Phosphate Additive Avoidance in Chronic Kidney Disease

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IN BRIEF Dietary guidelines for patients with diabetes extend beyond glycemic management to include recommendations for mitigating chronic disease risk. This review summarizes the literature suggesting that excess dietary phosphorus intake may increase the risk of skeletal and cardiovascular disease in patients who are in the early stages of chronic kidney disease (CKD) despite having normal serum phosphorus concentrations. It explores strategies for limiting dietary phosphorus, emphasizing that food additives, as a major source of highly bioavailable dietary phosphorus, may be a suitable target. Although the evidence for restricting phosphorus-based food additives in early CKD is limited, diabetes clinicians should monitor ongoing research aimed at assessing its efficacy.

Eating patterns are an important modifiable behavior in the management of patients with diabetes. Indeed, dietary modification is recommended as a first-line treatment for prediabetes (1) and is an integral component of ongoing diabetes care (2). Because patients with diabetes are at increased risk of chronic diseases such as chronic kidney disease (CKD) and cardiovascular disease (CVD), medical nutrition therapy for diabetes extends beyond glycemic control to include other cardiometabolic risk factors (e.g., weight, hypertension, and lipids) (2). These associations are important because dietary counseling with a registered dietitian for these conditions may be unavailable to patients until their condition becomes compromised. In fact, according to the U.S. Centers for Medicare & Medicaid Services Medical Evidence Report (June 2005 to May 2007, n = 156,400), 97% of CKD patients starting hemodialysis either were not under the care of a renal dietitian (88%) or had less than 12 months of renal dietitian care (9%) (3).

Dietary phosphorus restriction is recommended for patients with CKD but is not included in dietary guidelines for diabetes because hyperphosphatemia generally presents in the later stages of CKD (4,5). However, there is growing evidence that, even in earlier stages of CKD and in the absence of hyperphosphatemia, excess dietary phosphorus intake contributes to osteodystrophy and CVD. Although the majority of dietary phosphorus occurs naturally in foods and some can be leached out by wet cooking methods such as boiling, food additives in processed foods are a major source of dietary phosphorus; restricting their intake may be a suitable approach for limiting phosphorus exposure in earlier stages of CKD.

In this review, we discuss the evidence favoring dietary phosphorus restriction in earlier stages of CKD, with specific emphasis on phosphorus-based food additives. The intended purpose is to provide background information on an important and growing area of research in the

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renal nutrition field, which may become relevant to diabetes care in the near future.

Renal Phosphorus Handling in Health and CKD

Under normal conditions, dietary phosphorus intake exceeds physiological requirements, and the kidneys help to maintain phosphorus balance by eliminating excess phosphorus in urine. Plasma phosphorus is readily filtered by the glomeruli into the lumen of the renal tubules so that the concentration of phosphorus in the tubular filtrate is ~90% that in plasma (6). The majority of filtered phosphorus is reabsorbed in the proximal tubule under the regulation of several interconnected regulatory molecules (7), which control the proportion of filtered phosphorus that is excreted in urine (also known as the fractional excretion of phosphorus).

During CKD, the number and mass of functioning nephrons in the kidneys declines, causing a corresponding decrease in the amount of plasma, and therefore phosphorus, that is filtered. This is represented by a decrease in the estimated glomerular filtration rate (eGFR). To maintain normal excretion of excess phosphorus, the amount of phosphorus that is reabsorbed in the renal tubules decreases (i.e., the fractional excretion of phosphorus increases) (8). The fractional excretion of phosphorus can be upregulated dramatically such that only a small fraction (~10%) of filtered phosphorus is reabsorbed, and serum phosphorus concentrations can be maintained in a normal range until kidney function is severely reduced (eGFR <30 mL/min/1.73 m^2) (4,5,8). Concomitant changes in calcium metabolism occur (explained below), leading to a decline in serum calcium concentrations, which also leads to compensatory responses. The changes in regulatory factor concentrations that produce the decrease in phosphorus reabsorption and the decrease in serum calcium concentrations may have secondary consequences for CKD patients. The scenario in which serum phosphorus and calcium concentrations are maintained in the normal range at the expense of altered counterregulatory factors activity is known as the "trade-off hypothesis" (9).

Four key regulatory factors that generate the increase in fractional excretion of phosphorus in CKD are 1,25(OH)2-vitamin D (calcitriol), parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and its cofactor, klotho. The processes by which these regulatory factors work together to maintain phosphorus and calcium homeostasis and balance as CKD progresses are complex and incompletely understood. However, recent observational data, combined with mechanistic data, provide new insights into the pathways involved.

