Phosphorus and the Kidney: What Is Known and What Is Needed[1,2]

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ABSTRACT

A major role of the kidneys is to maintain phosphorus homeostasis. High serum phosphorus has been linked to all-cause and cardiovascular mortality in chronic kidney disease (CKD) both before and after initiation of renal replacement therapy. Considering the clinical implications of uncontrolled hyperphosphatemia, maintenance of phosphorus concentrations within an optimum range is standard of care in this patient population. Recently, the epidemiologic associations between serum phosphorus and worse outcome have been extended to the general population. This becomes even more important in view of the increasing dietary phosphorus intake in the American diet due in large part to the greater consumption of foods processed with phosphate additives. A greater understanding of mechanisms and epidemiology of altered phosphorus metabolism and disease in CKD may help clarify the possible role of excess dietary phosphorus as a health risk factor in the general population. *Adv. Nutr. 5: 98–103, 2014.*

Introduction

The kidneys play an essential role in the regulation of serum phosphorus concentration, ensuring that urinary phosphorus excretion matches the net absorption of phosphorus from the gastrointestinal tract. In the presence of normal kidney function, fasting serum phosphorus is maintained within a tight range despite wide fluctuations in dietary phosphorus intake through variations in the urinary phosphorus excretion. These considerations are important because of the evidence that the phosphorus content of the American diet has been increasing, mostly due to increased consumption of foods processed with phosphate additives (1).

Due to the important role of the kidneys in maintaining phosphorus homeostasis, an elevated serum phosphorus concentration is a common manifestation of advanced chronic kidney disease (CKD)[3], which can lead to substantial health problems in this population, most importantly bone and cardiovascular disease (CVD). Moreover, several longitudinal studies have linked hyperphosphatemia with CKD progression. In the current review, we discuss all of these areas as well as their implications for potential health risks in the general population.

Association between Serum Phosphorus and Bone Disease

Because the kidneys are major regulators of phosphorus in the body and are responsible for maintaining its serum concentrations within the physiologic range, it is not surprising that when renal function begins to decline, this homeostasis is disrupted and serum phosphorus begins to increase. An increase in serum phosphorus causes parathyroid hyperplasia leading to secondary hyperparathyroidism and ultimately bone disease. For some time during the course of renal disease progression, however, phosphorus retention and its physiologic effects may develop without overt fasting hyperphosphatemia.

High-turnover bone disease is a known clinical manifestation of advanced CKD resulting from secondary hyperparathyroidism. The term "renal osteodystrophy" was initially coined to describe this phenomenon. This disease is important because eventually it leads to bone fractures, and as a result, CKD patients have a higher risk of fractures, even in early stages. A recent report found that white women with CKD stages 3–4 had 2.5 times as many nonvertebral fractures as those without CKD, whereas the risk in black women with

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[3] Abbreviations used: Akt, protein kinase B; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; Pit-1, pituitary-specific positive transcription factor 1; PKC, protein kinase C.

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CKD was approximately double compared with those without CKD (2,3). Of interest, over time, bone biopsies in CKD patients have shown a shift toward more adynamic bone disease rather than high-turnover disease (2).

Currently, however, it is clearly recognized that these bone abnormalities are manifestations of disturbed mineral metabolism also affecting extraskeletal sites (vascular calcifications) and therefore the term "CKD-mineral and bone disorder" is now frequently used to describe this syndrome, which is very prevalent in CKD and dialysis patients.

Short-term oral phosphorus loading in healthy volunteers has shown a marked effect on stimulating release of parathyroid hormone, a potential marker of bone disease (4). Furthermore, an increase in dietary phosphorus has been associated with increased prevalence of bone fractures in the general population (5).

