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Dietary phosphorus intake and mortality in moderate chronic kidney disease: NHANES III

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Abstract

Background. Dietary phosphorus intake is usually restricted in dialysis patients but the associations of dietary phosphorus intake with mortality in moderate chronic kidney disease (CKD) are unknown. Therefore, we examined these associations in National Health and Nutrition Examination Survey III.

Methods. Dietary phosphorus intake was estimated from 24-h dietary recalls administered by trained personnel. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². Time to mortality was examined by Cox regression models taking into account the complex survey design.

Results. 1105 adults with CKD were studied. Phosphorus intake was 1033 ± 482 mg/day (mean ± SD), eGFR was 49.3 ± 9.5 mL/min/1.73 m² and serum phosphorus was 3.5 ± 0.5 mg/dL. Compared to those in the lowest tertile of phosphorus intake (mean 532 ± 161 mg/day), those in the highest third (1478 ± 378 mg/day) had similar serum phosphorus levels (3.6 ± 0.5 versus 3.5 ± 0.6 mg/dL, P = 0.113) and modestly higher eGFR (50.0 ± 8.1 versus 47.5 ± 12.0 mL/min/1.73 m², P = 0.014). After adjustment for demographics, comorbidity, eGFR, physical activity, energy intake and nutritional variables, phosphorus intake was not associated with mortality

[hazard ratio (HR) 0.98 per 100 mg/dL increase, 0.93–1.03].

Conclusions. High dietary phosphorus intake is not associated with increased mortality in moderate CKD, presumably because serum phosphorus levels are maintained in the normal range at this level of GFR. Interventional trials are needed to define optimal phosphorus intake in moderate CKD.

Keywords: dietary phosphorus intake; mortality; moderate chronic kidney disease

Introduction

Phosphorus is a critically important mineral, playing a vital role in energy metabolism, cellular signaling, nucleic acid metabolism, platelet aggregation and bone mineralization. An average adult contains <1 kg of phosphorus in the body. About 85% of that is present in bones and teeth in the form of apatite, and the most of the remainder is inside cells in soft tissues. Only ~0.1% of body phosphate circulates in the blood. A well-fed healthy adult consumes ~1.5 g of phosphorus/day and about two-thirds of that is excreted in the urine and the rest in the feces.

The serum phosphorus level is influenced by dietary intake, gastrointestinal absorption, distribution across the body compartments including uptake into bone and excretion [1]. Regulation of serum phosphorus levels involves vitamin D, parathyroid hormone and fibroblast-derived growth factor-23 (FGF-23). Increased serum phosphorus concentrations are associated with vascular calcification [2] and mortality in dialysis patients [3–6]. Reduction in dietary phosphorus intake by avoiding foods high in phosphorus such as colas or dairy products is considered critical in controlling serum phosphorus in dialysis population. Thus, the national guidelines recommend reduction in dietary phosphorus intake in dialysis patients.

As glomerular filtration rate (GFR) declines to about 40–45 mL/min/1.73 m², urinary excretion of phosphorus decreases and serum levels of phosphorus begin to increase [7, 8]. More recently, in non-dialysis-dependent chronic kidney disease (CKD) patients, higher serum phosphorus levels have been shown to be associated with increased mortality [9, 10]. These data raise the possibility that higher dietary phosphorus intake might be associated with increased mortality in non-dialysis CKD. To our knowledge, there are no prior studies on the associations of dietary phosphorus with mortality in moderate CKD. Therefore, we examined these associations in the moderate CKD population in the National Health and Nutrition Examination Survey (NHANES) III data.

Methods

Study population and baseline data

The NHANES is an ongoing series of the surveys of the non-institutionalized civilian population in the USA conducted by the National Center for Health Statistics. From 1988 to 1994, NHANES III, a cross-sectional survey of the US population was carried out. It used a complex, multistage

sampling design to obtain a sample that is representative of the non-institutionalized civilian US population of early 1990s [11].