In cross-sectional analyses of CKD populations, higher FGF-23 concentrations are detected in those with mildly reduced kidney function (as early as stage 2 [eGFR 60–89 mL/min/1.73 m^2]), often before any changes in calcitriol and PTH concentrations are evident (4,5). FGF-23 is a bone-derived regulatory factor that acts to increase the fractional excretion of phosphorus in the kidneys (7). Conversely, its cofactor klotho is decreased and may initiate the early increase in FGF-23 concentrations (10,11). As CKD progresses, calcitriol concentrations decrease (5). Although low calcitriol concentrations in CKD were traditionally attributed to a loss of the kidney's capacity to produce 1-α hydroxylase, the enzyme responsible for activating vitamin D, FGF-23 is a potent inhibitor of 1-α hydroxylase activity and may account for the decrease in calcitriol early on in CKD (12). The decrease in calcitriol both directly (by diminished inhibitory action on the parathyroid gland) and indirectly (by reducing intestinal calcium absorption) contributes to hyperparathyroidism, commonly seen in those with moderately reduced kidney function (eGFR <60 mL/min/1.73 m^2) (5). Similar to FGF-23, PTH inhibits tubular phosphorus transporters to further increase the fractional excretion of phosphorus (7). In addition, PTH helps to maintain normal serum calcium concentrations by mobilizing calcium from bone, reabsorbing calcium in the kidneys, and increasing calcium absorption in the intestines (by increasing 1-α hydroxylase activity/calcitriol synthesis in the kidneys) (13). Importantly, other factors influence renal phosphorus handling, and these regulatory factors are linked through several feedback loops. Consequently, the actual adaptation process is difficult to study in vivo and more complex than described here.

Potential Consequences of Excess Dietary Phosphorus

The observed changes in calcitriol, PTH, FGF-23, and klotho are all features of an altered metabolic state in CKD, which leads to osteodystrophy, vascular calcification, and cardiac abnormalities, referred to as CKD-mineral and bone disorder (CKD-MBD) (14). In prospective studies of CKD patients, abnormal concentrations of these regulatory factors, in particular FGF-23, have been linked to CKD progression and CVD and fracture risk (4,15–20). Furthermore, calcitriol, PTH, and FGF-23 have been shown to directly affect bone turnover (21,22), vascular calcification (23,24), and left ventricular hypertrophy (25), suggesting that they may have a mediating role in the pathogenesis of CKD-MBD and that this process may begin in early CKD with the observed changes in these regulatory factors (26).

Importantly, animal models of CKD demonstrate that restricting dietary phosphorus intake can prevent the regulatory factor changes seen in CKD-MBD and slow the progression of CKD (27–31). Because phosphorus is found in most foods, it is unlikely that the low phosphorus intakes in these studies could be achieved in humans without using

synthetic diets or compromising nutrition status. However, it may be possible to sufficiently reduce dietary phosphorus intake to delay or diminish the regulatory factor changes. Indeed, modifying dietary phosphorus intake has been found to alter FGF-23 concentrations in people with and without CKD (32–35) and to reduce secondary hyperparathyroidism in CKD patients (36,37). Addressing hyperparathyroidism earlier through dietary restriction may prevent the progression of glandular hyperplasia to nodular hyperplasia, which is more difficult to suppress (38). Avoiding more severe elevations in PTH is expected to improve bone mineral density and reduce fracture rates, while precluding the eventual need for parathyroidectomy. Despite the apparent biological link between dietary phosphorus and CKD-MBD, prospective studies of reported dietary phosphorus intake and 24-hour urine phosphorus content with CVD mortality have generated inconsistent findings (39–41).

Limiting Dietary Phosphorus Intake

As previously mentioned, dietary phosphorus restriction is an integral component of hyperphosphatemia treatment in patients with moderately to severely reduced kidney function (14) and therefore has been extensively studied and tested in practice. Renal dietitians in particular devote substantial time and effort to determining the phosphorus content of foods and beverages (especially commercial products), and counseling CKD patients on how they can best limit phosphorus in their diet. A low-phosphorus diet (<800–1,000 mg/day) may include any and all of the following: *1*) limiting foods naturally high in phosphorus, *2*) leaching phosphorus from foods using wet cooking methods (e.g., boiling meat), and most recently *3*) avoiding phosphorus-based food additives (42).

