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Dietary Phosphorus Intake and the Kidney

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Abstract

Although phosphorus is an essential nutrient required for multiple physiological functions, recent research raises concerns that high phosphorus intake could have detrimental effects on health. Phosphorus is abundant in the food supply of developed countries, occurring naturally in protein-rich foods and as an additive in processed foods. High phosphorus intake can cause vascular and renal calcification, renal tubular injury, and premature death in multiple animal models. Small studies in human suggest that high phosphorus intake may result in positive phosphorus balance and correlate with renal calcification and albuminuria. Although serum phosphorus is strongly associated with cardiovascular disease, progression of kidney disease, and death, limited data exist linking high phosphorus intake directly to adverse clinical outcomes. Further prospective studies are needed to determine whether phosphorus intake is a modifiable risk factor for kidney disease.

Keywords

phosphorus; phosphate; kidney function; GFR; glomerular filtration rate; chronic kidney disease

INTRODUCTION

Phosphorus is an essential mineral required for cell structure, signaling, energy transfer, and other important functions. Recent studies suggest that excessive phosphorus intake could have adverse consequences on the skeletal, renal, and cardiovascular systems. Individuals with chronic kidney disease (CKD) may be particularly susceptible to the effects of high phosphorus intake. As renal function decreases, levels of fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and serum phosphorus may become elevated. These disturbances of bone mineral metabolism have been linked to increased risk of end-stage renal disease (ESRD), cardiovascular disease (CVD), and death. Animal studies demonstrate a direct relationship between phosphorus load per nephron and renal parenchymal calcification and proximal tubular injury. Most human studies examining the relationship

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between phosphorus intake and adverse outcomes have been restricted to observational studies, which may be limited by reverse causation, measurement error, and residual confounding. In this article, we review emerging evidence from experimental, observational, and interventional studies suggesting high phosphorus intake may accelerate the course of CKD.

PHOSPHORUS REQUIREMENTS ACROSS THE LIFE CYCLE

Total body phosphorus in the adult is estimated at approximately 700 g, with 85% existing in the form of hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$, 14% existing in soft tissues, and only 1% existing extracellularly, including organic (70%) and inorganic (30%) forms of phosphate. Measured serum phosphorus values reflect phosphorus circulating freely as HPO_4 or H_2PO_4 , which comprises only 15% of the inorganic fraction, or approximately 15 mmol (465 mg). Phosphate serves as a reservoir for temporary storage and transfer of energy and as an acid-base buffer, and forms the structural components of cells (e.g., phospholipids, nucleotides, and nucleic acids).

The dietary reference intake for phosphorus was published in 1997 and outlines phosphorus requirements across the life span. Phosphorus content of the human body has been estimated to be approximately 17 g at birth with daily fetal phosphorus requirements of 62 mg/d (53). It is unknown whether there are any adverse effects of high phosphorus intake on pregnant women or on fetal development. Adequate intake (AI) between the ages of 0–6 and 7–12 months has been estimated at 100 mg/d and 275 mg/d, respectively, on the basis of studies measuring mean intake of human milk (Table 1) (1, 20, 38). Studies from the 1980s found that infants fed modified cow-milk-based formulas had threefold higher phosphorus intake and slightly higher levels of serum phosphorus compared with human-milk-fed infants (52). After 6 weeks, serum phosphorus in these phosphorus-rich-formula-fed infants decreased to levels similar to those of their human-milk-fed counterparts, with no apparent toxicity or significant differences in bone mineral content, weight, or length. However, some studies have suggested that infants less than 1 months may be at increased risk of hypocalcemia and late neonatal hypocalcemic tetany when fed modified cow milk formulas with high phosphorus content (37, 152, 164).

In children, accretion data estimating gains in lean and bone mass have been used to calculate estimated average requirements (EAR) (Table 1). As accretion of phosphorus increases during childhood, EAR increases from 380 mg/d in 1- to 3-year-olds to 1,055 mg/d for 9- to 18-year-olds. The EAR for adults is based on extrapolation from a study infusing a neutral phosphate solution intravenously in adults with normal renal function to estimate the phosphorus intake required to reach the lower end of the normal distribution of serum phosphorus levels in adults (2.7 mg/dL) (13). The UL was adjusted to slightly lower levels in pregnant women, accounting for increased phosphorus absorption in this state, and in adults older than 70 years, because of the increased prevalence of CKD in this population.

PHOSPHORUS METABOLISM IN HEALTH

In the United States, the average intake of phosphorus for men is 1,655 mg/d and 1,190 mg/d for women, with intake decreasing with increasing age (22). The main natural sources of phosphorus intake include dairy, meat, grain, and fish; inorganic phosphorus-based additives used by food manufacturers may contribute up to 10–30% of total phosphorus intake (23, 25, 27, 64, 102). Bioavailability varies depending on the source of phosphorus intake, with legumes estimated to have the lowest bioavailability (~40%) and inorganic phosphorus additives having the highest bioavailability (nearly 100% in some studies) (85–87, 163).

Phosphorus homeostasis is maintained through absorption/secretion in the gastrointestinal tract, filtration/absorption in the kidneys, and shifts into and out of bone (Figure 1). Net absorption of phosphorus (absorption/secretion from pancreatic and biliary fluids) is roughly 65% but may vary depending on the bioavailability of the phosphorus source, 25-hydroxyvitamin D [25(OH)D], and the relative amounts of phosphorus and calcium (69, 85–87, 139, 162). The entire intestinal tract absorbs phosphorus, although most of the absorption occurs in the small intestine (47, 66, 101, 132, 133). The two main pathways for intestinal phosphate absorption are a passive paracellular pathway and an active type II sodium-dependent phosphate transporter (*Npt2b*) in the intestine, which have been studied in mice and rats (70, 114). The passive paracellular pathway tends to be dependent on overall intake, proportionately increasing its role as phosphorus intake increases, whereas the active pathway predominates in the setting of low phosphorus intake (72). This active pathway via *Npt2b* is stimulated by 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] as well as by low phosphorus intake, which occurs independent of 1,25(OH)₂D₃ through a posttranscriptional mechanism (26, 142). A type III sodium-dependent transporter, *Pit1*, may also play a role in intestinal phosphate regulation, although it does not appear to be influenced by changes in phosphorus intake (6, 61, 88, 110).

