

Phosphorus Homeostasis in Normal Health and in Chronic Kidney Disease Patients with Special Emphasis on Dietary Phosphorus Intake

Jaime Uribarri

Division of Nephrology, Mount Sinai School of Medicine, New York

ABSTRACT

Elevated serum phosphorus has been identified as a cardiovascular risk factor in chronic kidney disease (CKD) patients and a clear understanding of phosphorus homeostasis is very important for practicing nephrologists. At any particular point, serum phosphorus levels reflect the balance between movements of this mineral from and into the intestine, bone, intracellular space, and kidneys. We briefly review here all these exchanges with a particular emphasis on dietary phosphorus intake. Despite all the oral phosphorus binders currently available in the market, dietary restriction of this mineral remains a cornerstone for the prevention and treatment of hyperphosphatemia. An effective restriction of dietary

intake of phosphorus requires prescription of a moderate protein intake (0.9–1.0 g/kg/day) and restricted consumption of highly processed fast and convenience foods. Phosphorus added during food processing is an important source of this mineral because of its magnitude and high bioavailability. Moreover, as food manufacturers are not required to label the amount of phosphorus added during food processing, a significant amount of the current daily phosphorus intake remains unaccounted when estimating phosphorus intake in CKD patients. The recent development of low phosphorus-containing food products represents a very useful addition for CKD patients.

Body Phosphorus Content and Distribution

The total phosphorus content in a 70 kg man is approximately 700 g. About 85% of this phosphorus is in the bone and teeth (in the form of hydroxyapatite), 14% in soft tissues and only 1% in the extracellular space. Phosphorus inside cells is present mostly in the form of organic compounds such as creatinine phosphate, ATP, nucleic acids, phospholipids, and phosphoproteins. In plasma, phosphorus is present in both organic and inorganic forms, but in the clinical laboratory it is only the “inorganic phosphate” that is measured with a normal range of 3.0–4.5 mg/dl. Less than 20% of the inorganic phosphate is protein-bound. Further, although the clinical laboratory usually expresses measured phosphorus as “phosphate”, only the weight of elemental phosphorus is considered. Because the atomic weight of phosphorus is 31, a phosphorus concentration of 4 mg/dl is 1.29 mmol/L ($4 \text{ mg/dl} = 40 \text{ mg/L} / 31 = 1.29$).

The concentration of extracellular phosphorus is not as tightly controlled as that of calcium and may vary widely over the course of a day with lowest values early

in the morning and peak values at about 8 PM; levels are also higher in summer months compared to the winter season.

Phosphorus concentration in the extracellular space is determined by the interactions among intestinal absorption, renal excretion, and exchanges with bone and the intracellular space (Fig. 1).

Intestinal Absorption

Phosphate is absorbed in the small intestine both by passive paracellular diffusion along an electrochemical gradient and actively across the cells by the luminal sodium phosphate cotransporter type 2b (1). This transporter is very similar to the sodium phosphate cotransporters found in the renal tubules and is also stimulated by $1,25(\text{OH})_2$ vitamin D. Nicotinamide is a well-known inhibitor of these transporters (2) and the oral administration of nicotinamide to hemodialysis patients has been shown to produce a significant reduction in serum phosphorus levels (3). The same effect reducing serum phosphorus concentration has been recently shown with oral nicotinic acid, which gets converted to nicotinamide inside the body (4).

Although vitamin D increases intestinal phosphorus absorption to some extent, it is not essential for gastrointestinal absorption of phosphorus. In the presence of renal failure, absorption of a test dose of phosphorus

Address correspondence to: Jaime Uribarri, MD, Division of Nephrology, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029, or e-mail: jaime.uribarri@mssm.edu.

Seminars in Dialysis—Vol 20, No 4 (July–August) 2007
pp. 295–301
DOI: 10.1111/j.1525-139X.2007.00309.x

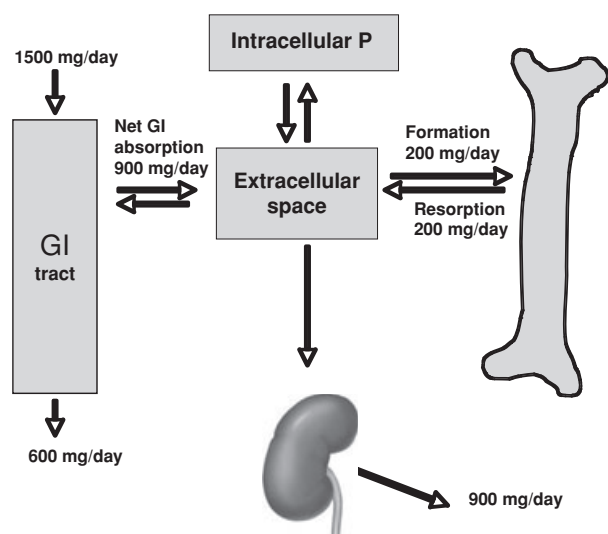


FIG. 1. Phosphorus homeostasis.

was 60% in comparison with 80% in controls; administration of 1,25(OH)₂ vitamin D to the renal failure patients increased the absorption from 60% to 86% (5).

