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Organic and Inorganic Dietary Phosphorus and Its Management in Chronic Kidney Disease

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Dietary phosphorus control is often a main strategy in the management of patients with chronic kidney disease. Dietary protein is a major source of phosphorus intake. Recent data indicate that imposed dietary phosphorus restriction may compromise the need for adequate protein intake, leading to protein-energy wasting and possibly to increased mortality. The two main sources of dietary phosphorus are organic, including animal and vegetarian proteins, and inorganic, mostly food preservatives. Animal-based foods and plant are abundant in organic phosphorus. Usually 40% to 60% of animal-based phosphorus is absorbed; this varies by degree of gastrointestinal vitamin-D-receptor activation, whereas plant phosphorus, mostly associated with phytates, is less absorbable by human gastrointestinal tract. Up to 100% of inorganic phosphorus in processed foods may be absorbed; ie, phosphorus in processed cheese and some soda (cola) drinks. A recent study suggests that a higher dietary phosphorus-protein intake ratio is associated with incremental death risk in patients on long-term hemodialysis. Hence, for phosphorus management in chronic kidney disease, in addition to absolute dietary phosphorus content, the chemical structure (inorganic versus organic), type (animal versus plant), and phosphorus-protein ratio should be considered. We recommend foods and supplements with no or lowest quantity of inorganic phosphorus additives, more plant-based proteins, and a dietary phosphorus-protein ratio of less than 10 mg/g. Fresh (nonprocessed) egg white (phosphorus-protein ratio less than 2 mg/g) is a good example of desirable food, which contains a high proportion of essential amino acids with low amounts of fat, cholesterol, and phosphorus.

INTRODUCTION

The progressive deterioration of kidney function in chronic kidney disease (CKD) leads to retention of many substances, including phosphorus. Serum phosphorus concentration, however, is usually maintained within the normal range of 2.5 mg/ dL to 4.5 mg/dL by a variety of compensatory mechanisms until CKD has progressed to about stage 5 or end-stage renal disease.[1] Therapeutic strategies aimed at phosphorus control typically include dietary phosphorus restriction, reducing intestinal absorption with phosphorus binders,

and removing phosphorus with dialysis therapy. Despite these approaches, normalization of serum phosphorus levels is often difficult and frequently not obtained. Recent data suggest that fewer than 50% of patients meet target levels for serum phosphorus.[2] Administration of phosphorus binders that contain calcium, aluminum, resin, or heavy metal may lead to excessive calcium burden, aluminum toxicity, gastrointestinal disturbances, or heavy metal accumulations, respectively, in addition to pill burden.[3] Even though restriction of dietary phosphate may conflict with the need to maintain adequate protein intake,[4,5] dietary strategies are still in the forefront of the phosphorus control interventions. Hence, sound knowledge of sources of dietary phosphorus is fundamental to the clinical and dietary management of patients with CKD.

DIETARY PHOSPHORUS
Sources of Phosphorus

Since phosphorus exists in virtually all living organisms, it is found in most foods. The main food sources of dietary phosphorus are diverse types of organic phosphorus in protein-rich foods, including animal foods such as dairy products, meat, and fish, as well as plant foods such as legumes, nuts, and chocolates; along with inorganic phosphorus in the form of food additives (Table 1).

Organic Phosphorus

Since organic phosphorus is largely bound in vivo to proteins and other intracellular carbon-containing molecules, it is naturally found in protein-rich foods.[10] As shown in Table 1, both animal- and plant-based foods are abundant in organic phosphorus. Organic phosphorus is hydrolyzed in the intestinal tract and then absorbed into the circulation as inorganic phosphate.[11] Usually, only 30% to 60% of organic dietary phosphorus is absorbed, varying by the digestibility of dietary nutrients and bioavailability of dietary phosphorus, degree of activation of vitamin D receptors in the gastrointestinal tract, and presence or absence of compounds that can bind to phosphorus or interfere with its gastrointestinal absorption such as aluminum or nicotinic acid.[12,13]

Phosphorus From Animal Proteins. In a nonvegetarian western diet, over one-half of the dietary phosphorus load originates from animal proteins.[14] The main food sources of phosphorus are the protein food groups of meat, poultry, fish, eggs,

Table 1. Selected Sources of Dietary Phosphorus[6-9]