Nearly 100% of phosphorus is filtered in the glomeruli, and typically 80–90% of phosphorus is reabsorbed via *Npt2a*, *Npt2c*, and *Pit2* transporters in the proximal tubule (16, 54, 166). In mouse models, *Npt2a* mediates approximately 70% of renal phosphate and *Npt2c* activity is estimated to account for the remaining 30% of phosphate reabsorption (8, 35, 54). *Npt2a* null mice develop hypophosphatemia, hypercalciuria, and nephrocalcinosis (8). *Npt2c* null mice develop hypercalcemia, hypercalciuria, and increased 1,25(OH)₂D₃ levels, but not hypophosphatemia, renal calcification, or significant bone abnormalities, suggesting a lesser role of *Npt2c* in phosphate regulation in mice (10).

Knowledge of sodium phosphate transporters in humans is limited. *NPT2A* expression in the human kidney proximal tubule is similar to that in its murine counterpart, with *NPT2A* expression occurring relatively late in development, reaching its highest point during the postnatal period and then falling with increasing age (100). Serum from patients with phosphate-wasting disorders such as autosomal dominant hypophosphatemic rickets presents decreased *NPT2A* expression and phosphate transport in cultured proximal tubule cells (21). Mutations in the *NPT2A* gene have been identified in a few patients, resulting in manifestations ranging from hypophosphatemic rickets to Fanconi syndrome and

nephrolithiasis (129). Mutations of the *NPT2C* gene cause hereditary hypophosphatemic rickets with hypercalciuria, suggesting perhaps a larger role of *NPT2C* in humans (10, 104).

A number of factors regulate renal phosphate handling. PTH and FGF23 are the most important of these hormones, reducing the activity of both *NPT2A* and *NPT2C*, resulting in increased urinary phosphate excretion (8, 54, 151). FGF23 requires membrane-bound Klotho, a cofactor found in the kidney (and in the choroid plexus, parathyroid gland, and other tissues), to bind to the FGF23 receptor and exert its phosphaturic effects (95, 96). The relative importance of these hormones in phosphorus regulation remains unclear.

Higher phosphorus intake results in increases in the phosphaturic hormones PTH, FGF23, and dopamine and decreases in $1,25(\text{OH})_2\text{D}_3$ (4, 19, 111, 112, 151, 167). However, the effect of phosphorus intake on FGF23 appears to be modest in human studies, with some studies unable to detect a significant effect (19, 32, 48, 78, 79, 94, 111, 161, 165). Recent human studies suggest that PTH rather than FGF23 explains the increased phosphaturia that occurs immediately after an acute phosphorus load (137). In the course of progressive CKD, FGF23 levels were shown to elevate before PTH levels (80). Renal expression of Klotho and soluble Klotho levels decrease before FGF23 levels rise as the glomerular filtration rate (GFR) declines, suggesting that increases in FGF23 levels in CKD could be partly secondary to Klotho deficiency (7, 74, 148).

The FGF23/Klotho pathway is of great importance, as evidenced by knockout mice lacking FGF23 or Klotho, in which the lack of either results in a complex aging-like phenotype characterized by hyperphosphatemia and vascular calcification (95, 96, 147). Patients with hyperphosphatemic familial tumoral calcinosis exhibit a similar phenotype due to mutations in the *GALNT3* gene, which encodes a glycosyl transferase, resulting in increased susceptibility of FGF23 to proteolytic degradation (57). Other factors that affect phosphate reabsorption include estrogen, insulin, growth hormone, thyroid hormone, and other phosphatonins such as matrix extracellular phosphoglycoprotein and Secreted frizzled protein-4 (11, 12).

DYSREGULATION OF PHOSPHORUS HOMEOSTASIS

Several factors may disrupt the mechanisms designed to maintain serum phosphorus levels, leading to periodic elevations in serum phosphorus (Figure 2). Adverse effects of high phosphorus intake may be magnified in the setting of CKD as nephron mass declines and calcium and phosphorus homeostasis is maintained by elevations in PTH and FGF23; the point at which these adaptive mechanisms become maladaptive is difficult to discern (45). If phosphorus intake remains unchanged while nephron mass and GFR decrease, an increasing amount of phosphorus must be excreted per individual nephron. High phosphorus intake from inorganic phosphorus additives may also lead to impaired bone turnover, as demonstrated in a recent crossover trial in humans with normal kidney function (24, 65). Both high and low bone turnover are common in CKD and can be exacerbated by secondary hyperparathyroidism (115) and metabolic acidosis (58, 92), leading to increased available calcium and phosphorus. Elevated PTH levels can also stimulate cytosolic free calcium concentrations, whereas metabolic acidosis results in decreased luminal citrate, an important

inhibitor of calcium phosphate precipitation (73, 99). Inflammation and deficiencies of inhibitors of calcification (i.e., fetuin-A) in combination with these imbalances in phosphorus homeostasis create a perfect storm for ectopic calcification, which can manifest in the vasculature and in the renal parenchyma (113, 116, 117, 138, 149).

EXCESSIVE PHOSPHORUS INTAKE: NEPHROCALCINOSIS AND PROXIMAL TUBULAR INJURY IN ANIMAL MODELS

The toxic effects of excessive phosphorus intake on the kidney were first demonstrated in the 1930s (107). High-phosphorus diets ranging from 2% to 6.5% administered to female albino rats resulted in renal tubular necrosis, nephrocalcinosis, inflammation, interstitial fibrosis, and albuminuria. When nephron mass was decreased by nephrectomy, the effects of phosphorus on the kidney were further magnified. These lesions were observed as early as within 1–3 days. Other studies using less extreme levels of phosphorus intake in rats have also demonstrated renal toxicity (59, 67, 75, 84, 98, 105, 134). In a study of nephrectomized, partially nephrectomized, and intact Sprague-Dawley rats, dietary phosphorus intakes of 0.5% (normal laboratory rat diet), 1%, and 2% were administered for 18 weeks (67). Calcium content measured in the aorta and in the kidney increased with higher phosphorus intake and decreased nephron mass. A strong correlation between phosphate load excreted per nephron and a histologic severity score ($r = 0.87$, $P < 0.01$) was observed. Restriction of phosphorus can prevent proteinuria, renal calcification, proximal tubular injury, and mortality in nephrectomized rats (49, 50, 75, 84, 105, 151). Similar findings have been demonstrated in dogs and cats (17, 50, 131).

