Dietary phosphorus intake and health\textsuperscript{1,3}

Jaime Uribarri and Mona S Calvo

Phosphorus is an essential nutrient, occurring in most foods both as a natural component and as an approved ingredient added during food processing. With an increase in the consumption of processed foods over the past decades in the United States, phosphorus consumption has increased and far exceeds the nutrient requirement of most men and women (1). Much of our understanding about the potential risks associated with high phosphorus intake comes from the clinical experience with chronic kidney disease (CKD)\textsuperscript{4} patients in whom high serum phosphate concentration has been shown to be significantly associated with cardiovascular and all-cause mortality. CKD patients are unable to clear excess phosphorus because of their impaired renal function, making their consumption of many processed foods a source of phosphate toxicity (2). More important to general public health, similar epidemiologic associations of cardiovascular disease (CVD) and all-cause mortality with excess phosphorus intake now have been described in the general population (3, 4).

Although dietary phosphorus intake is a major determinant of serum phosphate, it has been difficult to show an association between dietary phosphorus intake and fasting serum phosphate in most studies in healthy subjects, which raises the issue of whether elevated serum phosphate in these studies results from factors other than increased dietary phosphorus intake. We believe this lack of association results from the failure to consider several confounding factors in these studies. A first consideration is the rapid and effective handling of increases in serum phosphate by normal kidneys, a function that maintains constant serum concentrations despite wide variations in dietary phosphorus intakes. Changes in serum phosphate in response to marked increases in phosphorus intake can usually be detected by repeated measurements of serum phosphate throughout the day. Therefore, fasting serum phosphate, which is usually measured in epidemiologic studies, is not a good indicator of dietary phosphorus intake (5). A second important consideration is the questionable accuracy of the available databases used to estimate dietary phosphorus intake, which have been shown to significantly underestimate the phosphorus content of foods, in part because of the failure to capture phosphorus content from the ever-increasing use of phosphorus-containing food additives. Several studies comparing the accuracy of calculated estimates of dietary phosphorus with the use of popular software with direct chemical analyses support an underestimation of $\sim$25–30% by existing nutrient content databases, including those based on the updated USDA Nutrient Content Databases (5).

Even if we had accurate assessment of total dietary phosphorus intake, this may still not be the most appropriate variable to relate to serum phosphate, given the different bioavailability of phosphorus from different food sources. Phosphorus in food additives, for example, is rapidly and almost completely absorbed, whereas food-bound phosphorus, a natural constituent of protein and other nutrients, is more slowly and less efficiently absorbed. More important, phosphorus contained in plant protein sources, such as soy, is mostly present as phytate, which is not as easily digested as animal protein sources of phosphorus, such as meat. Therefore, the total amount of phosphorus absorbed from a vegetarian diet may be much less than that typically consumed by most Americans (6). The relative dietary intake of calcium in relation to that of phosphorus is another important factor that affects the physiologic regulation of serum phosphate and reactions to phosphorus intake. Independent of the absolute amount of calcium or phosphorus consumed, the relative ratio of these 2 nutrients needs to be in optimal balance (1:1, mg:mg) to avoid disrupting their hormonal regulation. For example, in observational studies, increases in potentially toxic hormones are more pronounced when the calcium-to-phosphorus dietary intake ratio is $<1:1$, as it is for a significant segment of the United States and other Western populations (5, 7).

Several acute studies in healthy adults have shown that oral phosphate loading has an effect of increasing markers of bone disease and/or CVD in healthy subjects (1). There are many potential mechanisms through which a high dietary phosphorus intake may induce disease with or without a measurable elevation within the normal range of fasting serum phosphate. The potential toxicity mechanism that has garnered the most attention is the disruption of the endocrine regulation of calcium and phosphorus. In both animal models and clinical studies, a high-phosphorus diet has been shown to induce parathyroid hormone

\textsuperscript{1}From the Mount Sinai School of Medicine, New York, NY (JU), and Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Department of Health and Human Services, Laurel, MD (MSC).

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\textsuperscript{3}Address correspondence to J Uribarri, 1 Gustave Levy Place, New York, NY 10029. E-mail: jaime.uribarri@mssm.edu.

\textsuperscript{4}Abbreviations used: CKD, chronic kidney disease; CVD, cardiovascular disease; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

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had calcium-to-phosphorus ratios of
weeks of consuming grocery foods high in phosphate additives, associated with all-cause mortality in healthy people who participated in a large national survey, NHANES III. Previously, dietary phosphorus intake was shown to be associated with biomarkers of cardiovascular outcome, such as left ventricular mass measured by cardiac MRI in healthy subjects from the Multi-Ethnic Study of Atherosclerosis and concentrations of FGF-23 among participants in the Health Professionals Follow-Up Study (3, 9).

In the study by Chang et al (4), the significant association found between total phosphorus intake or phosphorus density (mg/kcal) and all-cause mortality remained after adjusting for other lifestyle and demographic confounders. The strongest associations were found with phosphorus density, suggesting that expressing phosphorus intake as a function of caloric intake, another commonly underreported variable, compensated for its probable underestimation. However, it is likely that the authors have not uncovered all of the nutrient indexes that could influence the association of phosphorus intake with cardiovascular and all-cause mortality. As described earlier, calcium intake and the calcium-to-phosphorus ratio of habitual diets may also have influenced the impact of phosphorus intake on hormones other than FGF-23, as discussed by Chang et al, namely PTH. PTH concentrations within the normal range have been shown to be significantly associated with all-cause mortality and specifically with arteriosclerosis in older people (10). PTH is acutely elevated in response to oral phosphate loading, persistently elevated in response to weeks of consuming grocery foods high in phosphate additives, and significantly higher in young women whose habitual diets had calcium-to-phosphorus ratios of <0.6 (5). In fact, by using the mean calcium and phosphorus intakes in each quartile to approximately calculate the dietary calcium-to-phosphorus mass ratio in the study by Chang et al, we noted a marked decrease in the ratio, from 0.92 at the lowest dietary phosphorus quartile to 0.47 at the highest intake quartile, suggesting that elevated PTH may also be involved.

Epidemiologic studies are observational in design and therefore cannot be used to define causality. Whether phosphorus is a passive marker for other adverse events or a real toxin remains undetermined. Only randomized controlled intervention trials directly testing the effect of modifying dietary phosphorus intake on outcomes can establish causality. Before embarking on such studies, we must first try to tease apart all of the different factors involved in these associations to identify the active culprit or culprits or mechanisms of toxicity.

In summary, we believe the current study adds fuel to the premise that high dietary phosphorus intake is a risk factor for bone and CVD health, not just in CKD patients but also in the general population. The increased cumulative use of phosphorus ingredients in food processing clearly deserves further study in view of what is now being shown about the potential toxicity of excessive phosphorus intake. Further work is needed to define whether these associations represent real causality; however, in the meantime, we need to take some actions such as obligating food manufacturers to label the phosphorus content of their products on the required Nutrition Facts panel, which would enable consumers to determine their phosphorus intake. It is evident from the ever-increasing studies in the general population that the stakes are too high to simply ignore these associations.

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REFERENCES