Association between Serum Phosphorus and CVD

Advanced CKD, even in young patients, is associated with an increased propensity for calcifications (6). Although it has been known for decades that in end-stage renal disease (ESRD), hyperphosphatemia causes soft tissue calcification including vascular calcifications, until recently the impact of vascular calcification on survival in patients with CKD had not been appreciated. Currently, it is increasingly accepted that the presence of excess vascular calcification, particularly coronary artery calcification may play a pivotal role in the disproportionately high burden of CVD in this patient population (7–9). Attention to this problem was first raised by Block et al. (10) in 1998 when they examined the associations between serum phosphorus, calcium phosphorus product, and mortality in 6000 U.S. hemodialysis patients. This study showed that there was an independent association of serum phosphorus concentrations $\geq$5.5 mg/dL with all-cause and cardiovascular mortality. This association with mortality is not limited to hemodialysis patients. A large retrospective cohort study in 6730 CKD patients in the Veterans Affairs Medical Centers showed that a serum phosphate concentration >3.5 mg/dL was independently associated with mortality, and this risk increased linearly with each subsequent 0.5-mg/dL increase in concentration (11). This association between mortality and high phosphorus concentrations has been shown repeatedly, with a large study in >40,000 hemodialysis patients showing that serum phosphorus concentrations $\geq$5 mg/dL are associated with an increased risk of death (12). These findings have been corroborated independently in other countries. For example, an Italian group showed an association between serum phosphorus and the likelihood of death in >1700 CKD patients (13). A recent meta-analysis including 47 studies and 327,644 CKD participants further supports the evidence of an association between higher serum phosphorus and mortality in this population (14).

More recently, increasing evidence has extended the epidemiologic link between elevated serum phosphorus and adverse outcomes in patients who have only mild to moderate renal dysfunction or even apparent normal kidney function. In a post hoc analysis of data from the Cholesterol And Recurrent Events (CARE) Study, there was a graded independent relation between elevated phosphorus and risk of death in people with prior myocardial infarction (15). Interestingly, most of the participants in this study had baseline serum phosphorus in the normal range and the baseline estimated glomerular filtration rate (eGFR) was >60 mL/(min · 1.73 m^2) in each group analyzed. Also, there was a recent study (16) that examined the relation between time-averaged phosphorus concentrations over 11 y and mortality in participants with eGFR >60 mL/(min · 1.73 m^2). It was found that the risk of mortality increases by 1.09 (HR: 1.09; 95% CI: 1.06, 1.84) with every mg/dL increase in serum phosphorus.

The mechanism behind the association between hyperphosphatemia and adverse cardiovascular outcomes has been attributed to phosphorus-induced vascular calcification, but there may be many other potential explanations. An acute elevation of serum phosphorus might be associated with acute endothelial dysfunction. This was shown in a small group of healthy Japanese men (17). In a double-blind crossover study, 11 health men were alternately served 1 single meal containing either 400 or 1200 mg of phosphorus. Serum phosphorus concentrations and flow-mediated dilation of the brachial artery were measured before and 2 h after the meals. The high dietary phosphorus load increased serum phosphorus at 2 h (by an average of 0.8 mg/dL) and significantly decreased flow-mediated dilation (by an average of 4.5%). Moreover, in vitro experiments showed that high phosphorus loading inhibited NO production through increased reactive oxygen species production and endothelial NO synthase inactivation via conventional protein kinase C (PKC), resulting in impaired endothelium-dependent vasodilation (17). This suggests that a significant, acute postprandrial elevation of serum phosphorus secondary to oral phosphorus loading may be as important in the pathogenesis of CVD as average phosphorus concentration. There are also concerns that phosphorus might induce direct actions on the myocardium, inducing fibrosis (18). Although there have been in vitro studies demonstrating this, direct clinical evidence has been provided by studies that have linked hyperphosphatemia to left ventricular hypertrophy, both in CKD (19) and ESRD patients (20). There is also an association between higher serum phosphorus and arterial compliance (21), which may indirectly lead to left ventricular hypertrophy.

