A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease

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The diagnosis of chronic kidney disease (CKD) confers dismal clinical outcomes regardless of whether patients are initiating dialysis and face a median survival of only 2–3 years or they have earlier-stage CKD and face a risk of death that is greater than the risk of progression to dialysis. These poor outcomes are driven by extraordinarily high rates of cardiovascular disease that historically have not responded to risk-factor modification strategies proven to attenuate risk in the general population. Nor have measures aimed at increasing the dose or quality of dialysis made an appreciable dent in mortality. Still worse, interventions that were expected to be beneficial resulted in increased mortality in recent trials. Although this apparent lack of progress in advancing the care of CKD is discouraging, resignation is not an option. On the contrary, with the rising rates of CKD worldwide, there is an urgent need to rigorously test novel therapeutic strategies in randomized trials. The breadth of accumulating evidence linking disordered phosphorus metabolism to adverse outcomes spans *in vitro*, animal, and human studies, and positions phosphorus management as an attractive target for intervention. Although opinion-based practice guidelines promote phosphorus management strategies that are widely accepted in dialysis patients, there is a clear need to perform randomized controlled trials to prove or disprove the benefits of therapy. Perhaps even more important, the discovery of fibroblast growth factor 23 (FGF23) and its potential as a novel diagnostic to identify disordered phosphorus metabolism at an early, subclinical state has presented the opportunity to develop placebo-controlled randomized trials in pre-dialysis CKD patients with normal serum phosphate levels. This commentary considers the justification and challenges for such trials and presents a 'first-draft' blueprint of distinct trial approaches to initiate a dialog that will ultimately culminate in studies aimed at improving survival across the spectrum of CKD.

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Chronic kidney disease (CKD) is a growing public health epidemic that affects ~13% of the US population or ~26 million people,[1,2] and far more worldwide. Although the overwhelming economic and medical impact of the growing US dialysis population (stage 5 CKD: >350,000)[3] is widely recognized, >13,000,000 people in the United States alone suffer from CKD stages 3 or 4,[1,2] which are risk factors for cardiovascular disease (CVD) mortality.[4–7] CVD and CKD share common risk factors, the presence of CVD is associated with progressive CKD, *de novo* and recurrent CVD events are more common in all stages of CKD, and associated outcomes are far worse in CKD patients than in the general population.[8–10] As a result of these 'disease multiplying' interrelationships, stage 3–4 patients' risk of death due to CVD is significantly greater than their risk of progressing to dialysis.[11,12]

Given the links between CKD and CVD, considerable research efforts have focused on strategies to prevent CKD progression, modify traditional and CKD-specific risk factors for CVD, and improve survival. Although randomized studies showed the renoprotective benefits of blocking the renin–angiotensin system,[13–16] attempts to reduce CVD burden and mortality in CKD have been less successful.[17–23] Nevertheless, an accumulating body of exciting clinical and experimental evidence supports disordered phosphorus metabolism as a novel target worthy of interventional trials of renal and cardiac protection in CKD.

ROLE OF PHOSPHORUS EXCESS IN RENAL AND CARDIOVASCULAR INJURY

Hyperphosphatemia has long been known to exert adverse effects on bone and parathyroid glands.[24–27] During the last decade, hyperphosphatemia has also emerged as a novel risk factor for kidney disease progression, vascular calcification, left ventricular hypertrophy (LVH), and mortality across the spectrum of CKD.[28–31] Prospective studies of non-kidney disease populations yielded analogous results that provide strong corroborative evidence in support of the role of phosphorus in adverse outcomes in CKD.[32,33]

Phosphorus and kidney disease progression

Nephrocalcinosis is a pattern of kidney injury related to phosphorus toxicity,[34] and is associated with mitochondrial disorganization and mineralization of tubular cell membranes,[35] factors that may promote tubular cell death and consequent tubulointerstitial fibrosis.[35,36] Experiments in mildly uremic rats, administered diets with high phosphorus content,[37] showed accelerated kidney disease progression, and epidemiological studies suggest that higher serum phosphate levels predict more rapid CKD progression.[30,38,39] Moreover, animal and human studies suggest that phosphorus-restricted diets may slow the decline in kidney function.[40–42] An important limitation of the human studies, however, is that more advanced CKD at baseline is the strongest predictor of progression. Given the relative imprecision in quantifying renal function, it is possible that the higher serum phosphates that predicted more rapid progression actually reflected more advanced CKD at baseline. Whether the association between increased serum phosphate levels and renal progression is causal or because of residual confounding can only be definitively determined by randomized studies that test whether reducing dietary phosphorus absorption by decreased intake or by administration of phosphorus binders will slow the progression of CKD.

Phosphorus and vascular injury

Arterial stiffening due to calcification is an independent risk factor for mortality in the general population and in CKD.[43,44] Severe calcification is more common in CKD than in people with normal kidney function,[45] and has been associated with mortality on dialysis.[46–48] Hyperphosphatemia has been linked to arterial calcification in several dialysis cohorts,[45,49–51] in the pre-dialysis population,[52] and, more recently, in patients with preserved kidney function.[53] In support of the epidemiological link between hyperphosphatemia and arterial disease, experimental data indicate that vascular calcification is an organized cellular process that begins in early CKD,[45,54–58] and is mediated, in part, by upregulation of osteoblast factors in vascular smooth muscle cells exposed to high phosphorus concentrations.[59–64] Recent findings of an association between high normal serum phosphate levels and vascular calcification in pre-dialysis CKD[52] suggest that even lower phosphate concentrations may contribute to calcification. Further studies are needed to assess whether interventions targeting phosphorus metabolism in normophosphatemic CKD patients could prevent progression of vascular disease.

