Increased levels of phosphorus and fibroblast growth factor-23 (FGF-23) are strong predictors of cardiovascular morbidity and mortality. From a physiological perspective and supported by some data, phosphorus is the main driver for FGF-23 secretion. Therefore, it is conceivable that interventions aiming at restriction of phosphorus uptake from the gastrointestinal tract may lower serum FGF-23 levels and improve cardiovascular risk and subsequently survival. It is not currently known to what extent phosphorus and FGF-23 are independent risk factors, and therefore both need to be targeted. However, their respective metabolisms are tightly connected. Control of phosphorus levels in chronic kidney disease (CKD) patients is attempted mainly by restriction of dietary intake and the use of phosphorus binders. In this review, it is outlined that not just the amount of dietary phosphorus intake is important but also its type (organic vs. inorganic), its source (animal vs. plant derived), and the protein-to-phosphorus ratio in the bioavailability of phosphorus from food. This qualitative aspect of diet is likely a neglected aspect of dietary counseling in CKD. However, in more advanced stages of CKD, dietary restriction of phosphorus alone is usually not sufficient to control hyperphosphatemia, and phosphorus binders are indicated. The inexpensive, calcium-containing dietary phosphorus binders are used commonly worldwide. However, they are not suitable for every patient because of the association with elevated serum calcium, increase in vascular and valvular calcification scores, and cardiovascular and all-cause mortality. The calcium content itself in these binders has recently been implicated to upregulate FGF-23. For that reason, the noncalcium, aluminum-free agents such as sevelamer and lanthanum are being advocated. However, these drugs do not have a clearly defined effect on circulating levels of FGF-23. Although it is conceivable that targeting FGF-23 may lead to improved clinical outcomes, this remains speculative. Therefore, more studies are needed to answer the question if this can be achieved with any of the phosphorus binders, or by another (additional) pharmacological intervention.

Introduction

CHRONIC KIDNEY DISEASE (CKD) is associated with high cardiovascular morbidity and mortality. This increased risk is only partially explained by a higher prevalence of traditional risk factors in CKD, suggesting that some CKD-specific factors may play a causal role. Among these, hyperphosphatemia appears to be among the most important factors, being independently associated with mortality in dialysis patients and nondialysis patients with earlier stages of CKD. In the last decade, fibroblast growth factor-23 (FGF-23) emerged as the most important phosphorus-regulating hormone. Along with parathyroid hormone (PTH), FGF-23 reduces renal tubular reabsorption of filtered phosphorus in response to changes in gastrointestinal phosphorus uptake, thereby preventing major changes in serum phosphorus levels. As such, its function is comparable to PTH. However, FGF-23 function diverges from PTH effects on vitamin D metabolism, leading to a reduced level of active vitamin D, whereas this is increased under the influence of PTH. FGF-23 levels start to increase relatively early in the course of CKD, as early as stage II to III, long before hyperphosphatemia is detectable. As CKD progresses, FGF-23 levels increase further up to 2,000-fold above thereference limit in hemodialysis patients. The progressive rise in FGF-23 levels parallels the progressively increased risk of death and cardiovascular events with deteriorating renal function in CKD. In epidemiologic studies, increased levels of FGF-23 have consistently been related with progressive renal function decline and an increased risk of cardiovascular morbidity and mortality. Epidemiological data are inconclusive regarding the question whether all risks associated with FGF-23 are mediated through phosphorus metabolism, which would imply that FGF-23 is a sensitive biomarker of phosphorus...
load, or whether all presumed toxicity of phosphorus load are in fact due to its FGF-23 stimulating effects. Finally, synergism between FGF-23 and phosphorus in inducing pathology may also exist.

In addition to the above-mentioned epidemiological data, a recent study demonstrated a direct effect of FGF-23 on the development of left ventricular hypertrophy, an undisputed intermediate endpoint in clinical studies, in rodents. Therefore, it is conceivable that interventions aiming at restriction of phosphorus uptake from the gastrointestinal tract may lower serum FGF-23 levels and improve cardiovascular risk and subsequently survival. However, data on the potency of several dietary measures and various types of phosphorus binders to influence FGF-23 and phosphorus in different stages of CKD are scattered. Moreover, some of these measures may have different effects on these 2 targets.

