

FGF23: Is It Ready for Prime Time?

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Since the identification of fibroblast growth factor 23 (FGF23)² more than a decade ago, interest in this hormone has grown dramatically among both nephrologists and endocrinologists. FGF23, initially identified in patients with rare forms of hypophosphatemia, is also increased in patients with chronic kidney disease (CKD). A handful of studies have suggested that increased circulating concentrations of FGF23 not only play an important role in the development of secondary hyperparathyroidism but also are associated with adverse systemic effects, including increased mortality and deterioration of renal function—associations that have definitively been confirmed in a new prospective study of 3879 adult patients with CKD (1). Isakova et al. reported that circulating FGF23 concentrations were an independent predictor, over a 5-year period, of both (a) progression to end-stage renal disease in patients with a baseline estimated glomerular filtration rate $>30 \text{ mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ and (b) mortality in patients with predialysis CKD. These findings highlight the systemic importance of FGF23 and raise the question of whether FGF23 measurements should now be considered a clinically useful biomarker for diagnosing and managing CKD mineral and bone disorder (CKD-MBD).

Current algorithms for the diagnosis and treatment of CKD-MBD recommend periodic measurement of creatinine, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D concentrations in the plasma of patients at all stages of CKD. These biochemical variables are markers of altered mineral, bone, and/or vascular metabolism. FGF23 measurements, however, are not currently recommended by any guidelines, nor are they available in most clinical laboratories. Although the report by Isakova et al. (1) suggests that increased circulating FGF23 concentrations do predict mortality in patients with CKD, several major hurdles must be overcome before FGF23 can become a routine clinical test.

First, FGF23 assays are not harmonized and do not appear ready for clinical use. The current assays include the “intact” assays from Kainos and Immotopics International, both of which measure the full-length molecule, and the “C-terminal” assay from Immotopics, which detects both the intact molecule and C-terminal fragments. Interestingly, despite some initial concern as to whether values obtained with the Immotopics C-terminal assay overestimate the true amount of biologically active FGF23 in circulation, current data suggest that virtually all detectable FGF23 in advanced CKD circulates in the full-length, biologically active form of the molecule and thus that measurements obtained with the Kainos “intact” assay and the Immotopics “C-terminal” assay reflect the same circulating moiety (2). The measurements obtained with the 3 assays differ, however, not only in their absolute numerical readouts but also in the unit of measure reported (picograms per milliliter vs relative units per milliliter), and little information is available on the relationship between the results obtained with the 2 Immotopics assays and those obtained with the Kainos assay. Studies have yet to be performed to determine (a) whether it is possible to convert results obtained by one assay into results obtained by another, (b) how the 3 assays compare with respect to accuracy and reproducibility, and (c) what constitutes the reference interval for each assay. Thus, standardization of all 3 assays is necessary before they can be considered ready for routine clinical use and incorporation into clinical practice guidelines.

A second hurdle to the adoption of FGF23 values into mainstream clinical practice is a lack of a concrete cutoff point above which an increased risk has been documented. Indeed, the analysis by Isakova et al. (1) focuses on the relationship between FGF23 and mortality for one FGF23 assay—the Immotopics C-terminal assay—by using multivariable regression analysis. Although this form of analysis is powerful for assessing the independent relationships between different variables and outcomes, it is only one of the steps toward establishing useful cutpoints for clinical risk assessment and target intervals for management. Moreover, previous data have demonstrated that the risk of mortality is influenced by (a) phosphorus concentrations, (b) the calcium-phosphorus product, and (c) the use (or lack thereof) of active vitamin D sterols. Each of these 3 variables carries independent risks of mortality, at least in patients treated with maintenance dialysis

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² Nonstandard abbreviations: FGF23, fibroblast growth factor 23; CKD, chronic kidney disease; CKD-MBD, CKD mineral and bone disorder.

(and potentially in those with earlier stages of CKD as well), suggesting that these variables should also be considered as important, potentially modifiable factors in patients with CKD.

An interesting paradox exists in these data. Indeed, active vitamin D sterols stimulate skeletal FGF23 production; therefore, it would seem this form of therapy might increase mortality rates. Large epidemiologic studies, however, have demonstrated a survival advantage for dialysis patients treated with vitamin D sterols, compared with dialysis patients who do not receive any vitamin D therapy (3). Thus, although a combination of biochemical measurements and treatment algorithms probably will provide the most useful paradigm for predicting and treating disordered mineral metabolism in CKD patients, currently only a limited number of studies have defined optimal target intervals for biochemical measurements and optimal treatment regimens, including doses, types of phosphate binders, and vitamin D therapies. Such studies are needed and are certainly warranted.

The data on the value of FGF23 for diagnosing and managing CKD-MBD are even less clear than for its use as a biomarker of future risk. For a marker to be of value beyond prediction, data must show that interventions to alter the concentrations of that marker are associated with changes in clinical outcomes. FGF23 is a phosphaturic hormone that simultaneously reduces the production of renal 25-hydroxyvitamin D 1- α -hydroxylase and increases the production of the 24-hydroxylase, thereby decreasing the circulating concentration of 1,25-dihydroxyvitamin D. The increase in FGF23 concentrations early in the course of CKD is likely potentiated either by chronic increases in the total body burden of phosphate (due to decreased renal phosphate excretion) or by subclinical increases in parathyroid hormone. Thus, it is not surprising that short-term studies have demonstrated that early interventions to decrease FGF23 concentrations through preventing intestinal phosphate absorption may be effective in increasing endogenous 1,25-dihydroxyvitamin D and decreasing parathyroid hormone in patients with early CKD (4). These data suggest that the FGF23 concentration may be a useful target for clinicians in preventing the development of secondary hyperparathyroidism. It is tempting, in light

of the current data by Isakova et al. (1), to extrapolate to the conclusion that the same therapeutic strategy might mitigate the cardiovascular mortality rate associated with CKD, particularly given previous data from Isakova et al. suggesting a lower mortality rate in adults with predialysis CKD who were treated with phosphate binders (5). Nevertheless, long-term and well-controlled studies are badly needed to explore the potential benefits of such therapeutic strategies, both with respect to the long-term consequences of secondary hyperparathyroidism and on morbidity and mortality.

The powerful study by Isakova et al. confirms the role of FGF23 as a biomarker of renal disease progression and mortality in a very large cohort of patients with CKD—a chronic condition that affects as much as 15% of the US population—and highlights deficiencies in our current guidelines for both diagnosing and managing altered mineral metabolism in CKD. Indeed, not only do current FGF23 assays need to be evaluated and standardized more rigorously, but further studies are also needed to establish whether current guidelines should address the issue of FGF23 as both a risk factor and a therapeutic target. How concentrations of this new hormone fit into current treatment algorithms and whether targeting concentrations of this hormone can alter the course of CKD and the mortality rate remain unknown. Large, well-controlled interventional trials are therefore needed to definitively answer the question: Should FGF23 be a target of therapy in patients with CKD?

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