SERUM PHOSPHORUS AND RENAL AND CARDIOVASCULAR OUTCOMES

Many studies have shown a relationship between elevated serum phosphorus levels, even in the high-normal range, and risk of CVD and mortality across all levels of kidney function (29, 39, 123, 159). Several studies have also documented an association between higher serum phosphorus levels and risk of incident CKD, CKD progression, and ESRD (30, 36, 122, 140, 170). In a study of 28,355 patients with serum phosphorus measurements in the Geisinger Health System, Chang et al. (30) examined the association between serum phosphorus and kidney failure [defined as ESRD via linkage to the United States Renal Data System or estimated GFR (eGFR) < 15 mL/min/1.73 m²]. After multivariate adjustment for demographics, renal risk factors, and factors affecting serum phosphorus, the highest quartile of serum phosphorus (> 3.8 mg/dL) was associated with a 133% increased risk of kidney failure (aHR 2.33; 95% CI, 1.91–2.84; $P < 0.001$) compared with the lowest quartile (< 3.0 mg/dL). This association was significant even for patients with an eGFR of < 60 mL/min/1.73 m² (aHR 3.00; 95% CI, 1.63–5.53; $P < 0.001$). In continuous models, every 1 mg/dL increase above 3.5 mg/dL was associated with a 40% increased risk of kidney failure (aHR 1.40; 95% CI, 1.32–1.47; $P < 0.001$); below 3.5 mg/dL, the relationship was flat (aHR 0.99; 95% CI, 0.90–1.09; $P = 0.8$) (Figure 3).

Whether these findings can be extrapolated to implicate high phosphorus intake as a risk factor for cardiovascular or renal disease is unclear. In a study of patients with stages 3–4 CKD randomized to phosphorus binders or placebo, phosphorus binders lowered serum

phosphorus by only 0.2 mg/dL (14). However, serum phosphorus was measured only once and not at a specific time of day. Serum phosphorus follows a circadian pattern, and high dietary phosphorus intake can influence the circadian rhythm of serum phosphorus and increase time-averaged levels of serum phosphorus (Figure 4) (81, 127).

Portale et al. (127) first showed this in a crossover feeding study of 6 healthy men, in which high phosphorus intake accentuated the rise in serum phosphorus in the midafternoon as well as the early-morning hours. A similar study was repeated in a crossover feeding study of 11 participants with stage 3 CKD and 4 healthy controls (81) (Figure 4). Participants received a high-phosphorus diet (2,500 mg/d), normal phosphorus diet (1,500 mg/d), and low-phosphorus diet (1,000 mg/d with 1,000 mg lanthanum carbonate 3 times/d). Time-averaged mean serum phosphorus levels for the high, normal, and low periods were 4.3, 3.9, and 3.7 mg/dL, respectively, in healthy volunteers. Time-averaged mean serum phosphorus levels for the high, normal, and low periods were 4.3, 4.2, and 3.6 mg/dL, respectively, in the participants with stage 3 CKD. The largest difference in serum phosphorus levels of high-versus low-phosphorus diets was observed at 4 pm, whereas the smallest differences were observed at 8 am. Thus, the timing of measurements may be critical in evaluating the effects of phosphorus intake on serum phosphorus levels and may explain the weak relationship between dietary phosphorus intake and serum phosphorus levels, which are often measured in the fasting state in the morning or at nonstandardized times.

CALCIUM PHOSPHATE DEPOSITION IN HUMAN RENAL BIOPSY TISSUE

Intermittent rises in serum phosphorus levels throughout the day may predispose patients to ectopic calcification, particularly in the renal parenchyma. A human corollary to the extremely high phosphorus diets administered in the study by Mackay & Oliver (107) can be found in the setting of acute phosphate nephropathy, a complication ascribed to sodium phosphate bowel cleansing preparations (nearly 12 g of elemental phosphorus given over a 24-h period) used for colonoscopy (109). Sodium phosphate bowel cleansing preparations are associated with cases of acute kidney injury often resulting in permanent renal injury. Biopsy findings include acute and chronic tubular injury with tubular and interstitial calcium phosphate deposits. After several reports of acute phosphate nephropathy, oral sodium phosphate solution was removed from the market and tablets are now available only by prescription (<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103383.htm>).

It is less clear whether chronic consumption at the higher end of the distribution of dietary phosphorus intake in Western countries could lead to nephrocalcinosis. In support of a relationship between phosphorus load per nephron and nephrocalcinosis, a study of 246 renal biopsies found that renal calcium content was significantly associated with higher serum creatinine and phosphorus levels (60). Normal controls (autopsied patients without kidney disease) had tissue calcium content of 7.6 mg/100 g of tissue, compared with 35.7 mg/100 g and 85.3 mg/100 g of tissue for those with serum creatinine levels <1.5 and >1.5 mg/dL, respectively (60). A similar association between kidney function and prevalence of microscopic nephrocalcinosis was observed in a more recent renal biopsy study. Nephrocalcinosis (almost exclusively calcium phosphate crystals) was found in 4.6% of

deceased kidney donors, compared with 14.3%, 20.2%, and 54% for stages 1–2 CKD, stages 3–4 CKD, and stage 5 CKD or ESRD, respectively (44). According to the precipitation-calcification hypothesis, calcium phosphate crystal deposition in the renal parenchyma may lead to further inflammation and kidney injury (99). Although suggestive of this hypothesis, these retrospective observational studies are unable to prove a causal relationship between phosphorus intake, nephrocalcinosis, and subsequent CKD progression in humans.

