Nail in the Coffin for Fibroblast Growth Factor 23 as a Predictor of Kidney Function Decline

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Fibroblast growth factor 23 (FGF23) is a hormone derived from bone osteocytes; it regulates circulating levels of phosphorus and active vitamin D (1,25 dihydroxyvitamin D). Circulating levels of FGF23 are elevated in chronic kidney disease (CKD), progressively increase as glomerular filtration rate (GFR) falls, and are the highest among individuals with end-stage renal disease (ESRD). Among individuals with CKD, FGF23 is a potent and independent predictor of ESRD, cardiovascular disease outcomes, and all-cause mortality [1]. FGF23 is also associated with adverse cardiovascular outcomes in non-CKD populations [2], which may be in part due to its likely cardiac toxicity. Indeed, FGF23 directly causes cardiomyocyte hypertrophy [3].

In kidney disease, the stimulus for FGF23 is believed to be higher serum phosphorus levels resulting from nephron loss and reduced GFR; however, this has not been proven on the molecular level, and FGF23 may also be important for calcium regulation making our understanding of the stimulus for FGF23 all the more uncertain. What is certain is that circulating FGF23 levels increase early in the course of CKD, well before other ab-

normalities of mineral metabolism are noted [4], and FGF23 levels may be elevated even before any significant decrement in serum creatinine (e.g., at an eGFR of 77 mL/min/1.73 m²) [4], the main clinical measure of kidney function. Because FGF23 is strongly associated with progression to ESRD among individuals with CKD, is associated with adverse cardiovascular outcomes in non-CKD populations, and increases early in the course of CKD, the notion that FGF23 could mediate or predict kidney function decline and incident CKD among individuals with no or very mild kidney dysfunction is tempting to consider.

In this issue of the *American Journal of Nephrology*, Drew and colleagues report the results of a large observational study that examined the association between baseline circulating FGF23 levels and kidney function decline among 2,496 participants in the Health Aging and Body Composition Study (Health ABC Study) [5]. Glomerular filtration was estimated using cystatin C because it was calibrated across all Health ABC Study samples, and because it is less influenced by age, sex, race, and muscle mass. The mean estimated GFR (eGFR) of the entire co-

hort was 73 ± 18 mL/min/1.73 m². Twenty-three percent had an eGFR ≤ 60 mL/min/1.73 m² and 17% had urine albumin to creatinine ratio of ≥ 30 mg/g. Kidney function decline in the total cohort was defined as $\geq 30\%$ or ≥ 3 mL/min/year reduction in cystatin C-based eGFR, and incident CKD in participants with baseline eGFR > 60 mL/min/1.73 m² was defined as incident cystatin C-based eGFR ≤ 60 mL/min/1.73 m² and an eGFR decline of ≥ 1 mL/min/year. For all analyses, FGF23 was evaluated as a continuous variable and in quartiles. In logistic multivariable regression models, which included adjustment for baseline eGFR, there was no association between higher baseline FGF23 and kidney function decline in the entire cohort. Among participants with baseline eGFR > 60 mL/min/1.73 m², only the highest FGF23 quartile (> 60 pg/mL) was significantly associated with incident CKD (incident rate ratio: 1.27; 95% CI, 1.02–1.58). Factors hypothesized a priori to modify the relationship between baseline FGF23 and kidney function decline were evaluated using interaction terms; baseline eGFR and race did not modify any of the associations. Inflammation, assessed by baseline C-reactive protein, did not influence the relationship either – there were no changes in the ORs or incidence rate ratios when it was added to the final model. It is important to note that when FGF23 was modeled as a continuous variable, there was no significant association with incident CKD.

To determine kidney function decline, follow-up eGFR was obtained at year 3 and year 10, while FGF23 levels were assayed from samples obtained at year 2. Notably, a large proportion (43%) of the participants had only a single follow-up eGFR measured at year 3, and 10-year outcomes of these participants were not reported. Given the older age of the Health ABC Study participants (mean age of this cohort 75 ± 3 years), death may have been a considerable competing risk factor for kidney function decline. Furthermore, only 23% had an eGFR ≤ 60 mL/min/1.73 m²; thus, this small proportion of participants may have been insufficient to demonstrate any significant association of baseline FGF23 level and kidney function decline among those who had CKD at baseline. Moreover, even though studies show an association between FGF23 and progression of existing CKD, a single measure of FGF23 may not be sufficient to accurately predict progression of kidney function decline in CKD. A new analysis using trajectories of multiple FGF23 measures over time in the Chronic Renal Insufficiency Cohort (CRIC) demonstrates that only a certain proportion of individuals with CKD have rapidly increasing FGF23 over time and those with the steepest increase have a high

risk of death [6], suggesting that only a certain subset of individuals with CKD are at high risk for adverse outcomes. It is unlikely that this functional group of Health ABC Study participants, of which only 23% had prevalent CKD at baseline, would include enough individuals with rapidly increasing FGF23 to demonstrate an association between FGF23 and adverse outcomes such kidney function decline.

The use of cystatin C-based eGFR and the definitions of kidney function decline employed in this analysis are commendable. Cystatin C avoids the influence of age, sex, race, and muscles mass, and it is also associated with adverse outcomes in older adults. An eGFR decline of $\geq 30\%$ is in keeping with a recent decision by the United States Food and Drug Administration that this rate of decline is an acceptable clinical endpoint, while using an absolute eGFR decline of ≥ 3 mL/min/year makes this study comparable to others. Nonetheless, the loss of kidney function in older adults is an area of controversy and a median rate of eGFR decline of only 1.45 mL/min/year in the total cohort with mean baseline eGFR of 73 ± 18 mL/min/1.73 m² may not necessarily be pathologic [7]. Notably, FGF23 quartiles 2 (36–46 pg/mL) and 3 (47–60 pg/mL) appeared to be protective against a $\geq 30\%$ eGFR decline compared to quartile 1 (< 36 pg/mL).

Despite these factors, Drew et al. [5] concluded that FGF23 is a marker of kidney function but not a mediator (or predictor) of kidney function decline is appropriate. Indeed, all associations between baseline FGF23 and kidney function decline or incident CKD were either nonsignificant or substantially attenuated after adjustment for baseline eGFR, suggesting that high FGF23 was a marker of existing kidney dysfunction. Moreover, the results of their analysis agree with the results of other studies that demonstrate no substantial association between FGF23 and kidney function decline or incident CKD among individuals with no or mild baseline kidney dysfunction [8, 9]. Even though circulating FGF23 increases early in CKD, its ability to predict kidney function decline among individuals with no or mild CKD falls short.

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