

Second Chances in Mineral Metabolism

Myles Wolf

Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida

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The optimal management of disordered mineral metabolism in patients with chronic kidney disease has been among the most controversial topics in clinical nephrology during the past decade. The origins of the current controversies can be traced back to the initial reports from large-scale human studies of important associations between individual mineral metabolites—calcium, phosphorus, parathyroid hormone (PTH)—and adverse clinical outcomes (1,2). The volume of the mineral metabolism discourse escalated with the publication of complex pharmacoepidemiologic studies that suggested that therapy with active forms of vitamin D might improve survival (3,4). In the next wave of individual analyte studies that followed, deficiencies in the vitamin D axis were found to be associated with increased risk of cardiovascular disease and death (5,6). The introduction of cinacalcet into clinical practice doubled the number of available PTH-lowering therapies but, predictably, launched a new layer of jostling to identify the ideal therapeutic cocktail for dialysis patients. Unfortunately, it is doubtful that clear answers will ever emerge if we continue to assume that “better control” of individual mineral metabolism analytes, as judged by national and international practice guidelines, will translate into improved patient survival rather than directly comparing survival rates of different strategies in head-to-head studies.

How to best treat dialysis patients’ elevated serum phosphate levels is a related quagmire. Again, limited definitive data have promoted a dependence on nonvalidated surrogate markers and expert opinion (educated guessing), which has sparked seemingly never-ending controversy, including calcium *versus* noncalcium-based binders, metal *versus* polymer, efficacy *versus* safety, and so on. These issues have deflected attention from the most fundamental questions for which we also have no answers: Will reducing an elevated serum phosphate level improve survival and, if so, what is the optimal level to target? The imminent bundling of dialysis-related medications into a single dialysis reimbursement will surely add a new dimension of controversy. The only absolute certainty in this area is that the number of patients with renal failure and markedly abnor-

mal mineral metabolism who die soon after initiating dialysis will continue to grow.

Only randomized trials can defuse these controversies, but we might have already missed several windows of opportunity in mineral metabolism. Although the logistical difficulties of performing large-scale trials are well known, perhaps the greatest impediment in this particular area has been the insidious effect of the nephrology community’s propensity to package excellent hypothesis-generating animal and observational human data into plausible “stories” that are then prematurely integrated into clinical practice. For phosphorus and PTH control, the compelling yet unproven “stories” that have been ingrained in the nephrology vernacular and integrated into the standard of care limit our ability to go back and perform the placebo-controlled studies we desperately need but that many would now consider unethical. The argument that we must use the best available data today to treat our current patients is understandable, but it is that argument that engendered the current dilemma in mineral metabolism: we have gone too far (thereby preventing trials) but not far enough (we still do not have clear answers) in our research.

The discovery of fibroblast growth factor 23 (FGF23) injected a breath of fresh air and renewed optimism into the mineral metabolism dialogue. Secreted primarily by osteocytes, FGF23 is a phosphaturic hormone that counter-regulates the stimulatory effect of PTH on 1,25-dihydroxyvitamin D, stimulates the catabolism of 1,25-dihydroxyvitamin D by activating the 24-hydroxylase, and inhibits PTH secretion (7). The main stimuli of FGF23 secretion are dietary phosphorus intake and 1,25-dihydroxyvitamin D, which unite in several newly discovered classical negative endocrine feedback loops. FGF23 levels increase progressively as kidney function declines, which is possibly an adaptation to maintain neutral phosphorus balance and the most likely cause of early 1,25-dihydroxyvitamin D deficiency in chronic kidney disease (8). The FGF23 burden in kidney disease is dramatic: dialysis patients can routinely manifest 100- to 1000-fold elevations in biologically active FGF23 levels compared with healthy individuals (9).

As the latest addition to the family of measurable circulating analytes of mineral metabolism, several studies examined the relationship between FGF23 excess and adverse outcomes. Although the field is only in its infancy, FGF23 excess has been already associated with kidney disease progression, ventricular hypertrophy, vascular disease, and mortality (10–13). The results are strikingly consistent, particularly when contrasted

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Correspondence: Dr. Myles Wolf, Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 819, Miami, FL 33136. Phone: 305-243-7760; Fax: 305-243-8914; E-mail: mwolf2@med.miami.edu

with the less impressive results from similar studies of PTH. Thus, FGF23 is rapidly emerging as a novel candidate biomarker that could redefine phosphorus management across the spectrum of chronic kidney disease (14). Unfortunately, beneath the building momentum surrounding FGF23, a disturbingly familiar chatter is also beginning to surface—an effort to adapt the new FGF23 “story” into the existing mineral metabolism “story.” For example, a frequently voiced question is how to resolve the potential paradox whereby active vitamin D therapy is associated with improved survival if it raises FGF23 levels, and high FGF23 levels are associated with death?

