Understanding Sources of Dietary Phosphorus in the Treatment of Patients with Chronic Kidney Disease

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In individuals with chronic kidney disease, high dietary phosphorus (P) burden may worsen hyperparathyroidism and renal osteodystrophy, promote vascular calcification and cardiovascular events, and increase mortality. In addition to the absolute amount of dietary P, its type (organic *versus* inorganic), source (animal *versus* plant derived), and ratio to dietary protein may be important. Organic P in such plant foods as seeds and legumes is less bioavailable because of limited gastrointestinal absorption of phytate-based P. Inorganic P is more readily absorbed by intestine, and its presence in processed, preserved, or enhanced foods or soft drinks that contain additives may be underreported and not distinguished from the less readily absorbed organic P in nutrient databases. Hence, P burden from food additives is disproportionately high relative to its dietary content as compared with natural sources that are derived from organic (animal and vegetable) food proteins. Observational and metabolic studies indicate nutritional and longevity benefits of higher protein intake in dialysis patients. This presents challenges to providing appropriate nutrition because protein and P intakes are closely correlated. During dietary counseling of patients with chronic kidney disease, the absolute dietary P content as well as the P-to-protein ratio in foods should be addressed. Foods with the least amount of inorganic P, low P-to-protein ratios, and adequate protein content that are consistent with acceptable palatability and enjoyment to the individual patient should be recommended along with appropriate prescription of P binders. Provision of in-center and monitored meals during hemodialysis treatment sessions in the dialysis clinic may facilitate the achievement of these goals.

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Chronic kidney disease (CKD) affects >20 million Americans and is associated with high morbidity and mortality (1). The progressive deterioration of kidney function in CKD leads to retention of many substances, including phosphorus (P), that are normally excreted by the kidney. Serum P concentration, however, is usually maintained within the normal range of 2.5 to 4.5 mg/dl by a variety of compensatory mechanisms until renal disease has progressed to approximately stage 5 CKD or ESRD (2). An effective mechanism is the reduction in renal tubular absorption of phosphate (PO_4; *i.e.*, increased fractional excretion of P regulated by parathyroid hormone [PTH] and the phosphatonin fibroblast growth factor 23) (3,4).

In recent years, a number of epidemiologic studies have shown an association between high serum P levels and increased death risk in both dialysis-dependent patients with ESRD (5,6) and individuals with less advanced stages of CKD (7), hyperphosphatemia in these latter patients also seems to be associated with a faster rate of CKD progression (8). Indeed, emerging data indicate that in individuals who do not have apparent CKD and have high normal serum P levels, the risk for coronary artery calcification and mortality is increased (9–11). Hence, relative hyperphosphatemia may represent a novel cardiovascular and death risk factor (12). Similarly, it is possible, although not yet proved, that interventions aimed at dietary P restriction may improve cardiovascular profile and survival even in individuals with high-normal or borderline elevated serum P levels.

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The Element Phosphorus

P, a multivalent nonmetal element of the nitrogen group (group 15) of the periodic table, is naturally found in inorganic PO_4 rocks. Because of its high reactivity, P is almost never found as a free element in nature but is present almost exclu-

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sively in the anion form, PO_4. The first recorded generation of elemental P was in the late 17th century from a preparation of urine, which usually contains considerable quantities of dissolved PO_4 (13). Bone ash was another major source of P until the mid-19th century. The most important commercial use of P-based chemicals is the production of fertilizers. P compounds are also widely used in explosives, nerve toxins, friction matches, fireworks, pesticides, toothpastes, detergents, and food additives (14).

As an essential biologic element, P is required by all cells for normal function and is a critical component of all living organisms (15). In the body, the great preponderance of P is found as PO_4, 85% of which exists in bone and teeth as the calcium PO_4 salt hydroxyapatite. Phospholipids (*e.g.*, phosphatidylcholine) are major structural components of cell membranes (16). Energy production and chemical storage of energy are dependent on phosphorylated compounds, such as adenosine triphosphate and creatine PO_4. Nucleic acids are long chains of PO_4-containing molecules (17). A number of enzymes, hormones, and intracellular signaling molecules depend on phosphorylation for activity. P is an important buffer of hydrogen ion in body fluids. The P-containing molecule 2,3-diphosphoglycerate binds to hemoglobin in red blood cells and facilitates oxygen delivery to the tissues of the body (15).

Dietary P and its Metabolism

Because P exists in virtually all living organisms, it is found in most foods. The main food sources of P are the protein-rich food groups, including dairy products, meat, and fish (see below). According to the Food and Nutrition Board of the Institute of Medicine, the recommended dietary allowance for P is 700 mg/d in healthy adults; in older children and pregnant women, an allowance of up to 1250 mg/d has been suggested (17). There is net absorption of P through the intestinal tract (measured as diet minus feces) of approximately 40 to 80% of the dietary P, based on the type of the diet (see below) and the effects of such hormones as nonselective active vitamin D compounds (calcitriol), which increase the intestinal absorption of P (18).

After intestinal P absorption, only small amounts of P are excreted into the feces, sweat, and saliva, but this proportion of total P output can be increased with worsening renal function (19). In individuals without far advanced kidney failure, >95% of the excretion of the absorbed P is through urine (20). Normally, approximately 70 to 90% of the P filtered by glomeruli is reabsorbed by the renal tubular cells; this is controlled by PTH and fibroblast growth factor 23, both of which decrease the tubular P reabsorption (3). Hence, higher dietary P intake rarely leads to major changes in serum P concentrations in people with normal or partly attenuated renal function as long as the renal fractional excretion of P can be proportionately increased (21).