Phosphorus and LVH

Left ventricular hypertrophy is an independent risk factor for heart failure and mortality in virtually all populations, including non-CKD,[65] pre-dialysis CKD,[66] and dialysis.[67] Epidemiological studies estimate that the prevalence of LVH increases progressively with each stage of CKD such that up to 75% of incident dialysis patients are affected,[68] and death from heart failure accounts for >50% of CVD-related mortality on dialysis.[66] Disordered phosphorus metabolism, independent of its effects on vascular calcification, is associated with LVH in CKD,[69,70] and animal data support a direct effect. Rats that underwent parathyroidectomy, 5/6 nephrectomy, and were then administered physiological replacement doses of parathyroid hormone (PTH) and a high phosphorus diet developed hyperphosphatemia and LVH in the absence of vascular calcification[71] suggesting that excess dietary phosphorus resulting in hyperphosphatemia may be directly cardiotoxic. In contrast, intensive daily hemodialysis is an efficient modality for reversing hyperphosphatemia that was independently associated with regression of LVH.[72–74] Although investigators suggested a causal link between phosphorus control and regression of LVH, only randomized trials can offer definitive confirmation.

Phosphorus and mortality

On the basis of these potential mechanisms of vascular injury, it is not surprising that large observational studies have confirmed that hyperphosphatemia is an independent risk factor for CVD and mortality on dialysis.[28,75,76] These associations were subsequently validated in pre-dialysis populations[29–31] and even in non-kidney disease populations,[32,33] in which subtle increases in serum phosphate levels within the normal range were linked to increased risk of death. Although patients with lower serum phosphate levels were at lower risk of mortality as a group, whether reducing serum phosphate levels in individual patients would improve their clinical outcomes is often assumed, but remains completely unstudied and unknown.

CURRENT STANDARD OF CARE

The Kidney Disease Outcomes Quality Initiative (NKF/K-DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease recommend that serum phosphate levels be maintained between 2.7 and 4.6 mg per 100 ml in patients with CKD stages 3 and 4, and between 3.5 and 5.5 mg per 100 ml in dialysis patients.[77] Phosphorus reduction strategies, such as dietary phosphorus restriction or administration of dietary phosphorus binders, are recommended (although binders are not FDA (Food and Drug Administration)-approved in pre-dialysis) when serum phosphate levels exceed the target range (and secondarily, when PTH levels exceed its target range). It is critical to emphasize that these recommendations were published in 2003 by a working group of experts after meticulous assessment of the existing literature, which consisted largely of the aforementioned observational studies that related single measurements of serum phosphate to survival. The updated guidelines from the Kidney Disease Improving Global Outcomes group are expected to also focus on the initiation of treatment once serum phosphate levels exceed the normal range.[78] Thus, the current standard of care emphasizes the

management of overt hyperphosphatemia over disordered phosphorus metabolism in the setting of normal serum phosphate levels.

LIMITATIONS OF SERUM PHOSPHATE IN THE CLINICAL MANAGEMENT OF PHOSPHORUS METABOLISM

Although the evidence from large cohort studies linking hyperphosphatemia with adverse outcomes in pre-dialysis patients suggests that even subtle increases in serum phosphate levels within the normal range confer increased risk,[29,32,38] the small absolute differences in serum levels limit their utility for management decisions in individual patients. For example, the reported risk estimate for death in one of the pre-dialysis CKD studies was 23% per 1 mg per 100 ml increase in serum phosphate levels, yet 50% of patients had levels within the range of 2.5–3.5 mg per 100 ml.[29] By spanning such a large proportion of patients, relative risk estimates may sensationalize the actual absolute risk in clinical practice. Indeed, in a cohort of African-American patients, the hazard ratio for kidney disease progression was reported to be 1.07 for every 0.3 mg per 100 ml increase in serum phosphate levels, illustrating a lower absolute risk when a more realistic, lower per unit change in serum phosphate was used in the analysis.[38] The diurnal and postprandial variability in serum phosphate levels of up to 1 mg per 100 ml further complicates the clinical interpretation of risk attributable to smaller changes in serum phosphate levels.[79–81]

Furthermore, it is important to note that the widely-publicized independent association between increased serum phosphate levels and adverse clinical outcomes comes from heavily adjusted multivariate models.[29,38,53] Indeed, the results of phosphate and mortality are far less consistent in the unadjusted analyses reported in these same studies, with some showing a dampened association with mortality and others showing a reversed association, whereby higher serum phosphate levels were protective.[53] Significant negative confounding is clearly a common theme in this area. We must emphasize that the discrepancies between the unadjusted and adjusted analyses do not detract from the biological importance of phosphorus excess as an independent risk factor. Indeed, adjusting for potential confounding factor is critical to hone in on the true effect of an individual factor that is interrelated with others. However, the discrepancy is critical from a clinical perspective, as nephrologists do not perform multivariate analyses during clinical encounters. Furthermore, targeting certain serum phosphate ranges that seem most protective based on multivariate-adjusted models is fundamentally flawed. As an example, although a serum phosphate of 7 mg per 100 ml in a dialysis patient with a concurrent serum albumin of 4.5 g per 100 ml likely confers significantly less risk than an identical serum phosphate in a patient with a serum albumin of 2.5 g per 100 ml, clinical practice guidelines offer no specific dispensation for these very different situations. Complicating matters further for the clinician at the point of care is the fact that the same logic must be carried through to include upwards of 25 clinical covariates, an impossible task for clinical decision making. Less confounded biomarkers of phosphorus metabolism with greater resolution than the serum phosphate are desperately needed.

