Dietary Phosphorus Excess: A Risk Factor in Chronic Bone, Kidney, and Cardiovascular Disease?[1–3]

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ABSTRACT

There is growing evidence in the nephrology literature supporting the deleterious health effect of excess dietary phosphorus intake. This issue has largely escaped the attention of nutrition experts until this symposium, which raised the question of whether the same health concerns should be extended to the general population. The potential hazard of a high phosphorus intake in the healthy population is illustrated by findings from acute and epidemiologic studies. Acute studies in healthy young adults demonstrate that phosphorus intakes in excess of nutrient needs may significantly disrupt the hormonal regulation of phosphorus contributing to disordered mineral metabolism, vascular calcification, bone loss, and impaired kidney function. One of the hormonal factors acutely affected by dietary phosphorus loading is fibroblast growth factor-23, which may be a key factor responsible for many of the cardiovascular disease (CVD) complications of high phosphorus intake. Increasingly, large epidemiological studies suggest that mild elevations of serum phosphorus within the normal range are associated with CVD risk in healthy populations. Few population studies link high dietary phosphorus intake to mild changes in serum phosphorus due to study design issues specific to phosphorus and inaccurate nutrient composition databases. The increasing phosphorus intake due to the use of phosphorus-containing ingredients in processed food and the growing consumption of processed convenience and fast foods is an important factor that needs to be emphasized. *Adv. Nutr. 4: 542–544, 2013.*

Introduction

This symposium explored the potential adverse impact of the increasing phosphorus content of the American diet on the renal, cardiovascular, and bone health of the general population. Hyperphosphatemia in chronic kidney disease is recognized as a serious risk factor for bone disease, cardiovascular disease (CVD)[6], and mortality, with dietary phosphorus restriction and/or use of oral phosphate binders considered the best corrective care in this population. The role of dietary phosphorus in chronic kidney disease has been the focus of several conferences as well as numerous articles in prominent renal medical journals. The goal of this symposium was to bring this issue to the attention of the nutrition experts and, more importantly, to raise the question of whether the same health concerns should be extended to the general population. Five speakers from different areas of health care and nutrition science delved into each of the above elements, stimulating a robust audience discussion. The symposium speakers included: Mona S. Calvo, Center for Food Safety and Applied Nutrition, FDA, Laurel, MD; Orlando Gutierrez, Departments of Medicine and Epidemiology, University of Alabama, Birmingham, AL; Eiji Takeda, Department of Clinical Nutrition, Institute of Health Biosciences, University of Tokushima Graduate School, Tokushima, Japan; Katherine L. Tucker, Professor and Chair, Department of Health Sciences, Northeastern University, Boston, MA; and Jaime Uribarri, Department of Medicine, The Mount Sinai School of Medicine, New York, NY.

Increasing Phosphorus Content of the American Food Supply

Changes in the food supply over recent decades have led to increasing amounts of phosphorus in our diets. Although

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[3] The findings and conclusions presented in this review are those of the authors and do not necessarily represent the views and opinions of the USFDA.

[6] Abbreviations used: CVD, cardiovascular disease; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

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phosphorus is an important nutrient naturally found in most foods, it is now also added as a processing aid with many different and distinct functions that result in a variety of desirable characteristics in processed foods. The increasing cumulative use of phosphorus-containing additives is quite dramatic. Any average person's refrigerator or pantry will show that the majority of processed food products consumed for breakfast, lunch, dinner, or snacks contain phosphorus as one or more added ingredients. Although the actual amount of phosphorus in each item may be low, the total phosphorus consumed over a 24-h period may become quite considerable. Moreover, because manufacturers are not required to specify the amount of phosphorus added, it is not possible to estimate exactly how much phosphorus is consumed through the additives' contribution. Of note, the bioavailability of these phosphorus-containing additives is very high. Therefore, a given amount of phosphorus contained in food additives can contribute more phosphorus to the circulation than the same amount of phosphorus in a much less bioavailable form, such as phytate found in whole grains.