Briefly, participants provided informed consent and underwent a structured home interview conducted by trained personnel to ascertain self-reported medical history of conditions such as myocardial infarction, stroke, congestive heart failure and diabetes. This was followed by a physical examination, which included blood pressure measurement, extensive anthropometric and physiological assessments and blood draw for laboratory testing [11] at the NHANES Mobile Examination Center. The time of the blood draw and the number of hours of fasting before the blood draw were recorded. As detailed below, during this visit, participants also underwent a detailed diet interview.

Serum creatinine, albumin, calcium and phosphorus were analyzed on a Hitachi 737 automated analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) using reagents from Boehringer Mannheim Diagnostics. Serum creatinine measurements obtained using a kinetic rate Jaffe method in NHANES III were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH) as standard creatinine = $-0.184 + 0.960 \times \text{NHANES III measured serum creatinine}$ [12]. GFR was estimated as $175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the individual is woman) $\times 1.212$ (if the individual is African-American) [13]. CKD was defined as GFR <60 mL/min/1.73 m².

Dietary assessment

Details about dietary assessment methodology have been published elsewhere [11]. A computer-based interview system developed by the University of Minnesota's Nutrition Coordinating Center (Regents of the University of Minnesota) was used to conduct a 24-h dietary recall. The 24-h dietary recall was conducted by trained interviewers. The US Department of Agriculture's Survey Nutrient Data Base was used to calculate macro- and micronutrient content of the foods consumed during the 24-h recall period for each respondent.

Nutritional assessment

A trained technician carried out anthropometric measurements, while another trained technician assisted and recorded the measures. Weight was measured to the nearest 0.01 kg on an electronic scale. Standing height was measured to the nearest 0.1 cm with a stadiometer. Bioimpedance analysis (BIA) model 1990B (Valhalla Scientific, San Diego, CA) was used for the measurement of whole body electrical resistance and impedance. A standardized protocol for BIA procedure was carried out by trained observers and physicians in a standardized environment. Lean body mass (LBM) was estimated from prediction equations that were validated and cross-validated for men and women separately and for blacks and whites between the ages of 12 and 94 years. [men: LBM (kg) = $-10.68 + (0.65 \times S^2/\text{resistance}) + (0.26 \times \text{weight}) + (0.02 \times \text{resistance})$ and women: LBM (kg) = $-9.53 + (0.69 \times S^2/\text{resistance}) + (0.17 \times \text{weight}) + (0.02 \times \text{resistance})$ where $S^2/\text{resistance}$ is stature squared divided by resistance (cm²/Ω)] [14].

Follow-up data

The National Center for Health Statistics created an NHANES III Linked Mortality File that contains mortality follow-up data from the date of NHANES III survey participation (1988–1994) through December 31, 2000. This information was based upon the results from a probabilistic match between NHANES III and National Death Index death certificate records [15].

Statistical analyses

NHANES III utilized a complex multistage probability sample design. Several aspects of the NHANES design must be taken into account in data analysis, including the sampling weights and clustered sampling. We used the svy suite of commands in Stata 11 (Stata 11, College station, TX) and followed the analytical guidelines for NHANES data proposed by the Centers for Disease Control [16]. The svy commands in Stata accounts for the elements of NHANES sampling design to calculate the expected means and proportions of the entire US non-institutionalized civilian CKD population, which are presented with the estimated values and with associated 95% confidence intervals.

Using gender-specific tertiles, unadjusted associations of dietary phosphorus intake with baseline characteristics including dietary variables (calorie, protein, calcium and magnesium intake), nutritional variables (serum albumin and LBM) and serum calcium, phosphorus and

calcium–phosphorus product were examined using chi-square contingency table analysis for categorical variables and analysis of variance for continuous variables.