A normal diet contains approximately 1500 mg of phosphorus. Intestinal phosphorus absorption, in contrast to that of calcium, is linearly related to phosphorus intake over the range of 4–30 mg/kg/day (1). Thus, 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 or pharmacologic phosphorus binders. We will deal with this topic in more detail later in the Phosphorus Bioavailability section.

Renal Phosphorus Excretion

As phosphorus is not significantly bound to albumin, most is filtered at the glomerulus. The proximal tubule reabsorbs approximately 75% of filtered phosphorus, the distal tubule approximately 10%, and 15% is lost in the urine. The main phosphorus transporter in the luminal side of the proximal tubule is the 3Na-HPO₄ co-transporter type 2a (NPT-2a) (6). The activity of this transporter is increased by low serum P and 1,25(OH)₂ vitamin D and decreased by parathyroid hormone (PTH) and phosphatonins (see below). There are two other Na-P co-transporters, NPT-1 and NPT-3, which appear to be physiologically unimportant. Phosphorus is transported out of the renal cell by a phosphate-anion exchanger located in the basolateral membrane.

The main factors known to increase renal tubular phosphorus reabsorption include phosphate depletion, 1,25(OH)₂ vitamin D, volume depletion, metabolic alkalosis, chronic hypocalcemia and hormones such as insulin, estrogen, thyroid hormone, and growth hormone. Factors decreasing phosphorus tubular reabsorption include PTH, phosphatonins (see below), acidosis, hyperphosphatemia, chronic hypercalcemia, and volume expansion.

The term phosphatonin describes a factor originally observed in patients with tumor-induced osteomalacia responsible for the inhibition of renal phosphate reabsorption and altered 25-hydroxyvitamin D 1-hydroxylase regulation (7), but now shown to be present in normal plasma and increased in a variety of circumstances associated with altered phosphate reabsorption. We know now that there are several compounds that qualify as phosphatonins. The first two of these factors described were fibroblast growth factor 23 (FGF-23) and secreted frizzled related protein-4 (sFRP-4). FGF23 acts directly on the kidney to regulate the synthesis of 1,25-dihydroxyvitamin D3 and the surface expression of the sodium phosphate transporters NaP-2a and NaP-2c (8). Two more recently described factors, fibroblast growth factor 7 and matrix extracellular phosphoglycoprotein, have also been shown to inhibit phosphate transport in renal epithelial cells in culture, and in the case of matrix extracellular phosphorus glycoprotein, to induce phosphaturia in mice.

Fibroblast growth factor 23 behaves like a hormone produced by osteoblasts and acts on the renal tubules inhibiting phosphorus transport and calcitriol synthesis. More recently, it has been shown that the aging suppressor gene Klotho acts as a cofactor essential for activation of FGF signaling by FGF-23 (9).

Serum FGF-23 concentrations are elevated in patients with chronic renal failure and in patients on hemodialysis (10–12), but the stimulus driving this elevation remains uncertain. The potential regulatory effect of PTH has been tested by measuring FGF-23 levels in patients with primary hyperparathyroidism without chronic renal failure (13). No relationship between PTH and FGF-23 concentrations was found in these patients at baseline and parathyroidectomy did not significantly alter FGF-23, even though PTH concentrations decrease dramatically following surgery. It is attractive to postulate that the synthesis of FGF-23 is induced by the retention of phosphate that occurs in patients as renal disease progresses. Experiments attempting to demonstrate a direct regulatory effect of FGF-23 levels by changes in serum phosphate in response to changes in dietary phosphate intake in normal human subjects have supported this postulation (14,15), except for one study (11).

Exchange of Phosphorus with Bone and Intracellular Compartment

Exchanges between extracellular and bone phosphorus occur as a consequence of calcium homeostasis. Deposition and release of phosphorus in and from the bone is accompanied by movement of calcium in the same direction, but in a molar ratio of about 6:10 (as the deposited mineral phase is mostly hydroxyapatite, which contains phosphorus and calcium with that ratio). This molar ratio is important clinically as a given amount of calcium released from bone will be accompanied by much less phosphorus. For example, in a dialysis patient with no residual renal function and hyperparathyroidism daily bone release of 5 mmol of calcium (200 mg)

would result in a potential increase of serum calcium by 1.25 mg/dl (200 mg dissolved in 16 l of extracellular space), while serum phosphorus will only increase by 0.58 mg/dl (3 mmol or 93 mg in 16 l).