Although restricting high-phosphorus foods is commonly practiced in advanced CKD, this approach has several important limitations. First and foremost, many high-phosphorus foods are healthy choices for people with adiposity-based chronic diseases such as type 2 diabetes. Indeed, low-fat dairy products, nuts, seeds, legumes, and whole grains (all high-phosphorus foods) are key components of the DASH (Dietary Approaches to Stop Hypertension) diet (43) and of the American Diabetes Association's nutrition recommendations for individuals with diabetes (2).

Dietary guidelines for diabetes do not encourage a one-size-fits-all eating pattern, but instead advise that patients consume a variety of nutrient-dense foods (2). Many of the factors that reduce the nutrient density of foods (e.g., refining or adding sugars and fats) also reduce phosphorus density (Table 1). Consequently, patients who choose nutrient-dense foods as part of a diabetic diet may have a high phosphorus intake. Although not supported by the guidelines (2), individuals with diabetes who are aware of their diagnosis tend to report lower carbohydrate intakes than those who are unaware (44), perhaps because they are attempting to reduce postprandial glycemic excursions. This may result in a higher phosphorus intake because carbohydrates are replaced, in part, with protein (44), which is positively correlated with dietary phosphorus, even after adjusting for energy intake (42).

Another important issue with restricting high-phosphorus foods is that the crude phosphorus content of foods may not reflect the bioavailable (and therefore bioactive) fraction of dietary phosphorus. Notably, the majority of phosphorus compounds in plant foods are indigestible phytates, contributing to a lower overall phosphorus bioavailability than with animal-derived phosphorus (32,45,46). The issue of phosphorus bioavailability is still being explored, but it is likely that dietary recommendations for a low-phosphorus diet will change in the future to reflect bioavailability, as is already being suggested for whole grains (47). It may be possible for people with diabetes to reduce their dietary phosphorus intake by avoiding certain high-phosphorus foods that are already restricted on a diabetic diet, such as high-fat dairy products (e.g., ice cream and cheese). However, even if dietary phosphorus were demonstrated to promote CKD-MBD in early CKD without hyperphosphatemia, it is doubtful that limiting intake of healthy foods that are high in phosphorus would have a net beneficial effect in patients with diabetes and mildly reduced kidney function.

Leaching is another approach that has been explored for managing hyperphosphatemia in CKD patients (48,49). During leaching, foods undergo prolonged cooking with water (i.e., boiling for 30 minutes), causing minerals to diffuse out of foods and dissolve into the water, which is then discarded. In addition to reducing the phosphorus content of foods by up to half or more (48–50), cooking foods with water instead of fats avoids the added calories from fats and helps prevent high-temperature reactions that create potentially harmful compounds (e.g., hetercyclic amines, advanced glycation end-products, and trans fatty acids). However, leaching is time consuming and may be impractical for many high-phosphorus foods (e.g., dairy foods and peanut butter), or make them less palatable. Moreover, other water-soluble nutrients that may be beneficial for patients (e.g., potassium) are also removed by leaching (48).

Avoiding processed foods that contain phosphorus-based food additives may be the most appropriate means of reducing phosphorus intake in diabetes patients with mildly reduced kidney function. Phosphorus additives have many functional properties (51) and are used in almost every major processed food category (e.g.,

TABLE 1. Phosphorus Content of Foods According to Food Group

Food	Serving Size	Phosphorus (mg)	
		Per Serving	Per 100 kcal
Protein foods			
Chicken breast, roasted, skin removed	3 oz	194	139
Chicken breast, roasted	3 oz	182	109
Chicken breast, fried with batter	3 oz	157	71
Ground beef, 93% lean	3 oz	167	103
Ground beef, 70% lean	3 oz	141	69
Eggs	2 large	197	138
Black beans	1 cup	241	106
Peanut butter, creamy	2 Tbsp	107	56
Sesame seeds	1 oz	181	113
Dairy products			
Milk, skim	1 cup	247	298
Milk, whole	1 cup	205	138
Yogurt, low-fat, plain	1 cup	353	229
Yogurt, low-fat, vanilla	1 cup	331	159
Cheddar cheese	1.5 oz	193	112
Vanilla ice cream	1 cup	139	51
Grains			
Bread, white	1 slice	24	36
Bread, whole wheat	1 slice	68	84
Rice, brown	1 cup	208	84
Rice, white	1 cup	68	33
Cereal, Kellogg's Corn Flakes	1 cup	29	29
Cereal, Kellogg's All-Bran	1 cup	356	445
Bran muffin	1 medium	425	139
Croissant	1 medium	60	26
Fruits			
Apples	1 cup	12	21
Applesauce, sweetened	1 cup	18	9
Peaches	1 cup	31	52
Peaches, canned in juice	1 cup	42	38
Peaches, canned in heavy syrup	1 cup	29	15
Vegetables			
Carrots	1 cup	45	87
Broccoli	1 cup	60	194
Tomatoes	1 cup	43	134
Tomatoes, canned	1 cup	77	100
Tomatoes, canned, stewed	1 cup	51	77
Potatoes	1 medium	123	73
Potatoes, mashed	1 cup	101	43
Potatoes, French fries, McDonald's	1 medium	149	39