In a multivariable linear regression model, the association of dietary phosphorus with serum phosphorus was examined adjusted for demographics (age, gender and race), dietary variables (caloric intake and percent calories from protein), time of the day (morning: 7:00–11:59 AM, afternoon: 12:00–4:49 PM and evening: 5:00–11:00 PM) when the blood was drawn and the hours of fasting before the blood was drawn.

Survival analyses

The unadjusted association of dietary phosphorus intake with mortality was first examined in a Cox proportional hazards regression model without covariate adjustment. Next, this model was adjusted for age, gender and race to examine the extent to which demographic variables confound this association. A third Cox regression model was performed with further covariate adjustment for comorbid conditions (history of myocardial infarction, stroke, congestive heart failure, cancer and diabetes), lifestyle factors (smoking, alcohol use and physical activity), dietary variables (calorie intake and percent calories from protein) and estimated glomerular filtration rate (eGFR). Finally, as higher phosphorus intake might be associated with better nutritional status, the effects of further adjusting for nutritional variables [serum albumin, body mass index (BMI) and LBM] were examined in a fourth Cox regression model.

The assumption of proportional hazards was examined by comparing the logarithm of the hazard ratio (HR) for each predictor variable in the first 3 years of follow-up to the logarithm of the HR of the predictor

variables after Year 3. No models showed proportional hazards assumption violations with respect to dietary phosphorus intake.

The factors gender and stroke exhibited a significant deviation from proportional hazards ($P < 0.05$) in at least one of the models. Hence, rather than including these factors as covariates, each of the Cox regressions was stratified by each of these factors to allow separate baseline hazard functions within each stratum. In addition, quadratic terms were tested for each continuous covariate to test for the presence of nonlinear effects of that covariate. No quadratic terms were statistically significant.

Similar analyses were performed treating dietary phosphorus intake as a categorical variable with the lowest dietary phosphorus intake as the reference group.

Results

Of the 16 864 adults with valid data for GFR estimation, the subpopulation of 1105 CKD participants with nonmissing data for dietary intake, nutritional variables and mortality were included in this analysis.

Higher phosphorus intake was associated with younger age and non-African-American race (Table 1). GFR was modestly higher in the higher phosphorus intake group. There was a very small but statistically significant difference in calcium–phosphorus product.

Table 1. Participant demographics, pertinent lifestyle and medical history characteristics^a

	Lowest phosphorus intake tertile, 532 ± 161 (mg/day)	Middle phosphorus intake tertile, 912 ± 166 (mg/day)	Highest phosphorus intake tertile, 1478 ± 378 (mg/day)	P-value
Age (years)	70.8 ± 12.3	70.4 ± 12.4	67.4 ± 13.0	0.02
Women (%)	68 (63–73)	57 (49–64)	65 (57–73)	0.07
African-American (%)	12 (10–16)	6 (5–9)	4 (2–5)	<0.001
Myocardial infarction (%)	18 (13–25)	14 (9–21)	15 (11–19)	0.41
Congestive heart failure (%)	14 (9–19)	12 (8–19)	12 (8–16)	0.86
Stroke (%)	11 (7–16)	8 (6–12)	9 (6–13)	0.60
Diabetes (%)	18 (14–23)	21 (16–27)	22 (18–28)	0.51
History of malignancy (%)	11 (7–17)	9 (6–14)	12 (8–16)	0.73
Current smoker (%)	14 (10–20)	11 (7–16)	14 (10–20)	0.59
Current alcohol user (%)	20 (14–26)	32 (24–40)	35 (26–45)	0.02
Systolic BP (mmHg)	143.2 ± 23.5	141.6 ± 18.6	138.8 ± 20.7	0.04
Diastolic BP (mmHg)	75.6 ± 13.5	75.0 ± 11.3	74.7 ± 10.5	0.72
eGFR (mL/min/1.73 m ²)	47.5 ± 12.0	49.9 ± 8.7	50.0 ± 8.1	0.01
Serum phosphorus (mg/dL)	3.5 ± 0.6	3.4 ± 0.5	3.6 ± 0.5	0.11
Serum calcium (mg/dL)	9.3 ± 0.5	9.3 ± 0.5	9.4 ± 0.5	0.09
Calcium–phosphorus product (mg ² /dL ²)	32.8 ± 6.2	32.1 ± 5.1	33.4 ± 5.0	0.07

^aPercentages shown as percent (95% CI); continuous measures shown as mean ± SD. BP, blood pressure.

