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# Association of Dietary Phosphorus Intake and Phosphorus to Protein Ratio with Mortality in Hemodialysis Patients

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**Background and objectives:** Epidemiologic studies show an association between higher predialysis serum phosphorus and increased death risk in maintenance hemodialysis (MHD) patients. The hypothesis that higher dietary phosphorus intake and higher phosphorus content per gram of dietary protein intake are each associated with increased mortality in MHD patients was examined.

**Design, setting, participants, & measurements:** Food frequency questionnaires were used to conduct a cohort study to examine the survival predictability of dietary phosphorus and the ratio of phosphorus to protein intake. At the start of the cohort, Cox proportional hazard regression was used in 224 MHD patients, who were followed for up to 5 years (2001 to 2006).

**Results:** Both higher dietary phosphorus intake and a higher dietary phosphorus to protein ratio were associated with significantly increased death hazard ratios (HR) in the unadjusted models and after incremental adjustments for case-mix, diet, serum phosphorus, malnutrition-inflammation complex syndrome, and inflammatory markers. The HR of the highest (compared with lowest) dietary phosphorus intake tertile in the fully adjusted model was 2.37. Across categories of dietary phosphorus to protein ratios of <12, 12 to <14, 14 to <16, and  $\geq 16$  mg/g, death HRs were 1.13, 1.00 (reference value), 1.80, and 1.99, respectively. Cubic spline models of the survival analyses showed similar incremental associations.

**Conclusions:** Higher dietary phosphorus intake and higher dietary phosphorus to protein ratios are each associated with increased death risk in MHD patients, even after adjustments for serum phosphorus, phosphate binders and their types, and dietary protein, energy, and potassium intakes.

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The causes for the excessive mortality in people with chronic kidney disease (CKD) who undergo maintenance dialysis treatment are not clearly defined (1,2). Whereas the traditional cardiovascular risk factors do not account for the increased mortality in CKD patients (3,4), measures of mineral and bone disorders (MBD), including hyperphosphatemia, are associated with increased death risk (5–9). Hyperphosphatemia may be involved in the pathogenesis of vascular calcification (10–12). Hence, prevention and correction of hyperphosphatemia and dietary phosphorus burden are major components of the management of CKD. This goal is usually approached by restricting dietary phosphorus intake and administering phosphate binders (13–15).

There are few data concerning the association of dietary phosphorus intake with outcome. Restriction of dietary intake of phosphorus generally requires some reduction in the allow-

able protein intake (8) and restricted consumption of highly processed fast and convenience foods (16). However, imposing dietary phosphorus restriction can lead to obligatory reduction in dietary protein intake, which *per se* is associated with protein-energy wasting (PEW) (17) and increased mortality (8). Hence, it is difficult to determine the effect of dietary phosphorus on survival, because dietary protein intake tends to covary with phosphorus intake (18). However, dietary phosphorus to protein ratio may be a more appropriate metric to this end, as recommended by the Kidney Disease Outcomes Quality Initiative MBD guidelines for mineral and bone disorder of CKD (18,19). In this study, we examined the mortality-predictability of dietary phosphorus intake and the dietary phosphorus to protein ratio in a well-studied cohort of MHD patients who were followed for up to 5 years and in whom nutritional and inflammatory measures, including cytokines, and body composition were assessed. We hypothesized that higher dietary phosphorus intake and intake of foods with higher phosphorus to protein ratios are independently associated with increased death risk in MHD patients.

## Materials and Methods

### Patient Population

We studied MHD patients who participated in the National Institutes of Health-funded Nutritional and Inflammatory Evaluation in Dialysis

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(NIED) Study (20–24). The original patient cohort was derived from a pool of approximately 1300 MHD outpatients in eight DaVita dialysis clinics in the South Bay Los Angeles area (see the NIED Study website at [www.NIEDStudy.org](http://www.NIEDStudy.org) for more details). Inclusion criteria were outpatients who had been undergoing MHD for at least 8 weeks, were 18 years or older, and who signed a local Institutional Review Board approved-consent form. Patients with an anticipated life expectancy of less than 6 months (for example, because of metastatic malignancy or advanced HIV/AIDS) were excluded. From October 1, 2001, through December 31, 2006, 893 MHD patients from the eight clinics signed the informed consent form and started the study, of whom 224 patients filled in and returned the dietary questionnaires during the first 6 months of the study (see below) and were followed for up to 63 months; *i.e.*, until December 31, 2006. The medical chart of each MHD patient was thoroughly reviewed by a collaborating physician, and data pertaining to underlying kidney disease and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index was used to assess the severity of comorbidities (25,26).

### *Anthropometric and Body Composition Measures*

Anthropometric measurements were performed while patients were undergoing a hemodialysis treatment. Biceps and triceps skinfold thicknesses were measured with a conventional skinfold caliper using standard techniques as described previously (27,28). To estimate the percentage of body fat, portable near infrared interactance was used at the same time as the anthropometric measurements (29,30).

