Association of dietary phosphate and serum phosphorus concentration by levels of kidney function\textsuperscript{1,2}

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ABSTRACT

Background: The health implications of dietary phosphorus intake and the role of kidney function in managing serum phosphorus homeostasis are well studied. However, examining the source of dietary phosphorus intake and its impact on serum phosphorus has not been characterized in population studies.

Objective: This study aims to distinguish the association of food sources of organic phosphorus and inorganic phosphate additives on serum phosphorus concentration.

Design: A cross-sectional analysis of 24-h food recall data from 7895 adult participants of the National Health and Nutrition Examination Survey 2003–2006 was performed. Phosphorus content of foods was categorized as organic or inorganic. Correlations of serum phosphorus to clinical and dietary intake variables were achieved by using multiple regression analysis.

Results: Controlling for estimated glomerular filtration rate (eGFR), body mass index (BMI; in kg/m\textsuperscript{2}), and albumin-to-creatinine ratio, a significant increase in serum phosphorus occurred with dairy foods with inorganic phosphates [parameter estimate (PE) \pm SE: 0.07 \pm 0.02 mg/dL, \( P < 0.01 \)] or without inorganic phosphates (PE: 0.02 \pm 0.01, \( P < 0.001 \)) and cereals/grains with inorganic phosphates (PE: 0.005 \pm 0.002, \( P < 0.01 \)). A significantly higher serum phosphorus occurred when eGFR was <30 (PE: 0.24 \pm 0.08, \( P < 0.0001 \)), but eGFR 30–44 (PE: −0.11 \pm 0.04, \( P < 0.01 \)) and 45–60 (PE: −0.10 \pm 0.04, \( P < 0.01 \)) had lower serum phosphorus; higher serum phosphorus was associated with BMI <18.5 (PE: 0.18 \pm 0.05, \( P = 0.0009 \)) but lower with BMI \geq 35–39 (PE: −0.09 \pm 0.03, \( P = 0.0013 \)) or \( \geq 40 \) (PE: −0.10 \pm 0.03, \( P = 0.014 \)).

Conclusions: This analysis shows that dairy products and cereals/ grains having inorganic phosphate additives significantly increase serum phosphorus concentration, despite being consumed less frequently than foods without phosphate additives. It seems prudent for the Nutrient Facts Label to include phosphorus but also for food manufacturers to consider alternatives to phosphate additives. This trial was registered at clinicaltrials.gov as NCT02435017. Am J Clin Nutr doi: 10.3945/ajcn.114.102715.

Keywords: body mass index, chronic kidney disease, diet, dietary phosphorus, kidney disease

INTRODUCTION

The prevalence of kidney disease estimated to exist in the United States (1) and the role of kidney function in the metabolic balance of phosphorus have led to speculation that dietary factors might contribute to the burden of kidney disease (2–4). Some have postulated that increased dietary phosphorus intake increases risks for cardiovascular disease (5) as well as abnormal response to and presentation of growth factors, particularly fibroblast growth factor 23, associated with regulation of serum phosphorus (6). Serum phosphorus, even when within the normal range, has been associated with cardiovascular events, cardiovascular mortality, and all-cause mortality, both in healthy subjects (5) and in patients with chronic kidney disease (7). In these studies, a wide range of serum phosphorus concentrations has been reported. For example, in the Framingham Offspring Study, serum phosphorus concentrations ranging between 1.6 and 6.2 mg/dL were reported in healthy subjects with normal kidney function (5), but the reason for this wide variability is unclear. Dietary phosphorus has received substantial attention with regard to both the role of inorganic phosphate added to processed and enhanced foods (8, 9) and the difference in bioavailability of phosphorus from meats vs. vegetables (2).

Evaluations of National Health and Nutrition Examination Survey (NHANES)\textsuperscript{5} III data suggested a relation between dietary phosphorus intake and serum phosphorus (10). Assessing dietary phosphorus intake is complicated by an increasing inability for food and nutrient databases to accurately quantify dietary phosphorus, largely due to the increased use of inorganic phosphate additives in the US food supply (11). Currently, \( \sim 4.3\% \) of food additives generally recognized as safe by the US Food and Drug Administration (FDA) contain phosphates (12). To account for these additives and quantify the total phosphorus in foods, the amount of inorganic phosphorus added would need to be made available by food manufacturers, or all foods in the nutrient database would

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\textsuperscript{2}Supplemental Tables 1–4 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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\textsuperscript{5}Abbreviations used: ACR, albumin-to-creatinine ratio; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; NHANES, National Health and Nutrition Examination Survey; PE, parameter estimate.