Serum P levels can rise slightly with a high-P diet, especially immediately after a P-rich meal (3). High serum P concentrations inhibit the renal 1-α-hydroxylation of vitamin D, leading to a reduction in serum calcium (22). Elevated serum P may also suppress serum calcium by causing a saturated serum calcium-P product to precipitate in tissues. These factors can promote increased release of PTH (23). Frequent or sustained elevations of PTH levels can have adverse effects on bone mineral content and architecture, although the significance of such borderline or temporary hyperparathyroidism without kidney dysfunction is unclear (24). A controlled trial of young women found no adverse effects of a P-rich diet of up to 3000 mg/d on bone-related hormones and biochemical markers of bone reabsorption as long as dietary calcium intakes were maintained at almost 2000 mg/d (25). At present, there is no convincing evidence that the usual P intake in the United States adversely affects bone mineral density in individuals without CKD; however, a recent study that used a food frequency questionnaire showed that higher dietary P intake or P-to-protein ratio was associated with increased 5-year death risk in 224 prevalent hemodialysis patients (26).

Organic P and Dietary Protein

Because organic P is largely bound *in vivo* to proteins and other intracellular, carbon-containing molecules, P is naturally found in foods that are rich in protein (27). As shown in Table 1, animal-based foods that are abundant in organic P include dairy products, meat, poultry, and fish. Organic P is hydrolyzed in the intestinal tract and then absorbed into the circulation as inorganic PO_4 (28). Usually only 40 to 60% of organic dietary P is absorbed (29). Complexity is added by the variable digestibility of dietary nutrients and bioavailability of dietary P. Digestibility of P from animal-derived foods is higher than plant proteins (see below). Moreover, meat products are frequently "enhanced" by the addition of PO_4 additives (see below), which may markedly increase the total P content.

There is a strong and positive correlation between dietary protein and P intake, which is responsible for the frequent association of high protein intake in the diet with excessive ingestion of P and the development of hyperphosphatemia in people with CKD (27). Boaz and Smetana (27) examined the dietary intake of 104 Israeli patients with CKD, including 73 men (mean age 65.6 years), using a food frequency questionnaire. They developed the following regression equation for the relationship between protein and P intake, which can account for 84% of the variance in dietary P intake:

Dietary P (mg) = 128 mg P + (dietary protein in g) $\times$ 14 mg P/g protein

In a similar approach, we examined daily P and protein intake in 107 maintenance hemodialysis (MHD) patients from eight DaVita clinics in Southern California who participated in the Nutritional and Inflammatory Evaluation of Dialysis Patients (NIED) Study (30,31). Dietary intake was assessed by a 3-day diet diary associated with an interview with a dietitian; data were analyzed using Nutrition Data Systems for Research (NDSR), Version 2005 (Minneapolis, MN). Patients were 56.0 $\pm$ 12.4 years of age (mean $\pm$ SD) and included 60% men, 43% black and 36% Hispanic patients, and 62% with diabetes, with a dialysis vintage of 42.1 $\pm$ 33.7 months. Postdialysis dry weight was 75.1 $\pm$ 20.8 kg (minimum 42.6 kg, maximum 172.1 kg), and 3-month averaged Kt/V (single pool) was 1.58 $\pm$ 0.28. Calculated dietary P intake was 874 $\pm$ 352 mg/d (minimum 294

Table 1. Dietary P, protein, and potassium content of selected food items, ranked according to the P-to-protein ratio categories (64,65)