Source	Serving	Phosphorus, mg	Phosphorus-Protein Ratio, mg/g	Gastrointestinal Absorption, %
Organic				
Animal protein				
Milk, skim	8 ounces	247	29	40 to 60
Yogurt, plain nonfat	8 ounces	385	27	40 to 60
Cheese, mozzarella; part skim	1 ounces	131	20	40 to 60
Egg	1 large	86	14	40 to 60
Beef (cooked)	3 ounces*	173	7	40 to 60
Chicken	3 ounces	155	8	40 to 60
Turkey	3 ounces	173	8	40 to 60
Fish, halibut	3 ounces	242	9.3	40 to 60
Fish, salmon	3 ounces	282	13.4	40 to 60
Vegetarian protein†				
Bread, whole wheat	1 slice	57	Varies	10 to 30
Bread, enriched white	1 slice	25	Varies	10 to 30
Almonds	12 ounces	134	23	10 to 30
Peanuts	1 ounce	107	15	10 to 30
Lentils (cooked)	Half a cup	178	20	10 to 30
Chocolate	1.4 ounces	142 to 216	27	10 to 30
Inorganic (additives and preservatives)‡				
Carbonated cola drink	12 ounces	40	Not Applicable	80 to 100

*A 3-ounce serving is about the size of a deck of cards.
†Phytate leads to less absorbability.
‡Inorganic phosphorous may comprise 50% or more of daily dietary phosphorus load.

and dairy products.[6] Digestibility of phosphorus from animal-derived foods is higher than that of plant-based proteins (see below). Different sources of animal proteins contain different proportion of phosphorus. As an example, 1 large whole egg contains 6 g of protein and 86 mg of phosphorus, whereas egg white from 1 large egg (3.6 g protein) contains 5 mg of phosphorus, indicating that the bulk of egg phosphorus is in the egg yolk.[7] Poultry (such as chicken and turkey) contain less phosphorus than red meat (such as beef and veal) and fish. Each 100 g of salmon contains 21 g protein and 282 mg phosphorus.[7] Moreover, meat and dairy products are frequently "enhanced" by the addition of phosphate additives (see below), which may markedly increase the total phosphorus content. Similarly, different types of cheese may contain a range from less than 100 mg to almost 1000 mg per serving of combined organic and inorganic phosphorus based on the type of the cheese and its method of processing.[4,15] A high-fat animal-based diet may contain less phosphorus, but it also includes more saturated fat. However, there are currently no data indicating whether there are deleterious effects to a high-fat diet in patients with CKD. Indeed, a recent pilot trial by Ewers and colleagues suggested that prescribing a high-fat diet may be appropriate for patients with CKD stage 5, especially since the phosphorus and potassium content of such diets can be quite low.[16]

Phosphorus From Plant Protein and Phytates. Whereas many fruits and vegetables contain only small amounts of organic phosphate, it is naturally and abundantly occurring in some plant seeds, nuts, and legumes.[17] Chocolate is another phosphorus-rich plant-based food with an average of 142 mg to 216 mg phosphorus per serving size (40 g). The highest amount of phosphorus is found in black milk chocolate.[18] Cocoa is made from the seed of the cacao tree flower, referred to as cocoa beans. They are a rich source of phospholipids including lysophosphatidyl choline, phosphatidyl choline, phosphatidyl ethanolamine, and phosphatidyl inositol.[18] Unlike phosphorus in animal proteins that is present as organic phosphates in intracellular compartments and that is easily hydrolyzed and readily absorbed, phosphorus in plants, especially in beans, peas, cereals, and nuts, is mostly in the storage form of phytic acid or phytate.[17,19] Because humans do not express the degrading enzyme phytase, the bioavailability of phosphorus from plant-derived food is relatively low, usually less than 50%.[20] Hence, despite the "apparently" higher phosphorus content of some plant foods, such as beans, the actual rate of intestinal phosphorus absorption may be lower per gram of plant protein than per gram of animal-based protein (Table 1).[21] If healthy humans are given the same amount of dietary phosphorus from either animal or plant foods, urinary phosphorus excretion is higher with the animal-based diet.[22] Since usually only 20% to 50% of the plant-based phosphorus is absorbed in the human gastrointestinal tract, it is likely that prescribing patients with CKD a higher proportion of protein from plants may not only meet their required protein, but also lead to better management of their body phosphorus burden. There are however 3 important considerations in this regard. First, yeast-based phytase in whole grains makes the phosphorus content of leavened breads more effectively absorbed from the intestinal tract than cereals or flat breads.[23] Second, the effect of probiotics on enhancing phytate-associated phosphorus release and absorption is currently not clear. Third, the biological value (quality) of plant proteins tends to be lower than that of animal proteins, and for people with marginal protein intakes, this could lead to inadequate protein nutrition.