PHOSPHORUS BALANCE STUDIES IN HUMANS

Calcium supplementation induces a positive calcium balance, promoting increased bone mineral density (68, 157). However, concerns have been raised owing to associations between calcium supplements and an increased risk of vascular calcification and cardiovascular events (3, 15, 71). Phosphorus balance has not been studied as rigorously as calcium balance, although older metabolic studies suggest that high intakes of inorganic phosphorus additives could lead to positive phosphorus balance (46, 153). In a study of 7 patients with normal kidney function maintained on diets for 3–12 months in a metabolic ward, urine and stool were collected over 6 days to calculate calcium and phosphorus balances (153). Consumption of a diet with 685 mg/d of phosphorus and 1,517 mg/d of calcium resulted in a fairly even phosphorus balance (+72 mg/d). Consumption of the same diet supplemented with glycerophosphate (1,549 mg total phosphorus/d) resulted in a mean positive phosphorus balance of +228 mg/d. In more extreme cases, consumption of inorganic phosphorus loads of 7–9 g/d resulted in net positive phosphorus balances up to 2 gm/d (46). However, methods potentially underestimating fecal phosphorus could lead to overestimates of phosphorus balances (71, 169).

A randomized, placebo-controlled, crossover trial investigated the effect of calcium carbonate supplementation (2,457 mg calcium/d versus 957 mg/d) on calcium and phosphorus balances in 7 patients with stages 3–4 CKD (71). Calcium carbonate supplementation increased calcium balance compared with placebo (+550 versus +102 mg/d, $P = 0.002$). Mean phosphorus intake was 1,564 mg/d and no significant difference in phosphorus balance was observed. However, there was a nonsignificant trend toward higher phosphorus balance on calcium carbonate compared with placebo (+153 mg/d versus +95; $P = 0.2$), and the study may not have been adequately powered to study this question. Positive calcium and phosphorus balances could indicate deposition of calcium phosphate into extraskeletal tissues or the skeleton. More research is needed to understand phosphorus balance at different levels of phosphorus intake and kidney function.

FGF23 AND PTH: POTENTIAL MEDIATORS OF ADVERSE EFFECTS OF HIGH PHOSPHORUS INTAKE ON THE KIDNEY

Adverse effects of high phosphorus intake on the kidney may also be mediated by PTH and FGF23, which are stimulated by higher phosphorus intake (19, 78, 79, 151). Elevations in PTH may increase cytosolic calcium in the tubules and contribute to the pathogenesis of nephrocalcinosis (44, 73, 99). Observational studies have shown associations between elevated FGF23 levels and an increased risk of CKD progression (51, 106, 128, 141). Whether FGF23 is merely a strong risk marker or has a direct role in renal injury through a

yet unknown mechanism is unclear. Because elevations of PTH and FGF23 in the setting of CKD are adaptive mechanisms to maintain calcium and phosphorus homeostasis, it is difficult to determine when levels become maladaptive (45). For instance, neutralization of FGF23 with a monoclonal FGF23 antibody resulted in reduced hyperparathyroidism but increased serum phosphorus, aortic calcification, and mortality in a rat model (146).

PHOSPHORUS LOADING AND ENDOTHELIAL DYSFUNCTION

High phosphorus intake may also induce endothelial dysfunction, which has been hypothesized to manifest in the kidney as low-grade albuminuria (41, 136, 145, 150, 154, 155). Human studies from two groups (150, 155) have shown that oral phosphorus loading can impair endothelial function as measured by flow-mediated dilatation. Further, aortic endothelial cells and mesenteric blood vessels from rats exhibit impaired endothelium-dependent (nitric oxide-dependent) vasodilatation when exposed to high concentrations of phosphorus (150, 155). Stevens et al. (155) examined the effects of high concentrations of phosphorus on resistance vessels from subcutaneous abdominal fat from patients with normal kidney function and patients with stage 5 CKD. Endothelium-dependent vasodilatation was similarly impaired for vessels from both groups when exposed to high concentrations of phosphorus. The vessels from patients with stage 5 CKD relaxed normally when exposed to normal concentrations of phosphorus, suggesting that disruptive effects of chronic hyperphosphatemia on the endothelium may be partially reversible. Thus, a high-phosphorus diet may induce vascular dysfunction, which could theoretically manifest in the kidney as glomerular microvascular dysfunction and albuminuria (136, 145).

DIETARY PHOSPHORUS INTAKE AND PROTEINURIA

Di Iorio et al. (40) used observational data from Italian nephrology clinics with a special interest in dietary treatment of CKD to examine whether phosphorus modified the effects of a very low protein diet (VLPD) (0.3 g/kg protein supplemented with keto-analogs) on proteinuria. In this nonrandomized, sequential study of 1,198 patients compliant to LPD, mean proteinuria reduced from 1,910 mg/d on the last LPD visit to 987 mg/d on the last VLPD visit. Both serum phosphorus and 24-h urine phosphorus modified the protein-lowering effect of VLPD compared with LPD, even after adjustment for multiple confounders, including 24-h urine urea and sodium (*P* values for interaction: 0.04 for serum phosphorus, <0.001 for 24-h urine phosphorus). In other words, patients who had the lowest levels of serum phosphorus and 24-h urine phosphorus experienced the greatest reduction in proteinuria, suggesting a possible effect of phosphorus itself on proteinuria.

Chang et al. (28) examined the relationship between changes in dietary factors (assessed by 24-h urine collections) and obesity and changes in albuminuria in an observational analysis of the PREMIER trial, a randomized trial designed to lower blood pressure through counseling on weight loss, healthy diet, and exercise. In this trial of 481 patients with normal kidney function who had adequate 24-h urine collections, there was a significant association between changes in phosphorus excretion and albuminuria. Even after adjusting for multiple confounders, including protein intake estimated by 24-h urine urea excretion, every 314 mg/d reduction in phosphorus excretion was associated with a change in albuminuria of

–8.2% (–15.2% to –0.6%; $P = 0.03$). Although suggestive of a link between phosphorus intake/excretion and albuminuria, these observational studies are unable to prove a causal relationship.