Table 2. Association of phosphorus intake with dietary intake and nutritional status^a

	Lowest phosphorus intake tertile, 532 ± 161 (mg/day)	Middle phosphorus intake Tertile 912 ± 166 (mg/day)	Highest phosphorus intake tertile 1478 ± 378 (mg/day)	P-value
Calories (kcal/day)	1041 ± 411	1570 ± 521	2103 ± 698	<0.001
Dietary protein(% kcal)	15.3 ± 6.5	15.7 ± 4.4	17.3 ± 5.3	0.01
Dietary calcium (mg/day)	306 ± 164	568 ± 204	992 ± 413	<0.001
Dietary magnesium (mg/day)	146 ± 56	230 ± 71	346 ± 113	<0.001
Serum albumin (g/dL)	4.01 ± 0.4	4.04 ± 0.3	4.06 ± 0.4	0.51
BMI (kg/m ²)	27.1 ± 5.8	28.0 ± 5.5	27.7 ± 5.3	0.40
LBM (%) ^b	48.9 ± 10.3	53.2 ± 11.8	52.8 ± 10.8	<0.001

^aContinuous measures shown as mean ± SD.

^bLBM estimated from bioimpedance measurements.

As is expected, higher phosphorus intake was associated with higher intake of protein, energy, calcium and magnesium intake (Table 2). Of the anthropometric measures, higher phosphorus intake was associated with higher estimated LBM but not BMI or serum albumin (Table 2).

Dietary phosphorus was weakly associated with serum phosphorus after adjustment for demographics, calorie intake, percent calories from protein intake, time of blood draw and duration of fasting. A 100 mg/day increase in dietary phosphorus was associated with a corresponding change in serum phosphorus of 0.009 mg/dL (95% confidence limits: 0.006–0.011 mg/dL, Table 3).

There were 592 (54%) deaths over an average of 6.5 years of follow-up. The unadjusted hazard of death was lower with higher phosphorus intake (Figure 1). As shown in Figure 2, adjustment for age, gender and race attenuated the decrease in the HRs associated with higher phosphorus intake. Adjustment for comorbid conditions, eGFR, smoking, alcohol use, physical activity levels and energy intake further attenuated this association. Adjustment for nutritional status eliminated the lower hazard of mortality associated with high phosphorus intake.

The associations of phosphorus intake as a categorical variable with mortality were similar (Table 4).

Discussion

The results of the current study suggest that high dietary phosphorus levels are associated with very modest increase in serum phosphorus levels but not with increased mortality in early-stage III CKD. However, high dietary phosphorus is positively associated with LBM and intake of energy, protein, calcium and magnesium.

Higher levels of serum phosphorus was associated with increased risk of mortality in advanced CKD [9, 10] as well as hemodialysis patients [3, 5]. Furthermore, higher serum phosphorus levels were associated with lower ankle-brachial index (a marker of peripheral arterial disease) in individuals with normal kidney function or moderate kidney disease [17], increased risk of cardiovascular disease in individuals with eGFR >90 mL/min/1.73 m² and without proteinuria [18], and increased risk of stroke and death in healthy community-dwelling adults [19]. Therefore, there is much interest in strategies to reduce serum phosphorus

(either by decreasing dietary intake of phosphorus or use of phosphorus binders) not only in dialysis population but also in those with CKD [20–22].