Several studies have recently been published describing the different therapeutic approaches to lower serum phosphate levels in patients with CKD; however, none of these focused on their effect on modulating FGF-23. In this review, we summarize current data on dietary and pharmacological interventions to modulate FGF-23 levels and point out where these interventions may have different or undetermined effects on these 2 laboratory values.

Targeting FGF-23 via Lowering Phosphate Uptake in the Gastrointestinal Tract

The most described way of targeting FGF-23 is through lowering serum phosphate levels. This can be achieved by a phosphate–restricted diet and/or the administration of phosphate binders. Although the assumption that FGF-23 levels reflect phosphorus exposition over a preceding period has been recently challenged in hemodialysis patients, it is conceivable that targeting phosphorus as a means to lower FGF-23 is a justifiable approach.

Phosphorus Metabolism

Daily phosphorus ingestion is approximately 1,000 to 1,200 mg, of which approximately 950 mg is absorbed, mostly via the paracellular route. The total amount of phosphorus in humans is 500 to 700 g. More than 80% is stored in bone and teeth as an insoluble form of calcium salt. Phosphorus is also found in the intracellular compartment. The intracellular part is interchangeable with the extracellular fluid via specific channels. Less than 1% is present in the extracellular fluid, the compartment from which the phosphorus content is usually judged in clinical practice. Phosphorus is lost from the organism by the gastrointestinal tract (150 mg/day) and the urine (800 mg/day). In healthy people, a high dietary phosphorus intake leads to only a slight increase in plasma phosphorus level because of a rise of serum PTH and FGF-23 levels and increased urinary phosphorus excretion, thus balancing phosphorus intake and loss. However, in hemodialysis patients and those with predialysis CKD, the renal excretion of phosphorus is seriously impaired and the dietary intake of phosphorus exceeds the renal excretion capacity. Although the excretion via saliva and the gastrointestinal tract increases in CKD, it cannot outweigh the decrease in renal phosphorus excretion and almost always leads to hyperphosphatemia. Therefore, the potential ways to target the high phosphorus load are by dietary management, salivary and gastrointestinal phosphorus binding, or manipulating phosphorus transporters in the intestines (i.e., NaPi-IIb).

Phosphorus Intake From Different Sources and Its Availability

Phosphorus is naturally found in foods that are rich in protein. There is a close relationship between protein and phosphorus intake. A high protein intake may increase hyperphosphatemia and thus FGF-23 levels. In addition, a low dietary protein content slows the progression of kidney disease, especially in patients with proteinuria. Therefore, control of phosphorus load has been endeavored by restriction of dietary protein intake. However, if dietary protein restriction is too stringent, then this is associated with increased prevalence of malnutrition and higher morbidity and mortality. Thus, there is a delicate balance between low phosphorus intake and sufficient protein intake. Recent reports suggesting that the source of phosphorus, and not just its amount, in food is of importance for the bioavailability of phosphorus and this may be important to overcome this clinical dilemma.

Phosphorus in our diet exists in 2 different forms: inorganic or organic phosphorus. Inorganic phosphorus is mostly used as a preservative or additive for taste. It is interesting to realize that even foods such as ham also contain inorganic phosphorus, apart from protein–derived phosphorus, as an appetizing additive. Absorption of inorganic phosphorus is very high—above 90%. Unfortunately, the amount of inorganic phosphorus in processed foods is often unclear because manufacturers are not required to provide this information. An elegant clinical study demonstrated that teaching hemodialysis patients which products contain high amounts of inorganic phosphorus (e.g., sodas) and asking them to limit intake of such products significantly lowered serum phosphorus levels.

On the other hand, organic phosphorus found in protein has a relatively low absorption of approximately 40% to 60%. Phosphorus in meat is present within the cells as organic phosphorus, which is hydrolyzed in the intestinal tract and easily absorbed. By contrast, phosphorus in plants, especially beans, nuts, cereals, and peas, is mostly in the form of phytate. Because mammals lack the phytase-degrading enzyme phytase, the bioavailability of phosphorus from plant–derived foods is relatively low despite their high phosphorus content. For patients with CKD, this
Figure 1. Schematic representation of differences in bioavailability among different dietary sources of phosphorus. The sources that are low in the diagram represent the lowest uptake of phosphorus from the gastrointestinal tract. Dairy source is depicted separately because in general it has an unfavorable phosphorus-to-protein ratio. See text for detailed explanation.

difference of bioavailability of phosphorus may be of great importance (Fig. 1).