DIETARY PHOSPHORUS INTAKE, RISK OF ESRD, AND DEATH

A few observational studies have examined the relationship between dietary phosphorus intake and health outcomes (Table 2). In a study of patients with an eGFR of <60 mL/min/1.73 m² in the Third National Health Nutrition and Examination Survey (NHANES III), no relationship existed between dietary phosphorus intake and mortality (120). These findings contrast those of a study of 224 hemodialysis patients, in which higher dietary phosphorus intake, assessed by the Block Food Frequency Questionnaire (FFQ), was strongly associated with an increased risk of death whether unadjusted or adjusted for differences in comorbidities, inflammatory markers, and normalized protein nitrogen appearance (121). The highest tertile of phosphorus intake was associated with a 137% increased risk of death compared with the lowest tertile in the fully adjusted model.

One explanation for these disparate findings is that predialysis patients with CKD spontaneously decrease overall caloric protein (i.e., phosphorus) intake as kidney function declines. This was nicely demonstrated in a prospective, observational study of patients with CKD followed by a single renal dietician whose only dietary advice was to reduce potassium intake for patients who developed hyperkalemia (76). For each 10 mL/min decrease in creatinine clearance, dietary protein intake decreased an average of 0.06 g/kg/d (76). Thus, lower phosphorus intake in CKD patients may signify more severe kidney disease and overall poor health, making reverse causation a major problem in observational studies of CKD patients.

To minimize the issue of reverse causality, Chang et al. (31) conducted a study of healthy individuals, without cancer, diabetes, CVD, or kidney disease in NHANES III. Phosphorus consumption above 1,400 mg/d was directly associated with mortality; below 1,400 mg/d, there was no relationship between phosphorus intake and mortality (Figure 5). The highest quartile of phosphorus consumption (1,611 mg/d) was associated with a 37% ($P = 0.01$) increased risk of death compared with the lowest three quartiles. Results were consistent in subgroups of higher and lower Healthy Eating Index (HEI) scores, soda consumption, and fast-food consumption, and when models were additionally adjusted for sodium and saturated fat intake.

All these observational studies suffer from measurement error given the limitations of dietary databases to capture the contribution of phosphorus additives (25, 119, 135, 156). Further, dietary databases are unable to quantify bioavailable phosphorus, which varies across different sources of phosphorus (85–87, 139). Studies comparing FFQs and 24-h dietary recalls in various countries have reported moderate correlations between the two methods ($r = 0.4$ – 0.6) (2, 89, 143, 158). In a study of 44 healthy Italian patients who completed 7-day dietary records, three 24-h urine collections, and a semiquantitative FFQ, Spearman rank correlations between FFQ and 7-day dietary recall with 24-h urine phosphorus were 0.39 and 0.57, respectively (126). It is unclear which direction

measurement errors would have on these relationships, although we speculate that findings would be biased toward the null. Similar limitations and controversy of nutritional epidemiology studies can be found in literature examining the relationship between sodium intake and outcomes (168).

URINE PHOSPHORUS EXCRETION AND ADVERSE OUTCOMES

Several studies have tried to address measurement error of phosphorus intake by examining urinary phosphorus excretion as a marker of dietary intake (Table 2). Ix and colleagues (144) examined the relationship between phosphorus intake and ESRD and mortality in an observational analysis of 795 patients with moderate to severe CKD in the Modification of Diet in Renal Disease (MDRD) trial. A 24-h urine sample and 3-day dietary recall were collected at baseline prior to the intervention. Baseline phosphorus intake was weakly associated with 24-h urine phosphorus ($r = 0.25$). Baseline 24-h urine phosphorus was not significantly associated with ESRD [per 1 standard deviation (SD) increase in phosphorus intake: aHR 1.04 (0.94–1.15); $P = 0.5$] or death [per 1 SD increase in phosphorus intake: aHR 1.02 (0.90–1.16); $P = 0.8$].

The authors also conducted a post hoc analysis using the 3-day dietary recall data to examine the association between phosphorus intake and outcomes. Baseline phosphorus intake was marginally associated with ESRD (per 1 mg/kg/d increase in phosphorus intake: HR 1.10; 95% CI, 0.98–1.24; $P = 0.1$) and mortality (per 1 mg/kg/d increase in phosphorus intake: HR 1.19; 95% CI, 1.03–1.37; $P = 0.02$), even after adjustment for urea excretion. The weak correlation between phosphorus intake and 24-h urine phosphorus could reflect differences in renal phosphorus handling in moderate to severe CKD, errors in 24-h urine collections, or limitations of dietary databases, although prior studies have reported stronger correlations between dietary recalls and 24-h urine phosphorus (25, 102, 119, 156). Further, no follow-up 24-h urine phosphorus measurements were done during the trial period in this protein restriction trial, and reverse causation remains a concern.

In the Heart and Soul study, an observational study of 880 adults with a history of coronary heart disease, 24-h urine phosphorus excretion was not associated with mortality (third tertile versus first tertile aHR 0.78; 95% CI, 0.56–1.07) (124). However, data from this study suggest there may be serious issues with using 24-h urine phosphorus to estimate habitual phosphorus intake. First, if 24-h urine phosphorus excretion solely reflected dietary intake, one would expect serum phosphorus, FGF23, and/or PTH to be higher with higher 24-h urine phosphorus excretion. After adjustment for age, sex, race, and eGFR, mean PTH levels did not differ across tertiles (T) of 24-h urine phosphorus (T1–T3: 4.0 pg/mL; $P = 0.9$). Similarly, adjusted mean FGF23 levels did not differ across tertiles (T1: 3.8, T2: 3.8, T3: 3.9 RU/mL; $P = 0.4$), nor did serum phosphorus levels (T1: 3.6, T2: 3.7, T3: 3.7 mg/dL; $P = 0.1$). Second, for 24-h urine phosphorus excretion to reflect dietary intake, phosphorus balance must be neutral, which may not hold true at higher levels of phosphorus intake (46, 153). In another analysis of the Heart and Soul study, the same research group found that FGF23 was more strongly associated with mortality and CVD events when fractional excretion of phosphorus was lower, implying resistance to its actions (i.e., Klotho deficiency) (43, 148). Together, these findings suggest that 24-h urine phosphorus excretion

may be an imperfect measure of habitual phosphorus intake and could reflect other factors, particularly renal resistance to FGF23.