Fibroblast growth factor 23 (FGF23) is a relatively novel hormonal factor that plays an important role in phosphorus homeostasis. FGF23 concentrations increase progressively beginning in early CKD, presumably as a physiologic adaptation to maintain normal serum phosphate concentrations (22). Increased FGF23 concentrations have emerged as a risk factor for adverse outcomes including death in patients with CKD (23,24). Increased FGF23 concentrations have been also associated with higher risk of heart failure, stroke, and death among individuals with preserved renal function (25). Whether most of the CVD risk associated with elevated serum phosphorus could be explained by elevated

FGF23 remains an area of debate and an exciting area of future research.

Association between Serum Phosphorus and Progression of Kidney Dysfunction

Experimentally, high dietary phosphorus has been shown to initiate and/or worsen progression of kidney dysfunction (26), whereas dietary phosphate restriction reverses and/or restricts the dysfunction (27). Although the most common explanation has been phosphorus-induced calcification, there are other potential proposed mechanisms including phosphorus-dependent podocyte injury due to overexpression of pituitary-specific positive transcription factor 1 (Pit-1) transporter in rats (28). It is also possible that the deleterious effect of acute phosphorus loading on systemic endothelial function described above might also extend to the glomerular endothelium.

Much less is known clinically about the potential effect of serum phosphorus concentrations on rate of progression of CKD, but there have been a few clinical studies on this subject. O'Seaghdha et al. (29) demonstrated that the relative risk of developing ESRD was much higher in CKD patients with serum phosphorus concentrations >4 mg/dL in NHANES participants. On analysis of historical data by Schwarz et al. (30) in a cohort of U.S. veterans with CKD, patients with elevated serum phosphorus had a higher risk of developing ESRD or worsening CKD. In a post hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) Study, Zoccali et al. (31) found an independent risk of elevated serum phosphorus with progression to ESRD or worsening CKD in patients with proteinuric CKD and attenuation of the renoprotective action of ramipril. Chue et al. (32) showed that increased baseline serum phosphorus was an independent predictor of both decline of glomerular filtration rate and progression to ESRD. In a post hoc analysis of the African American Study of Hypertension and Kidney Disease (AASK) Study, elevated baseline serum phosphorus was independently related to decline in glomerular filtration rate and progression to ESRD (33). In a recent, large multiethnic study in ~100,000 patients, Sim et al. (16) showed that the incidence of ESRD was higher with higher concentrations of serum phosphorus.

As a counterpoint to these large studies associating phosphorus with progression of kidney dysfunction, there was another recent large study (34) using data from the Kidney Early Evaluation Program (KEEP) Study in which no independent association was found between serum phosphorus concentrations and progression to ESRD. In 10,672 patients, there was a higher prevalence of CVD among the highest quartile of serum phosphorus, but there was no increase in all-cause mortality or progression to ESRD after adjustment for demographic and clinical data in multivariable analysis. The limitations of this latter study include a shorter follow-up period compared with other follow-up studies, such as the AASK clinical trial (33), and measurement of serum phosphorus only at baseline and not averaged over time, such as in Sims et al. (16).

All of these studies have the limitation of being observational in nature and thus cannot be used to establish causation. This applies even for data from randomized controlled trials (31,33) because the initial randomization was for variables other than phosphorus.

Interestingly, elevated concentrations of FGF23 have also been associated with increased progression to ESRD. This was shown in 2011 in a large prospective study in 3879 participants with CKD stages 2–4, which showed that the risk of all-cause mortality and progression to ESRD increased with increasing quartiles of FGF23 (35). This association was previously shown in a smaller cohort of 227 nondiabetic patients with mild CKD (36). In both of these studies, the association remained constant despite adjusting for phosphorus concentrations, suggesting a more complex interrelation between FGF23, phosphorus, and CKD progression, which should be explored in more detail.

Recently, analyses of data from the Multi-Ethnic Study of Atherosclerosis (MESA) Study showed a strong, independent association between dietary phosphorus intake and left ventricular mass assessed by magnetic resonance (37). Acute oral phosphorus loads have been previously linked to impaired endothelial function as discussed earlier (17) as well as elevated FGF23 concentrations (38,39).