Parameter	Serving Amount	P (mg)	Protein (g)	K (g)	P-to-Protein Ratio (mg/g)	Comments[a]
P-to-protein ratio <5 mg						
egg white[b]	1 large	5	3.6	54	1.4	–
pork rinds	1 oz	24	17.4	36	1.4	521 mg Na
orange roughy fish	3 oz	87	19.2	154	4.5	–
P-to-protein ratio 5 to <10 mg/g						
lamb	3 oz	~170	~27.0	~203	6.3	[c]
tuna, canned in water	3 oz	139	21.7	201	6.4	–
chicken drumstick	1 drum	81	12.5	108	6.5	–
beef (excludes organ meats)	3 oz	~160	~23.0	~220	7.0	[c]
ground beef	3 oz	165	21.9	258	7.5	–
chicken breast	1/2 breast	199	26.7	220	7.5	–
turkey (excludes organ meats)	3 oz	~180	~24.0	~375	7.5	[c]
yellow fin tuna	3 oz	208	25.5	484	8.2	–
Nepro with Carb Steady (66)	8 oz	165	19.1	250	8.6	250 mg Na
pork sausage	2 links	44	5.1	~124	8.6	–
Novosource Renal (67)	8 oz	154	17.4	192	8.9	210 mg Na
lobster	3 oz	157	17.4	299	9.0	–
hotdog on bun, fast food[d]	1 sandwich	97	10.4	143	9.3	670 mg Na
pork (excludes organ meats)	3 oz	~185	~20.0	76	9.3	[c]
cod fish	3 oz	190	19.5	439	9.7	–
taco, fast food	1 small	203	20.7	474	9.8	802 mg Na
P-to-protein ratio 10 to <15 mg/g						
soy protein isolate[e]	1 oz	217	22.6	23	9.6	–
egg substitute[e]	1/4 cup	76	7.5	207	10.1	–
salmon, sockeye	3 oz	235	23.2	319	10.1	–
crab, blue[e]	3 oz	175	17.2	275	10.2	–
bagel (4″)[e]	1	89	8.7	132	10.2	–
cheeseburger, fast food[d,f]	1 sandwich	162	15.4	194	10.5	601 mg Na
bologna[f]	2 slices	92	8.6	179	10.7	417 mg Na
cottage cheese, 1% milkfat[f]	1/2 cup	151	14.0	194	10.7	–
halibut	3 oz	242	22.7	490	10.7	–
tuna, canned in oil	3 oz	265	24.8	176	10.7	–
tempeh	1/2 cup	171	15.8	305	10.8	–
rainbow trout	3 oz	226	20.6	375	11.0	–
tofu, raw[e]	1/2 cup	239	19.9	299	12.0	–
beef jerky	1 large piece	81	6.6	118	12.3	438 mg Na
peanut butter, chunky[e]	1 tbsp	51	3.9	119	13.1	–
swordfish	3 oz	286	21.6	314	13.2	–
whole egg	1 large	84	6.3	67	13.3	–
frankfurter, beef and pork[d]	1 frank	72	5.1	75	14.1[f]	504 mg Na
frankfurter, beef	1 frank	72	5.1	70	14.1	513 mg Na
peanut butter, smooth[e]	1 tbsp	57	4.0	104	14.3	–
lima beans[e]	1/2 cup	105	7.3	478	14.4	–
soybeans, cooked[e]	1/2 cup	211	14.3	443	14.7	–
P-to-protein ratio 15 to <25 mg/g						
peanuts[e]	1 oz	101	6.7	187	15.1	–
baked beans with franks[e]	1/2 cup	135	8.7	305	15.5	557 mg Na
edamame	1/2 cup	284	6.1	284	15.6	–
black beans[e]	1/2 cup	120	7.6	306	15.8	–
ricotta cheese, part skim[f]	1/2 cup	225	14.0	154	16.1	–
kidney beans[e]	1/2 cup	125	7.7	357	16.2	–
pinto beans[e]	1/2 cup	125	7.7	373	16.2	–

Table 1. (Continued)

Parameter	Serving Amount	P (mg)	Protein (g)	K (g)	P-to-Protein Ratio (mg/g)	Comments[a]
chicken liver	1 liver	79	4.8	52	16.5	–
cream cheese[f]	1 tbsp	15	0.9	20	16.7	–
soymilk[e]	4 fl oz	59	3.4	169	17.4	–
Camembert cheese[f]	1 wedge	132	7.5	71	17.6	–
bleu cheese[f]	1 oz	110	6.1	73	18.0	–
lentils[e]	1/2 cup	178	8.9	366	20.0	–
mozzarella cheese[f]	1 oz	149	7.4	27	20.1	–
Munster cheese[f]	1 oz	133	6.6	38	20.2	–
cheddar cheese[f]	1 oz	145	7.1	28	20.4	–
Swiss cheese[f]	1 oz	161	7.6	22	21.2	–
almonds[e]	24 nuts	137	6.0	48	23.0	–
walnuts[e]	14 halves	98	4.3	18	25.0	–
American cheese[d,f]	1 oz	145	6.3	200	22.8	–
egg yolk[b]	1 large	65	2.6	125	22.8	–
adzuki beans	1/2 cup	193	8.7	612	22.2	–
feta cheese, Persian	1 oz	96	40.0	18	24.0	–
P-to-protein ratio >25 mg/g						
biscuit, egg, sausage, sandwich, fast food[d,g]	1 biscuit	562	20.0	268	28.1	–
milk, low fat (2%)	1 fl cup	229	8.1	366	28.3	–
pecans[e]	20 halves	79	2.6	116	30.4	–
half and half	1 tbsp	14	0.44	20	31.8	–
cashews[e]	1 oz	139	4.3	160	32.3	–
tahini	2 tbsp	220	5.1	124	43.1	
sunflower seeds	3 tbsp	370	6.2	272	59.7	–
liquid nondairy creamer[d]	1 oz	19	0.3	0	63.3	

For more information on the nutrient content of foods, search the USDA food composition database.
[a]The quantitative sodium content is mentioned for high-sodium foods (>400 g of sodium per serving).
[b]P-to-protein ratio of egg varies considerably: Whole egg 13.4; egg yolk 24.7; egg white 1.4 mg/g.
[c]Values vary for cut of meat; average provided.
[d]Product contains phosphate additives (see text).
[e]P from nuts, seeds, and grains is ≤50% bioavailable than phosphorus from other sources (see text) (9).
[f]See also Table 4 for the role of additive in the variation of P content of various cheese types.
[g]High in sodium.

mg/d, maximum 2137 mg/d), and dietary protein intake was 66.6 ± 26.9 g/d (minimum 24.1 g/d, maximum 160.7 g/d). There was a strong linear association ($r = 0.91$, $P < 0.001$) between the dietary protein and P content (Figure 1). The following regression equation accounted for 83% of the variation ($R^2 = 0.83$)

Dietary P (mg) = 78 mg P + (dietary protein) × 11.8 mg P/g protein

It is important to note that high R^2 values in both our and Boaz and Smetana's (27) regression equations indicate a good model fit and not necessarily good prediction for individual values (32).

