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Role of fibroblast growth factor 23 in patients with chronic kidney disease

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Fibroblast growth factor 23 (FGF23) is a vital osteocyte-derived hormone that regulates the metabolism of phosphorus and 1, 25-dihydroxyvitamin D (1,25[OH]$_2$D). 1,25(OH)$_2$D and high dietary intake of phosphate up-regulate FGF23 expression, leading to increased renal phosphate excretion and decreased 1,25(OH)$_2$D synthesis, and then suppression of FGF23, thus completing a negative feedback loop. Several clinical studies of patients with kidney disease reported that an increased serum FGF23 level was associated with poor outcomes [Figure 1].[1,2]

FGF23 is a 251 amino acid protein that osteocytes secrete into the circulation after cleavage of a 24 amino acid leader sequence. The intact FGF23 (iFGF23) can then undergo cleavage into two fragments that are presumably biologically inactive, an N-terminal fragment and a C-terminal fragment (cFGF23). An excess of serum cFGF23 leads to competitive inhibition of the full-length FGF23 and prevents it from binding its receptors. FGF23 is the earliest biochemical abnormality that occurs when there is disordered mineral metabolism in patients with chronic kidney disease (CKD), and precedes the increases of parathyroid hormone and phosphate that occur when the estimated glomerular filtration rate (eGFR) declines. Thus, the early elevation of cFGF23[3] indicates its value in the diagnosis of CKD. A meta-analysis of 15 prospective cohort studies supports the strong positive association between FGF23 and cardiovascular mortality in CKD and dialysis patients,[4,5] indicating that FGF23 could be useful as a prognostic biomarker for CKD. Some studies demonstrated that cFGF23 was a better predictor of disease progression. For example, the cFGF23 level is higher in patients with lower eGFR and a high cFGF23 level is associated with a more rapid decline of eGFR.[6] However, Smith *et al*[7] observed that the level of iFGF23 increased as the level of cFGF23 decreased during disease progression, suggesting less cleavage of the intact form.

Taken together, FGF23 could be a promising prognostic biomarker and a possible target for clinical management of kidney disease. However, because of some conflicting studies, further investigations are needed to determine the mechanism by which FGF23 promotes kidney dysfunction and to identify the most suitable FGF23 fragment for prediction of prognosis. Further investigations should also investigate the effect of reducing the FGF23 level on the clinical outcomes of patients with CKD.

Although the mechanism by which FGF23 regulates CKD is still not fully understood, a previous study[7] showed that physiological retention of phosphate enhanced the expression of GalNac-transferase 3 (GALNT3), leading to O-glycosylation of iFGF23 and reducing its susceptibility to proteolysis by furin. Rabadi *et al*[8] also found a decreased level of *Galnt3* mRNA in mouse bone marrow after acute blood loss, and that this protected iFGF23 from proteolysis by furin, and thus increased the cleavage of FGF23 and the level of cFGF23. In addition, recent studies reported that iron deficiency[9,10] and erythropoietin (EPO)[11] also affected FGF23 production. Moreover, a study of mice reported that applying hypoxia inducible factor-proline hydroxylase inhibitors (HIF-PHIs) increased the serum level of FGF23.[9] Current studies show that iron deficiency seems to only increase the level of cFGF23, and that the level of iFGF23 may remain normal due to FGF23 cleavage.

However, there is an incomplete understanding of the factors that affect FGF23 cleavage. In particular, the functions of the two fragments, especially cFGF23, are incompletely understood in patients with CKD. The correction of iron deficiency, a major determinant of elevated FGF23 level, can reduce elevated FGF23 levels.