A recent study (40) showed a significant increase in FGF23 concentrations with increased dietary phosphorus intake in community-dwelling adults with preserved renal function. This is in contrast to another recent study in nearly 4000 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study (41), in which there was no association between dietary phosphorus intake and FGF23 concentrations. The reasons for this discrepancy might be that phosphorus intake is more strongly associated with FGF23 concentrations in individuals with normal kidney function compared with those with CKD. Another possibility for the different findings is that a larger proportion of individuals in the CRIC study were of lower socioeconomic status, who generally consume higher quantities of foods containing inorganic phosphorus additives, which are incompletely captured by standard dietary surveys.

Attention has been called to a potential association between phosphorus and cancer (42). High dietary phosphorus was found to promote tumorigenesis and altered protein kinase B (Akt) signaling in a lung cancer mouse model. The applicability of these experimental findings to the clinical situation, however, remains undefined. **Table 1** summarizes several potential mechanisms that may provide a mechanistic link between elevations of serum phosphate and tissue injury and therefore eventual clinical disease.

Do the Risks Associated with High Serum Phosphorus in CKD Patients Also Apply to the General Population?

The phosphorus content of the American diet has been increasing, mostly due to the consumption of foods processed with phosphate additives (1). We know from CKD patients that increasing serum phosphorus even with normal dietary phosphorus intake may be associated with worse outcome. We believe that increased dietary phosphorus intake beyond

TABLE 1 Postulated potential mechanisms of phosphate toxicity[1]

1. Increasing tissue calcification by increasing Ca × P product (26)
2. Increasing tissue calcification indirectly by several mechanisms including vascular smooth muscle cell osteoblastic differentiation by upregulation of transcription factors such as RUNX-2 and MSX2 (53)
3. Inducing cardiac fibrosis (18)
4. Increasing Ca × P product, which decreases serum Ca concentration and therefore increases PTH release (4)
5. Increasing FGF23 release, which in turn affects other cardiovascular tissues (25)
6. Increasing oxidative stress, which inhibits NO production leading to endothelial dysfunction (17)
7. Inducing overexpression of Pit-1 transporter, leading to podocyte injury (28)
8. Stimulation of Akt signaling, probably favoring tumorigenesis (54)

[1] Akt, protein kinase B; Ca, calcium; FGF23, fibroblast growth factor 23; MSX2, muscle segment homeobox transcription factor 2; P, phosphorus; Pit-1, pituitary-specific positive transcription factor 1; PTH, parathyroid hormone; RUNX-2, runt-related transcription factor 2.

nutritional needs seriously disrupts phosphate homeostasis in healthy individuals, which may have significant potential public health consequences in terms of bone, cardiovascular, and kidney disease, even in the presence of normal kidney function.

A direct relation between dietary intake and serum phosphorus can be clearly documented in dialysis patients. Dietary phosphorus restriction or the use of oral phosphate binders is clearly followed by a significant fall in serum phosphorus (43,44). Therefore, serum phosphorus could be used as a surrogate of dietary intake in this population. This relation, however, has not been clearly documented in healthy individuals or CKD patients not yet on dialysis. A cross-sectional study assessing 15,513 participants in NHANES III showed a statistically weak but significant association between dietary and fasting serum phosphorus concentrations (45).

Several factors may confound the relation between dietary intake and serum phosphorus concentrations and help explain the above-described negative findings (45). First, serum phosphorus undergoes significant circadian variation. The concentration might vary as much as 2 mg/dL during a 24-h period (46). The renal handling of dietary phosphorus is so precise that serum fasting phosphorus concentrations remain unchanged in the presence of wide variations in intake, which will be reflected only by repeated measurement of serum phosphorus throughout the day. Therefore, fasting serum phosphorus is a very poor indicator of dietary phosphorus intake. This does not prevent, however, the possibility that increased fluctuations of serum phosphorus during the daytime when an individual is consuming a high-phosphorus diet (46) would have significant negative effects: for example, an acute impairment of flow-mediated dilatation of the brachial artery (17).