Even though the above studies of serum phosphorus provide a strong rationale for targeting dietary phosphorus in advanced stages of kidney disease, there is a paucity of data on whether dietary phosphorus by itself is a risk factor for poor outcomes in those with normal kidney function or mild kidney dysfunction. In an earlier analysis of NHANES III data, there were no associations of dietary phosphorus with serum phosphorus in non institutionalized US general population [23]. Antonucci *et al.* [24] conducted a rigorous 4-week interventional study of dietary phosphorus in 13 healthy men. In that study, participants were admitted to a General Clinical Research Center and consumed a constant diet that provided 500 mg of phosphorus per day, which was supplemented to achieve three phosphorus intakes, each of 9 days duration: control = 1500 mg/day, supplemented = 2300 mg/day and restricted = 625 mg/day. Intakes of calcium, sodium, potassium, magnesium, and energy were constant. Dietary phosphorus intervention had no effects on serum phosphorus levels. Therefore, there is no clear evidence to support the notion that dietary phosphorus manipulation will impact on serum phosphorus levels in those with normal kidney function or those with moderate CKD.

Nonetheless, independent of serum phosphorus levels, high dietary phosphorus could have deleterious consequences through other mechanisms. In the phosphorus intervention study described above, high dietary phosphorus intake resulted in increased serum levels of FGF-23 [24]. Increased serum levels of FGF-23 have been shown to be independently associated with endothelial dysfunction [25], coronary artery disease [26], left ventricular hypertrophy [27] and mortality [28] in CKD or dialysis patients. Apart from its effects on serum FGF-23 levels, high dietary phosphorus could affect outcomes through other mechanisms. For instance, *in vitro*, bovine aortic endothelial cells exposed to a phosphorus load increased production of reactive oxygen species and decreased nitric oxide production [29]. Furthermore, flow-mediated dilation of the brachial artery was significantly decreased by dietary phosphorus load in healthy volunteers [29]. Apart from cardiovascular disease, high dietary phosphorus intake could also increase progression of kidney disease as uremic

Table 3. Adjusted associations of dietary phosphorus with serum phosphorus

	Regression coefficient (95% CI)	P-value
Each 100 mg/day increase of dietary phosphorus	0.009 (0.006, 0.011)	<0.001
Each year increase in age	−0.003 (−0.004, −0.003)	<0.001
Men	−0.157 (−0.1733, −0.141)	<0.001
African-American race	0.017 (−0.000, 0.034)	0.056
Each 100 kcal/day increase	−0.004 (−0.005, −0.002)	<0.001
Each increase in 5% kcal from dietary protein	−0.002 (−0.012, 0.007)	0.620
Time of blood draw		
Morning blood draw (7:00 AM–11:59 AM)	Reference	
Afternoon blood draw (12:00 PM–16:59 PM)	0.148 (0.129, 0.166)	<0.001
Evening blood draw (1700–2300)	0.195 (0.171, 0.218)	<0.001
Duration of fasting (h)	−0.008 (−0.010, −0.006)	<0.001

rats fed with low phosphorus diet had slower progression of kidney disease on renal histology [30].

Taken together, the above literature could be interpreted as evidence that high dietary phosphorus intake could be deleterious in those with moderate kidney disease. Indeed, in maintenance hemodialysis patients, high dietary phosphorus was associated with increased hazard of death [31]. However, to our knowledge, there are no published data on whether high dietary phosphorus intake is indeed associated with increased mortality in moderate CKD.

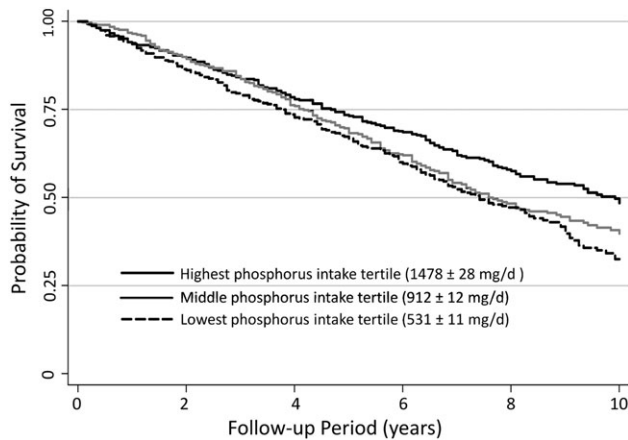


Fig. 1. Kaplan–Meier plot of unadjusted survival by phosphorus intake tertiles in moderate CKD.