The factors regulating cell phosphorus uptake have not been well defined. It is accepted that phosphorus moves passively into the cells driven by its chemical gradient. Carbohydrate feeding and acid base changes can cause rapid and profound changes in serum phosphorus by translocating phosphorus into and out of cells.

Dialysis Phosphorus Exchange

Phosphorus is relatively well dialyzed through most currently used hemodialyzers. For example, the manufacturer estimated phosphorus clearance with the Optiflux® F160 NR hollow fiber dialyzer (Fresenius Medical Care, Lexington, MA) is very similar to that of creatinine, about 230 ml/minute at a blood flow rate of 300 ml/minute. At a stable serum phosphorus concentration of 6 mg/dl this clearance should provide a total phosphorus removal of about 2898 mg per 210 minute session. As serum phosphorus concentration, however, falls precipitously during the first 2 hours of hemodialysis, the total dialytic phosphorus removal is compromised and amounts to only 800–1000 mg/session or about 300 mg/day (16). The situation is slightly better with peritoneal dialysis, where we demonstrated a daily phosphorus removal of about 423 mg in a group of 56 patients with average serum phosphorus of 5.2 mg/dl (17). In contrast, normal or low levels of serum phosphorus can be achieved with daily nocturnal hemodialysis (18), but unfortunately this modality of therapy currently applies to a very small percentage of dialysis patients.

Phosphorus Content of Foods

The usual daily intake of phosphorus varies significantly depending on the way people eat. For the typical American diet, young and middle-aged men consume about 1600 mg/day, while comparably aged women consume about 1000 mg/day (19). These estimates of dietary phosphorus intake reflect mostly the “natural” phosphorus content of foods. A true estimate of the dietary content of phosphorus, however, requires consideration of three major sources—natural phosphorus contained in raw or unprocessed food as cellular and protein constituents; phosphorus added to foods during processing; and phosphorus contained in dietary supplements.

Foods high in proteins such as meat, milk, dairy, eggs, and cereals are also naturally high in phosphorus and contribute the largest amounts to the total dietary phosphorus intake in an average diet. Table 1 gives a partial list of phosphorus content in different groups of foods. Recently, however, the increasing use of food processing practices, which include the addition of phosphorus, has produced significant increase in the daily intake of this mineral (19,20). In 1990, phosphorus-containing food

TABLE 1. Phosphorus content of selected foods*

Food	Portion size	P (mg)	Protein (g)	P/prot
Meats				
Veal	3 oz	212	31	6.8
Chicken	140 g	259	35	7.4
Lamb	3 oz	162	22	7.4
Beef	3 oz	200	26.4	7.6
Turkey	3 oz	208	24	8.7
Fish	3 oz	221	19.4	11.4
Pork	3 oz	224	18	12.4
Crab	3 oz	238	16.5	14.4
Breads, cereals, and nuts				
Bread	1 slice	25	3.4	7.3
Bagel	3.5"	68	7.5	9
Almonds	1 oz	134	6	22.3
Pistachio	1 oz	137	6	22.8
Walnuts	1 oz	98	4.3	22.8
Biscuits	2.5"	98	4.2	23.3
Cereals	1 cup	259	5.2	49.8
Milk, dairy, and eggs				
Egg white	1 large	5	3.6	1.4
Egg whole	1 large	96	6.3	15.3
Cheese	1 oz	133	6.6	20
Yogurt	8 fl oz	327	11.9	27.5
Milk	1 cup	222	7.9	28
Legumes and rice				
Peas	1 cup	114	7.5	15
Beans	1 cup	183	12	15
Lentils	1 cup	356	17.9	19.9
Rice, white	1 cup	74	4	18.4
Rice, brown	1 cup	162	5	32

*Individual values taken from the USDA National Nutrient Database. P/prot = ratio of phosphorus to protein content.

additives contributed an estimated 470 mg/day to the daily adult phosphorus intake in the United States, but this contribution will continue to increase as the people's demand for convenience and fast foods escalates (19). In fact, depending on individual food choices, phosphorus intake could be increased by as much as 1000 mg/day simply increasing the percentage of processed foods in the diet (21).