Inorganic Phosphorus and Food Additives

Phosphorus is the main component of many preservatives and additive salts found in processed foods.[24,25] Additives are used in food processing for a variety of reasons such as to extend shelf life, improve color, enhance flavor, and retain moisture.[21,26] Common sources of inorganic phosphorus include certain beverages, enhanced or restructured meats, frozen meals, cereals, snack bars, processed or spreadable cheeses, instant products, and refrigerated bakery products.[15,27] Currently, there is no accurate or reproducible method to distinguish between protein-based organic and preservative- or additive-based inorganic phosphorus in the food.[28,29]

Inorganic phosphorus, such as phosphorus additives, are not protein-bound; they are salts that more readily disassociate, and therefore, are more readily absorbed in the intestinal tract.[30] Indeed, it is believed that over 90% of inorganic phosphorus may be absorbed in the intestinal tract, as opposed

to only 40% to 60% of the organic phosphorus present in natural foods.[31,32] The major public health implication from these considerations is that the phosphorus burden from inorganic phosphorus-containing food additives is disproportionately high relative to organic phosphorus. In the early 1990s, phosphorus additives contributed approximately 500 mg of phosphorus per day to the American diet, whereas today phosphorus additives may contribute as much as 1000 mg of phosphorus per day to the average American diet.[21,31,33,34]

In the study of Bell and colleagues,[30] foods with a large amounts of phosphorus additives led to an increase in their total phosphorus intake from 979 mg/d to 2124 mg/d. These foods also led to increases in serum phosphorus levels and urinary phosphorus excretion and to decreases in serum calcium and urinary calcium concentrations.[30] These changes appear to be analogous to those seen in experimental animals fed high-phosphorus diets, which are associated with enhanced parathyroid hormone release, and create a syndrome similar to the secondary hyperparathyroidism observed in CKD.[35] Hence, not only processed foods may contain a high amount of phosphorus in addition to the phosphorus naturally present in those foods, but also their phosphorus is more readily absorbed, because it is in an inorganic form.

HOMEOSTASIS OF PHOSPHORUS
Intestinal Homeostasis

The cotransporters for phosphate absorption in the small intestine is similar to the sodium phosphate cotransporters found in the renal tubules and are also stimulated by 1,25(OH)2 vitamin D.[36] Factors that affect phosphorus absorption in the gastrointestinal tract are shown in Figure 1. The main determinants of how much phosphorus is absorbed in the intestine are the amount of phosphorus present in the diet, its bioavailability, and the presence of natural (see above) or pharmacologic phosphorus binders.

Renal Homeostasis

Because phosphorus is not significantly bound to albumin, phosphate is mostly filtered by the glomerulus. The proximal tubule reabsorbs approximately 75% of filtered phosphorus, the distal tubule reabsorbs approximately 10%, and 15% is lost in urine.[38] The activity of the phosphate transporter is
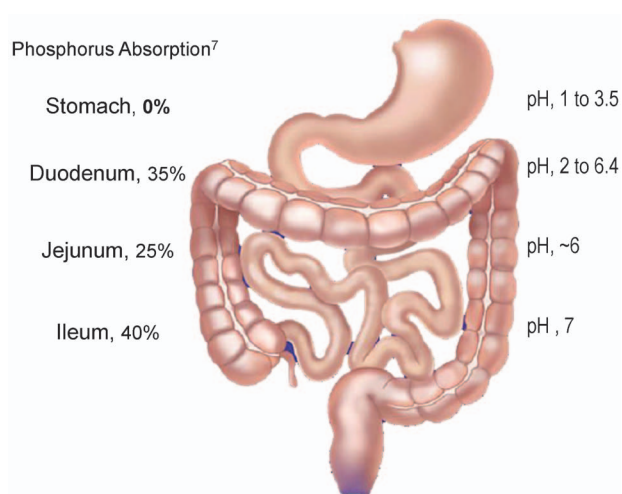