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need to be chemically analyzed, an impractical and expensive solution. The FDA does not require phosphorus to be reported on the Nutrient Facts Label, only that it be listed as an ingredient (13). In addition, foods (e.g., poultry) may be washed in phosphate-containing solutions to protect against contamination, which may contribute to the phosphorus content of the poultry product when consumed as food. However, this would not be reported as an ingredient (14). Furthermore, some commercial feed manufacturers have added phytase to the animal feed supply to avoid using inorganic phosphorus; this added phytase increases the bioavailability of organic phosphorus from the feed supply (15), which could affect human food composition. However, because only a portion of foods is selected annually for chemical analysis (16), the effect may not be readily detected in the nutrient databases.

The aim of this study was to examine the relation between dietary phosphorus intake—from both organic and inorganic sources—and serum phosphorus concentration in a large cohort of healthy subjects and subjects with reduced kidney function through quantifying foods by groups that supply organic sources of phosphorus or inorganic phosphate additives.

**METHODS**

**Study design**

The study was a cross-sectional evaluation of the serum phosphorus concentration compared with clinical characteristics and dietary intake reported for the 24-h period before blood draw.

**Study population**

The subjects in this study were from the continuous NHANES 2003–2006 cohort of 20,470 participants (17, 18). Analyses were restricted to adults aged 20–85 y (n = 10,020). Pregnant women (n = 569) and those who did not have laboratory values for serum creatinine and phosphorus, urine creatinine, and albumin or for whom 24-h dietary recall information was not available or accurate were excluded from this study (n = 1556). Population estimates were determined according to the NHANES analysis guidance by using the US census data for the years 2000–2006 (19).

**Ethics**

All participants in NHANES sign informed consent at the in-person interview, and data were coded to remove personal identifiers before public availability and protocols approved by the National Center for Health Services Research Ethics Board [protocols 98–12 and 2005–06 (20)].

**Dietary phosphorus assessment**

In this cohort, subjects underwent fasting blood and urine testing and were interviewed by trained dietary and health interviewers to provide a detailed history of their dietary intake the day before laboratory testing.

Dietary phosphorus, as well as its source (natural, considered organic phosphorus vs. processed foods with inorganic phosphate additives), was determined from the 24-h dietary recall taken on the day of serum sampling (21). Foods in NHANES are grouped according to the method used in the USDA nutrient database (22–24) and also listed by actual food item. Using that information, foods were further grouped into servings according to the Academy of Nutrition and Dietetics method to estimate quantity of food (25). Specifically, 140,251 foods consumed were collapsed into 9 food groups in the NHANES database as per the USDA method: milk and milk products; meat, poultry, fish, and mixtures; eggs; legumes, nuts, and seeds; grain products; fruits; vegetables; fats, oils, and salad dressings; and sugars, sweets, and beverages (16). Food groups were then subdivided into those that contained processed foods, in which inorganic phosphates are used as additives, into groups without additives and with additives (e.g., the milk and milk products food group was separated into 2 variables: nonprocessed dairy and processed dairy to account for added phosphates; **Table 1**). The portion size of the foods was standardized by using the Academy of Nutrition and Dietetics “Exchange Lists for Meal Planning” (25) by the amount of protein in 1 serving of milk (8 g protein); 1 ounce or 28 g of meat, fish, or poultry (7 g protein); 1 serving of eggs (7 g protein); 1 serving of legumes (7 g protein); 1 serving of grains (3 g protein); 1 serving of starchy vegetables (3 g protein); and 1 serving of nonstarchy vegetables (2 g protein). For food groups in which the protein content is generally <2 g/portion, the portion size was standardized based on energy or carbohydrate content or weight as follows: 1 serving of fruit (60 kcal); 1 serving of sweets, snacks, or noncola beverages (15 g carbohydrate); and 1 serving of cola beverages (245 g weight or 8 ounces, because kilocalories were not the concern, just potential phosphorus influence from the food item, and some of these beverages would be sugar sweetened, whereas others would be nonnutritive sweetened or unsweetened). A distinction was made between noncola and cola beverages because many cola beverages have phosphoric acid additives. Vegetables were subdivided into nonstarchy vegetables (2 g protein/portion) and starchy vegetables (3 g protein/portion), in which the phosphorus was 1) organic phosphorus with generally <100 mg phosphorus/100-g portion, 2) organic phosphorus that was generally >100 mg phosphorus/100-g portion or an organic phosphorus source was added to the food item (e.g., a cream sauce), and 3) inorganic phosphates that had been added in processing the food (e.g., frozen French fried potatoes). Fats (table fats, cooking fats, other fats, vegetable oils, and salad dressings) were also subdivided. Salad dressings were separated as having inorganic phosphates added if the dressing was not homemade and had a buttermilk or sour cream base or was labeled as Caesar or Thousand Island dressing or had modified food starch added. Sugars, sweets, and beverages were subdivided to account for 1) inorganic phosphates added (e.g., dark cola beverages) or 2) contained organic phosphate sources (e.g., candy bars, beer, wine; **Table 1**). The portion size of most foods in a food group is provided in **Supplemental Table 1**.