Phosphates for use in food are made from food-grade (pure) phosphoric acid, which is prepared from elemental phosphorus. Phosphoric acid is converted into sodium polyphosphates (and other compounds), which are used in the processing of many foods including meat. As meat producers increasingly raise leaner animals that contain significantly less fat, alternative processes are being developed to replace the flavor and moisture loss due to the reduction in fat on the animal, and one of the processes is enhancing meat (22). Enhanced meat is any meat product that has received injections of solutions such as water, salt and sodium phosphate to season the meat and to keep it from drying out. Although federal guidelines require manufacturers to include a notification statement of enhancement, most consumers are not aware that they are purchasing an altered product. The notification statement is usually written in small print, often not noticed by the purchaser. If the product has been repackaged into individual selling portions, the store is responsible for affixing the provided nutrition label on each individual packet and this step may be missed. Phosphate salts are also used in ham and bacon to reduce oxidation, stabilize proteins, and improve

color and flavor. When ham is cured in salt solution water is lost and adding the water back makes the ham soggy. Adding 5% sodium hydrogen phosphate to the curing medium prevents the loss of water and the ham is more tender and juicier. Phosphates are also used in canning fish to complex magnesium ions, which would otherwise cause over time the precipitation of crystals of struvite in the cans. Frozen fish is also rinsed before freezing in a solution of 12.5% sodium tripolyphosphate and 4% salt to prevent loss of proteins on thawing. Phosphate salts provide innumerable other functions in the food industry. The baking industry uses them in leavening systems, and soft drink manufacturers add phosphate to cola drinks to enhance flavor. One reason to use phosphoric acid is because it is cheaper and produces greater "sourness" than citric or tartaric acid. They work as emulsifiers in dairy products, to maintain condensed milk as liquid and as buffering agents in many different applications. Many of the processed foods we buy would be less acceptable and have shorter shelf lives without the use of phosphates by food manufacturers. As phosphates are already a necessary part of our diet, adding them to food theoretically should cause no problems in the general public, but this is obviously not the case in CKD patients. CKD patient also need to be aware that processed foods are significantly higher in sodium than the natural products.

Most multivitamin/mineral supplements do not contain phosphorus, because, for most people, such supplementation is unwarranted. However, some of them contain significant amounts of phosphorus, as shown in Table 2 and it is important to be aware of them when designing a diet with limited phosphorus intake.

The importance of the current practice of food additives is well illustrated in an experiment performed with eight normal volunteers (21). During a 4-week period, they were fed a diet free of phosphate additives. During a second 4-week period, commercially available foods very similar to those in the first period, but foods containing phosphate additives were substituted freely for items without added phosphate (for example, processed cheese for natural cheese, meats with added phosphates for unsupplemented meats, colas for citric acid-containing beverages, etc.). These substitutions increased the phosphorus intake by an average of 1154 mg/day while keeping the intake of protein and calcium unchanged. Interestingly, during the high phosphorus diet mild diarrhea was experienced by all the subjects during the first week and persisted throughout the 4 weeks in two subjects. The cathartic effect of phosphate salts is well

known as they have been used medicinally for this purpose for many years but it is interesting that it can manifest even with the amounts of phosphorus contained in diets commonly consumed in modern society. A fast screening of the ingredient labels in different items in your refrigerator will show that many national brand-name products used on a regular basis such as Oscar Mayer's ham, Campbell soup, and many others contain phosphate salts as additives. If you become curious to estimate your extra phosphorus intake from these sources you will not be able to satisfy this curiosity as the actual content of phosphorus is not stated. Thus, CKD patients cannot clearly estimate their dietary intake of phosphorus.

Phosphorus Bioavailability

The bioavailability of phosphorus from various food sources is a very important consideration in the analysis of dietary phosphorus intake. In plants a large fraction of the phosphorus (about 75%) is in the form of phytate. As the small intestine of humans does not secrete the enzyme phytase, which is necessary to degrade dietary phytate and release phosphorus, phytate phosphorus is not bioavailable in humans, unless the food has been processed with phytase such as in the leavening of bread with phytase-containing yeast. In contrast, phosphorus in meat is well absorbed as it is found mostly as intracellular organic compounds, which are easily hydrolyzed in the gastrointestinal tract releasing inorganic phosphorus for absorption. Phosphorus in milk is present in different fractions, each one of them with different bioavailability. Phosphorus added during food processing is mostly in the form of inorganic salts and hence is almost completely absorbed and therefore represents an even larger phosphorus burden (20).