Figure 1. Factors that affect phosphorus absorption[7] along the gastrointestinal tract with varying pH.[37]

increased by low serum phosphorous and 1,25(OH)2 vitamin D levels and decreased by parathyroid hormone and phosphatonins (fibroblast growth factor-23 [FGF-23] and secreted frizzled related protein-4). The main factors known to increase renal tubular phosphorous reabsorption include phosphate depletion, 1,25(OH)2 vitamin D, volume depletion, metabolic alkalosis, chronic hypocalcemia and the hormones insulin, estrogen, thyroid hormone, and growth hormone.[12] Factors decreasing renal tubular phosphate reabsorption include parathyroid hormone, phosphatonins, acidosis, hyperphosphatemia, chronic hypercalcemia, and volume expansion.[12] Fibroblast growth factor-23 is secreted by osteocytes and regulates phosphorus and vitamin D metabolism.[39,40] A sustained increase in dietary phosphorus intake stimulates FGF-23 secretion, which in turn increases phosphaturia[41,42] and inhibits renal 25-hydroxyvitamin D-1-a-hydroxylase, leading to decreased synthesis of 1,25-vitamin D.[41,42] A sustained reduction in phosphorus intake lowers FGF-23 secretion, which in turn enhances tubular phosphorus reabsorption and increases 1,25-vitamin D production. The main stimuli for FGF-23 secretion are high phosphorus intake, increased 1,25-vitamin D levels, and perhaps, parathyroid hormone (Figure 2).[40,41]

Exchanges of Phosphate Between Extracellular Fluid and Bone

Exchanges of phosphate between extracellular fluid and bone occur as a consequence of
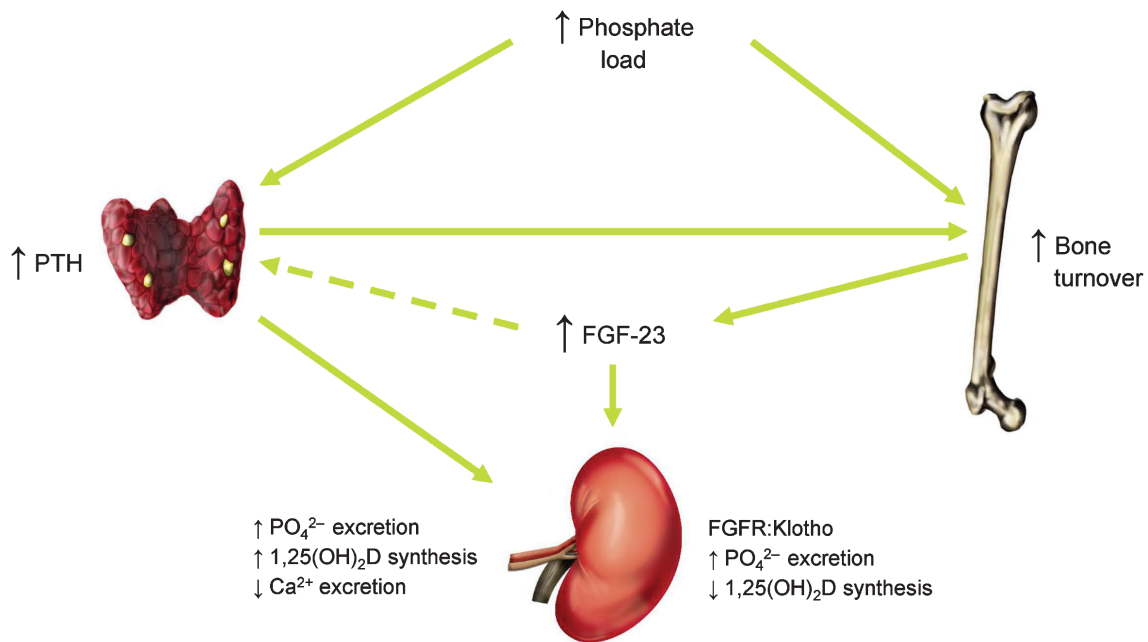
Figure 2. Effect of dietary phosphorus load on phosphorus metabolism in the body.[43]
1,25(OH)2D indicates 1,25-dihydroxyvitamin D3; Ca^{2+}, calcium; FGF-23, fibroblast growth factor-23; FGFR, fibroblast growth factor receptor; $PO4^{2-}$, phosphate; PTH, parathyroid hormone.

calcium homeostasis. Deposition in and release of phosphorus from bone are accompanied by movement of calcium in the same directions. The factors regulating cell phosphate uptake have not been well defined. It is accepted that phosphate moves passively into the cells driven by its chemical gradient. Carbohydrate feeding and acid-base changes also can cause rapid and profound changes in serum phosphorus by translocating phosphorus into and out of cells.