**Dietary supplement use**

The use of dietary supplements containing phosphorus was examined. The type of supplement (single component, mineral supplements, multivitamin with minerals) was recorded, and the amount and type of phosphorus in the supplement were assessed.

**Socioeconomic status**

Socioeconomic status was assessed as level of education and level of family income. Education level in adults
TABLE 1
General listing of food groups used in the USDA nutrient database adjusted according to phosphorus source

<table>
<thead>
<tr>
<th>Food group</th>
<th>Source of organic phosphorus</th>
<th>Source of inorganic phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk and dairy</td>
<td>No, very low, or medium phosphorus&lt;sup&gt;1&lt;/sup&gt;</td>
<td>High phosphorus&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Milk</td>
<td>Cheese, cottage</td>
<td>Cheese, yogurt</td>
</tr>
<tr>
<td>Meat, fish, poultry</td>
<td>Fresh or fresh-frozen</td>
<td>Salmon or other fish</td>
</tr>
<tr>
<td>Eggs</td>
<td>Eggs</td>
<td></td>
</tr>
<tr>
<td>Cereals and grains</td>
<td>Source of organic phosphorus</td>
<td></td>
</tr>
<tr>
<td>Bagel</td>
<td>Yeast breads</td>
<td></td>
</tr>
<tr>
<td>Barley</td>
<td>Noodles</td>
<td></td>
</tr>
<tr>
<td>Eggrolls</td>
<td>Noodle soup, not canned</td>
<td></td>
</tr>
<tr>
<td>Cream of wheat, oatmeal, grits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pastry, fruit pies</td>
<td>Pizza</td>
<td></td>
</tr>
<tr>
<td>Rice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semolina/couscous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish, fruits juices</td>
<td>Vegetable casseroles, homemade</td>
<td></td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn, chickpeas, peas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabbages, peppers</td>
<td>Lima beans, mixed vegetables</td>
<td></td>
</tr>
<tr>
<td>Mushrooms</td>
<td>Vegetable-pasta combinations, homemade</td>
<td></td>
</tr>
<tr>
<td>Sprouts</td>
<td>Soups (e.g., potato, carrot, broccoli with added cheese/milk)</td>
<td></td>
</tr>
<tr>
<td>Green beans, root vegetables (e.g., carrots, beets, onions, garlic), green-leafy vegetables</td>
<td>Potato, baked and stuffed</td>
<td></td>
</tr>
<tr>
<td>Stalks (e.g., celery, rhubarb), tomatoes, potato skins</td>
<td>Potato salad, with or without egg</td>
<td></td>
</tr>
<tr>
<td>Potatoes, white, russet, sweet, prepared from fresh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potato chips (not restructured)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olives, green or ripe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>Nuts, seeds</td>
<td></td>
</tr>
<tr>
<td>Italian dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French dressing</td>
<td></td>
<td></td>
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<tr>
<td>Mayonnaise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pesto</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweets and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tea, coffee, water (plain, flavored, or carbonated)</td>
<td>Beer, wine</td>
<td></td>
</tr>
<tr>
<td>Soft drinks, not dark</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination juice drinks (sweetener added)</td>
<td>Chocolate syrup, candy (with or without nuts)</td>
<td>Coffee drinks</td>
</tr>
<tr>
<td>Liquor</td>
<td>Coconut candy</td>
<td></td>
</tr>
<tr>
<td>Hard candy, chewing gum</td>
<td>Coffee beverages with milk added (e.g., cappuccino, latte)</td>
<td></td>
</tr>
<tr>
<td>Jam, jelly, preserves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar, sugar substitute</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Generally, a food item with <100 mg phosphorus/100 g of the food item.
<sup>2</sup>Generally, a food item with ≥100 mg phosphorus/100 g of the food item.
<sup>3</sup>Unknown amount of phosphorus from inorganic phosphate additives; food item may also contain organic phosphorus.
<sup>4</sup>TANG (Kraft Foods Group).

was recorded as less than a high school diploma, high school graduate or general education development test equivalent, some college or Associate of Arts degree, or college graduate or above. Annual family income was recorded as <$20,000, $20,000 to <$45,000, $45,000 to <$75,000, or $≥75,000.
Laboratory assessments

Serum for fasting creatinine and phosphorus, as well as urine for albumin and creatinine, was obtained at the examination center. Serum creatinine was analyzed by using the isotope dilution mass spectrophotometry–traceable Synchron LX Creatinine Reagent Kit, and phosphorus was analyzed by using the Synchron LX Phosphorus kit (Beckman Coulter) by Collaborative Laboratory Services. Urine was collected by the clean-catch technique as a “spot” urine sample, processed and shipped to the University of Minnesota. Urinary creatinine was measured on a CX3 analyzer (Beckman Coulter, Inc.) by using a Jaffé rate reaction, and urinary albumin was assessed by fluorescent immunoassay (18).