The low bioavailability of phosphorus from grains is very well known in the pig farming industry. Farmers know that only a fraction of this phosphorus will be absorbed and therefore they add supplemental phosphate in the diet in order to meet the phosphorus requirement for optimal growth and development of the animals. More importantly, the manure of these animals contains a higher concentration of phosphorus than is suitable for repetitive field application. Consequently, at high application rates of manure to land in areas of intensive pork production, the potential for pollution of local surface water and ground water with phosphorus can become a serious problem (23). Therefore, there is

TABLE 2. Phosphorus content of selected vitamins and nutritional supplements

Item	Serving size	P per serving (mg)
Centrum (Wyeth, Madison, NJ, USA)	1 tablet	48
Flintstones children multivitamins (Bayer Consumer Care, Morristown, NJ, USA)	1 tablet	100
Nature's Science (Scientific Fitness, Oakmont, PA, USA)	1 tablet	100
Vita complete multivitamin (Vita Health Products, Inc., Winnipeg, Manitoba, Canada)	1 tablet	125
TwinLab Carp-L care (TwinLab Corp., Manhattan, NY, USA)	1 tablet	163
Cell-Tech Punch (MuscleTech, Glendale, NY, USA)	2 scoops	100
Myoplex Deluxe Nutrition (Myoplex.co.uk, Bournemouth, Dorset, UK)	1 bar	200

great interest in the development of crops of grain that contain phytase as well as in the development of transgenic pigs that digest phytate (24).

In contrast to all the information available in the pig farming industry, the bioavailability of different dietary phosphorus sources has not been studied in humans. Therefore all our estimates of bioavailability are based on extrapolation from animal data. The only data in this area come from acute experiments (25) by H.J. Karp et al. from Helsinki who studied 16 female volunteers aged 20–30 at five separate 24-hour sessions with different dietary phosphorus intake. At the control session phosphate intake was low (500 mg/day of P), while at the other four sessions phosphorus intake was 1500 mg/day, but 1000 mg of it was taken in from meat, cheese, whole grains, or a phosphate supplement, respectively. Urinary phosphorus excretion was higher during the meat and phosphate supplement sessions when compared with the sessions when grain or cheese was given (25).

As a result of the different factors mentioned above, usually only 60% of phosphorus from a typical mixed diet is absorbed. Obviously, this percentage will change depending on the predominant food groups and the degree of processing of the foods present in selected diets. A diet with a predominance of fast food and processed meats as a protein source will provide higher fractional phosphorus absorption than a diet of similar “natural” phosphorus content but with a predominance of fresh, unprocessed foods.

Calcium Fortification

Patients with CKD need a certain amount of calcium in their diets. In fact, as renal insufficiency is associated with vitamin D deficiency and hence decreased intestinal absorption of calcium, greater amounts of oral calcium intake may be required in this condition. In the past, it has clearly been shown that untreated renal insufficiency leads to significant negative calcium balance (26). Over the past two decades, however, the increasing use of calcium-containing phosphorus binders and vitamin D or vitamin D analogs to control secondary hyperparathyroidism has markedly reduced the daily dietary requirements of calcium (27). In fact, the K/DOQI guidelines for bone metabolism and disease recommend a total daily calcium intake not higher than 2000 mg of elemental calcium, including diet and calcium supplements (28). A simple calculation can show that it is very easy to exceed the daily recommended calcium intake: a dialysis patient receiving CaCO_3 1250 mg t.i.d. (elemental calcium = 1500 mg) who eats one grilled cheese sandwich (using two slices of white bread and 1½ ounces cheese = 371 mg elemental calcium) and one cup of yogurt (elemental calcium = 450 mg) receives 2321 mg of elemental calcium daily! If this dialysis patient is anuric and dialyzed with 2.5 mEq/l calcium dialysate concentration, he/she will be in significant positive calcium balance which over time may lead to increased

vascular calcifications and potential vascular disease (29).

At the same time, a growing awareness of the importance of maintaining adequate calcium intake for bone health and the realization that total calcium intake may be inadequate for the general population has led to voluntary calcium fortification of an increasing number of foods. Manufacturers are making use of the marketing advantages reaped by adding calcium to a large variety of foods. Food products in the United States being fortified with calcium include beverages, especially fruit juices such as orange juice and isotonic/sports drinks. In addition, dairy drinks, breakfast drinks and soy-derived beverages are also good candidates for fortification. This increased dietary calcium intake resulting from calcium-fortified foods, however, is a cause for concern in the CKD population.

Increased use of calcium-fortified foods can have two potential effects on dietary phosphorus intake. On the one hand, a common salt used for calcium fortification is actually calcium phosphate, which obviously will directly increase phosphorus supply to the intestine. On the other hand, when calcium is fortified with nonphosphate salts such as carbonate or citrate, this extra calcium may act as a phosphorus binder and diminish the bioavailability of intestinal phosphorus. Moreover, although most people are clearly aware that milk and dairy products represent a good source of calcium, it is not easy to realize that foods that do not usually contain calcium such as orange juice, breads and cereals found in the supermarket are now usually fortified with calcium. Most companies place labels on the package to warn about these additions, but sometimes the labels may be nonspecific such as “added vitamins and minerals” and patients need to pay attention to details.