KIDNEY DISEASE AND PHOSPHORUS
Effect of Chronic Kidney Disease on Phosphorus Homeostasis

Fibroblast growth factor-23 levels are constitutively elevated in CKD, beginning as early as stages 2 and 3, long before hyperphosphatemia is detectable.[44-46] Increased FGF-23 augments fractional excretion of phosphate and decreases 1,25-vitamin D levels, thereby diminishing dietary phosphorus absorption. As a result, 1,25-vitamin D levels decline progressively in parallel with increasing FGF-23 beginning in early CKD and before there are any of the classical clinical manifestations of "insufficient renal mass." This suggests that, rather than not being able to produce adequate 1,25-vitamin D, the kidney is being signaled not to generate it. It is important to emphasize that the hypothesis that FGF-23 levels increase in early CKD as a compensatory response that maintain normal serum phosphate levels remains unproven. Decreased 1,25-vitamin D levels, in turn, lower gut phosphate absorption and reduce feedback inhibition of the parathyroid glands, This leads to increased circulating parathyroid hormone levels, which further augment urinary phosphate excretion.[47] The direct effects of FGF-23 on bone mineralization and on other organs are less clear. Although serum FGF-23 levels are often high in patients with tumor-induced osteomalacia, the highest concentrations are encountered in patients with CKD, and especially, in those undergoing maintenance dialysis, in whom serum FGF-23 levels can be more than 1000-fold above the normal range.[47]

Effect of Dialysis Treatment on Phosphorus

Phosphate is preferentially located in the intracellular space, and hence, the majority of the phosphorus for dialysis removal is derived from the intracellular pool. During the first phase of dialysis, serum phosphorus level is the main determinant of phosphate removal.[48] Within the initial 60 to 90 minutes of initiation of hemodialysis, there is a rapid

reduction in the serum phosphorus level, followed by a decreased phosphorus gradient between the plasma and dialysis solution, resulting in less efficient transfer. Throughout the treatment, the primary determinant of phosphate removal is the relatively slow movement of phosphorus from the intracellular pools to the extracellular pools. A large rebound of phosphorus occurs after termination of dialysis, often reaching about 80% of predialysis serum phosphorus values within several hours.[49] Phosphorus removal with standard thrice weekly 4 hours of hemodialysis ranges from 600 mg to 1200 mg per treatment (or 1800 mg to 3600 mg per week). Even though phosphate is mostly removed during the first hour of dialysis, the constant elimination during the later stages of treatment is frequently underappreciated. For example, one study found that a 4-hour hemodialysis treatment removed an average of 923 ± 12 mg of phosphorus versus 1127 ± 15 mg in a 5-hour session.[50] In comparison, phosphorus removal with continuous ambulatory peritoneal dialysis averages 300 mg to 360 mg of phosphorus per day or 2100 mg/w to 2520 mg/w.

High Serum Phosphorus and Outcomes in Chronic Kidney Disease

In the Multi-Ethic Study of Atherosclerosis, Adeney and coworkers[51] examined associations of serum phosphate concentrations with vascular and valvular calcification in 439 participants who had moderate CKD and no clinical cardiovascular disease. The prevalence of calcification in the coronary arteries, descending thoracic aorta, aortic valve, and mitral valve, determined by electron-beam or multidetector row computed tomography, was 67%, 49%, 25%, and 20%, respectively. Each 1-mg/dL increment in serum phosphate concentration was associated with a 21%, 33%, 25%, and 62% greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively. The authors suggested that higher serum phosphate concentrations, although still within the normal range, are associated with a greater prevalence of vascular and valvular calcification in people with moderate CKD. Tomiyama and colleagues[52] in 2006 assessed a total of 96 CKD outpatients who were not undergoing dialysis. Coronary calcification, defined as a coronary artery calcification score higher than zero Agatston units, was seen in 61 patients. The authors suggested that serum phosphorus levels were independent determinants of severe coronary calcification. Block and associates[46] in 2004 and Kalantar-Zadeh and coworkers[53] in 2006 showed that high serum phosphorus is an independent predictor of mortality in patients with CKD. Table 2 shows epidemiologic data of the levels of calcium, phosphorus, and parathyroid hormone at which death and cardiovascular events were observed.