Clinical assessments

Kidney function

Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for the estimated glomerular filtration rate (eGFR) (26). Kidney function is reported in 15-mL·min⁻¹·1.73 m⁻² increments as described in the Kidney Disease: Improving Global Outcomes guidelines (27). CKD-EPI >105 mL·min⁻¹·1.73 m⁻² was used as the reference group.

The albumin-to-creatinine ratio (ACR) was measured to detect kidney damage (a value >30 mg/g). However, only one urinary protein was available in this cohort for testing for kidney damage, so confirmation of the presence of kidney damage or chronicity of kidney function level was not possible. Instead, the data were handled as a general population cohort single assessment of ACR and kidney function (27).

Anthropometric measurements

BMI (in kg/m²) was categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25–24.9), or obese (≥30) (28). Obesity was further classified as class I (30–34.9), class II (35–39.9), or class III (≥40) (28).

Statistical analysis

Characteristics of the sample were summarized by using descriptive statistics, and comparisons across kidney function level groups were made by using ANOVA with Bonferroni correction for continuous variables. Categorical variables were compared across kidney function level groups by using the Wald log-linear χ² statistic. The population mean ± SE of servings of food from each food group was determined by using complex survey statistics with SAS Survey (SAS v 9.2; SAS Institute) with appropriate weighting variables and was correlated to serum phosphorus (dependent variable). Sociodemographic variables (education and family income), clinical variables (ACR, BMI, and kidney function level), and dietary intake variables [number of servings of foods from each food group according to the phosphorus source (none or very small, organic or inorganic phosphorus)] were used in a multiple-regression analysis to develop a model of the sociodemographic, clinical, and dietary variables that affect serum phosphorus. Age, sex, and race were accounted for in the CKD-EPI equation for kidney function, so these variables were not repeated in the demographic assessment. Multicollinearity was evaluated by using Pearson correlation coefficients (r ≥ 0.8), and, if present, the variable having the highest correlation was retained. The influence of these variables on the serum phosphorus concentration was reported as the parameter estimate (PE) for each variable retained in the model. Non-significant dietary variables were retained in the model to demonstrate the overall effect of dietary intake. Significance was held at P < 0.05, and for comparison of means of food groups across kidney function level groups, a Bonferroni correction was applied.

To assess for selection bias that serum phosphorus in the analyzed group might not reflect the US adult population because only those with a diet record were included in the main analysis, we compared the serum phosphorus of participants without a diet record with the main analyzed group by using Student’s t test.

The key assumption of this study was that types of foods consumed, as well as subdividing food groups into those known or assumed to have inorganic phosphate additives, would affect the serum phosphorus concentration. For sensitivity analysis, multiple regression was performed by using the nutrient values for dietary phosphorus reported in the USDA National Nutrient Database for Standard Reference (16) instead of the food groups described above. In this analysis, the phosphorus was reported in total milligrams consumed for the 24-h period. An additional multiple-regression analysis was performed in which food groups were entered without subdividing the foods into those with or without inorganic phosphate additives.

RESULTS

A total of 7895 participants had data available for inclusion in this study. The population mean ± SE age was 46.7 ± 0.5 y, and 52.8% were Caucasian (Table 2). The mean BMI was 28.4 ± 0.2, but 33.4% were obese. Hypertension was present in 41.6% of the population, and 11.8% had elevated serum glucose. The mean ACR was 27.7 ± 2.4 mg/g. The education level of 17.1% (n = 2204) was less than high school diploma, 26.1% (n = 1953) received a high school diploma or equivalent, 31.7% (n = 2215) had attended some college, and 25.2% (n = 1518) had a college degree or greater. The annual family income level of 19.5% (n = 2168) was <$20,000; 30.9% (n = 2585) reported an annual income of $20,000 to <$45,000, 22.9% (n = 1488) reported $45,000 to <$75,000, and 26.6% (n = 1457) reported ≥$75,000 annual income. Separating the cohort into kidney function level groups of 15-mL·min⁻¹·1.73 m⁻² increments demonstrated a higher proportion of men, an older age, and a greater proportion of the presence of hypertension and hyperglycemia in the lower kidney function level groups (Table 2).

The population mean serum phosphorus was 3.81 ± 0.01 mg/dL (median: 3.73; range: 1.9–6.8 mg/dL) (Figure 1 and Supplemental Table 2) and varied by kidney function level.

Bivariate analyses

Dietary phosphorus and correlates

The mean number of servings of foods from sources with none to very low amounts of phosphorus was 6.0 ± 0.01 servings/d, which represented 24.7% of servings of foods consumed. The mean number of servings of foods with organic phosphorus was 14.0 ± 0.01 servings/d, representing 52.4% of servings of food consumed. The mean number of servings of food with inorganic
phosphorus was 6.38 ± 0.01 servings/d, representing 22.9% of servings of food consumed.