### *Laboratory Tests*

Predialysis blood samples and postdialysis serum urea nitrogen were obtained on a midweek day. The single-pool Kt/V was used to represent the weekly dialysis dose (31). Except as indicated below, all laboratory measurements were performed by DaVita Laboratories (Deland, FL) using automated methods. In this study, 3-month averaged values were used, and all laboratory measurements used established assays with well-known coefficients of variation. Serum C-reactive protein (CRP) was measured by a turbidometric immunoassay (WPCI, Osaka, Japan; unit: milligrams per liter; normal range: <3.0 mg/L) (32,33). IL-6 and TNF- $\alpha$  were measured with immunoassay kits (R&D Systems, Minneapolis, MN; units: picograms per milliliter; normal range: IL-6: <9.9 pg/ml, TNF- $\alpha$ : <4.7 pg/ml) (34,35). CRP and the cytokines were measured in the General Clinical Research Center Laboratories of Harbor-UCLA. Total homocysteine was determined by high-performance liquid analysis and serum transthyretin (prealbumin) by immunoprecipitin analysis (1).

### *Food Frequency Questionnaires*

We used the dietary questionnaire known as Block Food Frequency Questionnaire (FFQ) at the start of the cohort study to examine the dietary intake of participating subjects over the past 6 to 12 months. The full-length Block FFQ was originally developed by Gladys Block, Ph.D., at the National Cancer Institute (36,37). Different versions of this questionnaire have been developed, extensively studied, and validated (36–38). The Block 98 version (developed and distributed by Block Dietary Data Systems, [www.Nutritionquest.com](http://www.Nutritionquest.com) in Berkeley, CA) is an eight-page paper and pencil form that can be completed at home or during outpatient visits, such as hemodialysis sessions, in 20 to 40 minutes. The FFQ includes 152 multiple-choice questions on the basis of 107 food items. The first five questions are general inquiries concerning types of fruits, vegetables, cereal, and fat or oil. Seventeen subsequent questions are about vitamins and minerals or herbal supplements. The next 130 items are detailed questions about food intake

habits and provide extensive coverage. Each of these questions has two sets of multiple-choice answers about the frequency of the food item (with up to nine options, from never to every day) and the quantity of the ingested food (with four distinct levels). All patients were also asked to answer a question concerning their intake of phosphate binders. In this study, a group of trained research assistants and dietitians supervised the FFQ administration while the MHD patients were undergoing routine hemodialysis treatment in the dialysis clinic. The completed FFQ booklets were reviewed immediately after they were returned, and if any question remained unanswered, the FFQ was returned to the patient with the request to answer the blank questions. All completed FFQs were scanned by an optical mark reader scanner, and the results were interpreted by using software specifically designed to analyze the FFQ information on the basis of food ingredient data from the United States Department of Agriculture. FFQs, as compared with standard dietary diary and recall techniques, often underestimate or sometimes overestimate intake (37,39–41). However, many studies demonstrate that nutrient intakes calculated from FFQs and from dietary diaries and recalls are closely correlated (37,39,41). Nutrient intakes from FFQs are therefore usually reported as tertiles, percentiles, or ratios rather than absolute values.

### *Statistical Analyses*

Pearson correlation coefficient (*r*) was used for analyses of linear associations. Simple linear regression analyses were used to examine trends across increments of phosphorus intake. Multivariate regression analyses were performed to obtain adjusted *P* values controlled for case mix and other covariates. A restricted cubic splines graph with two degrees of freedom was used to illustrate systematic relations between dietary phosphorus and mortality. This method also served to examine the nonlinear associations as continuous mortality predictors as an alternative to potential inappropriate assumptions concerning linearity (42). Death HRs were obtained using Cox proportional hazard models after controlling for the relevant covariates.

We performed incremental levels of multivariate adjustment. (1) Case-mix variables included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, insurance (Medicare *versus* others), marital status, modified Charlson comorbidity score, dialysis dose (single-pool Kt/V), intake of sevelamer HCl or calcium-based binders, and residual renal function. (2) Dietary intake variables included dietary energy, protein, and potassium intake. (3) Malnutrition-inflammation complex syndrome (MICS) variables included serum or blood levels of phosphorus, albumin, creatinine, bicarbonate, calcium, ferritin, hemoglobin, white blood count, and lymphocytes percent; prescribed erythropoietin and active vitamin D doses; normalized protein catabolic rate (nPCR), also known as normalized protein nitrogen appearance; and body mass index. (4) Additional adjustment was made for three inflammatory markers (CRP, IL-6, and TNF- $\alpha$ ). In our view, results from the unadjusted models are likely to be profoundly confounded because of omission of such potential confounders as age and gender, whereas results from the MICS or more adjusted models may be overadjusted because of possible inclusion of biologic intermediates that may be in the causal pathway. We thus prefer to base inferences on the case-mix-adjusted models. Because we cannot be certain of the *best* model, however, we have included four levels of adjustments in the presented analyses to provide the full spectrum of results. Descriptive and multivariate statistical analyses were carried out with the statistical software Stata version 10.0 (Stata Corporation, College Station, TX).