Recommendation for Dietary Phosphorus Intake in Chronic Kidney Disease

The Recommended Dietary Allowance for phosphorus in the normal population is summarized in Table 3. To our knowledge, there is only one study that has examined the effect of dietary phosphorus on clinical outcome in patients with CKD; Noori and colleagues in 2010 evaluated the effect of phosphorus intake on mortality in a cohort of 224 maintenance hemodialysis patients. They concluded that high phosphorus intake is an independent

Table 2. Epidemiologic Data of Serum Levels of Calcium, Phosphorus, and Parathyroid Hormone at Death in Patients on Hemodialysis*

Study	Level at which Increased Risk of Death Observed		
	Calcium, mg/dL	Phosphorus, mg/dL	Parathyroid Hormone, pg/mL
Lowrie and Lew (1990)[54]	< 9.0 and > 12.0	> 7.0	Not reported
Block et al (1998)[55]	…	> 6.5	…
Ganesh et al (2001)[56]	Not reported	> 6.5	< 33 and > 495
Block et al (2004)[46]	> 9.5	> 5.0	> 600
Young et al (2005)[57]	> 11.4	> 6.5	Not reported
Slinin et al (2005)[58]			
Death	> 9.7	> 6.3	> 480
Cardiovascular events	> 10.2	> 4.5	> 480
Kalantar-Zadeh et al (2006)[53]	< 8.5 and > 10.5	< 3.0 and > 7.0	< 200 and > 400
Noordzij et al (2006)[59]	…	> 5.5	...
Nakai et al (2008)[60]	> 10.0	> 5.5	> 120

*Ellipses indicate that there was no significant association of the measured parameter with death.

Table 3. Recommended Dietary Allowance for phosphorus (RDA)[61]

Age, y	RDA for Phosphorus, mg/d *	
	Men	Women
9 to 18	1250	1250
19 to 70	700	700
> 70	700	700

*The recommended intake of phosphorus for healthy adults is between 700 mg/d and 1250 mg/d. Example: 25% RDA for phosphorus on a food label means 175 mg.

predictor of mortality in these patients.[62] Hence controlling the amount of phosphorus in the diet may be critical in these patients. For patients who have a glomerular filtration rate (GFR) between 25 mL/min/1.73 m^2 and 70 mL/min/1.73 m^2 or who have a higher GFR with a documented progressive loss of kidney function, 8 mg/kg/d to 10 mg/kg/d of phosphorus may be prescribed with the 0.55 g/kg/d to 0.60 g/kg/d of protein.[63] These individuals generally are not given phosphate binders unless their serum phosphorus rises above normal levels.

For non-dialysis-dependent CKD patients with a GFR below 25 mL/min/1.73 m^2 who are prescribed a 0.55-g/kg/d to 0.60-g/kg/d protein diet, the phosphorus intake can be maintained at about 5 mg/kg/d to 10 mg/kg/d, although the lower range of this phosphorus intake will be burdensome for many individuals. Without phosphorus binders, there is a net intestinal phosphate absorption (diet minus fecal phosphorus) of roughly 60% of the phosphorus intake.[63] Therefore, this level of dietary phosphorus restriction usually will not maintain normal serum phosphorus level in patients with a GFR of less than about 15 mL/min, even with a substantial reduction in the fractional renal tubular reabsorption of phosphorus, unless phosphate binders are also used. Because amino acid and keto acid formulations do not contain phosphorus, one advantage of very-low protein diets supplemented with these preparations is the greater ease with which phosphorus intake can be reduced, often to as low as 4 mg/kg/d to 6 mg/kg/d.[63] To determine the effect of limiting the intake of phosphorus-containing food additives on serum phosphorus levels among patients with end-stage renal disease, Sullivan and colleagues[21] in 2009 assessed 279 patients with elevated baseline serum phosphorus levels (> 5.5 mg/dL). Intervention participants (n = 145) received education on avoiding foods with phosphorus additives. After

3 months, the decline in serum phosphorus levels was 0.6 mg/dL greater among the intervention versus the control participants (95% confidence interval, -1.0 mg/dL to -0.1 mg/dL). The authors suggested that educating patients with end-stage renal disease to avoid phosphorus-containing food additives resulted in modest improvements in hyperphosphatemia (Figure 3).

Estimating Dietary Phosphorus and Phosphorus-Protein Ratio

Dietary phosphorus intake is often underestimated. Oenning and coworkers[64] compared 3 methods for estimating dietary phosphorus content using both standard food tables and chemical analyses of 20 meals and found that all methods significantly underestimated the dietary phosphorus content by 15% to 25%. Available nutrient databases do not reflect the extra phosphorus content due to dietary additives. Such variations and inaccuracies in phosphorus content may make it difficult for patients and dietitians to accurately estimate phosphorus content.