A significant difference was demonstrated across the levels of kidney function for the number of servings consumed for dairy products without added phosphates; meat, fish, and poultry with added phosphates; legumes; cereals and grains; cereals and grains with inorganic phosphate additives; vegetables (non-starchy); fats without added phosphates; and sweets and beverages without added phosphates and with added phosphates (Table 3).

**Serum phosphorus and correlates**

Neither education level ($r = 0.006$, $P = 0.97$) nor income level ($r = 0.012$, $P = 0.71$) correlated with serum phosphorus.

Kidney function (CKD-EPI mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$) had a positive association with serum phosphorus concentration but was not statistically significant ($r = 0.027$, $P = 0.072$). However, separating the kidney function level into 15-mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ increments resulted in significance ($r = 0.084$, $P = 0.0007$) and delineated some expected differences. People whose eGFR was $<30$ mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ had significantly higher serum phosphorus than those with eGFR $\geq$ 105 mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ (reference group): $4.12 \pm 0.07$ vs. $3.83 \pm 0.02$, $P = 0.0009$.

Also different from the reference group were people with eGFR 30–44 mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ ($3.74 \pm 0.03$, $P = 0.0205$) and people with eGFR 45–59 mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ ($3.73 \pm 0.03$, $P = 0.0036$). No differences in serum phosphorus concentration were apparent for those with eGFR 60–74, 75–89, or 90–105 mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$ compared with the reference group ($P > 0.05$; Figure 1 and Supplemental Table 2).

The population mean ACR was $27.7 \pm 2.4$ mg/g and was positively correlated with serum phosphorus concentration ($r = 0.037$, $P = 0.0043$) and negatively associated with CKD-EPI level ($r = -0.089$, $P < 0.0001$).

BMI was negatively associated with the serum phosphorus concentration ($r = -0.070$, $P < 0.0001$); 1.6% ($n = 114$) were underweight (BMI <18.5), 31.2% ($n = 2263$) had a normal BMI (18.5–24.9), 33.8% ($n = 2718$) were overweight (BMI 25–29.9), 19.8% ($n = 1592$) were class I obese (BMI 30–34.9), 8.3% ($n = 641$) were class II obese (BMI 35–39.9), and 5.4% ($n = 426$) were class III obese (BMI $\geq$ 40).

**FIGURE 1** Median and range of serum phosphorus in mg/dL across kidney function level categories in NHANES 2003–2006 reported as the eGFR from the Chronic Kidney Disease Epidemiology Collaboration 2009 equation in mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$, $*P < 0.05$, $\dagger P < 0.01$, $\ddagger P < 0.001$; compared with reference group, eGFR $>105$ mL $\cdot$ min$^{-1} \cdot$ 1.73 m$^{-2}$, eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey.
were class III obese (BMI ≥40). Compared with those with a normal BMI, people who were underweight had a higher serum phosphorus concentration (β: 0.17; 95% CI: 0.06, 0.27; P = 0.003), and those who were overweight or obese had a lower serum phosphorus concentration (β: −0.06; 95% CI: −0.10, −0.03; P = 0.0007).

Approximately 25% of participants took a dietary supplement containing inorganic phosphates; the frequency was higher in the lower kidney function level groups than in those with the highest kidney function (CKD-EPI <30, 24.9%; CKD-EPI 30–44, 33.7%; CKD-EPI 45–59, 29.5%; CKD-EPI 60–74, 26.3%; CKD-EPI 75–89, 28.4%; CKD-EPI 90–105, 25.0%; and CKD-EPI >105, 15.7%; P < 0.001). The mean amount of phosphorus from dietary supplements was 126.3 ± 7.8 mg/dL in those who reported taking dietary supplements. The most common source of the phosphorus (in ∼33% of participants) was a complex multivitamin/mineral supplement (e.g., Centrum Silver Multivitamin/Multimineral Supplement; Pfizer or SpectraVite CVS Pharmacy) with dicalcium phosphate as a source for calcium and phosphorus. The mean serum phosphorus of participants taking dietary supplements containing phosphorus (3.81 ± 0.02 mg/dL) was not statistically different from those not taking supplements (3.80 ± 0.01, P = 0.50).

A small, positive association with the serum phosphorus concentration was apparent in the dietary intake of foods containing inorganic phosphates (r = 0.064, P < 0.0001) and foods containing organic phosphorus (r = 0.075, P = 0.024). However, no association was present between dietary intake of foods without phosphorus (r = 0.027, P = 0.31) and the serum phosphorus concentration in the population.