FGF23: AN EMERGING BIOMARKER OF PHOSPHORUS METABOLISM

Sensitive biomarkers are urgently needed for screening, early diagnosis, and initiation of therapy for disordered phosphorus metabolism before the development of end-organ damage. Fibroblast growth factor 23 (FGF23) is a key regulator of phosphorus and vitamin D metabolism that offers significant promise (Figure 1).[82,83] FGF23 is a 251 amino acid protein secreted by osteocytes in adults[84] and by other tissues during development.[85] FGF23 binding to FGF receptor 1c-klotho complex in the kidney[86,87] induces phosphaturia by decreasing phosphate reabsorption in the proximal tubule[88,89] and inhibits renal 25-hydroxyvitamin D-1-α-hydroxylase leading to decreased conversion of 25-hydroxyvitamin D (25D) to 1,25-dihydroxyvitamin D (1,25D), the biologically active hormonal form of vitamin D.[90,91] 'Primary' syndromes of FGF23 excess, in which FGF23 was originally discovered as the etiological factor, are marked by hypophosphatemia, renal phosphate wasting, and inappropriately low 1,25D levels for the degree of hypophosphatemia. These aspects of FGF23 physiology were confirmed in transgenic mice that overexpress a cleavage-resistant FGF23 molecule, in mice administered exogenous FGF23, and in humans with various syndromes of hypophosphatemia caused by excessive FGF23.[92–97] In contrast, FGF23 depletion states, such as FGF23-null mice and patients with inactivating FGF23 mutations, show hyperphosphatemia with excessive 1,25D.[96,98]

The central role of FGF23 in rare disorders of phosphorus metabolism suggested that it may also regulate phosphorus and 1,25D homeostasis in health. Through classic negative endocrine feedback loops, dietary phosphorus intake and 1,25D stimulate FGF23 secretion, which in turn inhibits 1,25D production and increases urinary phosphate excretion.[88,99] For example, several days of dietary phosphorus loading stimulates FGF23 secretion, which induces phosphaturia and suppresses renal 1,25D.[99–101] Phosphorus restriction exerts the opposite effects: FGF23 levels decrease leading to renal phosphate reabsorption and enhanced gut absorption of phosphorus due to increased 1,25D.[99–101] Thus, FGF23 seems to help maintain serum phosphate levels within a narrow range despite fluctuation in dietary phosphorus intake. Interestingly, it is unknown how the stimuli for FGF23 secretion are sensed by the secretory cells, and, perhaps counter-intuitively, changes in serum phosphate levels do not seem to be the intermediary step, given that human physiological studies did not observe a change in FGF23 levels when serum phosphate levels were independently altered through a variety of non-dietary strategies.[102,103] It is also important to acknowledge that regulatory mechanisms of urinary phosphate excretion that