Consistent with these data, a recent epidemiologic study of 30,075 MHD patients found that the predialysis serum P increased incrementally as the normalized protein nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), rose; the nPNA reflects the protein intake in MHD patients (Figure 2) (33). Hence, a higher dietary protein intake in patients with CKD not only predisposes to a greater P intake but also may lead to worsening hyperphosphatemia; however, it is important to appreciate the wide range of variation in the proportion of P from different types of protein-containing foods. A relevant example is the egg white, which has only 1.4 mg of P per gram of protein, whereas egg yolk contains 22.8 mg of P per gram of protein, or 16 times more P per gram of protein (see Table 1).

P Intake from Plant Foods: The Role of Phytate

Whereas many fruits and vegetables contain only small amounts of P, organic PO_4 is found naturally and abundantly in some plant seeds, nuts, and legumes. Unlike P in meat that is present as organic phosphates in intracellular compartments and that is easily hydrolyzed and readily absorbed, P in plants, especially in beans, peas, cereals, and nuts, is mostly in the form

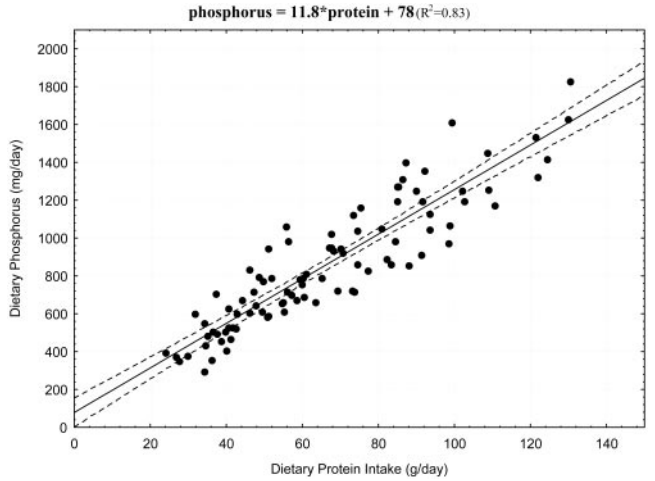

Figure 1. Estimated daily P intake (in mg/d) from daily protein intake (in g/d) in 107 MHD patients from the NIED Study (30). Regression equation: P = 11.8*protein + 78 (r = 0.91, $P <$ 0.001). Characteristics of the study population: 107 adult MHD patients from eight DaVita dialysis Clinics in Los Angeles area, 2001–2006. Dietary P intake 874 ± 1352 mg/d (range 294 to 2137 mg/d), dietary protein intake 66.6 ± 26.9 g/d (range 24.1 to 160.7 g/d), age 56.0 ± 12.4 years, men 60%, black patients 43%, Hispanic patients 36%, patients with diabetes 62%, dialysis vintage 42.1 ± 33.7 months, postdialysis dry weight 75.1 ± 20.8 kg (range 42.6 to 172.1 kg), single-pool Kt/V 1.58 ± 0.28. Dashed lines indicate predicated interval.

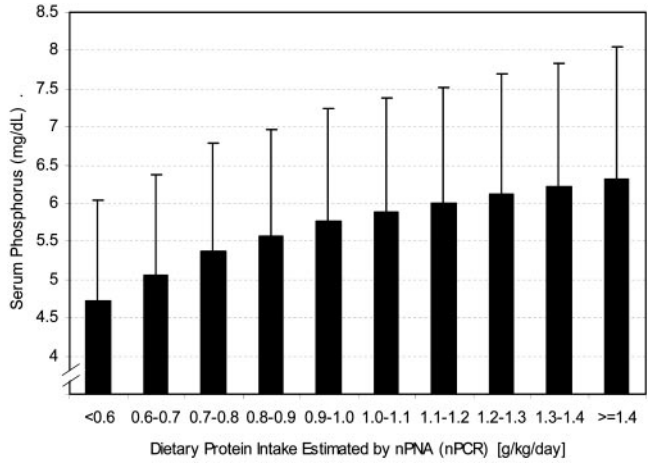

Figure 2. Association between the baseline dietary protein intake, represented by 13-week averaged nPNA (nPCR) and 13-week averaged serum P, in 30,075 DaVita MHD patients ($P <$ 0.001 for trend). Adapted from reference (33), with permission.

of phytic acid or phytate (34,35). Because humans do not express the degrading enzyme phytase, the bioavailability of P from plant-derived food is relatively low, usually <50% (36). Hence, despite the "apparently" higher P content of some plants (see Table 1), the actual result may be a lower rate of intestinal P absorption per gram of plant protein than animal-based protein (37). When healthy humans are given the same amount of dietary P from either animal or plant foods, urinary P excretion is higher with the meat-based diet (38).

The apparently high content of P in plants seeds (see Table 1) has traditionally led to an emphasis on restricting such plant foods as beans for fear of worsening hyperphosphatemia in patients with CKD (39). Notwithstanding the wisdom of such prudent recommendations, in our opinion and given the role of phyate in inhibiting the intestinal P absorption, plant foods are somewhat less likely to increase P burden. Nonetheless, even with a lower fractional rate of intestinal absorption with such foods as beans, a large bean intake can still lead to an excessive P burden. There are several important considerations in this regard. First, some seeds and beans have a high content of potassium (see Table 1), which may contribute to worsening hyperkalemia in patients with CKD. Second, yeast-based phytase in whole grains makes the P content of leavened breads more prone to intestinal absorption than cereals or flat breads (40). Finally, the effect of probiotics on enhancing phytate-associated P release and absorption is not clear.

