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Forging Forward with 10 Burning Questions on FGF23 in Kidney Disease

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ABSTRACT

The discovery of fibroblast growth factor 23 (FGF23) as the causal factor in the pathogenesis of rare forms of hypophosphatemic rickets is rapidly reshaping our understanding of disordered mineral metabolism in chronic kidney disease (CKD). Excessive production of FGF23 by osteocytes is an appropriate compensation to help maintain normal phosphorus metabolism in these patients. Beginning in early CKD, progressive increases in levels of FGF23 enhance phosphaturia on a per-nephron basis and inhibit calcitriol production, thereby contributing centrally to the predominant phosphorus phenotype of predialysis kidney disease: normal serum phosphate, increased fractional excretion of phosphate, and calcitriol deficiency. A proliferation of studies linking phosphorus and now FGF23 excess to adverse renal and cardiovascular outcomes in patients with CKD is setting the stage for novel clinical trials that could ultimately bring FGF23 testing into the clinic. Ten burning questions must be addressed to galvanize FGF23 research further in CKD.

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In only a few years, the discovery and characterization of fibroblast growth factor 23 (FGF23) is drastically changing our understanding of disordered mineral metabolism in chronic kidney disease (CKD). The journey of FGF23 from anonymity to center stage began with studies of a family of rare diseases that share a common phenotype, including hypophosphatemia, isolated urinary phosphate wasting, rickets or osteomalacia, and insufficient calcitriol production for the degree of hypophosphatemia. The main diseases in the group are X-linked hypophosphatemia (the most common), autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, fibrous dysplasia, and tumor-induced osteomalacia (TIO; a sporadic form).[1,2] With no known cause for the diseases, overexpression of one or more circulating phosphaturic factors, termed "phosphatonins" was hypothesized.

Genetic studies provided the breakthrough. Positional cloning revealed missense mutations in the gene encoding FGF23 on chromosome 12 in each of four families with autosomal dominant hypophosphatemic rickets, encompassing 26 affected individuals.[3] These mutations were later shown to protect FGF23 from proteolytic cleavage.[4,5] Confirmation of the causal role of FGF23 in the hypophosphatemic disorders came in 2001, when high expression of FGF23 was isolated from tumor cells from patients with TIO.[6] The development of high-precision assays for measuring FGF23 confirmed elevated circulating levels in patients with TIO, X-linked hypophosphatemia, and ESRD compared with healthy individuals (Figure 1)[7,8] and opened the door to a new era of human physiologic research on FGF23.

NORMAL FGF23 PHYSIOLOGY

FGF23 is primarily secreted by osteocytes[9] and has several endocrine effects on mineral metabolism (Figure 2): FGF23 induces phosphaturia by decreasing phosphate reabsorption in the proximal tubule through downregulation of luminal sodium-phosphate co-transporters[10,11]; FGF23 reduces circulating levels of calcitriol by inhibiting renal 1-α hydroxylase[10,11] and stimulating 24-hydroxylase,[11] which catalyzes the initial step in vitamin D degradation; and FGF23 inhibits secretion of parathyroid hormone (PTH).[12] These effects are dependent on the presence of klotho, which is highly expressed in the kidney and the parathyroid glands and acts as a co-receptor for FGF23 by markedly increasing the affinity of FGF23 for ubiquitous FGF receptors.[13,14] These aspects of FGF23 physiology were demonstrated in studies of animals that were administered FGF23,[4,10,12,15] transgenic mice that overexpress *FGF23*,[16–19] and *klotho*[20] and *FGF23* null mice.[21] Physiologic studies of normal humans were confirmatory,[22–24] as were observations from patients with

