Fibroblast Growth Factor-23 May Follow Cardiovascular Disease Rather than Causing It in Chronic Kidney Disease

We read the article "Fibroblast growth factor-23 and risks of cardiovascular and noncardiovascular diseases: A meta-analysis" by Marthi *et al.*[1] with great interest. The study provided an important demonstration that serum higher fibroblast growth factor-23 (FGF-23) level was positively associated with cardiovascular and noncardiovascular outcomes in populations with or without CKD.[1] In agreement with Marthi *et al.*,[1] our previous meta-analysis also pointed out that there might be predictive effects of FGF-23 on cardiovascular diseases (CVDs; including myocardial infarction, atrial fibrillation, myocardial ischemia, heart failure, and stroke) and mortality in patients with CKD.[2]

However, the absence of an exposure-response relationship and similarly sized associations between FGF-23 and different outcomes may not be strong enough to suggest a noncausal relationship between FGF-23 and CVD. Indeed, interactions between FGF-23 and CVD are complicated and remain inconclusive. Experimental studies have revealed that FGF-23 could induce left ventricular hypertrophy.[3] Both FGF-23 overexpression and Klotho deficiency showed cardiac remodeling effects in CKD.[4] However, Slavic *et al.*[5] found that genetic ablation of *FGF-23* or *Klotho* did not modulate heart hypertrophy, indicating other mediators as the real culprits. Recently, left ventricular hypertrophy in transgenic mice was found to elevate myocardial and serum levels of FGF-23.[3] Taken together, the mutual promotion between FGF-23 and CVD indicates a complex interaction between mineral metabolism and the cardiovascular system in CKD. FGF-23 may follow CVD rather than causing it in CKD.

In conclusion, the finding of this meta-analysis[1] is very important, because it brings us a deep and broad view of FGF-23 in CVD and mortality in patients with or without kidney disease. More mechanisms between FGF-23 and CVD will need to be studied to better understand the effect of FGF-23 on cardiovascular health in patients with CKD.

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DISCLOSURES

None.

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See related Letters to the Editor, "Fibroblast Growth Factor-23 Is Not a Single Bystander in Chronic Kidney Disease Mortality," and "Authors' Reply," on pages 2601 and 2602–2603, respectively.

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Authors' Reply

The published observational data show similarly sized epidemiologic associations between increased fibroblast growth factor-23 (FGF-23) concentration and risk of a range of cardio-

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