

New Insights to Fibroblast Growth Factor 23 in Kidney Transplant

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Some abnormalities in mineral metabolism are evident even at very early stages of chronic kidney disease (CKD) and are important determinants of subsequent bone and cardiovascular disease.1,2 A decade ago, fibroblast growth factor 23 (FGF23) was recognized by a few as the protein responsible for several rare inherited and acquired syndromes of osteomalacia and rickets.3,4 Only recently have studies demonstrated the significance of FGF23 in mineral metabolism in the larger population of patients with CKD and ESRD.5–7 In 2007, Fliser et al.8 reported that higher FGF23 levels were strongly associated with progression of non diabetic CKD. The next year, Gutierrez et al.9 published that incident hemodialysis patients with higher FGF23 levels were at substantially greater risk for all-cause mortality. These and other studies generated considerable interest in the role of FGF23 in mineral metabolism homeostasis in CKD.

Recent reports extend these findings by showing that FGF23 levels are elevated at very early stages of CKD,2 and the associations of FGF23 with all-cause mortality or cardiovascular disease extend to patients with stages 3 to 4 CKD,10 and even to individuals with ostensibly normal kidney function.11 In this issue of JASN, Wolf et al.12 report that higher FGF23 levels associate with the composite outcome of all-cause mortality or kidney allograft loss among 984 stable transplant recipients. Most of the participants were several years after transplantation. This finding is significant for several reasons. First, in conjunction with other literature, this study demonstrates that higher FGF23 levels identify patients at increased risk for adverse outcomes across the spectrum of CKD. Second, because most kidney transplant recipients have survived an extended period on dialysis before receiving an allograft and often have a high burden of vascular disease, the study demonstrates that FGF23 continues to provide risk information in this late stage of disease. Last, given the pattern of other mineral metabolism abnormalities observed in kidney transplant recipients, the study provides new insights into potential mechanisms, as described further next.

With these discoveries come new challenges. Among the most pressing is a better understanding of mechanisms responsible for the link of FGF23 with adverse outcomes.7 Several possibilities require special consideration. A main biological function of FGF23 is to increase urine phosphorus excretion.4,13 A wealth of data spanning from the laboratory to population-based studies implicates hyperphosphatemia as a key factor inducing and promoting arterial calcification.14–16 Thus, perhaps high FGF23 levels are linked with mortality through alterations in phosphorus homeostasis. Several studies have investigated this possibility. Consistently and observed again in the article by Wolf et al. in this issue, statistical adjustment for serum phosphorus levels measured concurrently with FGF23 does not attenuate its relationship with outcomes.8,12 However, phosphorus may remain an important intermediary nonetheless. Contemporary clinical laboratories precisely measure serum phosphorus levels, typically with coefficients of variation <3%. However, there is considerable biological variability in serum phosphorus levels within individuals over time.17 This is analogous to serum glucose, for which one can precisely determine the blood level at a given moment, but it gives a mere snapshot of average glucose levels over time. Thus,
one possibility is that higher FGF23 levels increase in response to higher phosphorus levels and may serve as a more accurate indicator of time-averaged serum phosphorus exposure than serum phosphorus levels themselves, analogous to a hemoglobin A1c as an indicator of time-averaged glucose levels. Future studies with repeated measurements of serum phosphorus over time are required to investigate this possibility. However, the study by Wolf et al. in this issue provides some early insights arguing against this hypothesis.

Kidney transplant recipients frequently develop posttransplantation hypophosphatemia. Although this abnormality often wanes with time, a subgroup remains persistently hypophosphatemic. In the study by Wolf et al. did not provide repeated measures of serum phosphorus, subgroup analysis demonstrated that higher FGF23 levels remain strongly associated with death or allograft loss in patients with serum phosphorus in the lowest tertile (<2.9 mg/dl) at study enrollment. Although not definitive, these data suggest that viewing FGF23 as a marker of time-averaged serum phosphorus may be too simplistic.

FGF23 also inhibits conversion of calcidiol to calcitriol. Calcitriol deficiency may also activate the renin-angiotensin-aldosterone axis, affecting inflammatory stress and glycemia, and low levels associate with adverse outcomes. Thus, perhaps high FGF23 levels lead to low calcitriol, which in turn may lead to adverse outcomes. This hypothesis has not been fully investigated. Calcitriol levels are found at approximately 1000-fold lower levels in circulation than calcidiol, making them difficult to measure precisely. Moreover, calcitriol has a short serum half-life. Thus, similar to serum phosphorus levels, future studies may require multiple measures of calcitriol and use more precise measurement techniques to evaluate whether it may represent a causal intermediary between FGF23 and adverse outcomes.

When FGF23 binds its receptor, it requires the co-factor klotho to exert its effect on target cells. Klotho is expressed in the kidney, parathyroid gland, and choroid plexus but can be cleaved from the cell surface and released into blood, and biological significance of soluble klotho is uncertain. A recent study demonstrated that plasma klotho levels were low in a rat CKD model and that klotho inhibited phosphorus uptake and mineralization of rat vascular smooth muscle cells in vitro. Whether klotho levels are low in humans with CKD and how klotho interacts with vascular smooth muscles to induce these changes are unknown. Nonetheless, if similar effects hold in humans, one can speculate about feedback mechanisms stimulating higher FGF23 to compensate for low klotho levels in patients with CKD. Perhaps those with the lowest soluble klotho have the greatest burden of arterial calcium deposition and higher adverse event rates, the higher FGF23 may be serving as a marker of klotho activity within vascular tissues. Thus, whether high FGF23 levels may serve as a marker of soluble klotho or may interact with klotho in vascular tissues are important topics for future research.

Additional challenges include identification of methods to safely and reliably lower FGF23 levels. Preliminary studies suggest that non–calcium-based oral phosphorus binders and cinacalcet may lower FGF23 levels in patients with ESRD. Short-term studies evaluating oral phosphorus binders in stages 3 to 4 CKD provide conflicting results regarding changes in FGF23 concentrations and short-term dietary phosphorus loading or restriction in patients with CKD have not resulted in significant changes in FGF23. To date, all studies in CKD have evaluated short-term interventions, and future studies with longer follow-up may provide different results. Nontraditional methods that alter phosphorus levels in individuals with or without CKD should also be investigated in regard to their effect on FGF23.

In summary, FGF23 has emerged as a robust risk marker for death, cardiovascular events, and kidney disease progression across the spectrum of CKD. Moving forward, the new challenge will be to elucidate mechanisms responsible for these associations, to identify safe and effective methods to alter serum FGF23 levels, and ultimately to determine whether such interventions translate into demonstrable improvements in health outcomes in our patients.

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REFERENCES