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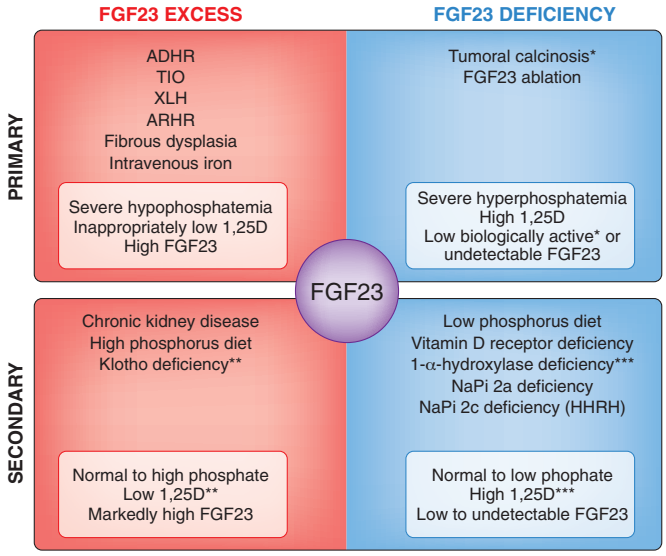

Figure 1. Causes of primary and secondary FGF23 excess and deficiency. Specific diseases and clinical settings and their characteristic metabolic features are listed in each quadrant corresponding to states of primary or secondary FGF23 excess or deficiency. The physiologic effects of FGF23 were originally identified in studies of rare hereditary and acquired diseases of primary FGF23 excess (left upper quadrant) and confirmed in human studies and animal models of FGF23 deficiency (right upper quadrant). Non–FGF23-dependent causes of phosphate wasting and impaired vitamin D signaling cause appropriate, secondary FGF23 deficiency (right lower quadrant), whereas CKD and deficiency of klotho, the FGF23 co-receptor, cause secondary FGF23 excess (left lower quadrant). Of all of the listed diseases and clinical settings, CKD is far and away the most common. *In contrast to absolute FGF23 deficiency, tumoral calcinosis can be caused by a defect in posttranslational glycosylation of FGF23, leading to high circulating levels of inactive C-terminal FGF23 fragments but absence of intact, biologically active FGF23. **Klotho deficiency differs metabolically from the other clinical settings in this quadrant in that 1,25 dihydroxyvitamin D (1,25D) levels are high as a result of lack of inhibition of the renal 1-α-hydroxylase by the faulty FGF23-klotho axis. Phenotypically, klotho deficiency causes a syndrome of tumoral calcinosis. ***In 1-α-hydroxylase deficiency, 1,25D levels are low, unlike the other clinical settings in this quadrant. ADHR, autosomal dominant hypophosphatemic rickets; XLH, X-linked hypophosphatemia; ARHR, autosomal recessive hypophosphatemic rickets; NaPi, sodium phosphate co-transporter; HHRH, hereditary hypophosphatemic rickets with hypercalciuria.

inactivating *FGF23* or *klotho* mutations (Figure 1).[25,26]

Oral phosphorus loading and calcitriol stimulate and dietary phosphorus restriction inhibits FGF23 secretion.[22–24,27] When a diet rich in phosphorus is consumed, high levels of FGF23 induce phosphaturia and inhibit calcitriol production, which decreases the efficiency of dietary phosphorus absorption. On a low-phosphorus diet, low FGF23 levels promote renal phosphate conservation and enhanced gut absorption of phosphorus as a result of increased calcitriol. Although this suggests serum phosphate levels are regulated within a narrow range by FGF23 despite wide fluctuation in phosphorus intake, how intake is sensed and how that signal is transduced to the FGF23-secreting osteocytes is unknown. Alternatively, FGF23 may not actually regulate serum phosphate levels. Indeed, FGF23 levels were unchanged by nondietary interventions that increased serum phosphate levels, such as intravenous phosphorus infusion[28] and medical orchiectomy.[29] In animal studies in which FGF23 and serum phosphate increased in parallel, it is likely that the intake of high-phosphorus chow was the primary stimulus.[30] Furthermore, patients with primary hypoparathyroidism[31] and those who had predialysis CKD and were given cinacalcet manifested persistent hyperphosphatemia,[32] suggesting that FGF23 alone is unable to maintain normal serum phosphate levels. Thus, two critical outstanding questions in normal FGF23 physiology, which themselves are undoubtedly intertwined, are, "How is phosphate sensed, and what is FGF23 primarily regulating: the serum phosphate, local phosphate concentrations near osteocytes, phosphorus balance, bone metabolism, or calcitriol levels?"