To our knowledge, only one general population cohort study has examined the association of urine phosphorus with health outcomes—the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study (160). In an abstract presented at the American Society of Nephrology 2013 Kidney Week, 11,116 individuals had available spot urine samples to measure phosphorus-to-creatinine ratios. Compared with the lowest quartile (Q) of urine phosphorus-to-creatinine ratio, the second, third, and fourth quartiles were significantly associated with increased risk of death [Q2: 1.27 (95% CI, 1.07–1.52), Q3: 1.54 (95% CI, 1.30–1.83), and Q4: 2.07 (95% CI, 1.76–2.44)]. However, spot urine phosphorus-to-creatinine ratios are poorly correlated with 24-h urine phosphorus and thus even less likely to reflect habitual phosphorus intake (118, 130). Future longitudinal, general population cohort studies should assess the association of 24-h urine phosphorus with adverse outcomes.

EFFECT OF PROTEIN RESTRICTION ON CKD PROGRESSION

Prospective randomized trials are the optimal study design to determine the effects of phosphorus intake on kidney function. Although it has been well-recognized that lowering both protein and phosphorus intakes could have beneficial effects on CKD, most human interventional studies have focused on restricting protein rather than isolating the effect of phosphorus intake alone while keeping protein intake constant. Thus, it is important to examine the body of data on protein restriction given the limited data for phosphorus-centered interventions.

The largest interventional study examining protein restriction, the MDRD study, was a complex randomized trial testing the effect of protein restriction and blood pressure control on CKD progression in 840 patients with moderate to severe, nondiabetic CKD (90, 103). In brief, primary analyses of this study failed to demonstrate a significant effect of a low protein diet (LPD) (<0.6 g/kg/d) on CKD progression, although event rates were low, resulting in inadequate power. Post hoc long-term analyses suggested a trend toward decreased risk of ESRD or death for the low-protein-diet group ($RR = 0.65$; 95% CI, 0.38–1.10; $P = 0.1$). Other randomized studies and meta-analyses of protein restriction trials suggest that LPDs may delay progression to ESRD (9, 33, 55, 56, 125). In a *Cochrane Systematic Review*, Fouque & Laville (55) examined 10 studies comparing two levels of protein intake in 2,000 nondiabetic adults with moderate to severe CKD for at least 1 year. Lowering protein intake reduced the risk of renal replacement therapy or death by 32% ($RR = 0.68$; 95% CI, 0.55–0.84; $P = 0.0002$).

EFFECT OF PROTEIN SOURCE ON CKD PROGRESSION

The source of protein may be as important as the quantity of protein in terms of effects on the kidney. Most but not all human feeding studies comparing the effects of vegetable versus animal sources of protein have found that vegetable sources of protein may reduce glomerular hyperfiltration and albuminuria (5, 63, 82, 83, 91). The salutary effect of replacing meat protein with vegetable protein could be due to differences in amino acids,

decreased dietary acid load, and/or decreased absorbable phosphorus. A recently published randomized trial compared a LPD (<0.6 g/kg protein/d) with a very-low-protein, vegetarian diet supplemented with ketoanalogues (KD) (<0.3 g/kg protein/d and 0.125 g/kg ketoanalogues/d) in 207 patients with stages 4–5 CKD (56). Significantly fewer patients in the KD arm developed the composite outcome of ESRD or a >50% decline in eGFR (13% versus 42%; $P < 0.001$). Patients in the KD group had lower serum urea and higher serum bicarbonate levels. Serum phosphorus decreased from 5.9 to 4.4 mg/dL in the KD group compared with an increase from 5.8 to 6.2 mg/dL in the LPD group ($P < 0.01$ for all comparisons). Whether the beneficial effect was driven primarily by differences in amino acids, dietary acid load, or phosphorus is unclear in this study and other protein restriction studies (62).

EFFECTS OF DIETARY PHOSPHORUS INTAKE ON THE KIDNEY

Because phosphorus additives may contribute as much as one-third of the total phosphorus in a diet high in processed foods (25, 27, 102), the question whether high phosphorus intake has adverse effects on the kidney is of significant public health importance. Surprisingly, there is a paucity of data on the effect of phosphorus intake (independent of protein intake) on CKD progression, although two studies are currently examining the effect of phosphorus binders on CKD progression and proteinuria (97, 108). However, phosphorus binders may have other effects beyond reducing absorption of phosphorus. For example, in a randomized trial by Block et al. (14) phosphorus binders increased vascular calcification compared with placebo, with the greatest effect in patients randomized to calcium acetate.

Chang et al. (32) recently conducted a randomized, crossover study examining the effects of phosphorus additives on urinary albumin excretion in 31 patients with eGFR < 45 mL/min/1.73 m² and albuminuria. Participants received unaltered, commercially available diet beverages and breakfast bars with and without phosphorus additives to produce a contrast of 998 mg/d of dietary phosphorus and 505 mg/d in 24-h urine phosphorus excretion between periods. The primary intention-to-treat analysis failed to find a significant association between higher phosphorus intake and albuminuria (14.3%, 95% CI, -2.5%, 34.0%; $P = 0.1$). However, in sensitivity analyses excluding two noncompliant patients, findings were strengthened and bordered on significance (17.3%, 95% CI, 0.08%, 37.5%; $P = 0.049$). Limitations included a population of mostly urban African Americans, although this could be viewed as a strength too since this population is at an increased risk of kidney disease and disproportionately live in areas with low access to healthy food (18, 34). Although the main findings of the study were negative, the sensitivity analyses suggested a possible effect on albuminuria, in line with findings in animal studies.

In conclusion, while excessive phosphorus intake causes renal injury in animal models, there is insufficient evidence implicating phosphorus consumption at the higher range of the current distribution of phosphorus intake in humans as a causal factor for CKD or CKD progression. Given the high use of phosphorus-based additives in the food supply, collaboration with food manufacturers is needed to provide accurate phosphorus information for patients with kidney disease to improve dietary phosphorus counseling and research (93).

More prospective interventional studies are needed to understand the potential adverse effects of high phosphorus intake on human health.

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Figure 1.