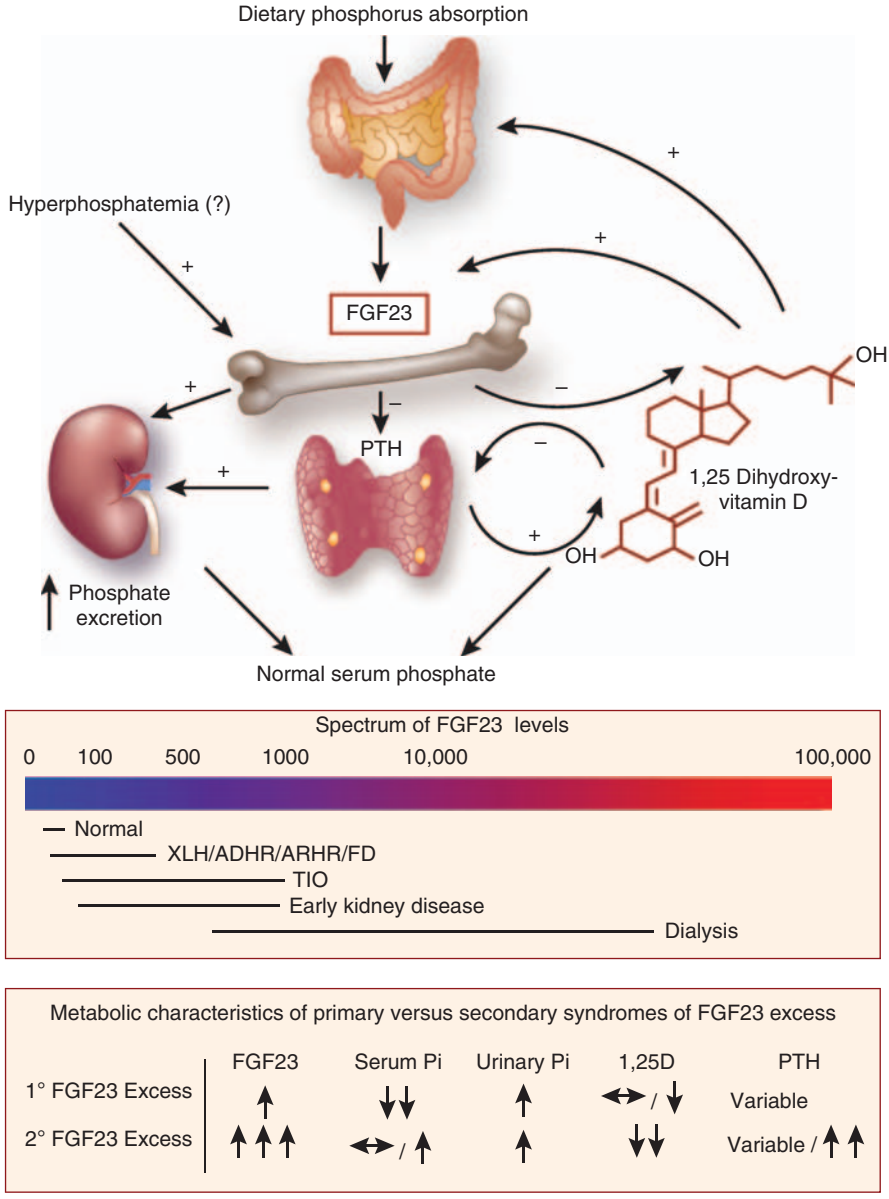

Figure 1 | Fibroblast growth factor 23 (FGF23) regulates serum phosphate levels within a narrow range, despite wide fluctuation in dietary intake, by a series of classic negative endocrine feedback loops involving 1,25-dihydroxyvitamin D (1,25D), parathyroid hormone (PTH), urinary phosphate excretion, and dietary phosphorus absorption. FGF23 secretion by osteocytes is primarily stimulated (+) by increased dietary phosphorus intake, exposure to 1,25D, and, possibly, by increased serum phosphate levels; FGF23 is inhibited (−) by low dietary phosphorus intake, hypophosphatemia, and low 1,25D levels. FGF23 binds FGF receptor with highest affinity in the presence of the co-receptor Klotho. In the renal proximal tubule, FGF23 binding increases urinary phosphate excretion by downregulating expression of luminal sodium–phosphate co-transporters, NaPi-2a and NaPi-2c. In addition, FGF23 inhibits secretion of PTH and inhibits 25-hydroxyvitamin D-1-α-hydroxylase, leading to decreased circulating levels of 1,25D. Decreased 1,25D levels, in turn, lower gut phosphorus absorption and release the parathyroid glands from feedback inhibition, thereby increasing circulating PTH levels, which further augment urinary phosphate excretion. The direct effects of FGF23 on bone mineralization and on other organs are less clear. The upper insert illustrates the spectrum of FGF23 levels that can be observed under normal conditions and in a variety of syndromes of FGF23 excess. Circulating FGF23 levels are 10- to 20-fold above normal (~30–60 RU/ml using a C-terminal FGF23 assay) in patients with hereditary hypophosphatemic rickets syndromes, including X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), and fibrous dysplasia (FD). Although FGF23 levels are often even higher in patients with tumor-induced osteomalacia (TIO), the highest levels are encountered in patients with kidney disease and especially in those on dialysis, in whom levels can reach concentrations more than 1000-fold above the normal range. The lower insert illustrates the differences in the metabolic characteristics of 'primary' syndromes of FGF23 excess, such as the hereditary diseases and TIO, versus 'secondary' syndromes of FGF23 excess, such as kidney disease. In addition to the severity of the FGF23 increase, the primary difference is normal to high serum phosphate (Pi) levels in patients with kidney disease compared to those with hypophosphatemia, which is the *sine qua non* of the hereditary syndromes. Although variable, 1,25D levels tend to be lower and PTH levels higher in patients with kidney disease than in those with the hereditary syndromes. Urinary fractional excretion of phosphate is high in both pre-dialysis kidney disease and genetic hypophosphatemic disorders.

are independent of FGF23 have been identified in the gut[104] and in the central nervous system[105] and, based on studies of primary hypoparathyroidism, FGF23 seems to require at least some PTH to maintain normal serum phosphate levels.[106] Unlike PTH, which changes dynamically in the postprandial state[107] and is affected by concurrent 25D levels,[108] FGF23 seems to be relatively stable over time within individual patients, including those with CKD,[107,109] an important characteristic of a clinically applicable biomarker.