In contrast, it is clear that the inhibitory effect of FGF23 to lower calcitriol production counterregulates the stimulatory effect of PTH, and calcitriol inhibits its PTH but stimulates FGF23 secretion (Figure 2).[33] Whether PTH and FGF23 share a classic negative endocrine feedback loop is likely but not yet proved. Whereas FGF23 inhibits PTH,[12] it is unknown whether PTH directly stimulates FGF23 production or does so indirectly through PTH-induced increases in calcitriol. A recent study of dialysis patients in whom FGF23 levels increased significantly in response to intravenous infusion of PTH in the absence of any change in calcitriol levels suggests a direct stimulatory effect of PTH on FGF23,[34] but further work is needed.

FGF23 PHYSIOLOGY IN CKD

Although originally discovered in studies of rare hypophosphatemic disorders, the greatest clinical application of FGF23 research may ultimately lie in the management of CKD. FGF23 levels increase progressively as GFR declines beginning in early CKD,[35–37] with some investigators observing significant increases already by stages 2 to 3 disease (Figure 3).[35,38] By the time patients reach dialysis, levels can be up to 1000-fold higher than in healthy individuals.[36] In a departure from the previous school of thought in which the gradual reduction in calcitriol levels that begins in early CKD was attributed to insufficient renal mass and thus insufficient 1-α-hydroxylase activity, it is now believed that "secondary" FGF23 excess is the primary mechanism. Likewise, "tertiary" FGF23 excess has supplanted

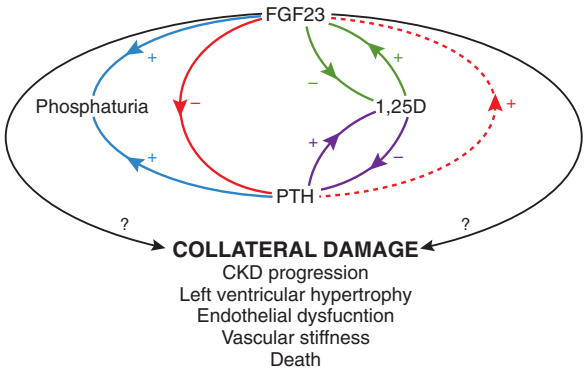

Figure 2. Physiologic actions of FGF23. FGF23 regulates phosphorus metabolism *via* a series of interrelated, classic negative endocrine feedback loops (individual feedback loops are color coded). Both FGF23 and PTH stimulate phosphaturia (blue), but their effects on 1,25D are counterregulatory (PTH and 1,25D, purple; FGF23 and 1,25D, green). Whereas FGF23 clearly inhibits PTH (solid red loop) and preliminary data suggest that PTH stimulates FGF23, the latter is unproved (dashed red loop). Whether markedly elevated FGF23 levels cause collateral damage with direct injury to nonclassical target cells such as in the heart, vessels, and kidney is hypothesized but unproved (black).