Although consumption of processed foods containing phosphorus additives has increased in recent decades, the mean phosphorus intake of healthy adults estimated from nationally representative surveys has remained relatively constant over the past decade, with the exception of the latest wave of intake data collected by the NHANES 2009–2010 survey. This most likely reflects an underestimate of dietary phosphorus intake by currently available food databases. The small increase observed in the last survey wave may be due to the re-analyses of nutrient content of certain processed foods recently undertaken by USDA. The inaccuracy of current food databases is suggested by several studies showing disagreement between dietary phosphorus intakes estimated using popular software and direct chemical analyses of different foods. These studies performed over the past 2 decades have consistently documented a significant underestimation of dietary phosphorus intake by the nutrient databases.

National surveys show that at least one-half of the U.S. population in all age groups, except adolescents, consumes phosphorus in excess of their Estimated Average Requirements, which is 400 mg/d for all age groups except rapidly growing adolescents. There is reason for concern, because current methods of estimating intake using computer programs actually underestimate the phosphorus content of foods, and therefore dietary intake, by 30% or more, placing some individuals close to the upper safe intake concentration of 4000 mg/d.

Evidence That Excess Dietary Phosphorus Can Cause Bone, Kidney, and CVD

Although phosphorus is an essential nutrient, its excess could be linked to tissue damage by a variety of mechanisms, including the secretion and action of fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH). Disordered regulation of these hormones by high dietary phosphorus may be key factors contributing to renal failure, atherosclerosis, and osteoporosis.

There is experimental work showing that high dietary phosphorus intake reduces bone mass, induces vascular calcification, and produces or worsens kidney disease, whereas dietary phosphorus restriction has the opposite effects in different animal models. No such studies exist in humans, but a few clinical studies have looked at the potential association between dietary phosphorus intake and clinical disease.

Several studies with oral phosphorus loading in healthy volunteers illustrate a significant effect stimulating PTH and FGF-23, both potential markers of bone and CVD. An acute oral phosphorus load was also shown to produce acute endothelial dysfunction as reflected by impaired flow-mediated vasodilatation.

An association between dietary phosphorus intake and left ventricular mass, a surrogate marker of heart disease, has been described among 4494 participants of the Multi-ethnic Study of Atherosclerosis. An increase in dietary phosphorus intake is also associated with prevalence of bone fractures. One study found that the risk of fractures increased by 9% for every 100 mg of phosphorus intake.

Many epidemiological studies show that mild elevations of serum phosphorus within the normal range are associated with CVD risk in healthy populations in the absence of apparent kidney disease. The latter studies must be considered only tentatively, because we cannot demonstrate with certainty that fasting serum phosphorus concentrations reflect mostly dietary phosphorus intake in these studies.

The epidemiological studies discussed above are observational in design and therefore cannot be used to define cause and effect. Only randomized interventional studies looking at the effects of decreasing dietary phosphorus intake or correction of serum phosphate on progression of disease will be able to clarify the role of phosphorus in causing these pathological conditions.

Factors Confounding the Association between Dietary Phosphorus Intakes and Fasting Serum Phosphorus Concentrations

Several factors may confound the association between dietary phosphorus intake and fasting serum phosphorus or concentrations of FGF-23 or PTH. An important confounder is the large circadian variation in the serum phosphorus concentration in the presence of normal kidney function. With any given oral load of dietary phosphorus, the kidneys so effectively eliminate phosphorus within the next 24 h that by the same time the next morning, the fasting serum phosphorus concentration has readjusted to the fasting concentration from the previous day. Only studies measuring several serum phosphorus concentrations during the course of 24 h are able to accurately assess daily oral load of phosphorus. Although not as much work has been conducted on the influence of dietary phosphorus on the circadian variation in the circulating concentrations of PTH and FGF-23, each of these hormones also demonstrates pronounced circadian rhythms. The patterns of circadian variations for phosphorus and PTH are almost superimposable.

Another factor that may affect any association between dietary phosphorus intake and serum phosphorus concentrations is what we already pointed out above: current databases used to estimate dietary phosphorus significantly underestimate it.