In a pilot study in rats with renal failure, Moe and colleagues showed lower serum phosphorus, urinary phosphorus excretion, and serum levels of FGF-23 in rats that were fed a grain-based protein diet compared with those that were fed a casein-based diet with comparable contents of protein and phosphorus. In a clinical crossover study, they further demonstrated the decreased bioavailability of phosphorus and a significant decrease in FGF-23 levels during a vegetarian diet period as compared with a meat diet period in patients with CKD Stage III and IV. This decrease in FGF-23 levels occurred despite normal levels of serum phosphorus and an equivalent phosphorus content in both diets. In addition, an observational cross-sectional study in 2,938 patients with CKD showed that the consumption of a higher percentage of protein from plant sources was associated with lower levels of FGF-23 without affecting serum phosphate, PTH, potassium, hemoglobin, or albumin.

The Kidney Disease Outcomes Quality Initiative guidelines recommend that dietary phosphorus intake should be restricted to 800 to 1000 mg/day for patients with CKD. However, this recommendation does not take into account the above-mentioned differences in bioavailability that are based on the source of phosphorus. Moreover, the quantity of dietary phosphorus intake is often underestimated. In addition, it leaves the clinician with the dilemma to balance between phosphorus loading and malnutrition. Therefore, the phosphorus- (in milligrams) to-protein (in grams) ratio would be more suitable for patients with CKD to compute their daily phosphorus intake because it is independent of the size of the food portion and it focuses on dietary phosphorus and protein. Unfortunately, this ratio also does not take into account the above-mentioned difference in bioavailability of the different phosphorus sources. In summary, a diet that is reasonably low in overall phosphorus content, but especially low in inorganic phosphorus, may be capable of preventing phosphorus loading while avoiding the malnutrition and higher morbidity and mortality induced by a protein intake that is too low. In the context of the current review, it is crucial to realize that virtually none of these potential dietary interventions have been evaluated for its effect on FGF-23 levels.

Effect of Different Phosphorus Binders on Serum Phosphorus and Their Effect on Mortality

In more advanced stages of CKD, especially from Stage IV onward, dietary restriction of phosphorus alone is usually not sufficient to control hyperphosphatemia, and phosphorus binders are indicated. Savica and colleagues reported on salivary phosphorus binding. Salivary phosphorus correlates with plasma phosphorus in hemodialysis patients, with a salivary phosphorus content being at least 5 times higher than the plasma phosphorus content. The salivary phosphorus content in CKD patients correlates negatively with glomerular filtration rate. The compensatory effect of increased salivary phosphorus excretion is nullified by swallowing the saliva including the phosphorus content, after which it is reabsorbed in the gut. For this reason, Savica and colleagues gave 13 hemodialysis patients 20 mg of chitosan-loaded chewing gum twice daily for 2 weeks in addition to their prescribed phosphorus binding regimen. Salivary phosphorus and serum phosphorus significantly decreased during this period. This suggests that salivary phosphorus binding could be a useful addition to dietary management and gastrointestinal phosphorus binders.

Administration of phosphorus binders is associated with lower mortality in patients with nondialysis-dependent and dialysis-dependent CKD. After abandoning aluminum as phosphorus binding therapy because of potential systemic aluminum toxicity, calcium-containing dietary phosphorus binders became the most commonly used compound for this indication worldwide. They are inexpensive and apart from their phosphorus binding capacity, they correct hypocalcemia, with the latter being considered advantageous for preventing or treating secondary hyperparathyroidism (SHPT). There is no meaningful difference between calcium acetate and calcium carbonate in their capacity to lower phosphorus. However, they may not be suitable for every patient because of their induction of a positive calcium balance and its associated progression of vascular calcification and a dose-limiting hypercalcemia.