## **Results**

Baseline demographic, clinical, and laboratory values in the 224 MHD patients are shown in Table 1. The patients' mean age

Table 1. Baseline demographic, clinical, and laboratory values in 224 MHD patients and according to the tertiles of their dietary phosphorus intake

Variables	All Patients ( <i>n</i> = 224)	Dietary Phosphorus Intake			
		Tertile 1 ( <i>n</i> = 74)	Tertile 2 ( <i>n</i> = 74)	Tertile 3 ( <i>n</i> = 76)	<i>P</i> for Trend <sup>a</sup>
Demographic					
age, yrs	55.0 ± 13.8	54.0 ± 12.8	57.7 ± 13.5	54.4 ± 15.0	0.69
women, %	48	57	46	41	0.05
race, % African-American	25	27	23	26	0.92
ethnicity, % Hispanic	54	47	54	59	0.14
primary insurance, %	50	47	48	54	0.45
Medicare					
diabetes mellitus, %	60	57	64	60	0.69
marital status, % married	49	48	47	51	0.68
Charlson comorbidity score	2.1 ± 1.4	2.0 ± 1.5	2.1 ± 1.3	2.1 ± 1.5	0.85
mortality, %	36	28	36	43	<0.05
Body composition					
body mass index	27.2 ± 6.8	26.6 ± 6.4	27.3 ± 6.8	27.6 ± 7.0	0.41
triceps skinfold, mm	17.9 ± 9.2	18.1 ± 8.4	17.8 ± 9.5	17.9 ± 9.9	0.57
biceps skinfold, mm	10.3 ± 9.3	11.1 ± 11.1	10.1 ± 9.1	9.8 ± 7.4	0.38
mid-arm muscle circumference, cm	20.7 ± 5.2	20.8 ± 5.6	21.5 ± 4.5	19.9 ± 5.4	0.29
near infrared measured body fat, %	27.2 ± 10.3	27.7 ± 9.6	27.6 ± 10.8	26.4 ± 10.5	0.42
Hemodialysis treatment measures					
dialysis vintage, mos	34.8 ± 29.5	34.2 ± 31.3	34.5 ± 30.3	35.7 ± 30.0	0.84
dialysis dose, Kt/V single pool	1.58 ± 0.30	1.59 ± 0.29	1.61 ± 0.34	1.55 ± 0.27	0.25
erythropoietin dose, 1000 U/wk	14.6 ± 11.3	13.2 ± 9.1	13.3 ± 9.0	17.2 ± 14.6	0.11
Serum measurements					
albumin, mg/dl	3.86 ± 0.34	3.87 ± 0.27	3.83 ± 0.36	3.89 ± 0.39	0.70
transthyretin (prealbumin), mg/dl	28.2 ± 9.1	27.8 ± 8.2	27.6 ± 9.2	29.3 ± 9.9	0.41
creatinine, mg/dl	10.7 ± 3.4	10.6 ± 3.1	10.4 ± 3.4	11.0 ± 3.7	0.79
calcium, mg/dl	9.3 ± 0.7	9.4 ± 0.6	9.3 ± 0.6	9.1 ± 0.7	<0.05
iron, mg/dl	65.2 ± 26.7	65.6 ± 25.6	65.3 ± 28.3	65.0 ± 26.3	0.69
phosphorus, mg/dl	5.8 ± 1.5	5.8 ± 1.3	5.7 ± 1.4	6.1 ± 1.6	0.26
ferritin, ng/ml	650 ± 488	617 ± 465	691 ± 539	642 ± 459	0.73
intact PTH (pg/ml)	337 ± 347	356 ± 331	288 ± 235	365 ± 440	0.46
bicarbonate, mg/dl	21.8 ± 2.5	21.9 ± 2.6	21.6 ± 2.5	22.0 ± 2.4	0.78
total homocysteine, μmol/L	24.1 ± 9.3	23.9 ± 9.5	23.5 ± 9.8	24.8 ± 8.6	0.20
CRP, mg/L	6.3 ± 7.9	6.5 ± 11.1	6.4 ± 6.2	6.0 ± 5.2	0.16
IL-6, pg/ml	24.6 ± 69.1	20.9 ± 54.6	29.8 ± 87.7	23.2 ± 61.4	0.95
TNF-α, pg/ml	7.8 ± 5.1	7.8 ± 5.1	7.0 ± 3.0	8.7 ± 6.5	0.62
blood hemoglobin, g/dl	11.9 ± 1.0	11.9 ± 1.0	11.8 ± 0.9	11.9 ± 1.1	0.50
white blood cell count, ×1000 cells/μl	7.2 ± 2.0	7.1 ± 1.9	7.3 ± 2.1	7.3 ± 2.0	0.60
lymphocytes, % of total white blood cells	21.2 ± 7.1	20.6 ± 7.1	21.3 ± 7.7	21.5 ± 6.8	0.32
Phosphorus binder administration					
sevelamer HCl, %	49	58	53	37	<0.01
calcium-based binders, %	20	22	17	22	0.90

All values are presented as mean ± SD or percentages. Kt/V indicates dialysis dose.

<sup>a</sup>*P* values for triceps and biceps skin fold thicknesses, dialysis dose (vintage), ferritin, erythropoietin dose, CRP, IL-6, and TNF-α are based on the logarithmic values of these measures.