Inorganic P in Additives

P is the main component of many preservatives and additive salts found in processed foods (39,41). Additives are used in food processing for a variety of reasons, including to extend shelf life, improve color, enhance flavor, and retain moisture (37,42). The presence of inorganic P is often obscured by the use of complex names for the ingredients (43,44). Commonly used additives, all containing PO_4 moiety, are listed in Table 2. Common sources of inorganic P include certain beverages, enhanced or restructured meats, frozen meals, cereals, snack bars, processed or spreadable cheeses, instant products, and refrigerated bakery products (45,46). Even though the PO_4 salts named in Table 2 may be listed under the ingredients of the food manufactured for consumption in the United States, the Food and Drug Administration does not require manufacturers to list the quantity of P per serving on food labels (47). There is no accurate or reproducible method to distinguish between protein-based organic and preservative-based inorganic P in food (48,49).

Implications of P Burden from Additives

Inorganic P, such as P additives, are not protein bound; they are salts that more readily disassociate and are absorbed in the intestinal tract (50). Indeed, it is believed that >90% of inorganic P may be absorbed in the intestinal tract, as opposed to only 40 to 60% of the organic P present in natural foods (51,52). The major public health implication from these considerations is that the P burden from inorganic P–containing food additives is disproportionately high relative to organic P. In the early 1990s, P additives contributed approximately 500 mg/d P to the American diet, whereas today P additives may contribute as much as 1000 mg/d P to the average American diet (37,51,53,54).

In one study, eight healthy volunteers were fed a diet that contained the same amount of dietary protein (95 g/d) and energy (2200 cal/d) for 4 weeks. Initially, the foods offered contained little or no P-containing food additives. After 4

Table 2. Common phosphate additives used by food industry

Phosphate Salt	Purpose	Found in
Dicalcium phosphate	Calcium and phosphorus supplementation, dough conditioner	Bakery mixes, yeast-raised bakery products, cereals, dry powder beverages, flour, food bars, infant food, milk-based beverages, multivitamin tablets, yogurt
Disodium phosphate	Sequestrant, emulsifier, buffering agent, absorbent, pH control agent, protein modifier, source of alkalinity, stabilizer	Breakfast cereal, cheese, condensed milk, cream, evaporated milk, flavored milk powders, gelatin, half and half, ice cream, imitation cheese, infant food, instant cheesecake, instant pudding, isotonic drinks, nonfat dry milk, pasta, pet food, processed cheese, starch, vitamin capsules, whipped topping
Monosodium phosphate	Acidulant, buffering agent, emulsifier, leavening agent, protein modifier and sequestrant, gelling aid	Cola beverages, dry powder beverages, egg yolks, gelatin, instant cheesecake, instant pudding, isotonic beverages, and process cheese custard pudding and no-bake cheesecake mixes
Phosphoric acid	Acidulant, pH control agent, buffering agent, flavor enhancer, flavoring agent, sequestrant, stabilizer, thickener, synergist	Cola beverages, carbonated and noncarbonated beverages
Sodium hexameta-phosphate	Sequestrant, curing agent, dough strengthener, emulsifier, firming agent, flavor enhancer, flavoring agent, humectant, nutrient supplement, processing aid, stabilizer, thickener, surface-active agent, synergist, texturizer, buffering agent.	Meat, seafood, poultry, vegetables, cream, half and half, ice cream, whey, processed cheese, eggs, table syrup, toppings
Sodium tripolyphosphate	Sequestrant, pH control agent, emulsifier, providing alkalinity, buffering agent, coagulant, dispersing agent, protein modifier, antioxidant, curing agent, flavor enhancer, humectant, thickener, stabilizer, texturizer	Meat products, seafood, poultry, vegetable proteins, processed cheese, sour cream, dips, yogurt, eggs, table syrups, whipped toppings, pet food, vegetables, whey
Tetrasodium pyrophosphate	Buffering agent, pH control agent, alkalinity source, dispersing agent, protein modifier, coagulant, sequestrant, emulsification, color stabilizer	Processed meat, poultry, seafood, processed cheese, potato products, ice cream, frozen desserts
Trisodium phosphate	Buffer, emulsifying agent, stabilizer, protein modifier, pH control, color stabilizer	Processed cheese, cheese products, imitation cheese, isotonic beverages, cooked breakfast cereals

Source: ICL Performance Products LP, St. Louis, MO 63141; http://www.perfperformancelp.com.

weeks, foods with a large amount of P additives were offered to the participants (50). This intervention led to an increase in their total P intake from 979 to 2124 mg/d. The introduction of foods that contain PO_4 additives was associated with intestinal distress, soft stools, and/or mild diarrhea and led to increases in serum P levels and urinary P excretion and decreases in serum calcium and urinary calcium concentrations (50). These changes are analogous to those seen in experimental animals that were fed high-P diets, which are associated with enhanced PTH release, similar to secondary hyperparathyroidism observed in CKD (55). Hence, not only may processed foods contain a high amount of P in addition to the P naturally present, (*i.e.*, up to 2 times higher), but also the P is also more readily absorbed because it is in an inorganic form.