Other factors to consider under this heading include the variable phosphorus bioavailability from different foods and the nature of the actual food consumed. In a widely quoted study, high dietary phosphorus intake at baseline was associated with lower systolic blood pressure and at follow-up with less incidence of hypertension. Further analyses showed that only higher phosphorus intake from dairy products, not from other dietary sources, was consistently associated with lower systolic blood pressure, suggesting that milk itself may play a role either independently of phosphorus or in conjunction with it.

The relative content of calcium and phosphorus in the diet is important. A diet containing low calcium or high phosphorus, an imbalance in the calcium:phosphorus intake ratio, has been shown in both humans and animals to lead to secondary hyperparathyroidism and bone loss. New acute loading studies presented at the symposium revealed that maintaining a balanced dietary calcium:phosphorus intake ratio (1000 mg calcium:1200 mg phosphorus) reduces the number of postprandial peaks in serum PTH and eliminates the peak normally observed in FGF-23 8 h after a high-phosphorus, low-calcium meal. These new findings indicate the importance of maintaining a balance in the dietary calcium:phosphorus intake ratio to suppress FGF-23 concentrations.

Assessment of Exposure to Dietary Phosphorus

When estimating dietary phosphorus intake, it may be useful to separate natural food phosphorus from added phosphorus in view of their different bioavailability. The current standard practice for estimates of phosphorus intake is to sum phosphorus measures in the nutrient database without adjustment for differences in bioavailability. Using this approach, very few individuals appear to exceed the upper concentration for phosphorus intake. Not only does the nutrient content of the databases underestimate total phosphorus intake, but it does not consider enhanced phosphorus bioavailability of added inorganic phosphorus compounds. This leads to underestimating the total amount of phosphorus that is absorbed from foods rich in inorganic phosphorus and overestimating the amount of phosphorus actually absorbed from foods rich in less bioavailable organic phosphorus. These variations suggest the need to develop an algorithm to consider phosphorus bioavailability when calculating total phosphorus exposure from nutrient databases for use in studies of diet and health.

A longitudinal study monitoring intake and bone mineral density illustrates the need to consider phosphorus bioavailability. The study showed that adjusted mean femoral neck bone mineral density, a surrogate for future bone fragility, decreased with the number of cola servings consumed per week by postmenopausal women but had no relationship with total daily dietary phosphorus intake. Colas are rich in highly bioavailable phosphoric acid but contain no calcium, magnesium, or other minerals. Due to the rapid and efficient absorption of phosphorus from phosphoric acid in cola beverages, we speculate that their consumption may lead to short periods of high phosphorus exposure that may have more negative health effects than the same amount of phosphorus from less efficiently absorbed phosphorus food sources.

Could FGF-23 Rather Than Serum Phosphate Be a Better Link between Increased Dietary Phosphorus and Poor Health Outcome?

FGF-23 has recently emerged as an important hormone regulating phosphorus metabolism. FGF-23 is rapidly secreted in response to oral phosphorus loads and it induces increased urinary excretion of phosphorus, decreased renal synthesis of 1,25-hydroxyvitamin D, and decreased PTH release. In vitro and experimental animal data show that FGF-23 can directly produce myocardial hypertrophy and an association between FGF-23 and left ventricular hypertrophy has been described in humans with normal renal function.

Several large epidemiological studies show an association between concentrations of FGF-23 and CVD outcome in dialysis and predialysis patients as well as in healthy individuals independent of serum phosphate concentrations. It remains to be established, however, whether the previous large studies showing a similar association between serum phosphate and CVD outcome will be modified if concentrations of FGF-23 were to be measured and introduced in the analyses.

In conclusion, although systematically underestimated in national surveys, phosphorus intake seemingly continues to rise as a result of growing consumption of highly processed foods, especially restaurant, convenience, and fast foods. The increased cumulative use of phosphorus ingredients in food processing merits further study given what is now being revealed about the potential toxicity of phosphorus intake when it exceeds nutrient needs. Clearly, we need more research to develop more accurate nutrient content databases and algorithms to better assess meaningful phosphorus exposure as well as a better understanding of the hormonal factors that influence this dysregulation of phosphorus homeostasis.

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