Although several hypotheses have been advanced to address this question (15), in this issue of *CJASN*, Wetmore *et al.* provide the first published data that directly compared the effects of routine PTH-lowering strategies on FGF23 levels (16). In a secondary analysis of the randomized ACHIEVE trial, which compared the likelihood of achieving a PTH level of 150 to 300 pg/ml when treated with fixed low-dose active vitamin D plus titrated doses of cinacalcet (Cinacalcet-D) *versus* titrated doses of active vitamin D alone (Flex-D), Wetmore *et al.* measured FGF23 levels at multiple time points in a subset of participants ($n = 91$). Although there was no difference in the primary endpoint in the parent study (17), patients treated with Cinacalcet-D experienced a statistically significant, albeit modest, approximately 10% reduction in FGF23 levels from baseline to the end of the 27-week follow-up period. Although this represented a statistically significant difference compared with the change observed in the Flex-D arm, surprisingly, FGF23 levels increased by only approximately 4% on Flex-D, which represented a nonsignificant change from baseline.

The authors provide an excellent discussion of the physiology of FGF23 and the potential mechanisms for the differences in change in FGF23 levels between the two treatment groups. They should also be commended for a balanced and comprehensive self-critique of their study’s limitations which, in fairness, primarily stem from the main limitations of the parent trial. In addition to its small sample size of prevalent dialysis patients and brief follow-up period, ACHIEVE undertreated patients randomized to Flex-D compared with those who received Cinacalcet-D. For example, although their average vitamin D dose before study entry was approximately 19 $\mu\text{g}/\text{wk}$, by protocol, Flex-D patients received only 6 $\mu\text{g}/\text{wk}$ after washout and never achieved their previous intensity of therapy, despite no significant changes in mean calcium or phosphorus levels and persistently high PTH levels. In addition, although the difference did not reach statistical significance, there was a trend toward greater PTH reduction in the Cinacalcet-D arm. Thus, it is important to note, as Wetmore *et al.* do, that the lack of expected increase in FGF23 levels on active vitamin D might have been due to insufficient dose. Indeed, during the washout period, when previous therapy with vitamin D was discontinued, FGF23 levels decreased by approximately 5% (figure 1), suggesting that vitamin D most likely does indeed raise FGF23 levels on dialysis as has been previously reported (18). However, along the same lines, the slope of the FGF23 curve from washout through study completion did not change once cina-

calcet was initiated, which suggests that the direct effect of cinacalcet was also minor.

As a first-in-class study, the most important contribution of this report to advancing FGF23 research in chronic kidney disease may be its quantitative rather than qualitative aspects. Even if we assume that cinacalcet does indeed directly lower and active vitamin D does directly raise FGF23 levels, the magnitude of their effects may be smaller than expected, perhaps trivial in the context of the marked FGF23 elevation that is already established among dialysis patients. This is a welcome finding for two critical reasons. First, an ideal biomarker should be minimally confounded by other factors and therapies. This study suggests that future analyses of FGF23 in chronic kidney disease may not be significantly confounded by concomitant cinacalcet or vitamin D therapy. Indeed, the two published studies on FGF23 and mortality had virtually identical results, despite one excluding vitamin D-treated patients and the other including many who were treated (11,19).

Second, the lack of a major effect of these common therapies on FGF23 levels should reinforce our ability to resist the temptation to prematurely drag FGF23-related hypotheses, however attractive, into our existing muddled view of how to manage mineral metabolism in kidney disease, a pitfall that could jeopardize the studies we desperately need and are poised to do. For now, FGF23 simply cannot be considered a surrogate marker of outcomes related to mineral metabolism. Instead, in FGF23 it seems we have been granted a rare “second chance” to revisit placebo-controlled trials of fundamental concepts in mineral metabolism. We must stay the research course and demand the trials needed to obtain definitive results that will drive lasting improvements in the treatment of chronic kidney disease.

Disclosures

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See related article, “Effects of Cinacalcet and Concurrent Low-Dose Vitamin D on FGF23 Levels in ESRD,” on pages 110–116.