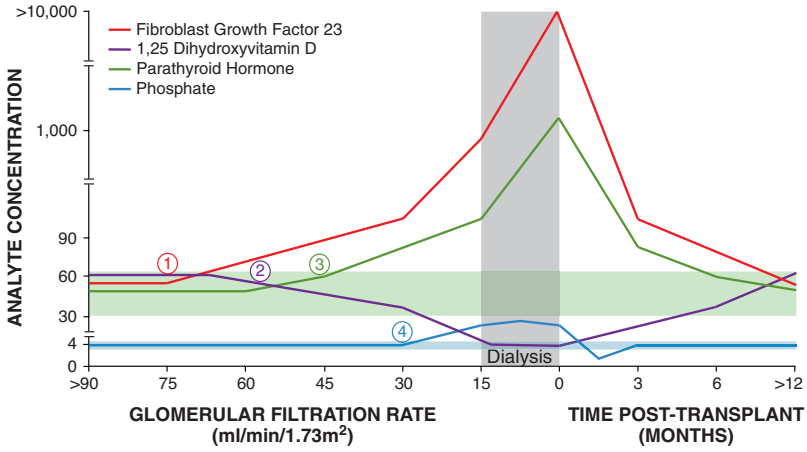

Figure 3. Temporal aspects of disordered phosphorus metabolism in progressive CKD and after kidney transplantation. The *x* axis in the predialysis period represents GFR (left); in the postdialysis period, it represents time after kidney transplantation (right). The *y* axis represents circulating concentrations of the individual analytes with the temporal changes in and normal ranges of individual analytes color coded (C-terminal FGF23 [RU/ml] in red; 1,25D [pg/ml] in purple; PTH [pg/ml] in green; and phosphate [mg/dl] in blue). Current hypotheses propose increased FGF23 as the earliest alteration in mineral metabolism in CKD (1). Gradually increasing FGF23 levels cause the early decline in 1,25D levels (2) that free PTH from feedback inhibition, leading to secondary hyperparathyroidism (3). All of these changes occur long before increases in serum phosphate levels are evident (4). FGF23 and PTH levels decline rapidly in the early posttransplantation period but variably thereafter. Persistent or tertiary FGF23 excess in the posttransplantation period contributes to posttransplantation hypophosphatemia and the sluggish recovery of normal 1,25D production.

tertiary hyperparathyroidism as the most likely mechanism of isolated posttransplantation hypophosphatemia and the associated delay in recovery of normal calcitriol production (Figure 3).[39,40]

The incorporation of FGF23 into our understanding of disordered mineral metabolism helps to explain classic studies in the area. For example, when phosphorus intake and renal mass are reduced in parallel, dogs do not develop secondary hyperparathyroidism, but severe hyperparathyroidism occurred when renal mass is reduced but usual phosphorus intake continues.[41] It is likely that differences in FGF23 levels account for these observations. It is also likely that a reduction in FGF23 levels as a result of decreased phosphorus intake accounted for the release of 1-α hydroxylase from feedback inhibition in studies that demonstrated a significant increase in calcitriol levels in response to dietary phosphorus restriction.[42,43]

Interestingly, efforts to reduce phosphorus intake as a treatment strategy to attenuate calcitriol deficiency and secondary hyperparathyroidism in CKD seem to have been mostly abandoned despite these and other promising studies suggesting benefits on bone mineralization and CKD progression.[44–46] By providing an easily measurable biomarker, FGF23 offers the opportunity to revisit these strategies with an eye toward large-scale use in day-to-day clinical practice. The proliferation of several exciting studies of FGF23 excess and adverse clinical outcomes increases the urgency of developing this approach.

FGF23 AND CLINICAL OUTCOMES IN CKD

Several large epidemiologic studies demonstrated significant associations between increased levels of serum phosphate and adverse clinical outcomes, including more rapid progression of kidney disease, cardiovascular disease, and death.[47–50] Although these studies illuminate disordered phosphorus metabolism as a therapeutic target, the serum phosphate is unlikely to be a viable biomarker in managing phosphorus metabolism in predialysis CKD because the magnitude of effect associated with changes in serum phosphate within the normal range is so small[47–50]; to the practicing clinician, impressive tests of significance are far less relevant than unimpressive relative risks. What is needed is a more sensitive biomarker of disordered phosphorus metabolism with greater

resolution for defining risk for adverse outcomes than serum phosphate, especially when the latter is normal as it usually is in predialysis CKD.[51] On the basis of initial epidemiologic studies, FGF23 is poised to fill this gap.

In a prospective study of 227 patients with nondiabetic CKD, increased FGF23 levels associated with significantly increased risk for progressive CKD.[52] The effect was independent of the mostly normal serum phosphate levels, and increased FGF23 was more predictive of CKD progression than serum phosphate. Among incident hemodialysis patients, increased FGF23 levels associated independently with increased risk for mortality during the first year of therapy.[53] Concomitant serum phosphate levels were only modestly associated with mortality and only among those with the most extremely elevated levels. In contrast, FGF23 demonstrated a monotonic increase in risk for mortality across the entire range of levels, and a high FGF23 level was most predictive among those with serum phosphate levels within the acceptable range. The dosage-response relationship between increasing FGF23 and mortality was confirmed in a study that extended these results to prevalent dialysis patients.[54] In aggregate, these data suggest that FGF23 excess is a more robust predictor of adverse outcomes in CKD than serum phosphate levels.