The Kidney Disease Outcome Quality Initiative guidelines of the National Kidney Foundation recommend that patients on maintenance dialysis take a relatively high protein intake of 1.2 g/kg/d.[65] Epidemiologic studies indicate that a higher normalized protein nitrogen appearance up to 1.4 g/kg/d (ie, equivalent to a dietary protein intake of roughly 1.5 g/kg/d to 1.6 g/kg/d) is
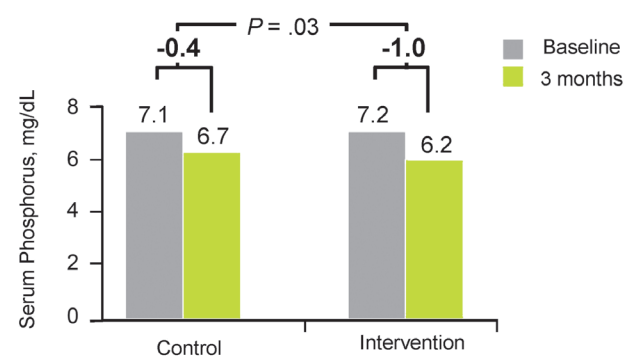
Figures 3. Schematic representation of the findings in the randomized controlled trial by Sullivan and colleagues[21] to examine the impact of nutritional education related to phosphorus additives on serum phosphorus in hyperphosphatemic patients on hemodialysis. The intervention group consisted of patients on dialysis who received education on avoidance of foods with phosphate additives or continue usual care, and the control group, patients on dialysis without this education.

associated with the greatest survival in patients on maintenance hemodialysis.[66] Nevertheless, as discussed above, a higher protein intake is usually associated with greater phosphorus intake and increased likelihood of hyperphosphatemia as shown in Figure 2.

It is important to note that dietary phosphorus restriction to control serum phosphorus is often associated with a reduction in protein intake, which is associated with protein wasting and poor survival.[5] A recent 3-year epidemiologic study in 30 075 prevalent patients on maintenance hemodialysis showed that a decline in predialysis serum phosphorus and a concomitant decline in dietary protein intake were associated with an increase in the risk of death.[5] In this latter study, the patients on maintenance hemodialysis whose protein intake rose while their serum phosphorus declined over time showed the greatest survival.[5] The authors speculated that the risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of lower serum phosphorus and might lead to greater mortality. Additional studies including randomized controlled trials should examine whether restriction of nonprotein sources of phosphorus is safer and more effective in this regard.

Boaz and Smetana[10] examined the dietary intake of 104 Israeli patients with CKD (73 men with a mean age of 65.6 years) using a food frequency questionnaire and suggested the following regression equation as the best-fitting equation that may account for 84% of the variance in dietary phosphorus intake:

Dietary phosphorus (mg) = 128 + 14 × protein intake (g)

In a similar approach, Kalantar-Zadeh and colleagues recently examined daily phosphorus and protein intake in 107 patients on maintenance hemodialysis from 8 DaVita clinics in Southern California, who participated in the Nutritional and Inflammatory Evaluation of Dialysis Patients Study.[67,68] Dietary intake was recorded via a 3-day diet diary accompanied by an interview and analyzed using the Nutrition Data Systems for Research, version 2005 (Minneapolis, MN, USA). Patients were 56.0 ± 12.4 years old, and included 60% men, 43% African-Americans, 36% Hispanics,

and 62% diabetics, with a dialysis vintage of 42.1 ± 33.7 months, postdialysis dry weight of 75.1 ± 20.8 kg (range, 42.6 kg to 172.1 kg), and 3-month averaged Kt/V (single pool) of 1.58 ± 0.28. Dietary phosphorus intake was 874 ± 352 mg/d (range, 294 mg/d to 2137 mg/d) and dietary protein intake was 66.6 ± 26.9 g/d (range, 24.1 g/d to 160.7 g/d). There was a strong association (r = 0.91, $P < .001$) between dietary protein and phosphorus intake (see Figure 1), and the following regression equation was able to explain 83% of the variation ($R^2 = 0.83$):

Dietary phosphorus (mg) = 78 + 11.8 × protein intake (g)

These results are strikingly similar to the findings of Boaz and Smetana.[10]

Because protein intake is an important component of the therapeutic management of patients with CKD and because foods with high-protein content are major sources of organic phosphorus, a more suitable dietary phosphorus metric for patients with CKD may be the ratio of phosphorus (mg) to protein in (g) for a given food item. The metric phosphorus-protein ratio, which is also recommended by the Kidney Disease Outcome Quality Initiative guidelines,[65] has several advantages: (1) the metric is independent of the size of food portion or serving; (2) it focuses simultaneous attention on both dietary phosphorus and protein, which are both important in the nutritional management of patients with CKD; (3) the ratio is higher for foods that have unusually high amounts of phosphorus additives but similar amounts of protein, eg, different types of cheese allowing for more commensurate comparison of food items by both patients with CKD and healthcare providers; and (4) the ratio calls attention to foods that are excessively high in phosphate and especially in phosphate additives, but contains little or no protein such as soft drinks. This should result in heightened awareness of these food sources of excessive phosphorus that are often of low nutritive value. A limitation of the absolute phosphorus content and phosphorus-protein ratio is that they do not provide information about the bio-availability or intestinal absorption of phosphorus in different food types, eg, vegetarian or primarily plant-based diet.