What Should Be the Daily Phosphorus Intake in CKD Patients?

Levels of serum phosphorus in patients with CKD remain within the normal range or even mildly below the normal range until the glomerular filtration rate (GFR) declines to 30 ml/minute (stage 4 of CKD). As hyperphosphatemia only becomes evident at GFRs below 30 ml/minute, it would appear that dietary phosphorus restriction is unnecessary in patients with stage 3 of CKD. Phosphorus retention, however, is known to occur very early in the course of CKD (30) and such phosphorus retention likely participates in the pathogenesis of secondary hyperparathyroidism. Indeed, the blood levels of PTH are elevated when GFR falls to 60 mL/minute/1.73 m², even though serum phosphorus levels are not elevated. Recently, a large study on stage 3 CKD patients (31) showed that serum phosphorus > 3.5 mg/dl, a normal value, was independently associated with increased mortality risk in this population. This finding supports dietary phosphate restriction in proportion to the decrease in GFR in stage 3, when blood levels of PTH are elevated and serum phosphorus levels are still normal. Based on this background the working group from K/DOQI concluded that: “Given

the lack of evidence of adverse effects, and the evidence of positive benefit of dietary phosphate restriction, it is the consensus of the Work Group that dietary phosphate restriction be initiated in patients with CKD when PTH levels are elevated (GFR < 60 ml/minute/1.73 m², stage 3) or with elevated blood levels of serum phosphorus (stages 4 and 5)" (28). The actual dietary recommendation is for less than 1000 mg phosphorus per day (28).

In practical terms, however, it is very difficult to provide a dietary phosphorus intake of less than 1000 mg/day because of the high levels of dietary protein intake advised as well as the large amount of unaccounted phosphorus in processed foods as discussed extensively above.

Dietary Phosphorus and Protein

The close association between phosphorus and protein content in food makes it very difficult to restrict dietary phosphorus content without simultaneously restricting dietary protein intake, especially protein of animal origin. We have previously shown that the current minimal daily protein intake of 1.2 g/kg/day set for dialysis patients by the DOQI guidelines will almost invariably lead to hyperphosphatemia in chronic peritoneal and hemodialysis patients (17,32). These guidelines for minimal protein intake are inappropriate as they prevent reaching reasonable levels of serum phosphorus and considering the lack of evidence of any benefit of this high protein intake (33).

Another related point is that the excessive emphasis on proteins of animal origin in CKD patients needs to be reanalyzed. For example, a dish made up of one cup of white rice and one cup of beans contains 16 g of protein and 257 mg of phosphorus. However, only 25% of this phosphorus (64 mg) actually gets absorbed. In contrast, the same amount of animal protein in meat will provide much more phosphorus into the circulation because of its almost complete bioavailability; specifically, 118, 122, 182, and 198 mg of phosphorus in 16 g of protein from chicken, beef, fish, and pork, respectively. It is important to note that all essential amino acids may be obtained from plant sources, and that even strict vegetarian diets can provide all dietary requirements, though careful monitoring of nutrient levels is important, as limiting factors become significant when no meat is present in the diet. We are not advising elimination of meat, but a mixed diet. The low bioavailability of phosphorus in plant proteins is an advantage that cannot be ignored when designing a diet limited in phosphorus.

Food Labeling for Phosphorus Content

An important tool needed to control dietary phosphorus intake is the listing of phosphorus content in the Nutrition Facts Panel that is required on all regulated foods. However, changes in the food labeling regulations no longer require manufacturers to list the phosphorus content in the Nutrition Facts Panel as they do for

sodium and potassium content, two nutrients whose intake must also be held under strict control in CKD patients (20). Therefore, patients have no means to determine the content of phosphorus of specific food items in the supermarket. The only current resource for patients is to read the ingredient list on food labels and select food products with no phosphate additives. Patients' advocacy groups should try to make food manufacturers aware of the importance of voluntary disclosure of their product's phosphorus content on the food label for the long-term health and maintenance of CKD patients.

Most of the software programs for estimating the patient's phosphorus intake and design individualized diets that are low in total phosphorus content are based on standard food composition tables, which usually do not include the phosphorus from these additives, leading to a consistent underestimation of dietary phosphorus intake. When the phosphorus content of several foods measured by chemical analysis was compared with the phosphorus content estimated by three software programs, the latter consistently underestimated the phosphorus content by an average of 250 mg/day (34). When the comparison was made only with menus including six or more processed foods, the underestimation of phosphorus content was greater than 350 mg/day (34).