Two food items are of special relevance to patients with CKD: Soft drinks and cheese. Substantial amounts of phosphoric acid are usually present in most colas and many other beverages but not in root beer, for instance (Table 3) (53). Many but not all clear-colored soft drinks or teas are low in P (Table 3) (46); however, most of these drinks contain little to no protein or other organic compounds, and the P is almost exclusively from additives. Being in liquid form, the inorganic P in these drinks are perhaps even more readily absorbable. The high additive-based P burden is a dietary challenge in almost all nations throughout the world. Table 4 illustrates variations in P content across diverse types of cheese in German-speaking regions of Europe. The quantity of P in a 50-g portion of cheese varies from <100 mg in Brie cheese to almost half a gram in processed soft cheese, which contains a significant amount of P salt (45,46).

Balancing Dietary Protein and P Intake in CKD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that maintenance dialysis patients take a relatively high protein intake of 1.2 g/kg body w per d (56). Epidemiologic studies indicate that a higher nPNA (nPCR) up to 1.4 g/kg per d (*i.e.*, equivalent to a dietary protein intake of roughly 1.5 to 1.6 g/kg per d) is associated with the greatest survival in MHD patients (57). Nevertheless, as discussed, a higher protein intake is usually associated with greater P intake and increased likelihood of hyperphosphatemia, as shown in Figure 2. Conversely, dietary P restriction to control serum P is often associated with a reduction in protein intake, which is associated with protein wasting and poor survival. A recent 3-yr epidemiologic study of 30,075 prevalent MHD patients showed that a decline in predialysis serum P and a concomitant decline in dietary protein intake were associated with an increase in the risk for death (33). In that study, serum P had a J-shaped association with mortality (Figure 3), whereas a combination of changes—drop *versus* rise—in predialysis serum P during 6 months and a change in the opposite direction—rise *versus* drop—in protein intake during the same period of time (measured by changes in nPNA or nPCR during 6 months) had a linear association with the survival, greater *versus* worse survival, respectively (Figure 4). In this study, the MHD patients whose protein intake rose while their serum P declined over time showed the greatest survival (33). The authors speculated that the risk of controlling serum P by restricting dietary protein intake may outweigh the benefit of lower serum P and might lead to greater mortality. Additional studies, including randomized, controlled trials, should examine whether restriction of nonprotein sources of P is safer and more effective. A recent randomized, controlled trial showed that P intake may be decreased by restricting intake of enhanced food with P-containing additives (37). Although it is possible that this dietary modification did not substantially reduce protein intake, the latter study did not present data on this question (37).

Metrics for Dietary P Management in CKD: P-to-Protein Ratio

The dietary P is usually expressed in milligrams per daily food intake. The recommended daily allowance for intake of P for healthy adults is between 700 and 1250 mg (17); however, a person who is ingesting 70 to 90 g/d protein will usually eat substantially more P than the daily allowance. The K/DOQI guidelines recommend up to 1000 mg/d dietary P for patients with CKD to allow for adequate palatability of the diet (56). Dietary P, however, is often underestimated. A study by Oenning *et al.* (58) compared three methods of estimating dietary P content using both standard food tables and chemical analyses of 20 meals and found that all methods significantly underestimated the dietary P content by 15 to 25%. In that study, the food tables underestimated the P content of the meals compared with the chemical analyses by an average of 272 mg/d (58). Assessment of P content of diets with more than five processed, convenience, or restaurant foods underestimated the measured P content by an average of approximately 350 mg/d. Available nutrient databases do not reflect the extra P content as a result of the dietary additives. Such variations and inaccuracies in P content may make it difficult for patients and dietitians to estimate P content accurately.

Because protein intake is an important component of the therapeutic treatment of patients with CKD and because foods with high protein content are major sources of organic P, a more suitable dietary P metric for patients with CKD may be the ratio of P (in mg) to protein (in g) for a given food item. The metric P-to-protein ratio, which is also recommended by the K/DOQI guidelines (56), has several advantages: (*1*) It is independent of the size of food portion or serving; (*2*) it focuses simultaneous attention on both dietary P and protein, which both are important in the nutritional treatment of patients with CKD; (*3*) the ratio is higher for foods that have unusually high amounts of P additives but similar amounts of protein (*e.g.*, different types of cheese; see Tables 1 and 4), allowing more commensurate comparison of food items by both patients with CKD and health care providers; and (*4*) it calls attention to foods that are excessively high in P and especially P additives, such as soft drinks, but contain little or no protein. This should result in heightened awareness of these food sources of excessive P that are often of low nutritive dietary value. A limitation of the absolute P content and P-to-protein ratio is that they do

Table 3. P content of selected beverages, mostly as a result of additives (based on 12-oz serving)