(±SD) was 55.0 ± 13.8 years; 48% of patients were women (*n* = 107), 54% (*n* = 120) were Hispanic, and 25% (*n* = 57) were African American. The mean dialysis vintage was 34.8 ± 29.5

months (median: 27.2 months). After ranking subjects according to their dietary phosphorus intake, we categorized them into tertiles of dietary phosphorus intake, with 74 to 76 patients

in each tertile. Table 1 shows the relevant demographic, clinical, and laboratory measures for the three tertiles of phosphorus intake. The proportion of women and patients using sevelamer HCl was higher in the groups with lower dietary phosphorus intake. There was no significant difference in the prevalence of diabetes mellitus and other comorbidities according to the modified Charlson comorbidity score. Table 2 shows the correlation coefficients of relevant measures with dietary phospho-

rus intake. Phosphorus intake was moderately to strongly correlated with the dietary energy, protein, and potassium intake, and marginally ( $r = 0.13$ ,  $P < 0.01$ ) with predialysis serum phosphorus (Figure 1). The correlation between dietary phosphorus intake and serum phosphorus did not persist after multivariate adjustment (Table 2).

Over the 5 years of the cohort, 81 patients (36%) died. Figure 2 shows the cubic splines graph illustrating the multivariate

Table 2. Unadjusted and multivariate-adjusted Pearson correlation coefficient of baseline phosphorus intake and other relevant variables in 224 MHD patients

Variable	Unadjusted	Case-Mix <sup>a</sup> Adjusted	Case-Mix + Diet <sup>b</sup> + MICS <sup>c</sup> Adjusted	Case-Mix + MICS + Diet + Inflammatory Markers (Full Model) <sup>d</sup>
General				
age	−0.04	−0.07	0.11 <sup>e</sup>	0.13 <sup>e</sup>
Charlson comorbidity score	0.07	−0.07	0.12 <sup>e</sup>	0.11 <sup>e</sup>
log erythropoietin dose	0.12 <sup>e</sup>	0.16 <sup>f</sup>	0.02	0.03
Nutritional variables				
body mass index	0.05	0.06	−0.04	−0.02
triceps skinfold	−0.02	0.04	−0.07	−0.07
biceps skinfold	−0.05	0.01	−0.11 <sup>e</sup>	−0.12 <sup>e</sup>
midarm muscle circumference	−0.07	−0.08	−0.06	−0.06
near infrared body fat%	−0.07	0.04	0.08	0.07
fat weight	−0.01	0.06	−0.01	−0.02
lean (fat- and edema-free) weight	0.09	0.02	−0.17 <sup>f</sup>	−0.17 <sup>f</sup>
normalized protein nitrogen appearance (nPCR)	0.01	0.03	0.05	0.04
energy intake	0.81 <sup>g</sup>	0.81 <sup>g</sup>	0.19 <sup>h</sup>	0.19 <sup>h</sup>
protein intake	0.88 <sup>g</sup>	0.89 <sup>g</sup>	0.71 <sup>g</sup>	0.72 <sup>g</sup>
potassium intake	0.76 <sup>g</sup>	0.75 <sup>g</sup>	0.27 <sup>g</sup>	0.28 <sup>g</sup>
Predialysis serum chemistries				
albumin	−0.01	−0.03	0.00	0.01
prealbumin (transthyretin)	−0.00	0.03	−0.02	0.01
creatinine	0.03	0.08	−0.03	0.00
ferritin	0.02	0.02	−0.01	−0.01
iron	0.03	0.00	−0.13 <sup>e</sup>	−0.14 <sup>f</sup>
calcium	−0.12 <sup>e</sup>	−0.07	−0.01	0.00
phosphorus	0.13 <sup>f</sup>	0.21 <sup>h</sup>	−0.01	−0.01
homocysteine	0.06	0.07	0.03	0.01
Inflammatory cytokines				
log CRP	0.09 <sup>e</sup>	0.07	−0.07	−0.09
log IL-6	0.02	0.01	0.08	0.09
log TNF- $\alpha$	0.00	−0.01	0.04	0.02

<sup>a</sup>Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of sevelamer HCl or calcium-based binders, and kidney residual urine.

<sup>b</sup>Diet includes calorie, protein, and potassium intakes.

<sup>c</sup>MICS variables include albumin, erythropoietin dose, creatinine, hemoglobin, phosphorus, nPCR, bicarbonate, calcium, ferritin, white blood cell, lymphocyte percent, body mass index, and vitamin D dose.

<sup>d</sup>Full model consists of case-mix variables, diet, MICS, and three inflammatory markers: CRP, IL-6, and TNF- $\alpha$ .

<sup>e</sup> $P$  value 0.20 to 0.05. Correlation coefficient  $>0.10$ .

<sup>f</sup> $P$  value 0.05 to 0.01. Correlation coefficient  $>0.10$ .

<sup>g</sup> $P < 0.001$ . Correlation coefficient  $>0.10$ .

<sup>h</sup> $P$  value 0.01 to 0.001. Correlation coefficient  $>0.10$ .