Food Demineralization

A method has been described to extract minerals from foods by soaking them in water (35). Mineral content was measured before and after water treatment. The phosphorus reduction was 51% for vegetables, 48% for legumes, 38% for meats, 70% for flours, and 19% for cheddar cheese. In my experience, however, patients complain of the extra work when cooking with this technique and the loss of taste of treated foods.

Boiling foods can also significantly reduce dietary phosphate while preserving protein intake, namely reducing the effective phosphate intake per gram of dietary protein. This can represent additional advice to the patient for limiting the dietary phosphorus load at the same protein intake (36).

Low-Phosphorus "Functional Foods"

The development of functional foods, with low phosphorus content, specially designed for CKD patients is a particularly appealing idea to help diversify food choices in CKD patients. The first of this kind of products, low phosphorus milk (Delicious Milk Company, Inc., New York, NY, USA), is already in the market for the past year. Each 8 fl oz pack of this milk contains only half the phosphorus and half the potassium of regular 2% fat milk. The daily use of this product for 1 month in a group of hemodialysis patients was associated with a marked statistically significant improvement in their sense of satisfaction with their diet, while their serum phosphorus and calcium remained unchanged (37). The use of this milk will clearly permit expansion of patients'

food choices adding variety to their diets. The same company is now offering very low phosphorus cheddar cheese sauce and the expectation is that several other low phosphorus cheese and food items will be developed in the near future. The CKD population in the United States alone is estimated at several millions making it an attractive and so far untapped market for the food industry.

In summary, current dialysis and phosphorus binder prescriptions are not sufficient to assure normal serum phosphorus levels in dialysis patients who are eating well. The important message is that limiting dietary intake of phosphorus requires prescription of a moderate protein intake (0.9–1.0 g/kg/day), increased consumption of a variety of fresh fruit and vegetables and restricted consumption of highly processed fast and convenience foods. Phosphorus added during food processing is an important source of this mineral because of its magnitude and high bioavailability. Because this information is often unknown to the consumer, it needs to be more extensively disseminated among healthcare professionals dealing with dialysis patients, a population of patients in whom a very precise determination of phosphorus intake is essential. Legislation to make content of phosphorus in the food ingredient list compulsory is needed. The recent development of low phosphorus-containing food products represents a very useful addition for these patients.