Brand Name	Specification/Flavors	P Content (mg)
Contain <10 mg of P per 12-oz serving[a]		
7 Up	All flavors	<10
Aquafina Essentials	(excluding tangerine pineapple)	<10
Barq's Root Beer	All flavors	<10
Dasani Water	All flavors	<10
Fanta	Most flavors	<10
Fresca	All flavors	<10
Vernors	Ginger ale	<10
Lipton Pure Leaf Teas	All flavors	<10
Mello Yellow	All flavors	<10
Minute Maid	Fruit punch	<10
Mountain Dew	Most flavors (excluding Code Red)	<10
Mug Root Beer	All flavors	<10
Nestea Tea	Lemon Sweet	<10
Pepsi	Pepsi Natural	<10
Root Beer	(excluding Hire's)	<10
Sierra Mist	All flavors	<10
Slice	All flavors	<10
SoBe Lifewater	All flavors	<10
Sprite	All flavors	<10
Tropicana Twister	All flavors	<10
Vault	All flavors	<10
Contain >10 mg of P per 12-oz serving		
AMP Energy	All flavors	30 to 207
Aquafina Flavorsplash	All flavors	93 to 128
Coca-Cola Classic	All types	62
Diet Coke (Coca-Cola)	All types	27
Dr. Pepper	All types	68
Fanta	Orange, red tangerine	11
Fruitworks	All flavors	53 to 140
Gatorade and G2	All flavors	36
Hawaiian Punch	All flavors	260
Lipton Brisk Tea	Green, lemon, raspberry, sweet tea, no calorie lemon	98 to 189
Lipton Iced Tea (plastic bottled)	All flavors	98 to 114
Lipton Sparkling	All flavors	98 to 104
Mountain Dew	Code Red	53
Mr. Pibb	Pibb Xtra, Pibb Zero	44
Nestea	Diet lemon, green tea citrus, diet green tea citrus, red tea pomegranate passion, raspberry	47 to 71
Pepsi	Most colas (except Pepsi Natural)	54
Diet Pepsi	All flavors	41 to 68
Propel Water	All flavors	89
Tropicana Fruit Drinks	All flavors	53 to 140

Source: Company websites and personal communication with manufacturers.
[a]Most drinks have no P.

not provide information about the bioavailability or intestinal absorption of P in different food types (*e.g.*, vegetarian diet).

Sherman *et al.* (43) recently measured the P and protein content of 44 foods, including 30 refrigerated or frozen pre-cooked meat, poultry, and fish items, using the Association of Analytical Communities official method and found that the ratio of P to protein ranged from 6.1 to 21.5 mg/g. The mean ratio was 14.6 mg/g in 19 food products that were labeled as

Table 4. Selected types of cheese consumed in German-speaking regions of Europe

Cheese	US English Equivalent Terminology	Fat in Dry Matter (%)	P (mg) in 50-g Serving
Cream and brie cheeses, 50-g serving			
Frischkäse	Cream cheese	50	94
Briekäse	Brie cheese	50	94
Soft cheese (*Weichkäse*), 50-g serving			
Butterkäse	(Danish) butter cheese	60	178
Gorgonzola	Gorgonzola (Italian blue cheese)		175
Camembert (45% *Fett i. Tr.*)	Camembert (soft, creamy French cheese)	45	175
Camembert (60% *Fett i. Tr.*)	See above	60	155
Mozzarella	Mozzarella		150
Limburgerkäse (20% *Fett i. Tr.*)	Limburger cheese with characteristic odor	20	143
Limburgerkäse (40% *Fett i. Tr.*)	See above	40	128
Münsterkäse	Munster-Géromé cheese	45	120
Hard and slicing cheese (*Hart- und Schnittkäse*), 50-g serving			
Edamerkäse (30% *Fett i. Tr.*)	(Dutch) Edam cheese	30	256
Edamerkäse (45% *Fett i. Tr.*)	See above	40	230
Gouda	Gouda cheese	45	220
Appenzeller Rahmstufe	Appenzeller cheese (hard cow milk cheese)	Varies	249
Emmentaler	Swiss (Emmental) cheese	45	291
Schmelzkäse, 62.5-g serving or 1 wedge (1 *Ecke*)			
Schmelzkäse	Processed soft (melted) cheese[a]	Varies	590[b]

Variations in phosphorus contents reflect mostly the contribution of additives. Contents of the table were developed on the basis of personal communication with Dr. Martin Kuhlmann (Berlin, Germany). English translation of the German words: *Käse*, cheese; *Weich*, soft; *Hart*, hard; *Schmelz*, melt (Schmelzkäse usually referrers to "processed" soft cheese); *Ecke*, wedge; *Fett i. Tr.*, fat in dry matter.

[a]There are different brands of processed soft cheese in the United States, such as Velveeta.

[b]For the processed soft cheese, the serving unit is 62.5 g (equivalent of 472 mg in 50 g of processed cheese).

having P as an additive as compared with 9.0 mg/g in the 11 items that did not list P additives. These authors also report that uncooked meat and poultry products that are "enhanced" may contain additives that increase P and potassium content by as much as almost two- and three-fold, respectively, and that this modification may not be stated in the food label (44).

As discussed, whereas inorganic P from additives are 90% absorbable, roughly 40 to 60% of P in foods derived from animals is absorbed by the intestine, and P in plant foods may have even lower bioavailability. Notwithstanding these limitations, the use of metric P-to-protein ratios still seems valuable for dietary treatment and education of patients with CKD. In Table 1, food items are ranked according to their P-to-protein ratio. The lowest amount of P in proportion to the quantity and quality of protein comes from animal-derived foods (average 11 mg of P per 1 g of protein), including egg whites and pork rinds, whereas whole eggs, dairy products, legumes, and lentils have higher P-to-protein ratios (average 20 mg of P per 1 g of protein). Egg white, an unusually rich source of high-biologic-value protein, has one of the lowest P-to-protein ratios and is also devoid of cholesterol; hence, it is a particularly healthful food source of protein for dialysis patients. In contrast, egg yolk is very high in both the P-to-protein ratio and cholesterol (see Table 1).

