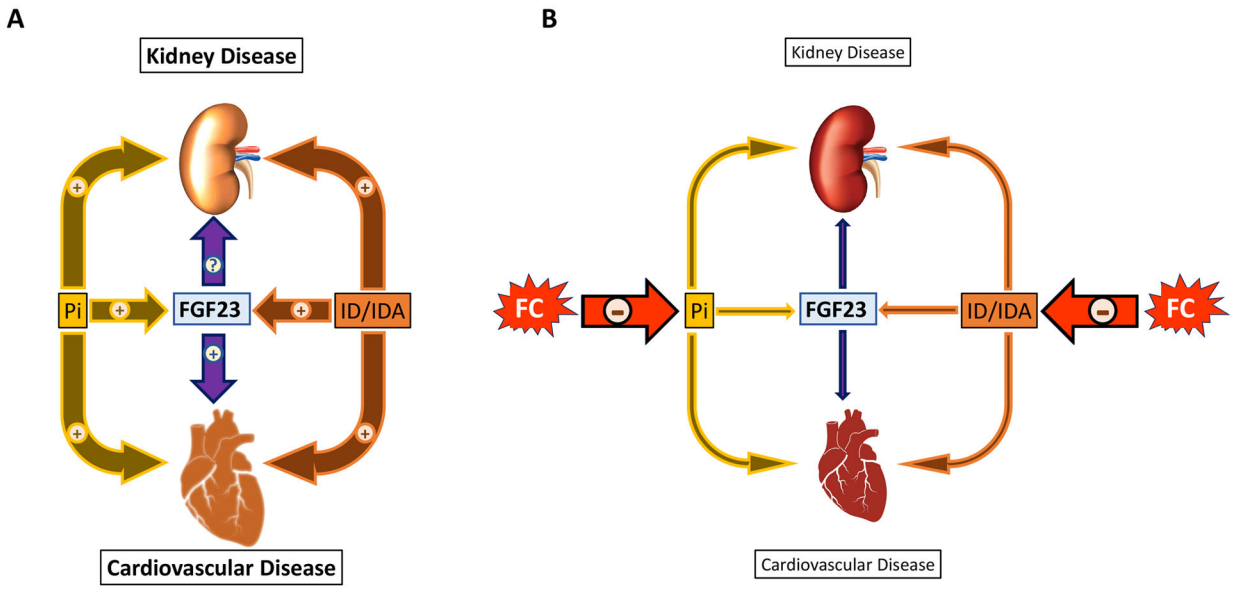

Figure 2: Kidney and cardiovascular effects of impaired phosphate and iron metabolism in CKD.

(A) In CKD, hyperphosphatemia, iron deficiency and anemia lead to progressive alterations in kidney and heart morphology and function and induce the production of FGF23. Excess FGF23 also targets the heart and contributes to development of cardiovascular disease and mortality may aggravate kidney disease progression. (B) Simultaneous reductions in phosphate and correction of iron balance and anemia by iron based phosphate binders, such as ferric citrate (FC), decrease FGF23 production and lead to improvement of kidney and cardiovascular disease.