Probably even more important is that several observational studies show an association between elevated serum calcium and the calcium-phosphorus product with all-cause and cardiovascular mortality.
these reasons, the much more expensive noncalcium-containing and aluminum-free agents, sevelamer and lanthanum, are being advocated. Sevelamer lowers serum phosphorus without promoting arterial calcification or even attenuating arterial calcification in contrast to calcium-containing binders.\textsuperscript{55,63-66} although this has not been confirmed by all studies.\textsuperscript{67-69} Data on the difference in all-cause mortality or cardiovascular mortality between noncalcium-based agents and calcium-based agents are still inconsistent.\textsuperscript{70-76}

**Phosphorus Binders and Their Effect on FGF-23**

Several studies reported about the effects of the different phosphorus binders on FGF-23. Oliveira and colleagues performed a pilot study assessing the effects of calcium acetate or sevelamer hydrochloride in patients with CKD Stages III to IV and normal serum phosphorus levels for a 6-week period. They showed that during treatment with both phosphorus binders there was a progressive decrease in serum PTH and 24-hour urinary phosphorus excretion, but no changes in serum calcium or serum phosphorus were seen. Serum FGF-23 was only significantly reduced at week 6 in the sevelamer hydrochloride group.\textsuperscript{77}

In a short study of 2 weeks, Isakova and colleagues assessed the capability of lanthanum carbonate, phosphorus-restricted diet, or a combination the 2 to lower FGF-23 levels.\textsuperscript{78} Although a substantial and statistically significant decrease in 24-hour urine phosphorus excretion was achieved in both treatment arms, this was not accompanied by a decrease in FGF-23 levels. This finding can be explained by too short of follow-up, or it could lead to the conclusion that the assumption that phosphorus is the main driver of FGF-23 secretion is a misconception. To test the first hypothesis, Gonzalez-Parra and colleagues added lanthanum carbonate for another 4 weeks after a phosphorus-restricted diet of 4 weeks. Indeed, although serum phosphorus did not change, 24-hour urinary phosphorus excretion and serum FGF-23 levels decreased.\textsuperscript{79} This was confirmed in a recently published additional study of Isakova and colleagues in which they extended the treatment period to 3 months. In this study there was no difference in FGF-23 levels with either a 900-mg phosphate diet or lanthanum carbonate alone, but a combination of these interventions significantly decreased FGF-23 levels.\textsuperscript{80} Yilmaz and colleagues compared an 8-week intervention with calcium acetate to sevelamer in hyperphosphatemic patients with CKD Stage IV. In both arms a decrease in serum phosphorus was found, but more markedly in the sevelamer group. However, it is important to note that FGF-23 changes were reciprocal: a decrease in those treated with sevelamer and an increase in those treated with calcium acetate. An interesting finding was that a decrease in FGF-23 levels was associated with increased flow-mediated vasodilation.\textsuperscript{81} Bleskestad and colleagues performed a crossover trial in which 21 patients with CKD Stage IIIb and a normal phosphate level were split in 2 groups: group 1 was treated with alphacalcidol for 2 weeks followed by sevelamer carbonate for 2 weeks after a 2-week washout period; group 2 was treated vice versa. The patients in group 2 had a nonsignificant increase of intact fibroblast growth factor 23 (iFGF-23) levels after treatment with sevelamer. However, the patients treated in group 1 had a significantly lower iFGF-23 level after treatment with sevelamer compared with baseline levels.\textsuperscript{82}

The very recently published data of the prospective cohort study of Spatz and colleagues in patients with CKD Stages III and IV with hyperphosphatemia did not show a change in serum FGF-23 levels after 3 months of treatment with sevelamer carbonate despite a significant difference in phosphorus. However, the phosphorus decrease, although statistically significant, was only modest. Because no forced uptitration of sevelamer was applied, 62% remained on the initial low dose of the phosphorus binder. Finally, the change in 24-hour urinary phosphorus excretion after the initiation of sevelamer was not reported. Therefore, it is uncertain if dosing was adequate to induce a FGF-23 reduction.\textsuperscript{83}

A recent study that compared 3 groups of phosphorus binders with placebo did not show a statistically significant decrease in serum FGF-23 in the 3 pooled treatment arms. However, the effects on intact FGF-23 differed by binder type; only patients treated with sevelamer carbonate had a significant decrease in intact FGF-23 from baseline, but this study was not powered to detect differences between groups.\textsuperscript{84} Presumed differences between effects of phosphorus binders on FGF-23 level may be explained by differences in phosphorus binding capacity. However, despite similar reductions in serum phosphorus levels, sevelamer lowers FGF-23 more than calcium-containing phosphorus binders.\textsuperscript{77,84} Even more, calcium-based phosphorus binders are associated with higher serum FGF-23 levels.\textsuperscript{85} It is suggested that serum calcium itself is a direct regulator of the FGF-23 levels.\textsuperscript{86-88} From a teleological point of view, the reason for this may be another hypercalcemia-induced way to inhibit vitamin D activation by FGF-23 action.