Because cardiovascular disease is the leading cause of death in patients with CKD,[55] it is likely the association between FGF23 excess and mortality is mediated by increased cardiovascular risk. Several studies support this view. In a population of predialysis patients with CKD and healthy patients with normal serum phosphate levels, increased FGF23 associated independently with increased left ventricular mass index and significantly greater prevalence of left ventricular hypertrophy.[56] These results were confirmed and extended to a large population of elderly patients who had preserved renal function and in whom increased FGF23 levels were also independently associated with endothelial dysfunction and vascular stiffness.[57,58] On the basis of presentations at the American Society of Nephrology's Renal Week 2009,[59–61] we can expect numerous additional reports confirming the association between FGF23 excess and adverse outcomes.

POTENTIAL CLINICAL IMPLICATIONS OF FGF23 IN CKD

Current data suggest that FGF23 could herald a new paradigm in the treatment of patients with CKD. Just as PTH screening is used to determine which patients with CKD and normal serum calcium levels should be considered for vitamin D therapy, so, too, could FGF23 screening help to identify which patients with CKD and normal serum phosphate levels benefit from dietary phosphorus restriction and phosphorus binders. This would represent a significant departure from current standards of care, which emphasize initiating treatment when overt hyperphosphatemia develops, which is often long after FGF23 levels have already increased substantially (Figure 3).[35] Thus, FGF23 screening could identify far more candidates for phosphorus-related therapies far earlier in their course of CKD, when the benefits of early intervention are maximal. Conservatively assuming that 50% of patients with stages 2 through 4 CKD in the United States manifest an elevated FGF23 level,[62] FGF23 screening could expand the target population for phosphorus-related therapies from approximately 0.4 million dialysis patients and predialysis patients with hyperphosphatemia to >7 million individuals, nearly a 2000% increase.

Before FGF23 can be integrated into CKD practice, it must traverse additional milestones. We must demonstrate that increased FGF23 is a risk factor for adverse outcomes in predialysis CKD and that elevated FGF23 levels can be safely lowered in this population. Then, we must prove in a randomized trial that lowering elevated FGF23 levels reduces the risk for adverse outcomes compared with placebo. These critical issues were presented in detail in recent reviews that focused on the clinical aspects of FGF23 in the future.[62] The next section highlights 10 burning questions on FGF23 in CKD, the answers to which will likely shape the FGF23 research portfolio in upcoming years.

TEN BURNING QUESTIONS ON FGF23 IN CKD

1. What Is the Normal Range of FGF23, and What Is the Prevalence of an Abnormally High Level at Various Stages of CKD?

These are among the most basic and important outstanding questions in human FGF23 research. The ability to recognize which patients with CKD have high FGF23 levels requires knowledge of what is normal, yet there have been no population-based studies to define normal FGF23 ranges across various ages, genders, and races and in health, CKD, or other disease states.

2. Besides Dietary Phosphorus and Calcitriol, What Are the Determinants of FGF23 Levels in CKD?

Although serum phosphate and FGF23 levels correlate strongly,[36,54] there are no data to support a direct effect of serum phosphate on FGF23 secretion in health or CKD. Although it is possible that prolonged severe hyperphosphatemia in dialysis patients might theoretically stimulate FGF23 secretion directly, existing data suggest that FGF23 may not be primarily regulating (and thus stimulated by perturbations in) serum phosphate levels, but perhaps, instead, it regulates phosphorus balance, vitamin D physiology, or bone metabolism, as recent studies suggested.[38,63,64]

Whether kidney disease itself contributes to raising FGF23 levels directly is also unclear. For example, the ailing kidney could express a factor that stimulates FGF23, decrease expression of an inhibitor, or contribute to diminished uptake or decreased urinary clearance of the hormone. Current evidence suggests there is indeed increased production of FGF23 as early as stage 2 CKD,[38] and the concept of increased production is supported by persistently elevated FGF23

levels 12 months after kidney transplantation despite a well-functioning allograft.[39] The clearance of FGF23 in CKD by cellular uptake, urinary excretion, or dialysis must be studied, and we must also determine the impact of residual renal function and dialysis vintage before FGF23 levels in dialysis patients can be accurately interpreted. Finally, intravenous iron stimulates FGF23 secretion.[65] Although the mechanism and relevance require further study, this could have important implications for dialysis patients who are frequently administered iron.