Small studies suggest that FGF23 levels are constitutively elevated in CKD, presumably as a compensatory response to maintain normophosphatemia.[110–112] Under this hypothesis, the early and progressive reduction in 1,25D levels in CKD is less likely due to insufficient renal mass[113] and is more likely due to inhibition by 'secondary' FGF23 excess[110] in addition to other factors, such as vitamin D deficiency, down-regulation of the PTH receptor in the kidney, and accelerated 1,25D degradation.[108,114–117] This hypothesis is supported by cross-sectional studies that showed extremely low rates of hyperphosphatemia, yet markedly increased FGF23 levels in pre-dialysis CKD patients, and independent associations between high FGF23 levels and increased phosphaturia, and between decreased glomerular filtration rate (GFR) and 1,25D levels.[110–112] Moreover, the observation of persistently low 1,25D levels in the posttransplant period despite markedly elevated PTH levels and a high prevalence of hypophosphatemia, each of which should stimulate 1,25D production by the healthy allograft,[118,119] supports an important role for FGF23 in the early development of 1,25D deficiency in CKD.[120,121] Importantly, as increased FGF23 levels are detectable in early CKD long before hyperphosphatemia first develops,[110] increased FGF23 may represent an early, more sensitive biomarker of disordered phosphorus metabolism than concomitant serum phosphate measurements. A number of recent studies highlight this potential.

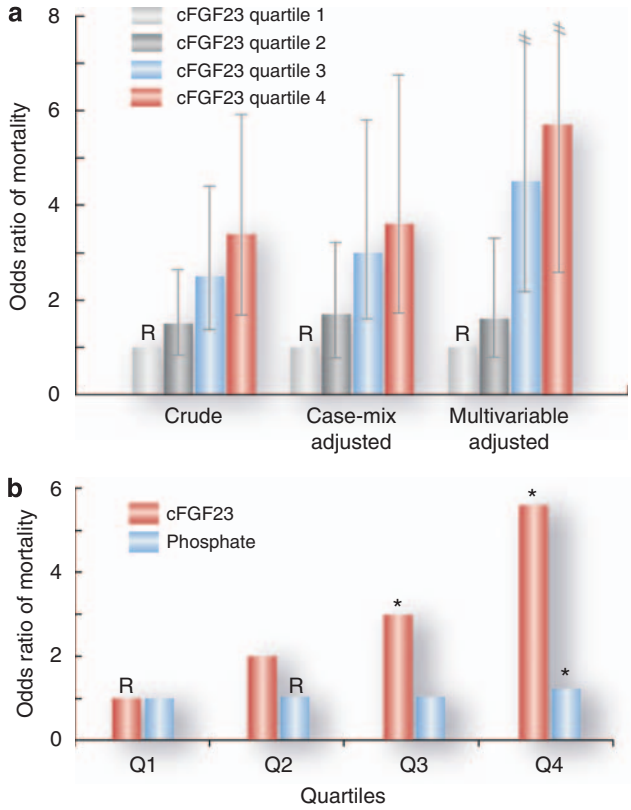

Figure 2 | Associations between FGF23, phosphate, and mortality. (**a**) Crude, case-mix-adjusted, and multivariate-adjusted odds ratio of mortality according to quartiles of cFGF23 levels (quartile 1, <1090 RU/ml; quartile 2, 1090–1750 RU/ml; quartile 3, 1751–4010 RU/ml; quartile 4, >4010 RU/ml). The case-mix-adjusted analysis included the following variables: age, sex, race, ethnicity, blood pressure, body mass index, standardized mortality rates, vascular access, history of diabetes, and congestive heart failure. The multivariate-adjusted analysis included the case-mix variables plus phosphate, calcium, log PTH, albumin, creatinine, and ferritin. Quartile 1 is the reference group in all models. Vertical lines represent 95% confidence intervals. This figure is reproduced from Gutiérrez *et al*,[122] with permission from the Massachusetts Medical Society. (**b**) Multivariate-adjusted odds ratio of mortality according to quartiles of serum phosphate (quartile 1, <3.5 mg per 100 ml; quartile 2, 3.5–4.4 mg per 100 ml (reference group, R); quartile 3, 4.5–5.5 mg per 100 ml; quartile 4, >5.5 mg per 100 ml); and quartiles of cFGF23 (quartile 1, <1090 RU/ml (reference group, R); quartile 2, 1090–1750 RU/ml; quartile 3, 1751–4010 RU/ml; quartile 4, >4010 RU/ml). *$P<0.05$ compared with the respective reference group.

FGF23 AND CLINICAL OUTCOMES

FGF23 and mortality

Given the well-established association between serum phosphate and mortality,[28,29] the relationship between FGF23 levels and mortality was examined in a prospective, nested case–control study of 400 incident hemodialysis patients.[122] As hyperphosphatemia is a risk factor for mortality that correlates with FGF23,[110] confounding by serum phosphate was minimized through frequency matching to randomly select 50 cases and 50 controls within each quartile of baseline serum phosphate in the overall cohort. As therapy with activated vitamin D can stimulate FGF23 secretion[88,100,101] and has been associated with improved survival on hemodialysis,[76,123–125] patients who initiated therapy with activated vitamin D before collection of their baseline blood sample were excluded from the study.

