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## Fibroblast growth factor 23 and cardiovascular events in chronic kidney disease patients

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### Introduction

Fibroblast growth factor (FGF)-23 is a circulating endocrine hormone which is secreted by osteocytes, primarily in response to rise in dietary phosphate intake and circulating level of 1, 25(OH)2D3, the hormonally active form of vitamin D (1,2). The classic actions of FGF-23 on bone and mineral metabolism are interceded by binding of FGF-23 to heterodimeric complexes containing of FGF receptors and the specific FGF-23 co-receptor, Klotho (3). Activation of Klotho–FGF receptor complexes in the kidney enhances urinary phosphate excretion by downregulating the activity and expression of the sodium-dependent phosphate transporters NaPi-2a and NaPi-2c in the proximal renal tubule apical membrane. FGF-23 also reduces presentation of CYP27B1, which encodes 25-hydroxyvitamin D3 1 $\alpha$ -hydroxylase, and stimulates expression of CYP24A1, which encodes the catabolic 1,25-(OH)2D3 24-hydroxylase. Consequently, 1,25(OH)2D3 levels will reduce (4,5).

Studies have shown, concentration of FGF-23 increases increasingly in patients with chronic renal failure as their glomerular filtration rate (GFR) decreases (6,7). The stronger associations in chronic renal failure might relate to Klotho deficiency, which could either accentuate Klotho-independent toxic effects of FGF-23, or eliminate Klotho-dependent protective properties. Furthermore, the relationship between higher serum FGF-23 levels and cardiovascular disease was particularly strong in patients with low fractional excretion of phosphate, which could imply tubular cell resistance to the actions of FGF-23 due to underlying Klotho deficiency (8,9). Higher serum phosphate values are also modestly associated with a risen risk of cardiovascular events even after accounting for FGF-23 levels (10). This finding suggests that FGF-23 and phosphate might promote distinct mechanisms of cardiovascular toxicity. Higher serum phosphate level is strongly associated with endothelial dysfunction and atherosclerosis, and higher FGF-23 level is potently associated with left ventricular hypertrophy (LVH) and congestive heart failure (CHF) (11). Several investigations have detected stronger associations among higher serum FGF-23 levels and adverse outcomes in patients with chronic renal failure than in those without renal failure (9,12).

For example in the Heart and Soul Study, more FGF-23 serum value was associated with increased risk of a complex of transient ischemic attack, myocardial infarction, stroke, and hospitalization for CHF in individuals with a history of

### ■ Implication for health policy/practice/research/medical education

Disorders of phosphate homeostasis are popular in patients with chronic renal failure. As renal function deteriorates, circulating levels of phosphate and the phosphate-regulatory hormone, fibroblast growth factor (FGF)-23, increase gradually. Higher serum levels of phosphate and FGF 23 are accompanied with an increased risk of adverse outcomes, comprising all-cause mortality and cardiovascular disease. The association of higher levels of FGF 23 and adverse cardiovascular outcomes are commonly independent of serum phosphate levels. High levels of FGF-23, hyperparathyroidism, and hyperphosphatemia have all been related to an increased risk of cardiovascular mortality and morbidity chronic renal failure individuals.

■ **Keywords:** Kidney, Chronic kidney disease, Fibroblast growth factor-23, Left ventricular hypertrophy, Congestive heart failure

stable coronary artery disease (13). Other investigations suggest that, cardiac myocytes are able to express FGF-23 under circumstances of stress and also in atherosclerotic plaques. Additionally, this study showed, FGF-23 levels are raised in patients with systolic heart failure (14). Higher serum value of FGF-23 are constantly accompanied by a graded increase in all-cause mortality in prospective investigation of different population of patients, either with or without chronic kidney disease (2-7).

In one cross-sectional investigation tested the correlation among FGF23 level with serum lipid profile and body mass index and some of the other cardiovascular risk factors in individuals with non-dialysis chronic renal failure. This study detected, that there are not any significant association between FGF23 with body mass index and also with lipid profile. However, they found a significant associations of FGF23 with serum albumin and also with systolic blood pressure. In another cross-sectional study the association of FGF23 level with various biochemical parameters and cardiovascular status, in non-dialysis chronic renal failure and stage 5 of CKD, showed higher cardiac death, which was directly proportionate to the rising FGF23 levels. Patients with low ejection fraction, higher interventricular septal thickness and higher left ventricular mass index (LVMi) on 2D-Echo had a higher FGF23 (15). Similar observation was observed in a larger cohort of 292 individuals with chronic kidney disease stages 1