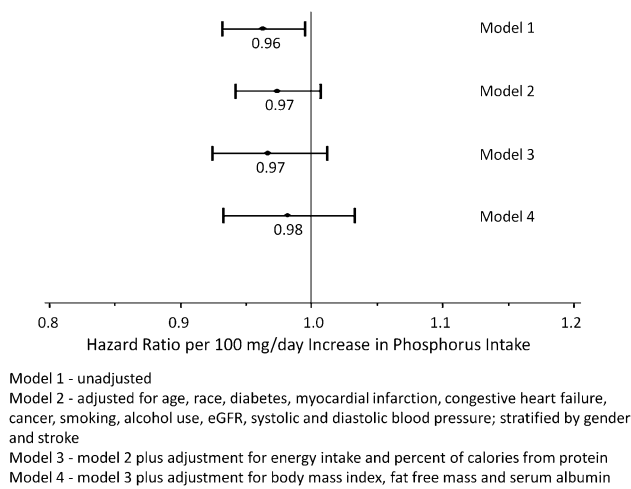


Fig. 2. HR of death associated with phosphorus intake in moderate CKD.

As GFR declines to about 40–45 mL/min/1.73 m², urinary excretion of phosphorus decreases and serum levels of phosphorus begins to increase [7, 8]. In this sample of people with moderate kidney disease (eGFR, 49.3 ± 9.5 mL/min/1.73 m²), higher reported dietary phosphorus intake was associated with lower hazard of death in unadjusted models (Table 3 and Figure 2). With adjustment, dietary phosphorus intake was not significantly associated with mortality. It is possible that the magnitude of the Cox regression coefficients for dietary phosphorus were attenuated due to effects of measurement error [32] or short-term variation in diet. However, because the estimated HRs corresponding to higher phosphorus levels were <1 in each model considered (Figure 2), it is unlikely that attenuation due to measurement error obscured a direct association of higher phosphorus with increased mortality. Thus, the results of this study suggest that spontaneously higher phosphorus intake is not associated with increased mortality at this level of eGFR. It is still conceivable that dietary phosphorus restriction might improve outcomes in those with more advanced CKD with decreased ability to excrete phosphorus. Interventional studies are warranted to conclusively establish the potential benefit or harm of low phosphorus diet in early-stage III CKD.

Another therapeutic strategy is the use of phosphorus binders to decrease dietary phosphorus absorption in those with early stages of CKD and normal serum phosphorus levels [33]. In individuals with advanced CKD (eGFR, 26.3 ± 15.6 mL/min) and normal serum phosphorus (4.5 ± 0.7 mg/dL), therapy with sevelamer was associated with decreased progression of coronary calcification compared to individuals treated with a low phosphorus diet alone [34]. Since low phosphorus diet was associated with increased coronary calcification in that study, the decreased calcification with sevelamer may be through mechanisms independent of its dietary phosphorus-binding effect. Therefore, it is unclear whether dietary phosphorus restriction would improve coronary calcification and cardiovascular outcomes in CKD. In a retrospective analysis of hemodialysis patients, patients treated with phosphorus binders were matched with those who were not treated with phosphorus binders by their baseline serum phosphate levels and propensity score of receiving phosphorus binders during the first 90 days [33]. In that study, therapy with phosphorus binders was independently associated with lower mortality. This was presumably because phosphorus binders suppressed serum FGF-23 levels. Similarly, in men with moderate to advanced non-dialysis CKD, phosphorus binder therapy was associated with decreased risk of all-cause mortality which