Conclusions

Dietary intake of P is derived largely from foods with high protein content or food additives and is an important determinant of P balance in patients who have CKD and have a greatly reduced GFR. PO_4 additives can dramatically increase the amount of P consumed in the daily diet, especially because P is more readily absorbed in its inorganic form. In contrast, plant foods, including seeds and legumes that are high in P, are usually associated with the least intestinal P absorption because of the phytate in these foods. Hence, the P burden from food additives in fast foods, soft drinks, and processed cheese and snacks is disproportionately high relative to its dietary P content compared with natural P sources from animal and plant protein. Information about the P content and type in prepared foods is often unavailable or misleading. In a recent random-

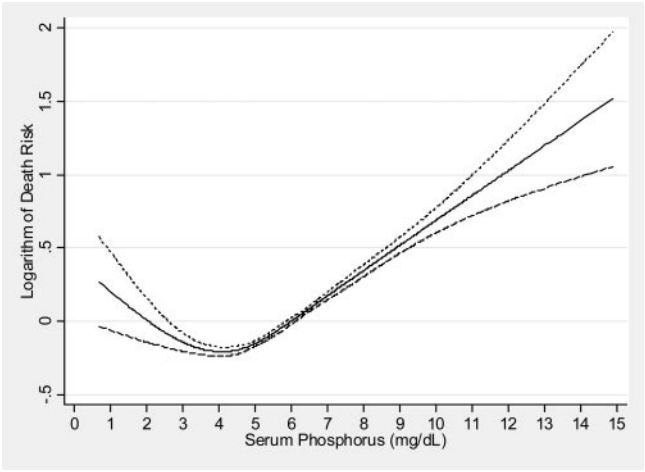

Figure 3. Mortality predictability of 3-month averaged predialysis serum P concentration in 30,075 DaVita MHD patients. The *y* axis shows the logarithm of the risk ratio of all-cause mortality during 3 years of observation (July 2001 through June 2004). The multivariable regression spline models are adjusted for case mix and measures of nutritional status and inflammation. Dashed lines are 95% point-wise confidence levels. Adapted from reference (33), with permission.

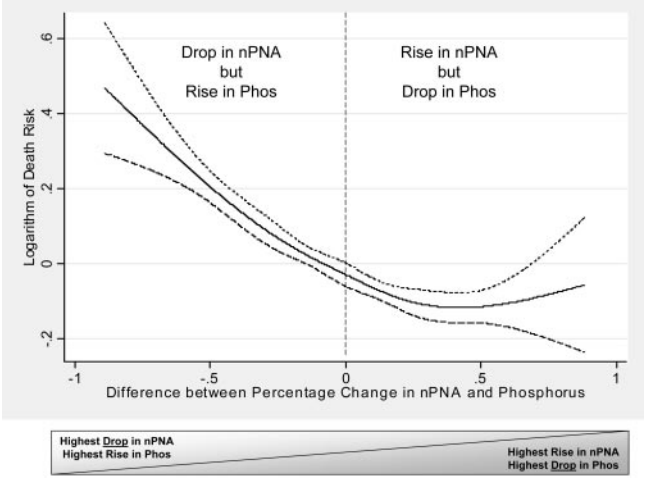

Figure 4. Mortality predictability of the difference of the percentiles of the changes in dietary protein intake, represented by nPNA (nPCR), and serum P concentration in 30,075 MHD patients. The difference between nPNA and serum P concentration in each patient is a number between −0.98 and 0.98. The *y* axis shows the logarithm of the risk ratio of all-cause mortality during 3 years on the basis of a multivariable Cox regression spline model, adjusted for case mix and measures of nutritional status and inflammation. Dashed lines are 95% point-wise confidence levels. Each patient received a percentile score between 0.01 and 0.99 according to the percentile rank of the change in nPNA or serum P. Adapted from reference (33), with permission.

ized, controlled trial, inorganic P in processed food contributed significantly to the P burden of dialysis patients (37). The foregoing considerations strongly suggest that in patients with CKD, a mixed composition of dietary animal and plant foods that are rich in phytic acid should be encouraged, whereas the intake of processed foods should be limited. Of course, it is most important to restrict intake of P in all of its forms in the diet of patients with CKD.

The increased use of P additives in food, coupled with the increased popularity of convenience foods and frequenting of fast food restaurants, has greatly increased the amount of P consumed by both the general population and patients with CKD. When health care workers and members of the population at large develop menus and meal plans for patients with CKD, we recommend that they consider both the absolute dietary P content and the P-to-protein ratio of foods and meals. More accurate reporting of P content of foods by manufacturers, especially when mandated by the Food and Drug Administration, may result in improved public health nutrition and healthier control of dietary P intake with less risk for developing protein malnutrition in people with illnesses that render them more P intolerant (43,44). Because a high protein intake and a concurrent low P intake and normal serum P seems to be associated with the lowest mortality in patients with ESRD (33), cooking modalities that can reduce P content (*e.g.*, boiling) (48), use of selective vitamin D activators that lead to less intestinal P absorption (23), diligent use of potent P binders with less pill burden (59–62), and patient-friendly educational tools such as the concept of dietary "phosphate unit" and its relationship with binder dosage (63) also are helpful. Meals that have lower amounts of organic and particularly inorganic P and are rich in high-value protein, along with P binders, can be provided during long hemodialysis treatment sessions to patients with CKD within inside dialysis clinics and monitored in-center by renal dietitians and nephrologists. Well-designed trials are needed to examine these hypotheses (4).

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