Phosphorus metabolism in health. Average phosphorus intake is approximately 1,000–1,500 mg/d. Approximately 65% of phosphorus is absorbed in the gastrointestinal tract, although the exact amount is dependent on the vitamin D status, source, and bioavailability of the dietary phosphorus, and on the ratio of calcium to phosphorus intake. Nearly 100% of phosphorus is filtered in the glomeruli and ~80–90% is reabsorbed, depending on the activity of PTH and FGF23 in the kidneys. Assuming a steady state with neutral bone balance in a healthy adult, 24-h urinary phosphorus should approximate daily phosphorus intake. Abbreviations: FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

Figure 2.

Dysregulation of phosphorus homeostasis. High phosphorus intake leads to increased time-averaged 24-h serum phosphorus, particularly resulting in exaggerated peaks in the afternoon and early morning. In the setting of CKD, nephron mass is decreased, leading to compensatory mechanisms, including elevations in PTH and FGF23 to maintain phosphate homeostasis. Klotho, a cofactor found in the kidney, is required by FGF23 to exert its phosphaturic effects, and appears to decrease before PTH and FGF23 in CKD (95, 148). Renal acid excretory capacity is diminished in CKD, resulting in decreased luminal citrate, an important inhibitor of calcium phosphate precipitation, whereas PTH levels can stimulate cytosolic free calcium concentrations; both of these factors increase the chances of intratubular calcium phosphate precipitation (99). Elevated levels of PTH and phosphorus intake can impair bone metabolism, increasing available calcium and phosphorus (65, 115). All these factors in combination with inflammation and decreased levels of calcification inhibitors may result in a perfect storm for ectopic calcification in blood vessels and the renal parenchyma. Another potential mechanism leading to kidney injury and albuminuria is endothelial dysfunction, which occurs with phosphorus loading through the nitric oxide pathway (41, 145, 150, 155). Abbreviations: 1,25(OH)₂D₃, 1,25-dihydroxyvitamin D₃; CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

Figure 3.

Distribution and risk of ESRD by serum phosphorus levels. We modeled serum phosphorus using linear splines (knot at 3.5 mg/dL), adjusted Cox regression models for demographics, time of day, fasting status, menopause, renal risk factors (e.g., smoking, body mass index, systolic blood pressure, diabetes, cholesterol, eGFR, urine albumin/creatinine ratio, cardiovascular disease), and medications affecting serum phosphorus levels (e.g., estrogens, testosterone, vitamin D, calcium, and phosphorus binders). Above 3.5 mg/dL, higher serum phosphorus was associated with an increased risk of kidney failure (per 1 mg/dL increase: aHR 1.40; 95% CI, 1.32–1.47; $P < 0.001$). Below 3.5 mg/dL, there was no relationship between phosphorus and kidney failure (per 1 mg/dL increase: aHR 0.99; 95% CI, 0.90–1.09; $P = 0.8$). Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Figure 4.

Serum phosphate concentration and urine phosphate-to-creatinine ratio in healthy controls ($n = 4$) and CKD patients ($n = 11$) throughout the day and across high-, normal-, and low-phosphate diets. Point estimates reflect mean concentrations, and error bars reflect standard errors. The top panels show serum phosphate concentrations in healthy control and CKD participants. P values for diet $\times$ time interactions were 0.02 in the healthy control group and 0.02 in CKD participants. The bottom panels show urine phosphate-to-creatinine ratios in healthy control and CKD participants. P values for the diet $\times$ time interactions were 0.11 and 0.48 in the healthy control group and in CKD participants, respectively. Abbreviations: CKD, chronic kidney disease. Image reproduced with permission from AJCN [Ix JH, Anderson CA, Smits G, Persky MS, Block GA. Effect of dietary phosphate intake on the circadian rhythm of serum phosphate concentrations in chronic kidney disease: a crossover study. *Am J Clin Nutr*. 2014 Nov;100(5):1392–7.].

Figure 5.

Distribution and adjusted hazard ratio of death by absolute phosphorus intake in a healthy U.S. adult population: NHANES III. Cox proportional hazards regression was used to estimate hazard ratios of mortality by absolute phosphorus intake using linear splines with a knot at 1,400 mg/d adjusted for age, gender, race, ethnicity, poverty/income ratio, total energy intake, BMI, systolic blood pressure, current and former smoking, physical activity, non-HDL cholesterol, log ACR, eGFR, and low vitamin D level. The values were centered at 700 mg/d, and the graph is truncated at 200 and 4,000 mg/d for ease of presentation. *The Recommended Daily Allowance (700 mg/d) represents the daily dietary intake of phosphorus considered sufficient by the Food and Nutrition Board to meet the requirements of nearly all (97.5%) of healthy adults. **The tolerable upper intake level (4,000 mg/d) is the highest average phosphorus intake that is likely to pose no adverse health effects to almost all individuals in a general population. Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; NHANES III, Third National Health and Nutrition Examination Survey. Image reproduced with permission from AJCN [Chang AR, Lazo M, Appel LJ, Gutiérrez OM, Grams ME. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. *Am J Clin. Nutr.* 2014 Feb;99(2):320–7.].

Table 1EAR, RDA, and UL of phosphorus across the life cycle^a

Age categories	EAR ^b or AI ^c (mg/d)	RDA ^d (mg/d)	UL ^e
0–6 months	100 mg/d (AI)	–	Not established
7–12 months	275 mg/d (AI)	275 mg/d (AI)	Not established
1–3 y	380 mg/d	460 mg/d	3,000 mg/d
4–8 y	405 mg/d	500 mg/d	3,000 mg/d
9–18 y	1,055 mg/d	1,250 mg/d	4,000 mg/d
19–70 y	580 mg/d	700 mg/d	4,000 mg/d
70+ y	580 mg/d	700 mg/d	3,000 mg/d
Pregnancy, <18 y	1,055 mg/d	1,250 mg/d	3,500 mg/d
Pregnancy, 19+ y	580 mg/d	700 mg/d	3,500 mg/d
Breastfeeding, <18 y	1,055 mg/d	1,250 mg/d	4,000 mg/d
Breastfeeding, 19+ y	580 mg/d	700 mg/d	4,000 mg/d

^a Adapted from the dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.

^b Estimated average requirement (EAR): the intake that meets the estimated nutrient need of 50% of the individuals in the group.