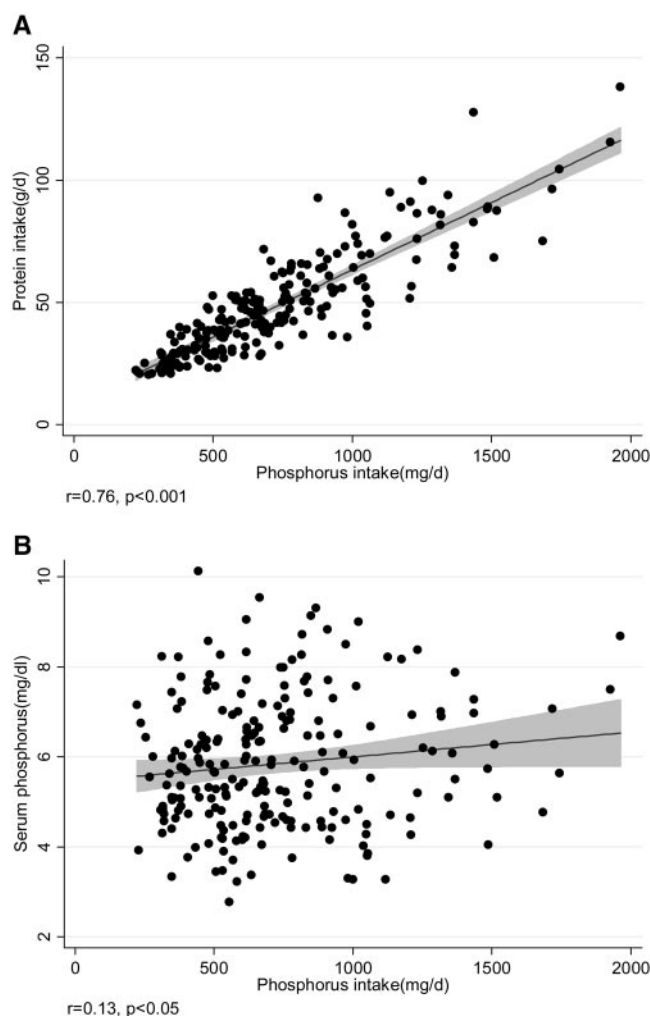


Figure 1. Scatter plots (including the regression line and 95% CI) reflecting the correlations of dietary phosphorus intake with dietary protein intake (upper panel) and serum phosphorus concentration (lower panel).

adjusted association between baseline dietary phosphorus intake and mortality. A trend toward increased risk of death was observed in the MHD patients with higher dietary phosphorus intakes. The death HRs are shown in Table 3. The highest tertile of dietary phosphorus intake was associated with significantly increased death risk [HR (95% confidence interval [CI]) in the unadjusted [1.84 (1.07, 3.19)], case-mix-adjusted [1.89 (1.04, 3.43)], case-mix plus diet plus serum phosphorus-adjusted [2.59 (1.10, 6.08)], and case-mix plus diet plus MICS plus inflammatory markers-adjusted [2.37 (1.01, 6.32)] analyses ( $P < 0.05$  for trend for all levels of multivariate adjustment). These associations remain essentially unchanged after adjustment for additional potential confounders, including serum cholesterol level (data not shown).

To examine the mortality predictability of the dietary phosphorus content per unit of protein intake, we examined the cubic splines graphs for the multivariate-adjusted mortality—predictability of dietary phosphorus to protein ratio (Figure 3). The ratio had close association with dietary phosphorus:  $r =$

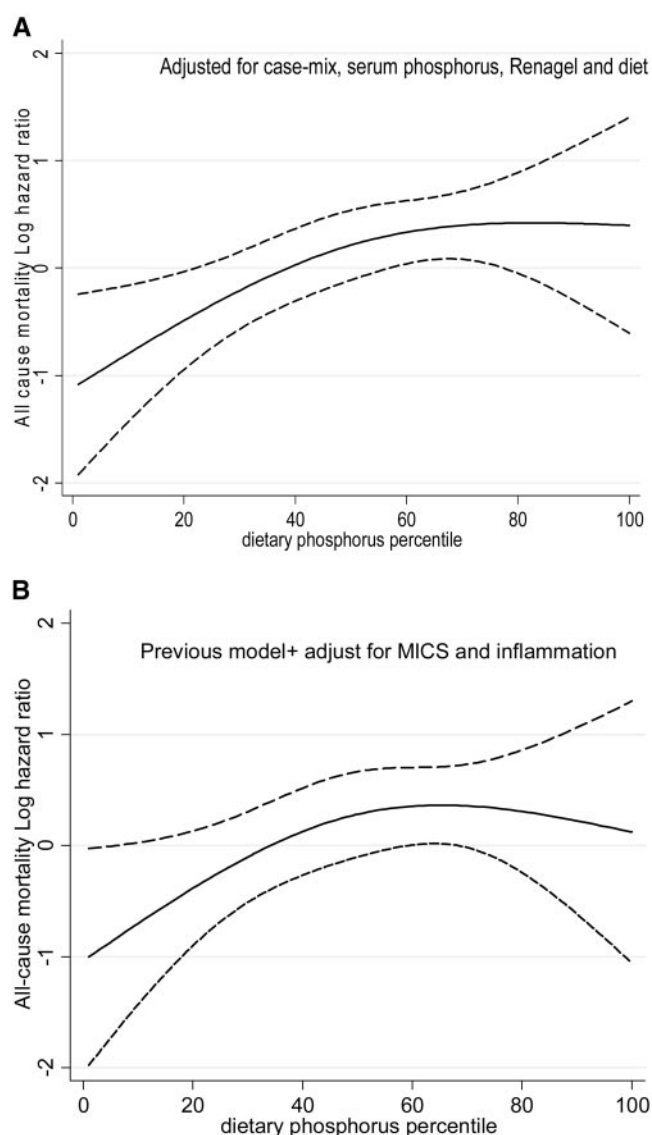


Figure 2. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality predictability (with 95% CI) according to the percentile of the patient's dietary phosphorus intake in the entire cohort of 224 MHD patients over 5 years (from October 2001 to January 2007). Spline models are with two degrees of freedom. Case-mix variables include age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of phosphorus binders, and residual urine. Dietary variables include energy, protein, and potassium intake. MICS variables include serum concentrations of albumin, creatinine, bicarbonate, ferritin, calcium, and phosphorus, blood levels of hemoglobin, white blood cell, and lymphocyte percent; and nPCR, body mass index, and averaged doses of erythropoietin and injected active vitamin D. Inflammatory markers include serum concentrations of CRP, IL-6, and TNF- $\alpha$ .