Sherman and associates[69] recently measured

the phosphorus and protein content of 44 foods, including 30 refrigerated or frozen precooked meat, poultry, and fish items, using the Association of Analytical Communities' official method. They found that the ratio of phosphorus to protein ranged from 6.1 mg/g to 21.5 mg/g. The mean ratio was 14.6 mg/g in 19 food products that were labeled as having phosphorus as an additive as compared to 9.0 mg/g in the 11 items that did not list phosphorus additives. These authors also reported that uncooked meat and poultry products that are "enhanced" may contain additives that increase phosphorus and potassium content by as much as almost two- to three-fold, respectively, and that this modification may not be stated in the food label.[70]

As discussed above, whereas inorganic phosphate from additives is approximately 90% absorbable, roughly 40% to 60% of phosphorus in foods derived from animals is absorbed by the intestine, and phosphorus in plant foods may have even lower bioavailability. Notwithstanding these limitations, the use of the phosphorus-protein ratio still appears to be a valuable method for the dietary management and education of patients with CKD. The lowest amount of phosphorus in proportion to the quantity and quality of protein comes from nondairy products, animal-derived foods (average, 11 mg of phosphorus per 1 g of protein), including egg whites and pork rinds. Lamb, beef, chicken breast, and lobster have low phosphorus-protein ratio (5 mg/g to < 10 mg/g). Soy protein and soy bean, salmon, peanut butter, and cheeseburger sandwich have higher phosphorus-protein ratios (10 mg/g to < 15 mg/g). Whole eggs, dairy products (including whole milk and cheese), legumes (including beans and lentils), walnut, sausage, and fast foods have even higher phosphorus-protein ratios (average, 20 mg/g). Egg white, an unusually rich source of high biological value protein, has one of the lowest phosphorus-protein ratios and is also devoid of cholesterol; therefore, it is a particularly healthy food source of protein for patients on dialysis. In contrast, egg yolk has a very high phosphorus-protein ratio and is also very high in cholesterol.

CONCLUSIONS

Dietary intake of phosphate is derived largely from foods with high protein content or food additives and is an important determinant of phosphorus balance in patients with CKD who have a greatly reduced GFR. Almost all phosphorus ingested or that is found in the human body is in the form of phosphate. Phosphate additives can dramatically increase the amount of phosphorus consumed in the daily diet, especially since inorganic phosphate is more readily absorbed. In contrast, plant foods, including seeds and legumes high in phosphorus, are usually associated with the least intestinal phosphorus absorption because of the phytate contained in these foods. Hence, the phosphate burden from food additives in fast foods, soft drinks, and processed cheese and snacks is disproportionately high relative to their dietary phosphorus content compared to natural phosphorus sources from animal-based (excluding dairy products) and plant-derived foods.

The foregoing considerations strongly suggest that in patients with CKD, a mixed composition of dietary animal and plant foods rich in phytic acid should be encouraged, while the intake of processed foods should be limited. Dietary prescription for patients with CKD should take into consideration both the absolute dietary phosphorus content and the phosphorus-protein ratio of foods and meals. More accurate reporting of phosphorus content of foods by manufacturers may result in improved public health nutrition and healthier control of dietary phosphorus intake with less risk of developing protein malnutrition in people with types of illnesses that render them more phosphorus intolerant.[69,70] Cooking modalities that can reduce phosphorus content (such as boiling),[28] use of selective vitamin D activators that lead to less intestinal phosphorus absorption,[71] diligent use of potent phosphorus binders with less pill burden,[72-75] and patient-friendly educational tools such as the concept of dietary "phosphate unit" and its relationship with binder dose[76] could also be helpful.

CONFLICT OF INTEREST

and/or Amgen, Inc, the manufacturer of Cinacalcet hydrochloride (Sensipar™). Joel D Kopple receives the consultation fees from Nephroceuticals.

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