Increased FGF23 levels at the initiation of dialysis were independently associated with significantly increased risk of subsequent mortality during the first year on dialysis. The results were independent of serum phosphate and showed a strong 'dose–response'-type relationship such that ascending quartiles of FGF23 were associated with a linear increase in risk of mortality (Figure 2a). The highest FGF23 quartile was associated with a nearly 600% increased risk of death, which was markedly greater than parallel analyses of phosphate, in which mortality risk was only 20% greater in the highest versus the lower quartiles (Figure 2b). Furthermore, in contrast to the current and previous analyses of serum phosphate levels and mortality, the association between FGF23 and mortality was mostly 'unconfounded', with

minimal change in the risk estimates comparing the crude and multivariate-adjusted analyses (Figure 2a). Finally, the strongest associations between FGF23 and mortality were observed in the three lower phosphate quartiles (<5.5 mg per 100 ml), which coincide with the target range of serum phosphate when therapy is not recommended. The latter supports a potential role for FGF23 screening as a novel biomarker to detect which normophosphatemic patients are, nevertheless, at increased risk of mortality, and thus should be considered for therapy. In other words, FGF23 could prove to be a more sensitive and specific marker than the serum phosphate to guide treatment of disordered phosphorus metabolism.

At first glance, the increased mortality associated with high FGF23 levels may seem to be at odds with the survival benefit attributed to active vitamin D therapy,[76,123–125] given that the latter raises FGF23 levels.[88,100,101] However, these seemingly contradictory findings can be reconciled in a number of ways. It is possible that the effect of FGF23 excess on mortality could be modified by treatment with active vitamin D such that both are independently important, as we have shown previously for PTH.[124] It is also possible that patients who die early on dialysis despite active vitamin D therapy might be those with the highest baseline FGF23 levels or those whose FGF23 levels rose the most in response to therapy. Finally, it is likely that there is a therapeutic window for active vitamin D therapy, whereby too high a dose could be harmful by raising FGF23 excessively, but lower doses might promote less elevation of FGF23 while garnering the many proposed benefits of vitamin D.[126] Further studies that include active vitamin D treated and untreated patients are needed to address these issues.

FGF23 and cardiovascular disease

As CVD is the leading cause of death on dialysis, the relationship between increased FGF23 levels and mortality likely involves a cardiovascular mechanism. Three recent studies support a relationship between FGF23 and vascular disease and LVH.[127–129] In the first study, higher FGF23 levels were independently associated with impaired vasoreactivity in 759 patients with normal kidney function and with arterial stiffness in 208 patients with estimated GFR (eGFR) <60 ml/min/1.73 m^2.[127] In the second study of 124 prevalent hemodialysis patients, higher FGF23, but not serum phosphate levels, were independently associated with LVH and increased left ventricular mass index.[128] Most recently, elevated FGF23 levels were associated with increased left ventricular mass index and increased prevalence of LVH in 162 pre-dialysis CKD patients, independent of traditional risk factors and serum phosphate levels, which were not associated with left ventricular mass index or LVH.[129] In addition, although the highest versus lowest tertile of FGF23 levels was associated with significantly increased risk of severe coronary artery calcification,[129] the statistical significance was attenuated in multivariate analyses, suggesting a need for additional studies with greater power. Underlying these observations, FGF23 could represent a biomarker of total phosphorus or vascular disease burden,[64,122] could exert direct cardiac and vascular toxicity,[64,122] or could act indirectly by inducing 1,25D deficiency, which is a risk factor for LVH[130] and impaired vascular function in CKD.[131] Importantly, although previous studies found serum phosphate levels to be associated with vascular stiffness, LVH, and left ventricular mass index, the results of these studies again suggest that FGF23 may be superior to serum phosphate as a marker of the pathophysiological mechanisms that link disordered phosphorus metabolism with CVD in CKD.

FGF23 and kidney disease progression

To date, one prospective study of 177 non-diabetic CKD patients examined the association between FGF23 levels and kidney disease progression, defined as doubling of serum creatinine and/or terminal kidney failure.[132] During a median follow-up of 53 months, C-terminal FGF23 levels >104 RU/ml (or intact FGF23 levels >35 pg/ml) compared with lower levels were associated with more rapid progression of CKD independent of age, gender, baseline eGFR, proteinuria, and serum levels of calcium, phosphate, and PTH. Although residual confounding by baseline renal function, and earlier therapy with active vitamin D and phosphate binders may be potential limitations, if confirmed, this report suggests that FGF23 may also be a novel marker for CKD progression. Again, the vast majority of patients with elevated FGF23 levels had a normal serum phosphate, highlighting the potential superiority of FGF23 as a marker of disordered phosphorus metabolism when serum phosphate levels are normal.

PHOSPHORUS BINDERS AND CLINICAL OUTCOMES

The evidence linking hyperphosphatemia with adverse outcomes suggests that lowering serum phosphate levels in individual patients will improve their clinical outcomes. However, the survival effects of dietary phosphorus restriction and dietary phosphorus binders have not been evaluated in randomized controlled trials. In fact, all of the phosphorus binders used in clinical practice were approved by the FDA on the basis of their efficacy in lowering serum phosphate levels in short-term studies on dialysis patients rather than in long-term outcome trials.[133–137] Although several trials aimed to determine which specific phosphorus binder is best for dialysis patients,[138–142] until recently, no studies assessed whether any phosphorus binder therapy versus none alters mortality on dialysis.[143] In a prospective observational cohort study of 1-year all-cause mortality in 8610 incident hemodialysis patients, treatment with phosphorus binders during the first 90 days of dialysis was independently associated with an 18–30% lower risk of mortality compared with no treatment. The results were unchanged in an analysis that matched treated and untreated patients on their baseline serum phosphate levels and propensity score of receiving phosphorus binders. Importantly, the survival benefit was

independent of serum phosphate levels, suggesting potential benefits beyond the control of the serum phosphate. Indeed, recent studies show that phosphorus binders lower FGF23 levels in animals,[144] healthy humans,[101] dialysis patients,[145] and in patients with pre-dialysis CKD.[146] Whether aiming to reduce FGF23 levels using combinations of phosphorus binders, dietary counseling,[147] or salivary phosphate-binding chewing gum,[148] might improve outcomes directly or whether FGF23 can be used to guide these therapies in patients with CKD and relatively normal serum phosphate levels are critical questions with public health implications that require rigorous testing in randomized trials.