0.35 ( $P < 0.001$ ). As shown in Figure 3, higher ratio was associated with increased death risk. We then divided the dietary phosphorus to protein ratio into four *a priori* selected incre-

Table 3. HRs and 95% CIs of 5-year mortality according to tertiles of dietary phosphorus intake in 224 MHD patients (October 2001 to January 2007)

Death HR (95% CI) [ <i>P</i> ]	Dietary Phosphorus Intake Tertiles			<i>P</i> for trend
	Tertile 1 ( <i>n</i> = 74)	Tertile 2 ( <i>n</i> = 74)	Tertile 3 ( <i>n</i> = 76)	
Unadjusted	1.00	1.49 (0.84, 2.64) [0.16]	1.84 (1.07, 3.19) [0.02]	0.02
Case-mix <sup>a</sup> adjusted	1.00	1.66 (0.91, 3.02) [0.09]	1.89 (1.04, 3.43) [0.03]	0.02
Case-mix + diet <sup>b</sup> + serum phosphorus	1.00	1.96 (1.02, 3.74) [0.04]	2.59 (1.10, 6.08) [0.02]	0.03
Case-mix + diet + MICS <sup>c</sup> + inflammation <sup>d</sup> adjusted	1.00	1.88 (0.89, 3.95) [0.09]	2.37 (1.01, 6.32) [0.04]	0.04

<sup>a</sup>Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of sevelamer HCl or calcium-based binders, and kidney residual urine.

<sup>b</sup>Diet includes calorie, protein, and potassium intakes.

<sup>c</sup>MICS variables include albumin, erythropoietin dose, creatinine, hemoglobin, serum phosphorus, nPCR, bicarbonate, calcium, ferritin, white blood cell, lymphocyte percent, body mass index, and vitamin D dose.

<sup>d</sup>Inflammatory markers include CRP, IL-6, and TNF- $\alpha$ .

ments of <12, 12 to <14 (reference), 14 to <16 and  $\geq$ 16 mg/g. The death HRs of the four selected phosphorus to protein ratios are shown in Table 4. The MHD patients in the highest group, whose daily food intake contained >16 mg of dietary phosphorus per gram of food protein, exhibited almost two times increased death risk compared with the 12 to <14 mg/g group in the fully adjusted model.

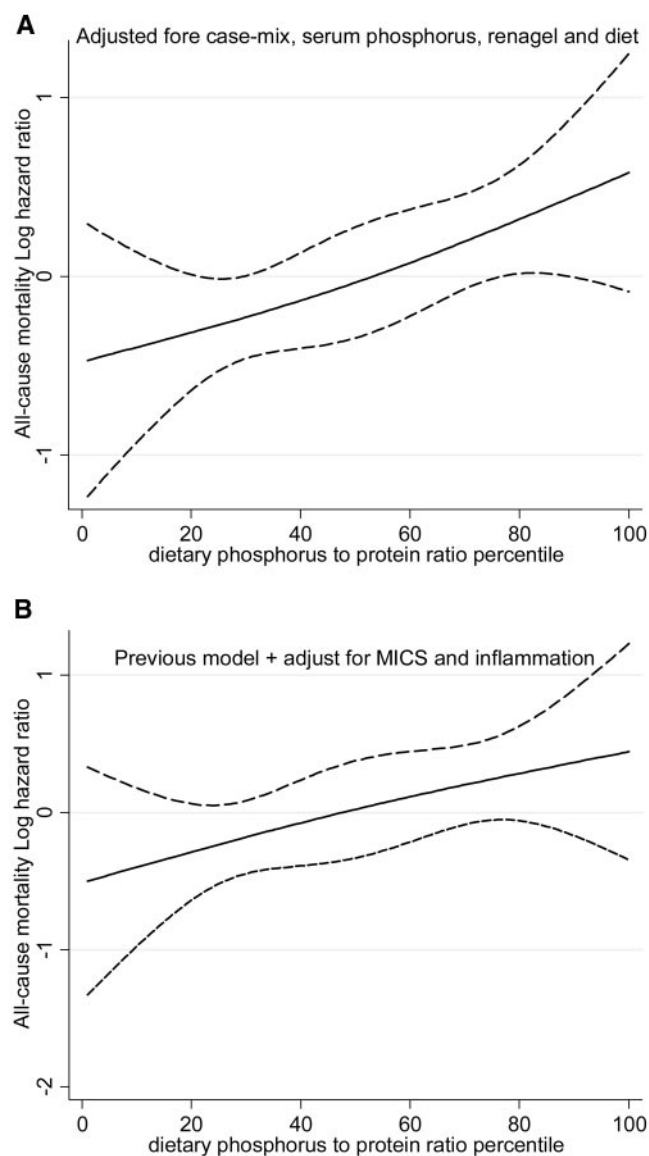
## Discussion

Using an FFQ to estimate daily nutrient intake in 224 MHD patients, we found that both absolute dietary phosphorus intake and the ratio of dietary phosphorus to protein in the ingested food were correlated with 5-year mortality. Although there are a number of reports of the association between the predialysis serum phosphorus and outcomes in CKD patients, (43–45), to our knowledge this is the first investigation in MHD patients to describe an association between dietary phosphorus intake, both by itself and in relationship to the amount of protein ingested, with mortality.

