



## FGF 23 and cardiovascular outcome in chronic kidney disease

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A high level of fibroblast growth factor-23 (FGF-23) is the initial abnormality of mineral metabolism in chronic kidney disease (CKD). Chronic renal failure, is a growing public health alert, which is accompanied with a markedly increased risk of cardiovascular disease and mortality. Left ventricular hypertrophy (LVH) and diffuse arterial calcification are common manifestations of cardiovascular disease and mortality in patients with CKD. FGF23 levels gradually increase in parallel with failing kidney function. High circulating FGF23, both in patients with moderate decreasing of the glomerular filtration rate (GFR) and dialysis, is associated with an increased risk for mortality and progression of chronic renal failure (1).

Results of several studies indicate a relation between FGF23 and LVH. Cardiovascular disease is an important cause of death in patients with CKD, and elevated FGF-23 is a strong predictor of mortality. Additionally, FGF23 was independently connected to an increased risk for cardiovascular mortality in individuals with renal failure with manifest coronary artery disease (2). Additional support for vascular influences of FGF23 derives from cross-sectional investigations in CKD patients and healthy individuals, in which FGF23 has been associated with different degrees of calcification and/or atherosclerosis in peripheral arteries, aorta, and coronary arteries (3). In humans, FGF23 related to increased risk for the presence of LVH and increasing of left ventricular mass in chronic renal failure patients and also in individuals without CKD (4). In the HOST study, elevated FGF23 was strongly associated with augmented risk of the composite outcome of myocardial infarction, amputation, or stroke (5). Several investigations detected strong associations between FGF23 and cardiovascular risk factors. Higher FGF23 levels were independently associated with endothelial cell dysfunction and vascular calcification. In addition to vascular calcification, higher FGF23 is associated with LVH, which is a principal mechanism of congestive heart failure (CHF) and arrhythmia, and a potent risk factor for mortality and morbidity in CKD. Several cross-sectional studies in CKD, end-stage renal failure (ESRD), and non-CKD populations showed that elevated FGF23 levels are independently associated with greater left ventricular mass index (LVMI) and greater prevalence of LVH. In an analysis

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

A high level of fibroblast growth factor-23 (FGF-23) is the initial abnormality of mineral metabolism in chronic kidney disease (CKD). Results of several studies indicate a relation between FGF23 and LVH. Cardiovascular disease is an important cause of death in patients with CKD and elevated FGF-23 is a strong predictor of mortality. Additionally, FGF23 was independently connected to an increased risk for cardiovascular mortality in individuals with renal failure with manifest coronary artery disease.

■ **Keywords:** Kidney, Chronic kidney disease, Fibroblast growth factor 23

of 3879 participants in the CRIC study (mean estimated GFR  $43 \pm 14$  ml/min per  $1.73 \text{ m}^2$ ) with median cFGF23 of 146 RU/ml (nearly three times the normal range value), there were 266 deaths during a median follow-up of 3.5 years (20/1000 person-years). CRIC study showed association between FGF23 and cardiac damage in chronic renal failure. Higher FGF23 levels were independently related to reduced ejection fraction, greater left ventricular mass index, and greater prevalence of concentric and eccentric LVH (6). In experimental study injection of FGF23 into the left ventricular myocardium or intravenously in wild-type mice, induced LVH. These results confirmed the concept of klotho-independent, direct end-organ toxicity of FGF23, and a potentially obvious role of FGF23 in the pathogenesis of uremic cardiomyopathy. Importantly, FGF23 was detected to directly promote cardiomyocyte growth in vitro and to induce hypertrophy of left ventricle in mice with normal renal function (7).

In fact, elevated plasma fibroblast growth factor 23, is a prognostic marker in CKD. Recently, FGF23 was reported to also be a predictive factor in chronic CHF too. In 149 patients with mean eGFR of 36 ml/min per  $1.73 \text{ m}^2$ , elevated FGF23 was independently accompanying with higher risk of the complex of carotid or lower limb revascularization, myocardial infarction, stroke, coronary, lower extremity amputation or even death (8). In an analysis of 833 individuals in the Heart and Soul Study that recruited predominantly non-CKD patients (22% had eGFR < 60 ml/min per  $1.73 \text{ m}^2$ ) with a history of coronary artery disease, the median cFGF23 was relatively normal (43 RU/ml), but

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those with higher levels had, independently increased risk of death and risk of developing the complex of myocardial infarction, cerebrovascular event, or hospitalization for CHF (9). Therefore, elevated FGF-23 is independently associated with occurrence of cardiovascular disease events in CKD stages 2–4 and elevated FGF-23 is more strongly associated with risk of CHF than atherosclerotic events (10). The strong association between FGF-23 and CHF may be a clinical result of the direct hypertrophic influence of FGF-23 on the myocardium, however, other possibilities could also contribute to our results. While, FGF-23 correlates with GFR, it is possible that unmeasured confounding related to intensity of CKD could mediate the association. In the study conducted by Shibata et al, circulating levels of FGF23 were positively correlated with LV mass, LV hypertrophy, reduced LV systolic function, and plasma brain-type natriuretic peptide (BNP) concentration (11). Among cardiac disease patients with preserved left ventricular ejection fraction (LVEF) and sinus rhythm, serum  $\alpha$ -Klotho, but not FGF23, showed a significant negative correlation with diastolic dysfunction, and this relationship was independent of age, estimated GFR (eGFR), blood hemoglobin level, and serum albumin (12). Yuvaraj et al in the current issue of *Journal of Parathyroid Disease*, concluded that patients with low ejection fraction, higher interventricular septal thickness and higher left ventricular mass index had a higher FGF23 levels (13). Therefore, clinical trials are now needed to verify whether reduction of excessive FGF23 activity would improve cardiac outcome in such a high risk population (13).

#### Author's contribution

FA 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 the author.

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#### References

1. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal

- function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int.* 2003;64:2272-79.
2. Seiler S, Reichart B, Roth D, Seibert E, Fliser D, Heine GH. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol Dial Transplant.* 2010;25:3983-9.
3. Yilmaz MI, Sonmez A, Saglam M, Yaman H, Kilic S, Demirkaya E, et al. FGF-23 and vascular dysfunction in patients with stage 3 and 4 chronic kidney disease. *Kidney Int.* 2010; 78:679-85.
4. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest.* 2011;121:4393-408.
5. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol.* 2011;22:1913-22.
6. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA.* 2011;305:2432-9.
7. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest.* 2011;121:4393-44
8. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol.* 2011;22:1913-22.
9. 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.
10. 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.
11. Shibata k, Fujita S, Morita H, Okamoto Y, Sohmiya K, Hoshiga M, et al. Association between circulating fibroblast growth factor 23,  $\alpha$ -Klotho, and the left ventricular ejection fraction and left ventricular mass in cardiology inpatients. *PLoS One.* 2013;8:e73184.
12. Okamoto Y, Fujita S, Morita H, Kizawa S, Ito T, Sakane K, et al. Association between circulating FGF23,  $\alpha$ -Klotho, and left ventricular diastolic dysfunction among patients with preserved ejection fraction. *Heart Vessels.* 2016;31:66-73.
13. 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.

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