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See related article, "Vascular Access Choice in Incident Hemodialysis Patients: A Decision Analysis," on pages 183–191.

## The Biomarker Niche for Fibroblast Growth Factor 23 Testing in CKD

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Identifying strategies to prevent progression of CKD, reduce risk of its cardiovascular complications, and improve survival is

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among the highest priorities in nephrology. Progress on these initiatives has been impeded by lack of validated biomarkers of early kidney injury that offer prognostic value beyond quantification of eGFR and albuminuria. Given its strong independent associations with CKD progression, cardiovascular disease, and death, fibroblast growth factor-23 (FGF-23) has emerged as a novel biomarker candidate in CKD.<sup>1–3</sup>

FGF-23 was originally discovered in studies of autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia, which are rare disorders caused by high circulating concentrations of FGF-23.<sup>4,5</sup> Since these seminal findings, an explosion of laboratory-based, patient-oriented, and epidemiologic research has helped characterize many aspects of FGF-23 regulation, its classic functions and off-target effects, and the potential clinical implications of high circulating levels.<sup>6</sup> Among the many important themes to emerge from this body of translational research is that CKD is one of the ripest clinical settings for developing FGF-23 as a clinical test of the future. A large epidemiologic study reported in this issue of *JASN* adds an important new chapter to the FGF-23 chronicle in CKD.<sup>7</sup>

Numerous studies have demonstrated that FGF-23 levels rise early in the course of CKD,<sup>8,9</sup> but few have tested the converse: Can the early increase in FGF-23 be leveraged as a diagnostic or confirmatory test for the presence of early CKD itself? Representing the Chronic Kidney Disease Biomarkers Consortium, Rebholz *et al.* tested the hypothesis that higher FGF-23 levels are associated with increased risk of developing kidney disease.<sup>7</sup> They conducted their analyses within the Atherosclerosis in Communities (ARIC) study, a large, community-based, prospective cohort study. In their primary analyses, the investigators examined a single measurement of baseline intact FGF-23 as a risk factor for incident ESRD in 13,448 participants who had a mean baseline eGFR of 97 ml/min per 1.73 m<sup>2</sup>; 2% were <60 ml/min per 1.73 m<sup>2</sup>. During a median follow-up period of 19 years, 267 (2%) participants developed ESRD. In unadjusted analyses, the highest versus the lowest quintile of FGF-23 was associated with a nearly 5-fold higher risk of developing ESRD. As expected, baseline eGFR was the most important confounding variable, but the significant association between higher FGF-23 and risk of incident ESRD persisted after adjusting for eGFR, regardless of which estimating equation was used. Further adjustment for other risk factors, including calcium, phosphate, and parathyroid hormone levels, did not alter the results. In a sensitivity analysis, the results remained qualitatively unchanged after additional adjustment for albuminuria in the subgroup of approximately 80% of participants in whom these assessments were available. Emphasizing the eGFR-independent effect, higher FGF-23 levels (only on the continuous scale) remained independently associated with higher risk of ESRD when the analysis was restricted to individuals with baseline eGFR >90 ml/min per 1.73 m<sup>2</sup>.

In their secondary analyses, the research team tested whether higher FGF-23 levels were also independently asso-

ciated with incident CKD using a definition that combined International Classification of Diseases hospitalization diagnostic codes and measures of eGFR conducted at regularly scheduled ARIC study visits. A total of 1818 patients (14.4% of the population) were identified. The unadjusted hazard ratio of incident CKD was only 1.7 in the highest versus the lowest FGF-23 quintile, which contrasted sharply with the comparable hazard ratio of 4.9 in analyses of ESRD. The CKD effect was fully attenuated with further adjustment, also in stark contrast with ESRD. Analyses of incident CKD according to FGF-23 on a continuous scale yielded similarly modest effects of borderline statistical significance. Unlike the analyses of ESRD, no eGFR-stratified, high eGFR-restricted, or albuminuria-adjusted analyses were presented. On the basis of the other incident CKD results, it is likely that these would have been null.

To summarize, higher FGF-23 measured at a single remote time point was associated with significantly higher risk of developing ESRD many years later, independently of known risk factors for ESRD including baseline kidney function as assessed by eGFR. By contrast, FGF-23 was not particularly predictive of incident CKD.