FFQs are widely used in epidemiologic studies to estimate food intake-associated relative risk for disease conditions because of the ease with which they can be administered and information on food intake can be entered into computer databases. Also, FFQs can provide estimates of the long-term, usual dietary intake of certain foods and nutrients in populations of subjects (46). Whereas the FFQ is a reliable tool for ranking individuals according to their dietary intake, the Food and Nutrition Board cautions that FFQ data may not be accurate enough to use to assess the adequacy of dietary intakes of individuals or small groups of people, because of three limitations: (1) lack of direct quantitative assessment of individual amounts of nutrients consumed; thus, precise quantification of intake is not feasible, and the calculated intake of nutrients may underestimate the total intake of that nutrient; (2) inadequate coverage of FFQ items to include all available food items; and (3) inclusion of diverse varieties of a given food under one single food item question, and hence failure to capture significant differences among different subtypes (46).

However, assessment of dietary phosphorus by FFQ in MHD patients may be considered a more valid approach for estimating exposure to excess phosphorus than serum phosphorus *per se*. The serum phosphorus value is usually measured predialysis on one occasion during the week and fluctuates both during the day in response to intake of specific nutrients as well as throughout the dialysis cycle (47). The dose and schedule of hemodialysis treatments as well as degree of residual renal function may also affect the predialysis phosphorus (47). Moreover, in the MHD patient, serum phosphorus concentration will also fluctuate in response to net bone reabsorption; *i.e.* the degree and type of a patient's bone mineral disease, and the serum calcium level as well as the use of intestinal phosphate binders and the magnitude of net intestinal phosphorus absorption (48). Thus, predialysis serum phosphorus can be considered to provide only a rough and short-term estimate of whether there is excess phosphorus concentration in plasma, and whether dietary phosphorus intake might be excessive. Indeed, it is pertinent that in our current study the predialysis serum phosphorus correlated to a low degree with the calculated dietary phosphorus intake and only without adjustment ( $r = 0.13$ ) or with adjustment only for case-mix ( $r = 0.21$ ; see Table 2). It is likely that dietary phosphorus intake does affect serum phosphorus in MHD patients, but perhaps this relationship would only be strong when the serum phosphorus concentrations are time averaged throughout the day, or possibly even over the course of the week. Nonetheless, our data are in agreement with epidemiologic studies relating hyperphosphatemia to increased mortality in CKD (5–9,12,49,50) and maintenance dialysis patients (51,52).

The mechanisms underlying the increased mortality associated with higher dietary phosphorus intake are unclear. Several reports have described the ability of elevated serum phosphorus to stimulate the phenotypic transformation of vascular smooth muscle cells into osteoblasts capable of producing a prominerizing milieu and actual bone tissue (9). Supersaturation of extracellular calcium and phosphorus may accelerate the development of medial wall vascular calcification, leading



**Figure 3.** Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality predictability (with 95% CI) according to the percentile of the patient's dietary phosphorus to protein ratio in the entire cohort of 224 MHD patients over 5 years (from October 2001 to January 2007). Spline models are with two degrees of freedom. Case-mix variables include age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of phosphorus binders, and residual urine. Dietary variables include energy, protein, and potassium intake. MICS variables include serum concentrations of albumin, creatinine, bicarbonate, ferritin, calcium, and phosphorus, blood levels of hemoglobin, white blood cell, and lymphocyte percent; and nPCR, body mass index, and averaged doses of erythropoietin and injected active vitamin D. Inflammatory markers include serum concentrations of CRP, IL-6, and TNF- $\alpha$ .

to arterial stiffness, aortic pulse wave velocity, left ventricular size, and mortality in MHD patients (9). Visceral myocardial calcification may enhance the risk of arrhythmic events and

sudden death. Phosphate excess may increase circulating parathyroid hormone (PTH) and/or decrease 1,25-dihydroxyvitamin D levels (6). Hyperparathyroidism is associated with cardiovascular disease (6). Animal studies of experimental renal failure have linked PTH excess to intracellular calcium overload, cardiac fibrosis, and impaired myocardial energy production (53–55). Circulating PTH excess is associated with increased prevalence of left ventricular hypertrophy (56) and the risk for cardiovascular and all-cause mortality (50). Decreased vitamin D levels may also contribute to the increased risk for adverse cardiovascular outcomes associated with higher phosphorus intake. 1,25-Dihydroxyvitamin D levels are suppressed with high serum phosphorus concentrations (57) and have also been inversely correlated with the extent of coronary artery calcification among individuals who are at risk for coronary disease without CKD (57).