A second important factor affecting the relation between dietary phosphorus intake and serum phosphorus is a fact we have previously reported: the current databases used to estimate dietary phosphorus intake might significantly underestimate it (1,47). At least part of this underestimation results from the increasing use of phosphorus-containing ingredients that are not captured in the national food consumption surveys, including those in NHANES III.

The different bioavailability of phosphorus from various food sources is an important confounder of the relation between dietary phosphorus and serum phosphorus. Thus, phosphorus in cereals will be less absorbed than the same amount of phosphorus in meat. Yet another confounder is the ratio between calcium and phosphorus dietary intake. The lower the calcium:phosphorus ratio, the higher the chance of adverse events for any dietary phosphorus intake (48).

What Is Needed Now?

Despite the large number of observational studies on the relation between serum phosphorus and adverse outcomes described above, there yet have been no randomized controlled interventional trials testing directly the effect of modifying phosphorus serum concentrations/dietary intake on outcomes. Therefore, it remains undetermined whether phosphorus is a passive marker for adverse events or a real toxin.

Although there have been no clinical trials in which reducing dietary phosphorus intake was the primary intervention, indirectly we can look for answers in clinical trials with dietary protein restriction that is directly linked to phosphorus intake. The Modification of Diet in Renal Disease (MDRD) Study was a large multicenter clinical trial in which modification of intake of dietary protein, and thus intake of dietary phosphorus, was the primary intervention. Although the study failed to achieve its end point of reducing GFR loss in CKD patients (49), a significant reduction in the risk of ESRD or death was observed during extended follow-up of several months in those patients with reduced dietary protein intake ($P = 0.05$). In a meta-analysis of 5 studies of nondiabetic renal disease, a low-protein diet significantly reduced the risk of renal failure or death (RR: 0.67; 95% CI: 0.50, 0.89) (50). Also, in a recent prospective randomized study in 82 type 1 diabetic CKD patients followed for 4 y with either a daily protein intake of 1.02 g/(kg · d) or 0.89 g/(kg · d), ESRD or death occurred in 27% of patients receiving the higher protein diet compared with 10% of those consuming a low-protein diet (log-rank test, $P = 0.042$) (51). After adjustment for the presence of CVD at baseline, the RR of ESRD or death was 0.23 (95% CI: 0.07, 0.72) for patients assigned to the low-protein diet ($P = 0.01$). Thus, all of these comparisons of randomized groups are consistent with, but do not prove, a beneficial effect of either protein restriction or, by extension, of phosphorus restriction on mortality

A reasonable approach would be to randomly assign a group of incident dialysis patients to 2 amounts of serum phosphorus over 1–2 y and then determine the cardiovascular mortality in both groups. Considering the high cardiovascular mortality in this particular patient population, conducting such a trial would not need a large sample size. However, conducting a similar trial in CKD patients or patients with preserved renal function would require a huge sample size because the incidence of cardiovascular mortality is much less. If we found significant results in the dialysis patients,

we could possibly extrapolate them to the remaining target populations.

Importantly, even if patients wanted to attempt a tight control of dietary phosphorus intake, it would be difficult because the extra phosphorus added for food processing remains unaccounted for. Therefore, an important tool needed to control dietary phosphorus intake would be the listing of phosphorus content on the product's Nutrition Facts panel, a listing that is currently required for other essential nutrients and minerals. The FDA has just enacted legislation forcing food manufacturers to precisely define the gluten content in foods, an important achievement for the estimated 4 million patients with celiac disease in this country (52). Because the CKD population is estimated at ~16 million, it is hoped that the FDA will eventually enact similar rules to define the actual content of phosphorus in food, an essential component of limiting dietary phosphorus intake in this country.

In summary, altered phosphorus homeostasis in CKD is associated with bad outcomes. Potentially, the same abnormalities could develop in people with normal kidney function, but consuming unnecessarily large amounts of dietary phosphorus. Further research is still needed to precisely delineate the underlying pathophysiologic mechanisms and, more importantly, to formulate interventions that would help reduce the adverse outcomes due to phosphorus.

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