The mean serum phosphorus was 3.80 ± 0.02 mg/dL for people with less than a high school education, 3.81 ± 0.02 mg/dL for people with a high school diploma or general education development test equivalent, 3.81 ± 0.02 mg/dL for people with some college education, and 3.81 ± 0.01 mg/dL for people with a college degree or greater (r = 0.006, P = 0.97). The mean serum phosphorus was 3.82 ± 0.01 mg/dL for people whose family income was <$20,000, 3.80 ± 0.01 mg/dL for family income between $20,000 and $44,999, 3.80 ± 0.02 mg/dL for family income between $45,000 and $74,999, and 3.81 ± 0.01 mg/dL for family income ≥$75,000 (r = 0.013, P = 0.71).

**Multiple-regression analysis**

Developing a prediction model for serum phosphorus was performed to quantitatively describe the contribution of the studied variables to the population mean serum phosphorus.

Analysis of the relation to serum phosphorus of the combined clinical factors (BMI, ACR, and kidney function level) and dietary factors demonstrated a small but statistically significant,
positive effect on serum phosphorus of the following variables ($R^2 = 0.027, P < 0.0001$; Table 4): CKD-EPI <30 mL · min$^{-1} · 1.73$ m$^{-2}$, BMI <18.5, and number of servings of milk and dairy foods, milk and dairy foods with added inorganic phosphorus, and cereals and grains with added inorganic phosphorus. A significant negative association was demonstrated with having CKD-EPI 30–44 and 45–59 mL · min$^{-1} · 1.73$ m$^{-2}$ and with having a BMI $\geq 35$ (Table 4).

Accounting for all the variables in the model, the strongest association with serum phosphorus was CKD-EPI <30 (increased serum phosphorus by 0.24 mg/dL), followed by BMI <18.5 (increased serum phosphorus by 0.18 mg/dL). For each additional serving of dairy foods with inorganic phosphorus added, an increase in the serum phosphorus by 0.07 mg/dL ($P = 0.0098$) would occur, and for each additional serving of dairy foods without added inorganic phosphorus, the increase in serum phosphorus was 0.02 mg/dL ($P = 0.0002$). A small but significant increase in serum phosphorus was also associated with servings of cereals and grains with added inorganic phosphates (0.005 mg/dL, $P = 0.0084$).

Other analyses

To test whether excluded cases would affect the generalizability of the results, we performed a comparison of the serum phosphates (0.005 mg/dL, Table 4): CKD-EPI <30 mL · min$^{-1} · 1.73$ m$^{-2}$, BMI <18.5, and number of servings of milk and dairy foods, milk and dairy foods with added inorganic phosphorus, and cereals and grains with added inorganic phosphorus. A significant negative association was demonstrated with having CKD-EPI 30–44 and 45–59 mL · min$^{-1} · 1.73$ m$^{-2}$ and with having a BMI $\geq 35$ (Table 4).

Accounting for all the variables in the model, the strongest association with serum phosphorus was CKD-EPI <30 (increased serum phosphorus by 0.24 mg/dL), followed by BMI <18.5 (increased serum phosphorus by 0.18 mg/dL). For each additional serving of dairy foods with inorganic phosphorus added, an increase in the serum phosphorus by 0.07 mg/dL ($P = 0.0098$) would occur, and for each additional serving of dairy foods without added inorganic phosphorus, the increase in serum phosphorus was 0.02 mg/dL ($P = 0.0002$). A small but significant increase in serum phosphorus was also associated with servings of cereals and grains with added inorganic phosphates (0.005 mg/dL, $P = 0.0084$).

DISCUSSION

The NHANES data were chosen for this study to better understand the relation of dietary intake to serum phosphorus concentration. The results demonstrated that being underweight, having a low eGFR, having an elevated ACR, and having a dietary intake of dairy foods with or without inorganic phosphates