^c Adequate intake (AI): the observed or experimentally derived intake by a defined population that appears to sustain a defined nutritional state.

^d Recommended daily allowance (RDA): the estimated nutrient need of nearly all (97.5%) individuals in the group.

^e Tolerable upper intake level (UL): the highest level of daily nutrient intake likely to pose no risk of adverse health effects to almost all individuals in the general population.

Longitudinal studies examining the effect of phosphorus intake on kidney outcomes or death in humans^a

Table 2

Study design	Study population	Exposure	Outcome	Results	Strengths/limitations	Reference
Observational	228 hemodialysis patients	Phosphorus intake, Block FFQ	Death	3rd tertile versus 1st tertile: aHR 2.37 (95% CI, 1.01–6.32)	Adjusted for many variables, including inflammatory markers and normalized protein nitrogen appearance FFQ may underestimate phosphorus intake Small sample size	121
Observational	1,105 adults with CKD from NHANES III, mean eGFR 49 mL/min/1.73 m ²	Phosphorus intake, single 24-h dietary recall	Death	3rd tertile versus 1st tertile: aHR 1.07 (95% CI, 0.67–1.70)	Nationally representative sample Reverse causation a concern Residual confounding possible although adjusted for many potential confounders 24-h dietary recall may also underestimate phosphorus intake	120
Observational	880 adults with CAD, mean eGFR 71 mL/min/1.73 m ²	24-h urine phosphorus	Death	3rd tertile versus 1st tertile: aHR 0.78 (95% CI, 0.56–1.07)	24-h urine collections a strength, although phosphaturia may reflect factors beyond habitual phosphorus intake Residual confounding and reverse causation a concern	124
Observational	1,325 men 65 years, mean eGFR 75 mL/min/1.73 m ²	Urine P _i /Cr ratio FE _{Pi}	Death	3rd tertile versus 1st tertile of urine P _i /Cr: aHR 1.22 (95% CI, 0.90–1.65) 3rd tertile versus 1st tertile of FE _{Pi} : aHR 0.88 (95% CI, 0.64–1.23)	Spot urine sample poorly correlated with 24-h urine phosphorus and unlikely to capture habitual phosphorus intake well Residual confounding and reverse causation possible	42
Observational analysis of nonrandomized, sequential study of LPD (0.6 g/kg) and then VLPD (0.3 g/kg) supplemented with keto-analogs	99 individuals with proteinuric CKD, mean eGFR 38 mL/min/1.73 m ²	24-h urine phosphorus	24-h urine protein	Change in 24-h urine phosphorus from LPD to VLPD associated with change in 24-h urine protein ($r = -0.27$, $P = 0.007$) 24-h urine phosphorus modified effect of VLPD on 24-h urine protein ($P < 0.001$)	24-h urine collections a strength, although phosphaturia may reflect factors beyond habitual phosphorus intake Confounding by time period possible although adjusted for many confounders including 24-h urine sodium and urea excretion Limited generalizability (highly motivated patients)	40
Observational analysis of a RCT of behavioral modifications to lower BP	481 individuals with BP 120–159/80–95, eGFR 60 mL/min/1.73 m ²	24-h urine phosphorus	24-h urine albumin excretion	Reduction in 24-h urine phosphorus associated with decreased albuminuria (–8.2% per 314 mg/d lower phosphorus intake; $P = 0.03$)	24-h urine collections a strength, although phosphaturia may reflect factors beyond habitual phosphorus intake Residual confounding possible although adjusted for many confounders including protein intake estimated from urea excretion	28

Study design	Study population	Exposure	Outcome	Results	Strengths/limitations	Reference
Observational	9,686 individuals without diabetes, cancer, kidney, or cardiovascular disease, eGFR 103 mL/min/1.73 m ²	Phosphorus intake, single 24-h dietary recall	Death	Phosphorus intake above 1,400 mg/d associated with death (Figure 3) Q4 (1,611 mg/d) versus Q1–Q3 (<1,611 mg/d): aHR 1.37; <i>P</i> = 0.01	Nationally representative sample Use of a healthy sample to limit concerns of reverse causation Residual confounding possible although adjusted for many confounders 24-h dietary recall may underestimate phosphorus intake	31
Observational analysis of a complex RCT examining the effect of protein intake on CKD progression	795 individuals with nondiabetic CKD, mean measured GFR 33 mL/min/1.73 m ²	Primary: 24-h urine phosphorus Secondary: phosphorus intake, 3-day dietary recall	ESRD, death	24-h urine phosphorus (per higher SD) ESRD: aHR 1.04 (0.94–1.15); <i>P</i> = 0.5 Death: aHR 1.02 (0.90–1.16); <i>P</i> = 0.8 Phosphorus intake (per 1 mg/kg/d increase) ESRD: aHR 1.10 (0.98, 1.24); <i>P</i> = 0.1 Death: aHR 1.19 (1.03, 1.37); <i>P</i> = 0.02	24-h urine collections a strength, although phosphaturia may reflect factors beyond habitual phosphorus intake 3-day dietary recall a strength, but this analysis was post hoc Reverse causation a concern	144
RCT comparing effects of high consumption of phosphorus additive on albuminuria	31 adults with albuminuria, mean eGFR 74.6 mL/min/1.73 m ²	Commercially available products with or without phosphorus additives (~1 g/d contrast)	Primary: 24-h urine albumin	Higher versus lower phosphorus period: albuminuria increased by 14.3% (from –2.5% to 34.0%; <i>P</i> = 0.1) Sensitivity analysis excluding 2 noncompliant patients: albuminuria increased by 17.3% (from 0.08% to 37.5%; <i>P</i> = 0.05)	Small sample size Short duration of intervention Change in background diet during intervention	32

^a Only studies examining the relationship between phosphorus intake (independent of protein or phosphorus binders) on kidney outcomes or mortality were included in this table.

Abbreviations: aHR, adjusted hazard ratio; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; ESRD, end-stage renal disease; FE_{Pi}, fractional excretional of phosphorus; LPD, low protein diet; P_i/Cr, phosphorus/creatinine ratio; Q, quartile; RCT, randomized controlled trial; SD, standard deviation; VLPD, very low protein diet.