Additional mechanisms independent of ionized calcium or 1,25-dihydroxyvitamin D concentrations may also participate causally in the association between excess body phosphorus burden and mortality (58,59). Fibroblast growth factor 23 (FGF-23) is a hormone that increases the rate of urinary excretion of phosphate and inhibits renal production of 1,25-dihydroxyvitamin D, thus helping to mitigate hyperphosphatemia in patients with kidney disease. Increased fibroblast growth factor 23 levels appear to be independently associated with mortality among patients who are beginning hemodialysis treatment (60). Because individuals with CKD have a high mortality and are at particularly high risk for cardiovascular morbidity and death, these considerations are of substantial clinical relevance (1,61).

Intake of phosphate binders in CKD patients and the close association between phosphorus, potassium, and protein content in foods make it somewhat difficult to evaluate the independent effect of dietary phosphorus intake on mortality (62). Furthermore, it is likely that patients who have a higher phosphorus intake are those who have more appetite, and hence are also more likely to ingest a higher dietary protein and energy intake. However, in our study both high phosphorus intake and a higher phosphorus to protein ratio in daily ingested food, even after simultaneous multivariate adjustment for phosphate binders and for energy, potassium, and protein intake as well as other factors, were associated with increased risk of death in subsequent years.

Some limitations should be considered in interpreting our findings. First is the limited sample size, which excludes further analysis on the association of phosphorus intake and CVD mortality or subgroup analysis. Second is the selection bias during enrollment, in that more malnourished patients were less likely to enroll. However, selection bias in this direction would lead to bias toward the null; therefore, without this bias, our results may have been even stronger. Third is the lack of information regarding dialysis access, dialysis membrane, and several other known or unknown confounders. Fourth, the FFQ has not been validated in patients undergoing maintenance dialysis, who may differ in their food intakes from dialysis to nondialysis days (63) and who may take more and different supplements (e.g., renal vitamin pills and phosphate binders) than do healthy persons or other types of patients. Furthermore, FFQs may underestimate the amount of daily protein (46)



**Table 4.** HRs of 5-year mortality according to four increments of dietary phosphorus to protein intake ratio in 224 MHD patients (October 2001 to January 2007)

Death HR (95% CI) [P]	Dietary Phosphorus to Protein Ratio (mg/g)				P for Trend
	<12 (n = 33)	12 to <14 (n = 64)	14 to <16 (n = 45)	≥16 (n = 82)	
Unadjusted	0.73 (0.32, 1.66) [0.45]	1.00	1.46 (0.76, 2.83) [0.25]	1.55 (1.01, 2.68) [0.06]	0.02
Case-mix <sup>a</sup> adjusted	0.83 (0.35, 1.99) [0.67]	1.00	1.56 (0.74, 3.28) [0.24]	1.74 (1.06, 3.13) [0.04]	0.02
Case-mix + diet <sup>b</sup> + serum phosphorus	0.88 (0.36, 2.16) [0.78]	1.00	1.50 (0.70, 3.20) [0.29]	2.09 (1.08, 4.05) [0.03]	0.02
Case-mix + diet + MICS <sup>c</sup> + inflammation <sup>d</sup> adjusted	1.13 (0.41, 3.12) [0.81]	1.00	1.80 (0.77, 4.22) [0.17]	1.99 (1.03, 4.25) [0.02]	0.08

<sup>a</sup>Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of sevelamer HCl or calcium-based binders, and kidney residual urine.

<sup>b</sup>Diet includes calorie, protein, and potassium intakes.

<sup>c</sup>MICS variables include albumin, erythropoietin dose, creatinine, hemoglobin, serum phosphorus, nPCR, bicarbonate, calcium, ferritin, white blood cell, lymphocyte percent, body mass index, and vitamin D dose.

<sup>d</sup>Inflammatory markers include CRP, IL-6, and TNF- $\alpha$ .

and phosphorus intake (64). However, our findings are given on the basis of ranked data, tertiles, and ratios rather than absolute amounts of dietary intakes. Finally, higher dietary phosphorus intake may be a surrogate of nonadherence to dietary restrictions and other recommendations, and hence related to mortality indirectly; however, the associations held even after comprehensive multivariate adjustment

There are several strengths to this study, including the relatively long follow-up period (63 months), the comprehensive laboratory evaluations, the concomitant assessments of body composition, and the detailed evaluation of the clinical and comorbid states of the patients by study physicians at baseline. Our cohort has been extensively characterized for markers of inflammation and nutritional status, energy intake, protein and potassium intake, and direct total body fat measurements. A unique feature of this study is its novelty in assessing phosphorus intake measured by FFQ, which is a validated method to estimate long-term usual dietary intake at a population basis and almost certainly a more valid tool for estimating overall phosphorus burden, rather than serum phosphorus, which is an intermittent predialysis blood measure. Furthermore, the dietary phosphorus to protein ratio reported in this paper should be less affected by any systematic underestimation of total food intake. Finally, participants were selected randomly without having prior knowledge of their inflammatory status.

### Conclusions

Both higher dietary phosphorus intake and a greater dietary phosphorus to protein ratio are associated with increased death risk in MHD patients, even after adjustments for serum phosphorus, type of phosphate binder used, and dietary protein, energy, and potassium intake. These findings, if verified in additional studies, suggest that the least possible phosphorus content with an adequate protein supply should be recommended to MHD patients. Future studies can also examine

diverse cooking procedures that discharge more phosphorus while preserving protein content, thus attenuating the dietary phosphorus to protein ratio.

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