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Parameter estimates of clinical and dietary variables associated with serum phosphorus concentration from NHANES 2003–2006$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Estimate (SE)</td>
</tr>
<tr>
<td>CKD-EPI &lt;30</td>
<td>0.2447 (0.0824)</td>
</tr>
<tr>
<td>BMI &lt;18.5</td>
<td>0.1795 (0.0486)</td>
</tr>
<tr>
<td>CKD-EPI 30–44</td>
<td>$-0.1097 (0.0383)$</td>
</tr>
<tr>
<td>CKD-EPI 45–59</td>
<td>$-0.1044 (0.0354)$</td>
</tr>
<tr>
<td>BMI $\geq 40$</td>
<td>$-0.1018 (0.0391)$</td>
</tr>
<tr>
<td>BMI 35–39</td>
<td>$-0.0938 (0.0265)$</td>
</tr>
<tr>
<td>Milk and dairy with IOP</td>
<td>0.0676 (0.0244)</td>
</tr>
<tr>
<td>Milk 25–29</td>
<td>$-0.0335 (0.0193)$</td>
</tr>
<tr>
<td>Milk and dairy</td>
<td>0.0245 (0.0060)</td>
</tr>
<tr>
<td>CKD-EPI 90–105</td>
<td>$-0.0211 (0.0213)$</td>
</tr>
<tr>
<td>BMI 30–34</td>
<td>$-0.0180 (0.0279)$</td>
</tr>
<tr>
<td>CKD-EPI 60–74</td>
<td>0.0116 (0.0255)</td>
</tr>
<tr>
<td>Meat, fish, and poultry with IOP</td>
<td>$-0.0114 (0.0075)$</td>
</tr>
<tr>
<td>Legumes</td>
<td>$-0.0103 (0.0076)$</td>
</tr>
<tr>
<td>CKD-EPI 75–89</td>
<td>0.0059 (0.0241)</td>
</tr>
<tr>
<td>Starchy vegetables, low to medium organic phosphorus</td>
<td>$-0.0053 (0.0078)$</td>
</tr>
<tr>
<td>Cereals and grains with IOP</td>
<td>0.0048 (0.0018)</td>
</tr>
<tr>
<td>Fats with IOP</td>
<td>0.0037 (0.0064)</td>
</tr>
<tr>
<td>Sweets and beverages with inorganic phosphates added</td>
<td>0.0032 (0.0043)</td>
</tr>
<tr>
<td>Starchy vegetables, high organic phosphorus</td>
<td>$-0.0030 (0.0103)$</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.0027 (0.0069)</td>
</tr>
<tr>
<td>Vegetables with IOP</td>
<td>0.0017 (0.0031)</td>
</tr>
<tr>
<td>Meats, fish, and poultry</td>
<td>$-0.0013 (0.0019)$</td>
</tr>
<tr>
<td>Fruits, vegetables, fats, sweets, and beverages without IOP</td>
<td>$-0.0013 (0.0017)$</td>
</tr>
<tr>
<td>Chocolate, candy, gelatin, beer, and wine</td>
<td>$-0.0008 (0.0043)$</td>
</tr>
<tr>
<td>ACR</td>
<td>0.0001 (0.0000)</td>
</tr>
</tbody>
</table>

$^1$Multiple-regression model; $R^2 = 0.02693, P < 0.0001$. BMI is in kg/m$^2$. ACR, albumin-to-creatinine ratio; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration estimation formula for kidney function level, in mL · min$^{-1} · 1.73$ m$^{-2}$; IOP, inorganic phosphates added; NHANES, National Health and Nutrition Examination Survey.
added, as well as foods categorized as cereals and grains with inorganic phosphates added, had a positive and significant effect on serum phosphorus. Furthermore, the effect of dairy foods with inorganic phosphates was stronger than that of dairy foods without inorganic phosphates, despite consuming fewer portions of the former. Although the model explained only 2.7% of the variance in serum phosphorus, controlling for level of kidney function, an estimator for kidney damage (ACR), and BMI, certain food groups were associated with increasing the serum phosphorus concentration. In particular, milk and dairy products with inorganic phosphate (a 0.005-mg/dL increase for each additional serving was also related to cereal and grain products with added inorganic phosphates (a 0.005-mg/dL increase for each additional serving of this food group). A serum phosphorus increase was also related to cereal and grain products with added inorganic phosphates (a 0.005-mg/dL increase for each additional serving of foods from this group). In addition, when controlling for dietary intake, BMI, and the ACR, having an eGFR of 30 mL min⁻¹ 1.73 m⁻² was associated with a 0.244-mg/dL increase in serum phosphorus concentration.

The data demonstrate a wide range of serum phosphorus, even at very good kidney function levels (e.g., eGFR ≥90 mL min⁻¹ 1.73 m⁻²), and that the overall impact of dietary intake, although significant, was small. This indicates that other factors (e.g., parathyroid hormone, vitamin D, fibroblast growth factor 23, and others) should also be evaluated, if possible, to improve our understanding of the intra- and interindividual variation in serum phosphorus concentration. In fact, the study demonstrated a lower serum phosphorus in people with obesity (BMI ≥35), which is similar to a finding by Kalaitzidis et al. (29), who also noted that serum phosphorus was lower in patients with higher BMI than in controls. This finding warrants additional research.

No claim as to the chronicity of kidney disease can be exerted onto these data because the kidney variables were measured only once (27). Other markers of kidney damage (e.g., presence of urinary casts, urine-specific gravity, and sedimentation rate) are not available in NHANES. Furthermore, the dietary intake was assessed only once, so no assumption that the results represent the usual dietary intake could be made. However, because phosphorus is cleared rapidly by the kidney, the assumption that the data represent a 24-h period was considered tenable.

Different from other reports (3, 10, 30), the current analysis found no association of income or education on the serum phosphorus concentration. Gutiérrez et al. (10) evaluated NHANES III (representing data from 1988 to 1994) by using a poverty-to-income ratio. Their study reported a significantly greater proportion of people with hyperphosphatemia in the lowest poverty-to-income group. These investigators had also shown a relation between income and serum phosphorus in a cohort of people recruited from local medical clinics (30). These important studies hypothesize a potential risk of people living in poverty to have higher serum phosphorus concentration than the rest of society. The current study does not refute their findings, but the relation was not apparent in the NHANES 2003–2006 cohort.