frozen foods, dry food mixes, packaged meats, bread and baked goods, and soups) (52). A 2013 study analyzing the amount of phosphorus in 56 pairs of similar food products (one with and one without phosphorus additives) (52) found that products containing phosphorus additives contained ~60% more phosphorus (178 ±202 vs. 111 ±112 mg/100 g). However, the absolute and relative differences in phosphorus content varied substantially between and even within food product categories. For example, the difference in phosphorus among cheese products (n = 4 pairs) was +347 mg/100 g (+85%), with an SD of 158 mg/100 g (52). It is difficult to obtain a clear estimate of usual intake of phosphorus from food additives, but analyses of menus selecting foods containing phosphorus additives suggest that they may contribute up to ~600–700 mg/day of inorganic phosphorus (52,53), which is thought to be highly bioavailable (51). Such additives may, with further study, constitute an important target for efforts to restrict dietary phosphorus intake. Importantly, there are usually phosphorus additive–free alternatives, albeit at a slightly higher cost (52).

Most phosphorus additives are easily identified in ingredients lists by the root "phos" (e.g., phosphoric acid, phosphates, diphosphates, and polyphosphates), although some are either indistinguishable (e.g., modified food starch) (54) or unlisted, as in the case of certain enhanced meats (55,56). Consequently, if patients are willing and able to read the ingredients lists of food products, they can often eliminate the majority of phosphorus additives from their diet. Avoiding processed foods may be difficult for most patients but has the additional benefit of helping to limit other potentially harmful compounds commonly found in these products (e.g., added sugars and sodium).

For now, the public health impact of phosphorus additives is largely unknown, in part because food manufacturers are not required to report

the amount of phosphorus additives used or the total phosphorus content of their products (because the evidence linking excess phosphorus to health outcomes has been deemed inadequate). Without this information, conventional nutrition assessment methods are unable to estimate phosphorus additive intake, preventing epidemiological studies, which would be needed to evaluate the public health impact of these additives. However, there is evidence that clinically relevant reductions in phosphorus intake can be achieved by eliminating phosphorus additives. In a landmark study (57), Sullivan et al. found that educating hemodialysis patients with hyperphosphatemia to avoid phosphorus additives reduced serum phosphorus concentrations compared to usual care. Similar studies are underway, including a 6-month, technology-supported, behavioral intervention targeting weight loss, physical activity, sodium restriction, and avoidance of phosphorus additives in overweight patients with type 2 diabetes and stages 1–4 CKD by members of our group (clinicaltrials.gov identifier NCT02276742).

Conclusion

In this review, we have discussed the potential health consequences of excess dietary phosphorus intake in patients with early CKD, an emerging area of research interest. In particular, there is growing concern that the compensatory changes in regulatory factors, which maintain phosphorus balance in patients with high dietary phosphorus intake and diminished glomerular filtration by increasing the fractional excretion of phosphorus in the kidneys, may contribute to CKD progression, as well as to skeletal and vascular disorders (i.e., CKD-MBD). More research is needed to determine whether reducing dietary phosphorus intake is beneficial in CKD patients without hyperphosphatemia. However, even if excess phosphorus were demonstrated to be harmful in this population, the conventional low-phosphorus diet may be inappropriate for diabetes patients with early CKD because it restricts the intake of many foods recommended for these patients.

Phosphorus additives in processed foods are major sources of highly bioavailable dietary phosphorus, which may become a novel target for diabetes patients in the future, particularly those with reduced kidney function. Current regulations require that the presence of food additives be indicated in the ingredients list of food products, but the amount of phosphorus is not required to be included in the nutrition facts panel. Given that phosphorus additives are widely used in processed foods and excess phosphorus intake may cause harm in individuals with kidney disease, mandatory labeling of phosphorus on food products may be an important public health intervention.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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