References

- Allen LH, Wood RJ: Calcium and phosphorus in modern nutrition. In: Shils ME, Olson JA, Shike M (eds). *Health and Disease*, 8th edn, 144–163. Philadelphia: Lea & Febiger
- Kempson SA, Colon-Otero G, Ou SY, Turner ST, Dousa TP: Possible role of nicotinamide adenine dinucleotide as an intracellular regulator of renal transport of phosphate in the rat. *J Clin Invest* 67:1347–1360, 1981
- Takahashi Y, Tanaka A, Nakamura T, Fukuwatari T, Shibata K, Shimada N, Ebihara I, Koide H: Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. *Kidney Int* 65:1099–1104, 2005
- Sampathkumar K, Selvam M, Sooraj YS, Gowthaman S, Ajeshkumar RNP: Extended release nicotinic acid – a novel oral agent for phosphate control. *Int Urol Nephrol* 38:171–174, 2006
- Ramirez JA, Emmett M, White MG, Fathi N, Santa Ana CA, Morawski SG, Fordtran JS: The absorption of dietary phosphorus and calcium in hemodialysis patients. *Kidney Int* 30:753–759, 1986
- Tenenhouse HS: Regulation of phosphorus homeostasis by the type iia na/phosphate cotransporter. *Annu Rev Nutr* 25:197–214, 2005
- Cai Q, Hodgson SF, Kao PC, Lennon VA, Klee GG, Zinsmeister AR, Kumar R: Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med* 330:1645–1649, 1994
- Bernd TJ, Schiavi S, Kumar R: “Phosphatonins” and the regulation of phosphorus homeostasis. *Am J Physiol Renal Physiol* 289:F1170–F1182, 2005
- Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu M, Moe OW, Kuro-o M: Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem* 281:6120–6123, 2006
- Shigematsu T, Kazama JJ, Yamashita T, Fukumoto S, Hosoya T, Gejyo F, Fukagawa M: Possible involvement of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism associated with renal insufficiency. *Am J Kidney Dis* 44:250–256, 2004
- Larsson T, Nisbeth U, Ljunggren O, Juppner H, Jonsson KB: Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int* 64:2272–2279, 2003
- Imanishi Y, Inaba M, Nakatsuka K, Nagasue K, Okuno S, Yoshihara A, Miura M, Miyauchi A, Kobayashi K, Miki T, Shoji T, Ishimura E, Nishizawa Y: FGF-23 in patients with end-stage renal disease on hemodialysis. *Kidney Int* 65:1943–1946, 2004
- Yamashita H, Yamashita T, Miyamoto M, Shigematsu T, Kazama JJ, Shimada T, Yamazaki Y, Fukumoto S, Fukagawa M, Noguchi S: Fibroblast growth factor (FGF)-23 in patients with primary hyperparathyroidism. *Eur J Endocrinol* 151:55–60, 2004
- Ferrari SL, Bonjour JP, Rizzoli R: Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. *J Clin Endocrinol Metab* 9:1519–1524, 2004
- Antonucci DM, Yamashita T, Portale AA: Dietary phosphorus regulates serum FGF-23 concentrations in healthy men. *J Clin Endocrinol Metab* 91:3144–3149, 2006
- Chauveau P, Poignet JL, Kuno T, Bonete R, Kerembrun A, Naret C, Delons S, Man NK, Rist E: Phosphate removal rate: a comparative study of five high-flux dialyzers. *Nephrol Dial Transplant* 6(Suppl. 2):114–115, 1991
- Sedlacek M, Dimaano F, Uribarri J: Relationship between phosphorus and creatinine clearance in peritoneal dialysis: clinical implications. *Am J Kid Dis* 36:1166–1174, 2000
- Pierratos A: Daily hemodialysis: an update. *Curr Opin Nephrol Hypertens* 11:165–171, 2002
- Calvo MS, Park YK: Changing phosphorus content of the US diet: potential for adverse effects on bone. *J Nutr* 126:S1168–S1180, 1996
- Uribarri J, Calvo MS: Hidden sources of phosphorus in the typical American diet; does it matter in nephrology. *Semin Dial* 16:35–41, 2003
- Bell RR, Draper HH, Tzeng DYM, Shin HK, Schmidt GR: Physiological responses of human adults to foods containing phosphate additives. *J Nutr* 107:42–50, 1977
- Murphy-Gutekunst L, Uribarri J: Hidden phosphorus-enhanced meats: part 3. *J Ren Nutr* 15:E1–E4, 2005
- Dou Z, Ferguson JD, Fiorini J, Toth JD, Alexander SM, Chase LE, Ryan CM, Knowlton KF, Kohn RA, Peterson AB, Sims JT, Wu Z: Phosphorus feeding levels and critical control points on dairy farms. *J Dairy Sci* 86:3787–3795, 2003
- Golovan SP, Meidinger RG, Ajakaiye A, Cottrill M, Wiederkehr MZ, Barney DJ, Plante C, Pollard JW, Fan MZ, Hayes MA, Laursen J, Hjorth JP, Hacker RR, Phillips JP, Forsberg CW: Pigs expressing salivary phytase produce low-phosphorus manure. *Nat Biotechnol* 19:979, 2001
- Karp HJ, Vahia KP, Karkkainen MU, Niemisto MJ, Lamberg-Allardt CJ: Acute effects of different phosphorus sources on calcium and bone metabolism in young women: a whole-foods approach. *Calcif Tissue Int* 2007 April 1, Epub ahead of print
- Hosking DJ, Chamberlain MJ: Calcium balance in chronic renal failure. A study using in vivo neutron activation analysis. *QJM* 42:467–479, 1973
- Hsu CH: Are we mismanaging calcium and phosphate metabolism in renal failure? *Am J Kidney Dis* 29:641–649, 1997
- Eknoyan G, Levin A, Levin NW: Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42(Suppl. 3):1–201, 2003
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 31:607–617, 1998
- Hsu CY, Chertow GM: Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant* 17:1419–1425, 2002
- Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Yong B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16:520–528, 2005
- Uribarri J: DOQI guidelines for nutrition in long-term peritoneal dialysis patients: a dissenting view. *Am J Kidney Dis* 37:1313–1318, 2001
- Uribarri J: The obsession with high dietary protein intake in ESRD patients on dialysis: is it justified? *Nephron Physiol* 86:105–108, 2000
- Oenning LL, Vogel J, Calvo MS: Accuracy of methods estimating calcium and phosphorus intake in daily diets. *J Am Diet Assoc* 88:1076–1080, 1988
- Jones WL: Demineralization of a wide variety of foods for the renal patient. *J Ren Nutr* 11:90–96, 2001
- Cupisti A, Comar F, Benini O, Lupetti S, D'Alessandro C, Barsotti G, Gianfaldoni D: Effect of boiling on dietary phosphate and nitrogen intake. *J Ren Nutr* 16:36–40, 2006
- Oliverio S, Atcher L: Regular use of low-phosphorus milk significantly improves dietary satisfaction of patients without changing their serum phosphorus. *Dial Transplant* 35:215–219, 2006