How should *JASN* readers interpret the seemingly contradictory CKD and ESRD results? One possibility is that biologic mechanisms are operative, and elevated FGF-23 levels contribute more to progression of established CKD than to initiation of *de novo* CKD. For example, FGF-23 increases phosphaturia by downregulating proximal tubular phosphate reabsorption.<sup>6</sup> Despite the lower filtered load of phosphate imposed by reduced GFR, elevated FGF-23 helps maintain normal serum phosphate levels in CKD by markedly increasing phosphate excretion from the remaining nephrons.<sup>10</sup> Perhaps, enhanced FGF-23-mediated phosphaturia exposes tubules to intraluminal phosphate concentrations that are sufficiently high to induce tubular toxicity only in established CKD.<sup>11</sup> Perhaps, other known metabolic consequences of elevated FGF-23, including suppression of renal production of calcitriol and *klotho*,<sup>6</sup> activate a series of secondary pathways that culminate in more rapid progression of CKD to ESRD. Most speculatively, perhaps elevated FGF-23 directly accelerates progression to ESRD by stimulating fibroblast-induced tubulointerstitial fibrosis in established CKD. Whether FGF-23 has direct effects on fibroblasts has not been studied, but is an intriguing possibility given its direct effects on other nonclassic target cells.<sup>12,13</sup>

Alternatively, methodologic factors may underlie the differential results for incident CKD versus ESRD. Insufficient power can be dismissed as a reason for the weaker CKD data because the incidence of CKD was nearly 7-fold higher than the incidence of ESRD, yet the ESRD analyses were clearly adequately powered. Misclassification of incident CKD that biased the analyses to the null is possible. Although one would expect that a large proportion of the ESRD cases previously met criteria for CKD, we are not told to what extent the 267 individuals who developed ESRD overlapped with the 1818 categorized as having developed incident CKD. It would have been interesting to know the frequencies of the different per-

mutations of renal outcomes and to compare baseline FGF-23 levels across the groups: those who developed incident CKD and ESRD, those who developed one but not the other, and those who remained CKD free and ESRD free throughout follow-up. Finally, the very definition of incident CKD, which relies on some amount of absolute reduction or change from baseline in eGFR, boosts the potency of baseline eGFR as a confounder. A high bar must be surmounted to define biomarkers for incident CKD that add substantial value beyond tried and mostly true eGFR.

At first blush, many of the limitations of incident CKD as an endpoint appear to be overcome by analyzing incident ESRD instead, as the authors did. Unlike incident CKD, which is imprecisely defined by somewhat artificial thresholds of eGFR that are based on variable serum creatinine or cystatin C levels, ESRD is a “hard” endpoint that is virtually impossible to misclassify when accessing high-quality databases. Furthermore, the longer latency period between assessment of FGF-23 and ESRD probably weakens the confounding potency of baseline eGFR in incident ESRD versus CKD analyses. However, incident ESRD as an endpoint also poses its own unique problem. In a general population, such as the ARIC study, individuals with prevalent CKD are undoubtedly those most likely to develop ESRD.<sup>14</sup> Because FGF-23 will be significantly higher among individuals with CKD than those without it, identifying elevated FGF-23 as a risk factor for ESRD may simply be synonymous with identifying CKD as a risk factor for ESRD.

But maybe this is an opportunity. Maybe FGF-23 testing of the general population could add value by segregating individuals with occult CKD belied by relatively preserved eGFR who truly are at risk of ESRD from those with normal renal function who are at minimal risk. Given the low rates of ESRD in the general population and the insufficiently low rates of false positive and false negative FGF-23 tests for ESRD that would be expected based on the overlapping FGF-23 distributions and modest effect sizes reported by Rebholz *et al.*, the number of seemingly normal individuals that FGF-23 testing would correctly reclassify as being at risk for ESRD is likely too small to support cost-effective testing of wide swaths of the general population. Furthermore, screening the general population for presence of CKD altogether is controversial.<sup>15</sup> Moving the needle on this issue will likely depend more on successfully developing disease modifying therapies that would secondarily create a need to identify treatment candidates than on developing new and improved biomarkers *a priori*.

In contrast with the general population, the value proposition and cost-effectiveness arguments may shift in favor of FGF-23 testing in established CKD. In this group, low eGFR and proteinuria are a given, but many patients progress quickly and others slowly, many develop cardiovascular events and others do not, and many die prematurely while others enjoy greater longevity. Here, FGF-23 may be an invaluable biomarker, capable of stratifying risk of these feared and common complications of CKD. This could help practicing

nephrologists to identify high-risk patients not otherwise detectable using current clinical and laboratory algorithms, and tailor treatment accordingly. This could also help the research community to design more efficient randomized trials that test novel therapeutic approaches aimed at improving clinical outcomes in CKD, which is our primary duty and goal.

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See related article, "Serum Fibroblast Growth Factor-23 Is Associated with Incident Kidney Disease," on pages 192–200.