Evaluation of serum phosphorus from previous NHANES years reported lower mean serum phosphorus concentrations than recorded in the more recent NHANES years (10, 31, 32). In each of these reports, the mean serum phosphorus of groups was lower (3.4–3.6 mg/dL) than that measured in the more recent NHANES; the current analysis demonstrated a population mean serum phosphorus of 3.81 mg/dL, and the mean in each kidney function level subgroup did not dip into the 3.4–3.6 range of mean values reported from previous NHANES reports. Several possibilities exist that might explain this difference: 1) analytic differences in the measurement of serum phosphorus. In the NHANES III cohort, the serum phosphorus concentration analysis quantitated phosphorus at an absorbance of 340 nm (33). The analytic method used in NHANES 2003–2006 used an absorbance measured at 365 nm (34, 35). 2) Population differences in the method used for sampling NHANES III and the NHANES 2003–2006 might explain some dissimilarity or differences in the analytic methods recommended (e.g., balanced repeated replication in NHANES III vs. Taylor linearization in NHANES 2003–2006) (36). 3) Diet and food processing may be different in more recent years than that available in NHANES III. In the United States, more phosphates have been added to foods in recent years than were being used 3 decades ago (37). The type of phosphorus in foods plays a role in the amount of phosphorus absorbed. Moe et al. (2) demonstrated that meals having equivalent amounts of phosphorus but of different sources (meats vs. grains) resulted in serum phosphorus differences. Phytates in grains reduce absorption of phosphorus and other minerals (2). However, of greater concern is the fact that phosphate additives are maximally absorbed; up to 100% of some phosphate additives are absorbable, whereas only 40–60% of naturally occurring phosphorus is absorbed during a mixed meal (38). Based on our results, it would be hard to conceive that analytic differences or population differences (e.g., BMI, kidney function, dietary intake) could cause such a change in the serum phosphorus concentration, but changes in food consumption and handling would support such an increase in serum phosphorus. Changing serum phosphorus concentration from 3.4 to 3.8 mg/dL might have public health implications, but further evaluations are needed.

The data presented in this report represent estimations of dietary phosphorus intake because the national food databases are currently unable to accurately provide phosphorus content of foods (11). Estimations of up to 66% misrepresentation of dietary phosphorus in the databases lead to inaccuracies in reported phosphorus intakes (9, 11, 39–41). In contrast to reports of considerable underestimation of phosphorus in the food databases, Carrigan et al. (42) found little difference in the phosphorus content of foods used in their study. They evaluated the phosphorus content in a normal diet and a phosphorus additive–enhanced diet by using the USDA nutrient database and performed a chemical analysis of the foods for comparison. Although the phosphorus additive–enhanced diet proved to provide more dietary phosphorus than the normal diet (~54%), these researchers found only a ~15–17% difference in the estimated values from the USDA nutrient database and the chemically measured values.

Phosphorus reporting on nutrition facts labels is not required by the FDA (13). However, manufacturers do report phosphorus used as an ingredient in the food. Whether the additives are necessary or improve the safety of the food supply is outside the scope of this report.

This study has limitations, primarily the cross-sectional nature of the study design. A randomized controlled trial, such as the one performed by Carrigan et al. (42) but in a larger sample size and
with a greater variety of foods, might be helpful to fully delineate the finding of a phosphate additive effect on serum phosphorus concentration. Another limitation is that the estimate of foods having inorganic phosphate additives is conservative. Not all foods with inorganic phosphate additives were known. Confirmation of the findings would require food manufacturers to report the amount of phosphates used in food production or chemical analysis of all foods in the nutrient database. In addition, the single-day dietary intake analysis and comparison to a single day’s serum phosphorus concentration cannot evaluate the long-term exposure to phosphate additives. However, the design of NHANES for producing a representative sample of the US population provides compelling data for hypothesis generation and future research.

In conclusion, the goal of this research was to assess whether foods having phosphate additives might have an effect on serum phosphorus. Despite the exquisite phosphorus balance provided by the kidney until late in kidney failure, adjusting for kidney disease revealed a dietary component related to the serum phosphorus concentration that is stronger in foods having phosphate additives than those without phosphate additives. It seems prudent for the FDA to consider adding phosphorus to the Nutrient Facts Label but also for food manufacturers to consider alternatives to phosphate additives.

The authors’ responsibilities were as follows—LWM, JVN, and WNS: designed research; LWM and JVN: conducted research; LWM: analyzed data; LWM, JVN, AOG, and WNS: wrote paper; LWM: had primary responsibility for final content. All authors read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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