to 5, in whom serum FGF-23 level were inversely correlated with estimated glomerular filtration rate (eGFR), while serum Klotho levels were positively associated with eGFR (16), and level of Klotho was even significantly reduced in chronic kidney disease stage two compared to stage one. Accordingly, the utility of serum FGF-23 for predicting a decline in kidney function was studied in a cohort of 180 individuals with IgA nephropathy. Elevated FGF-23 level was meaningfully associated with albuminuria, and was an independent predictor of chronic kidney disease progression (17). Likewise to study, the value of Klotho for predicting chronic kidney disease progression in 243 chronic renal failure patients Isakova et al, that low serum Klotho level was associated with adverse kidney outcomes, recommending that Klotho might be a biomarker of chronic kidney disease progression (18). Chronic kidney disease is often associated with dysregulated phosphate metabolism, which is firstly showed by high circulating levels of FGF-23 that becomes evident with eGFR below 60 ml/min/1.73 m<sup>2</sup> (6). Hyperparathyroidism and hyperphosphatemia develop in more progressive stages of CKD, which further promote FGF-23 overexpression in bone cells.

### Conclusion

High levels of FGF-23, hyperparathyroidism, and hyperphosphatemia have all been related to an increased risk of cardiovascular mortality and morbidity chronic renal failure individuals. Hence, FGF-23 could represent a promising therapeutic target which may shows the prognosis of patients with chronic kidney disease.

### Authors' contribution

FY was the single author of the paper.

### Conflicts of interest

The author declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by author.

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### References

- Saito H, Maeda A, Ohtomo S-i, Hirata M, Kusano K, Kato S, et al. Circulating FGF-23 is regulated by 1 $\alpha$ , 25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem*. 2005;280:2543-9.
- Saji F, Shigematsu T, Sakaguchi T, Ohya M, Orita H, Maeda Y, et al. Fibroblast growth factor 23 production in bone is directly regulated by 1 $\alpha$ , 25-dihydroxyvitamin D, but not PTH. *Am J Physiol Renal Physiol*. 2010;299:F1212-F7.
- Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;444:770-4.
- Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu Rev Physiol*. 2013;75:503.
- Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest*. 2004; 113:561-8.
- Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*. 2011;79:1370-8.
- Scialla JJ, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. *J Am Soc Nephrol*. 2013;24:125-35.
- Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L, et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. *Kidney Int*. 2013;83:160-6.
- Scialla JJ, Wolf M. Roles of phosphate and fibroblast growth factor 23 in cardiovascular disease. *Nature Rev Nephrol*. 2014;10:268-78.
- Scialla JJ, Xie H, Rahman M, Anderson AH, Isakova T, Ojo A, et al. Fibroblast growth factor-23 and cardiovascular events in CKD. *J Am Soc Nephrol*. 2014;25:349-60.
- Shalhoub V, Shatzken EM, Ward SC, Davis J, Stevens J, Bi V, et al. FGF23 neutralization improves chronic kidney disease-associated hyperparathyroidism yet increases mortality. *J Clin Invest*. 2012;122:2543-53.
- Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol*. 2012;60:200-7.
- Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. *Ann Intern Med*. 2010; 152:640-8.
- Gruson D, Lepoutre T, Ketelslegers J-M, Cumps J, Ahn SA, Rousseau MF. C-terminal FGF23 is a strong predictor of survival in systolic heart failure. *Peptides*. 2012;37:258-62.
- Yuvaraj A, Abraham G, Vijayan M, Jayapal J, Kulanthaipandian S, Nair S. Correlation of fibroblast growth factor 23 in chronic kidney disease patients with biochemical parameters and outcomes. *J Parathyroid Dis*. 2016;4:7-10.
- Shimamura Y, Hamada K, Inoue K, Ogata K, Ishihara M, Kagawa T, et al. Serum levels of soluble secreted  $\alpha$ -Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. *Clin Exp Nephrol*. 2012; 16:722-9.
- Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. *Clin J Am Soc Nephrol*. 2012;7:727-34.
- Kim HR, Nam BY, Kim DW, Kang MW, Han J-H, Lee MJ, et al. Circulating  $\alpha$ -klotho levels in CKD and relationship to progression. *Am J Kidney Dis*. 2013;61:899-909.

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