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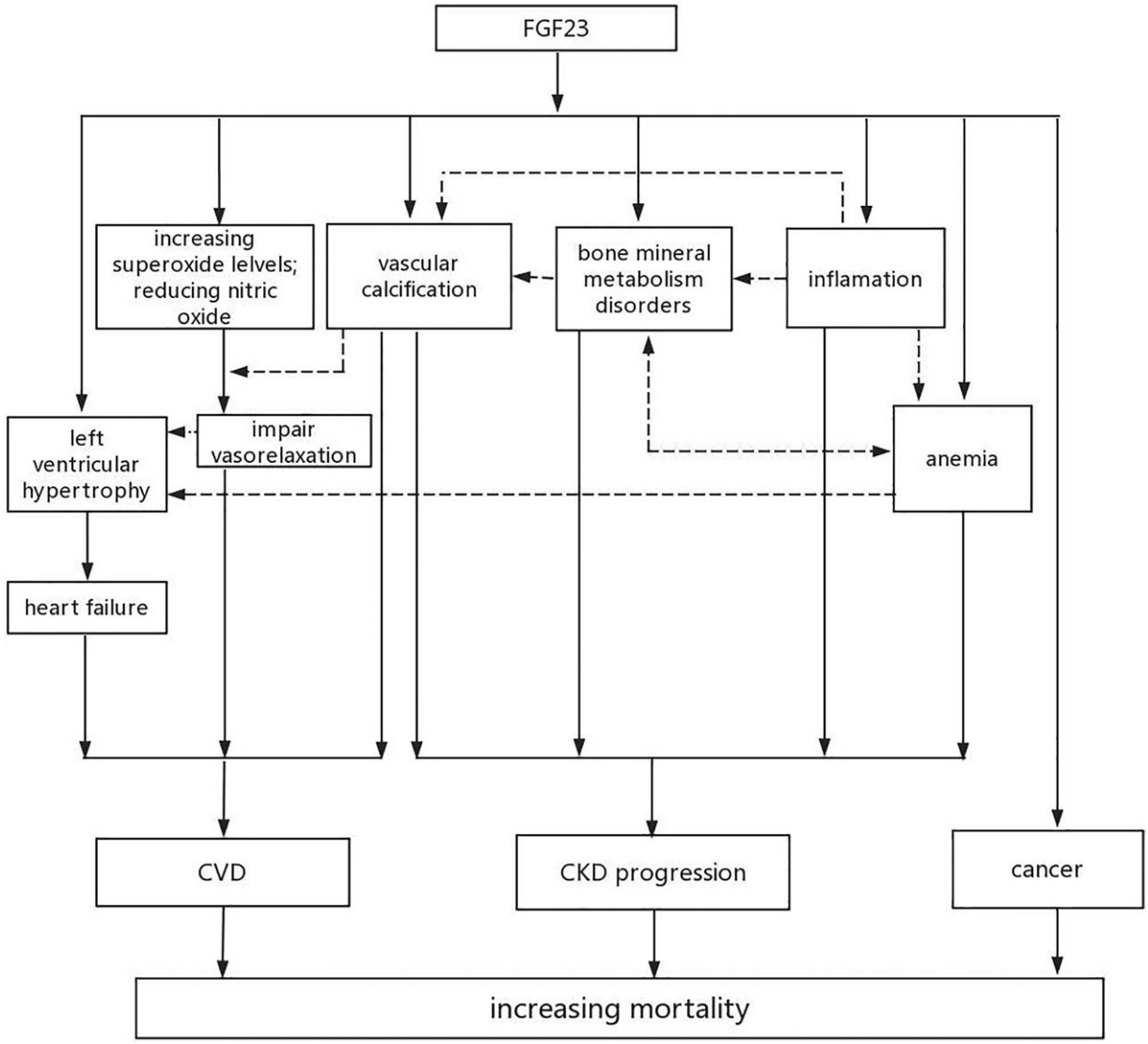

Figure 1: Physiological mechanisms underlying the association of increased FGF23 level with mortality. Solid lines indicate direct effects and dashed lines indicate indirect effects. CVD: Cardiovascular disease; CKD: Chronic kidney disease; FGF23: Fibroblast growth factor 23.

Clinical studies indicated that oral iron is superior to intravenous iron,[12] and that iron-based phosphate binders were especially effective.[13] It is thus possible that iron-based phosphate binders, which simultaneously reduce serum phosphorus and correct iron deficiency, also reduce serum FGF23 levels and improve the long-term outcomes of these patients. Iron deficiency, mediated by HIF1α and EPO, independently increases the FGF23 level and promotes the cleavage of FGF23, and these depend on renal function. HIF-PHI induces the transcription of endogenous EPO, although it remains within its normal physiological range, and it also affects FGF23 expression and cleavage. Future studies are needed to confirm the mechanisms by which endogenous or exogenous EPO increases FGF23 expression and affects FGF23 cleavage. Generally, endogenous EPO levels are elevated during early-stage CKD, and exogenous EPO is typically administered to patients with late-stage CKD, because of the presence of renal anemia, and FGF23 cleavage may decline as renal function declines. iFGF23 is usually considered the bioactive form, and a high cFGF23 level is associated with an increased risk of adverse outcomes in CKD patients.[14] Future studies should thus elucidate the biologic activity of the cFGF23. Intriguingly, a recent study suggested that blockade of FGF23 signaling prevented renal anemia in a murine model of CKD.[15] Future studies should also examine the effect of therapeutic strategies that control the level of FGF23 in patients with CKD.

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Conflicts of interest

None.

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