3. Elevated FGF23 and PTH Levels in CKD: Which Comes First?

Although FGF23 and PTH are often both elevated in CKD, it remains unknown which rises first and whether the pattern is uniform across all patients. Although the distinction may be purely academic for most patients with CKD in whom both are high, defining the sequence of early pathophysiologic events could shed light on the optimal initial therapeutic management of disordered mineral metabolism: whether to start with vitamin D, phosphorus therapies, or a combination of both. To date, limited data suggest that FGF23 excess precedes significant elevations in PTH levels,[66] but there are dissenting views.[67]

4. What Is the Ideal Assay to Measure Circulating FGF23 Levels in CKD?

There are currently two types of assays for measuring FGF23. C-terminal assays, which recognize two epitopes in the C-terminus, capture both intact FGF23 and its C-terminal fragment.[7] Intact assays capture only intact FGF23 because the two epitopes flank the cleavage site.[68] Although several studies demonstrated high correlation between the two assays even in CKD,[23,52,53,68] it is often assumed that the markedly elevated FGF23 levels in patients with CKD may represent accumulation of inactive C-terminal fragments. This view likely stems from the experience with PTH assays; however, unlike PTH, there are limited data in support of accumulation of FGF23 fragments in CKD.[8] Indeed, a recent study found virtually all circulating FGF23 is intact and biologically active in peritoneal dialysis patients.[68] This suggests that FGF23 is secreted intact exclusively and undergoes little if any degradation in circulation, both features in sharp contrast to PTH. Although additional confirmatory studies are needed, it seems clear that reliable results in CKD can be gleaned from either assay strategy.

5. How Do FGF23 Levels Differ in Specific CKD Subpopulations?

Most clinical studies of FGF23 have been relatively small, and the few larger studies were racially and ethnically homogeneous. In the mortality study of 400 incident hemodialysis patients, black and Hispanic patients demonstrated approximately 20 to 30% lower FGF23 levels compared with white patients.[53] Although large population-based validation studies are needed, these differences are plausible when considering the known racial and ethnic differences in mineral metabolism, whereby nonwhite groups have higher serum phosphate and calcitriol levels despite higher rates of nutritional vitamin D deficiency and elevated PTH levels compared with white groups.[69–71]

Whether FGF23 levels differ according to the cause of kidney disease is unknown. Most studies have found no association between FGF23 and age, but pediatric studies involving very young participants are needed given the differences in phosphorus physiology in infants and toddlers, who manifest markedly higher serum phosphate levels and growth rates than adults. Finally, estradiol stimulates FGF23,[72] and one study reported higher levels in healthy women,[7] but this, too, requires systematic study.

6. Is FGF23 Excess or Klotho Deficiency the True Risk Factor?

Deficiency of klotho, the co-receptor for FGF23, associates with hyperphosphatemia and markedly elevated levels of FGF23.[20,26] Just as FGF23 levels rise with progressive loss of kidney function, it is thought that renal expression of klotho declines.[73] This suggests that CKD may be a state of progressive renal resistance to FGF23.[74] Given the association between klotho deficiency and vascular calcification, accelerated aging, and premature death,[75] it is proposed that the association between FGF23 excess and adverse outcomes in CKD is mediated by klotho deficiency.[74] The main limitations to addressing this important hypothesis are the lack of a reliable *in vivo* assay for circulating klotho and uncertainty over the relative importance of the transmembrane *versus* the soluble form.