**Cinacalcet and FGF-23**

SHPT is a common complication in CKD patients. As kidney function declines, the synthesis of active vitamin D is suppressed because of increased levels of serum FGF-23. This deficiency of active vitamin D stimulates PTH secretion and triggers the early development of SHPT.\textsuperscript{89,90} FGF-23 also acts directly on the parathyroid to decrease PTH synthesis and secretion.\textsuperscript{91} However, in uremic patients with SHPT, this inhibitory effect of FGF-23 on the parathyroid is blunted.\textsuperscript{10,92} There are data suggesting that this is caused by local Klotho downregulation, mediated by hypermethylation in the Klotho gene promoter region.
because of uremic toxins, leading to resistance to FGF-23 inhibition in the parathyroid glands.\textsuperscript{93-95} It is important to note that PTH in turn induces FGF-23 transcription and secretion,\textsuperscript{96} thus forming a negative feedback loop. In CKD, because of the relative resistance of the parathyroid gland to the inhibitory effect of FGF-23, this negative feedback control is interrupted and actually leads to an amplification of PTH and FGF-23 production. For this reason it is conceivable that lowering PTH might lead to a decrease in FGF-23 levels.

Cinacalcet is a calcimimetic drug that acts by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. Cinacalcet effectively lowers PTH levels and serum calcium and phosphorus in patients with SHPT.\textsuperscript{97-100} Indeed as expected, it also lowers serum FGF-23 levels.\textsuperscript{101,102}

**Vitamin D and FGF-23**

In vitro and in vivo calcitriol administration raises the production of FGF-23 in bone and osteoblasts, leading to increased FGF-23 levels.\textsuperscript{103,104} Wolf pointed to the paradox of elevated FGF-23 levels that are associated with a higher mortality while active vitamin D therapy, which also is associated with improved survival, increases the production of FGF-23. He hypothesized that individuals have variable responses to active vitamin D in terms of FGF-23 increments. Thus, if a patient with a high baseline FGF-23 level reacts with only a modest increase in FGF-23 after active vitamin D, the benefits of the latter outweigh the dismal effects of a slight increase in FGF-23.\textsuperscript{11} However, the interacting effects of vitamin D and FGF-23 are far from clarified, both from a physiological perspective and in their effects on clinical outcome.

**Conclusion**

The independent roles of phosphorus and FGF-23 on clinical endpoints are far from elucidated. Epidemiological data strongly suggest a role for both. In clinical practice, especially from stage IV CKD onward, control of these 2 potentially toxic compounds is increasingly challenging. The currently available interventions controlling phosphorus and FGF-23 are dietary interventions and phosphorus binding therapy. This review outlines that data are available that show that not just the amount of dietary phosphorus intake is important but also its type (organic vs. inorganic), its source (animal vs. plant derived), and the protein-to-phosphorus ratio in the bioavailability of phosphorus from food. However, in daily practice this knowledge is barely translated in therapeutic strategies, and patients with CKD are too little educated to apply this knowledge. In more advanced stages of CKD, dietary restriction of phosphorus alone is usually not sufficient to control hyperphosphatemia, and phosphorus binders are indicated. Data are emerging that, although phosphorus binding capacity may be comparable between several binders, their effects on FGF-23 may differ entirely (i.e., increase with calcium-containing binders). It is currently unknown whether clinical application of these new insights will ultimately lead to improved outcome. At present, it is unfortunately not even well described if additional interventions or uptitrating of phosphorus binder therapy lead to a stepwise decrease in phosphorus and FGF-23 levels. Therefore, more detailed research is needed to elucidate the effects of diet and phosphorus binder therapy on FGF-23 levels and the feasibility to induce an effective, predictable, and sustained decrease in FGF-23 level in patients with different stages of CKD without inducing hypophosphatemia. Such knowledge is crucial to define safe treatment targets for optimal risk reduction in the burden of CKD.

**Practical Application**

The most practical approach to modify FGF-23 levels currently appears to be through phosphorus control. Novel insights about phosphorus availability are likely underused, although its effects on FGF-23 are unproven. It is important to note that important differences exist among phosphorus binders and their capability to lower FGF-23 levels. In particular, calcium-containing binders counterintuitively appear to increase levels of FGF-23.

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