BLUEPRINT FOR RANDOMIZED TRIALS

Dialysis

Given the large body of observational and supportive experimental data linking phosphorus excess and adverse outcomes, a clinical trial of phosphorus binders and hard clinical end points is long overdue for the dialysis population. However, conducting a placebo-controlled randomized trial of phosphorus binders on dialysis would likely be viewed as unethical given the wide acceptance of the current practice guidelines for maintaining serum phosphate levels between 3.5 and 5.5 mg per 100 ml.[77] Although normophosphatemic dialysis patients could be randomized, many of those in the placebo arm would soon develop hyperphosphatemia requiring treatment or withdrawal from the trial, substantially limiting power. Selecting surrogate end points would shorten the duration of follow-up and thereby prevent attrition in the placebo arm, but agreeing on an acceptable surrogate that would obviate the need for hard clinical end points may not be possible given previous conflicting results with surrogate markers.[138–141]

An alternative study design is a randomized controlled trial to compare the survival of 'intensive' versus 'conventional' serum phosphate control, for example, comparing a target serum phosphate level of 4–5 mg per 100 ml with a target of 6–7 mg per 100 ml. Although the exact target phosphate levels should be debated, the study design might mirror diabetes trials targeting different hemoglobin A1C ranges.[149,150] Although some resistance to the possibility of randomization to a 'conventional' arm might be encountered, we believe clinical equipoise can be justified. First, the current 'standard of care' is largely based on expert opinion.[77] Second, there is no data to suggest that reducing an individual's serum phosphate level increases their chance of survival. Third, it is possible that excessive treatment to achieve potentially unattainable target phosphate levels in certain patients might be harmful if it contributed to excessive calcium loading, osteomalacia, early satiety that exacerbated malnutrition, or exorbitant cost of medications and nutritional counseling.[77,151,152] Not to be discounted is the more subtle adverse effect on the dialysis team–patient relationship resulting from the stigmatization of certain patients who chronically fail to achieve desired, but perhaps unnecessary, phosphate targets as 'non-compliant.' Finally, important lessons can be learnt from the diabetes literature, in which intensive glycemic control was beneficial on a variety of clinical end points,[153,154] but even tighter control to achieve normalization of hemoglobin A1C was actually harmful.[150]

Pre-dialysis CKD

From a public health perspective, the greatest opportunity for improving the management of phosphorus metabolism in CKD resides in the millions of stage 3 and 4 patients, 90% of whom maintain normal serum phosphate levels[155] despite abnormal phosphorus metabolism marked by elevated FGF23 levels.[110] Clinical equipoise permits a placebo-controlled trial, as this population is rarely treated with phosphorus binders based on current guidelines. Indeed, a recent poll of practicing nephrologists indicates that only ~30% of stage 4 CKD patients and less than 20% of stage 3 CKD patients are treated with phosphorus binders.[156] Over 80% of physicians wait until serum phosphate levels exceed the normal range

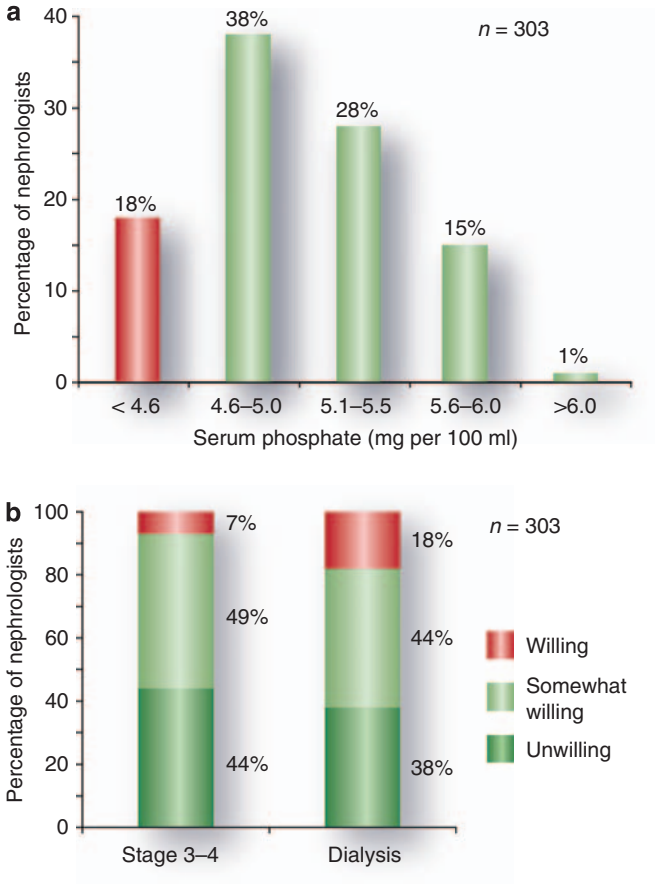

Figure 3 | Nephrologists' attitudes toward phosphorus management. (**a**) Serum phosphate levels when nephrologists ($n = 303$) initiate phosphorus binders in pre-dialysis, chronic kidney disease patients. (**b**) Relative willingness of practicing nephrologists ($n = 303$) to initiate phosphorus binders in patients with normal serum phosphate levels and pre-dialysis or dialysis-dependent chronic kidney disease. Data courtesy of the BioTrends Research Group.[156]