Table 4. Associations of phosphorus intake as a categorical variable with mortality in the CKD subpopulation using Cox regression models^a

Phosphorus intake tertiles	Model 1	Model 2	Model 3	Model 4
Lowest (531 ± 11 mg/day)	Reference	Reference	Reference	Reference
Middle (912 ± 12 mg/day)	0.88 (0.68–1.14)	1.03 (0.76–1.40)	1.07 (0.77–1.50)	1.25 (0.87–1.78)
Highest (1478 ± 28 mg/day)	0.64 (0.46–0.90)	0.84 (0.60–1.18)	0.92 (0.61–1.40)	1.07 (0.67–1.70)

^aModel 1—unadjusted; Model 2—adjusted for age, race, diabetes, myocardial infarction, congestive heart failure, cancer, smoking, alcohol use, eGFR, systolic and diastolic blood pressure; stratified by gender and stroke; Model 3—model 2 plus adjustment for energy intake and percent of calories from protein and Model 4—model 3 plus adjustment for BMI, LBM and serum albumin.

was most pronounced in men with higher baseline serum phosphate levels [22]. However, in a small randomized controlled trial of CKD patients, the use of lanthanum, a phosphorus binder was associated with decrease in urinary phosphorus excretion but not that of serum FGF-23 levels [35]. Thus, it is unclear whether the use of phosphorus binders in early-stage CKD patients with normal serum phosphorus levels would impact on hard end-points.

Higher protein intake is associated with higher phosphorus intake. Therefore, zealous restriction of phosphorus intake might decrease protein intake and adversely affect nutritional status [36]. Indeed, in this study, higher phosphorus intake was associated with higher LBM (Table 2). Dietary approaches to maximizing nutritional status while controlling phosphorus intake include maximizing the organic phosphorus to protein ratio and minimizing inorganic sources [31]. An organic Italian Mediterranean diet was reported to both decrease serum phosphorus and increase LBM among patients with Stages 2 and 3 kidney disease [37]. Adjustment of phosphate binder use based on dietary phosphate intake is reported to result in improved phosphorus levels in children without influencing phosphorus intake [22, 33, 35, 38].

Strengths of this study include the representative sample and rigorous methodology of the NHANES study. Limitations of the study include the observational nature, which limits causal inferences. Despite its common use, the Modification of Diet in Renal Disease equation has several limitations when used in specific groups and may result in the over diagnosis of CKD [39]. Furthermore, there were only single baseline measurements of dietary intake with a single 24-h recall at baseline. Conventional nutrient databases may not account for the consumption of food additives laden with highly bioavailable phosphorus [40–43], which might result in underestimation of phosphorus [36]. Imprecise estimates of dietary phosphorus intake might bias the study toward null hypothesis. However, given that the total calorie intake was lower in the lowest phosphorus group and higher in the highest phosphorus group, it is unlikely that there was systematic underestimation of dietary phosphorus in the low phosphorus intake group compared to the high phosphorus intake group. Fasting durations and time of day in blood collection varied between participants and these might affect serum phosphorus levels. However, when adjusted for these variables, dietary phosphorus had statistically significant but clinically not meaningful association with serum phosphorus at this level of eGFR. In addition, there are no data available in this NHANES dataset on serum parathyroid hormone or FGF-23 levels.

We conclude that spontaneously higher dietary phosphorus intake is not associated with increased mortality in moderate CKD in the USA. We conjecture that this absence of association reflects the maintenance of serum phosphorus levels in the normal range at this level of GFR. However, interventional trials are needed to establish the optimal level of dietary phosphorus intake in moderate CKD. Demonstration of sustainable dietary and supplement approaches to maximizing nutritional status and phosphorus metabolism may play a role in improving both clinical outcomes and quality of life of patients with CKD.

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Conflict of interest statement. T.G. currently acts as a consultant for Amgen Inc., Comedix Inc., Eli Lilly and Co., Kery Biopharmaceuticals, and NephroGenex.

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