7. Does FGF23 Exert Direct Toxicity on Tissues, or Is It Simply a Biomarker?

Underlying its association with adverse outcomes, FGF23 excess could be a biomarker of phosphorus excess or calcitriol deficiency, or it could be directly toxic to nontraditional target organs such as the cardiovascular system. Given the lack of klotho expression in the cardiovascular system, any direct effect of FGF23 would presumably be independent of klotho. There are reports of low-affinity, klotho-independent binding of FGF23 to FGF receptors,[76,77] suggesting the markedly elevated FGF23 concentrations observed in CKD could theoretically mimic the effects of basic FGF (FGF2), which has been implicated in myocardial hypertrophy.[78,79] Additional research is required to examine this question, which has substantial clinical implications.

8. Can FGF23 Levels be Lowered in CKD with Standard or Emerging Therapies?

If a markedly elevated FGF23 level is directly toxic, then reducing the level or blocking its effect would emerge as a novel therapeutic target in CKD. Short-term studies of dialysis patients demonstrated a modest reduction in FGF23 levels in response to cinacalcet and a modest increase in levels after treatment with active vitamin D.[80,81] Whether these effects prove to be clinically relevant when considered against the background of massive elevations in levels of FGF23 in dialysis patients is unclear. Administering a more targeted mAb that neutralizes FGF23 is theoretically attractive (but not yet available) for dialysis patients who do

not depend on native renal clearance of phosphorus. In predialysis CKD, alternative strategies would be needed because effective FGF23 blockade could replicate the physiology of FGF23 null mice[21] or patients with tumoral calcinosis[25]: severe hyperphosphatemia and hypercalcemia as a result of increased calcitriol levels with extensive calcification. In that setting, it would be essential to reduce the root cause of FGF23 elevation, likely by using dietary phosphorus restriction and phosphorus binders. Unlike neutralizing antibodies, these interventions would also be expected to be beneficial if FGF23 is a biomarker of adverse outcomes associated with phosphorus excess rather than a direct toxin. Animal and pilot studies of patients with CKD demonstrated the potential efficacy of binders,[82–84] but larger, more prolonged studies that also emphasize the impact of dietary restriction are needed.

9. Does Excessive FGF23 Inhibit Peripheral 1-α-Hydroxylase?

The optimum approach to treating deficiencies in the vitamin D axis in CKD is controversial. Although active vitamin D therapy associated with a significant survival benefit in observational studies,[85] there is growing interest in treating patients with inactive vitamin D precursors to decrease or obviate altogether the requirement for exogenous active vitamin D.[86] The basis for this approach is that peripheral activation of vitamin D precursors by extrarenal cells that express CYP27B1 (1-α-hydroxylase) will generate adequate amounts of calcitriol locally[87]; however, few studies have examined the regulation of peripheral CYP27B1 and whether it functions normally in CKD in the setting of very high FGF23 levels. In a recent report,[88] cholecalciferol repletion in dialysis patients induced calcitriol-dependent protein expression in monocytes, suggesting intact peripheral CYP27B1, but the effect could have been mediated by the increase in systemic (from the kidney) calcitriol levels that were observed. Determining whether a markedly increased FGF23 level inhibits peripheral CYP27B1 will strengthen the physiologic basis for designing optimal vitamin D regimens in CKD.

10. What Is the Role of FGF23 in Acute Renal Failure?

There are no systematic studies of FGF23 levels or its possible effects in acute renal failure. There is only a single report of increased FGF23 levels in a case of acute renal failure that was caused by rhabdomyolysis.[89] Observational studies should measure FGF23 levels at multiple time points in the course of acute renal failure, in several of its varied etiologies, and should determine whether there is any relationship between levels and subsequent outcomes.

CONCLUSIONS

In less than a decade since its discovery, FGF23 has been elevated to the forefront of CKD research and has the potential to transform the clinical management of disordered mineral metabolism in CKD. Such rapid progress represents an extraordinary case study in the power of modern multidisciplinary translational research in which human genomics, sophisticated cell biology, human physiologic research, epidemiology, and clinical trials unite with old-fashioned clinical observation. Expectedly, there is still much to learn about fundamental aspects of FGF23 physiology in general and in CKD in particular, and many more human studies are needed before FGF23 testing can be integrated into clinical practice. What is clear is that disordered phosphorus metabolism in CKD will continue to be an active and exciting area for years to come.

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DISCLOSURES

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