before initiating binders, and less than 8% of the surveyed nephrologists were willing to initiate binder therapy in normophosphatemic patients (Figures 3a and b).[156] The combination of alarmingly high mortality rates in CKD stages 3–4,[10] clinical equipoise for a placebo-controlled study, and the emergence of FGF23 as a marker to help identify which of the millions of normophosphatemic CKD patients might benefit from FGF23/phosphorus reduction strategies sets the stage for an innovative randomized trial in nephrology with implications for the public health.

We propose a placebo-controlled randomized trial of phosphorus binders in normophosphatemic CKD stage 3B and 4 (eGFR 15–44 ml/min/1.73 m^2) patients.[10] Broadly speaking, eligible patients would have a serum phosphate <4.6 mg per 100 ml without previous phosphorus binder therapy, and an FGF23 level above a certain threshold to be determined. Although hypophosphatemia will likely be an uncommon event given previous reports of use of phosphorus binders in pre-dialysis CKD patients in whom serum phosphate levels remained in the normal range,[157] patients who develop hypophosphatemia would reduce or discontinue the use of phosphorus binders. A total of 1000 patients in each arm and a follow-up time of 2 years would provide 90% power with a two-sided alpha of 0.05 to detect a 20% reduction in mortality in the treatment group, assuming an incidence density of 10 deaths per 100 person years in the placebo group, which is equivalent to a median survival of 5 years.[10] A smaller sample size could be used if the power is reduced to 80%, the follow-up duration is extended to allow more events, or a composite end point including major CVD events and renal progression is used, as has been done previously.[17,21] Internal data from our group support the feasibility of identifying a large sample of patients meeting these inclusion criteria: among normophosphatemic pre-dialysis CKD patients, 69% of patients with stage 3b and 4 CKD had C-terminal FGF23 levels $\geqslant 100$ RU/ml and 46% had levels $\geqslant 150$ RU/ml, which are roughly 2–3 times the normal range, respectively.

Additional questions will need to be addressed before embarking on a costly, albeit critically important, randomized, controlled trial. First, it must be shown that the association between increased FGF23 and mortality observed among incident dialysis patients is also detectable in the population to be targeted by the clinical trial, namely patients in stages 3–4. This could be accomplished in large prospective cohorts of CKD patients. Second, it must be shown that treatment with the proposed intervention, specifically phosphorus binders, can lead to sustained reductions in FGF23 levels in the target population. Finally, it will be important to further develop the plausible biological mechanisms to explain the potential beneficial effects of reduction of FGF23 and/or dietary phosphorus absorption, for example, reduction of vascular stiffness[127] or attenuation of LVH.[128,129]

The outlined objectives will require the mobilization of the nephrology community and significant resources. As the findings from the proposed clinical trials, positive or negative, will certainly affect the management of millions of patients worldwide, all of the shareholders in the care of CKD, who will stand to benefit from the results, should contribute to the support of such a monumental effort. Thus, financial and logistical support for the trials should come from a consortium that could include United States government sources such as NIH and Medicare, corresponding international government agencies, pharmaceutical companies with interests in CKD, especially those that manufacture phosphorus binders, large dialysis providers, and United States and international nephrology societies and foundations. Although industry sponsorship is essential, their involvement in the actual design of the specific studies should be kept at arm's length to minimize the possibility of real or, more likely, perceived conflict of interest. Thus, the design of the study and its management must be led by a multidisciplinary team of academic nephrologists, nutritionists, and other health professionals with specific expertise in phosphorus metabolism, FGF23, renal nutrition, biostatistics, and clinical trial conduct.

CONCLUSION

The high prevalence of CKD with its associated CVD risk and high mortality rates has prompted measures to increase awareness, promote early diagnosis, and create guidelines for clinical practice across the spectrum of CKD. The guidelines for phosphorus management that were driven by the need to improve the dismal clinical outcomes in CKD are largely based on expert interpretation of an impressive body of observational data, but minimal confirmatory randomized trials. The publication of the guidelines has focused the nephrology community's clinical efforts, but equally importantly, they have helped crystallize areas of critical gaps in our approach. Although it might be tempting to rapidly advance novel and potentially beneficial therapeutic paradigms into the clinical setting, especially in such a sick population as that of CKD, premature adoption of new 'standards of care' will further hamper the ability to perform definitive randomized trials. Nephrologists and regulatory agencies owe it to their patients to demand these studies. We propose a first-draft of a blueprint of potential randomized, controlled trials of different phosphorus management strategies aimed at improving survival in CKD. Although the optimal study strategies should be debated, such trials are urgently needed, a growing body of evidence supports their feasibility, and the results could dramatically alter the management of kidney disease patients worldwide.

DISCLOSURE

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