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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 ≥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 allowable 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.

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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 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-α were measured with immunoassay kits (R&D Systems, Minneapolis, MN; units: picograms per milliliter; normal range: IL-6: <9.9 pg/ml, TNF-α: <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 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-α). 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 (n = 224)	Dietary Phosphorus Intake			
		Tertile 1 (n = 74)	Tertile 2 (n = 74)	Tertile 3 (n = 76)	P for Trend[a]
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.

[a]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 phosphorus 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[a] Adjusted	Case-Mix + Diet[b] + MICS[c] Adjusted	Case-Mix + MICS + Diet + Inflammatory Markers (Full Model)[d]
General				
age	−0.04	−0.07	0.11[e]	0.13[e]
Charlson comorbidity score	0.07	−0.07	0.12[e]	0.11[e]
log erythropoietin dose	0.12[e]	0.16[f]	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[e]	−0.12[e]
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[f]	−0.17[f]
normalized protein nitrogen appearance (nPCR)	0.01	0.03	0.05	0.04
energy intake	0.81[g]	0.81[g]	0.19[h]	0.19[h]
protein intake	0.88[g]	0.89[g]	0.71[g]	0.72[g]
potassium intake	0.76[g]	0.75[g]	0.27[g]	0.28[g]
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[e]	−0.14[f]
calcium	−0.12[e]	−0.07	−0.01	0.00
phosphorus	0.13[f]	0.21[h]	−0.01	−0.01
homocysteine	0.06	0.07	0.03	0.01
Inflammatory cytokines				
log CRP	0.09[e]	0.07	−0.07	−0.09
log IL-6	0.02	0.01	0.08	0.09
log TNF-α	0.00	−0.01	0.04	0.02

[a]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.

[b]Diet includes calorie, protein, and potassium intakes.

[c]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.

[d]Full model consists of case-mix variables, diet, MICS, and three inflammatory markers: CRP, IL-6, and TNF-α.

[e]P value 0.20 to 0.05. Correlation coefficient >0.10.

[f]P value 0.05 to 0.01. Correlation coefficient >0.10.

[g]$P < 0.001$.Correlation coefficient >0.10.

[h]P value 0.01 to 0.001. Correlation coefficient >0.10.

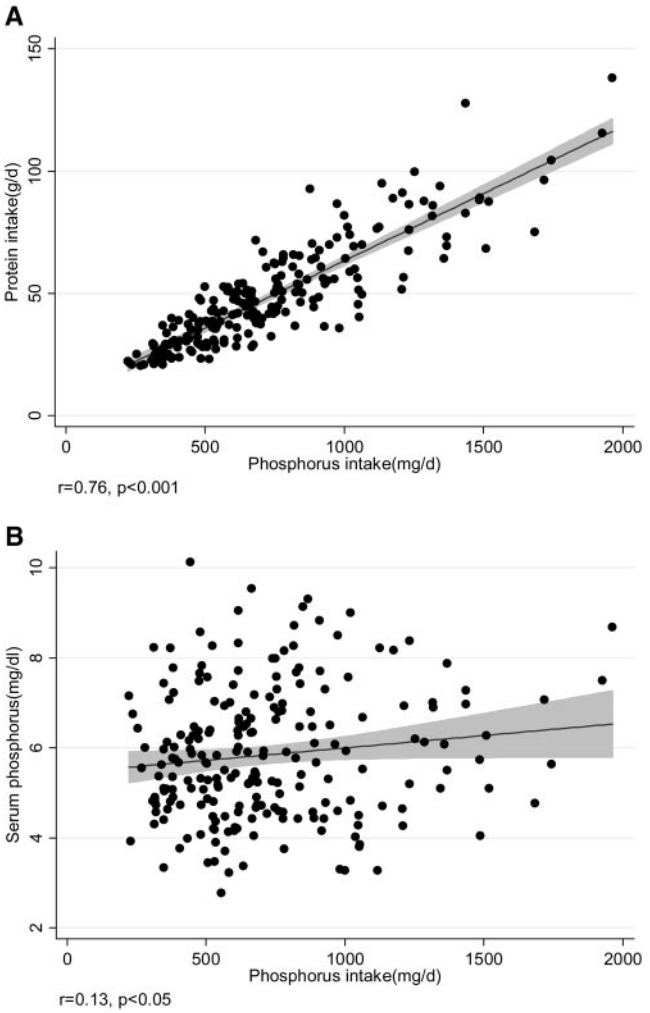

Figure 1. Scatter plots (including the regression line and 95% CI) reflecting the correlations of dietary phosphorus intake with dietary protein intake (upper panel) and serum phosphorus concentration (lower panel).

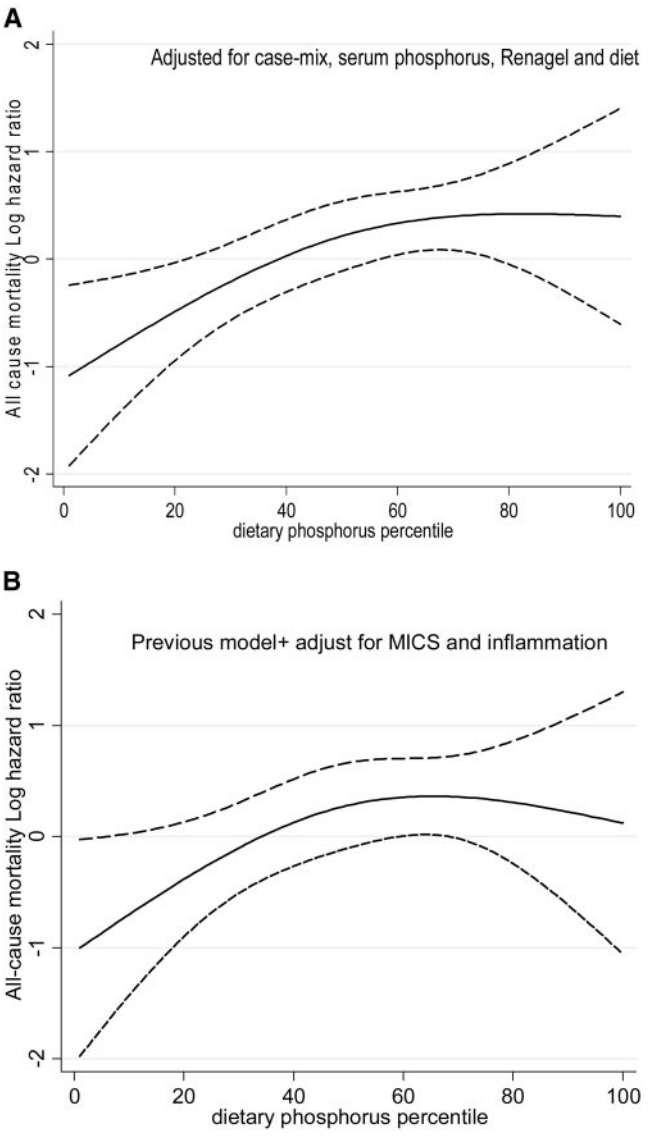

Figure 2. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality predictability (with 95% CI) according to the percentile of the patient's dietary phosphorus intake in the entire cohort of 224 MHD patients over 5 years (from October 2001 to January 2007). Spline 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-α.

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: $r = 0.35$ ($P < 0.001$). 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) [*P*]	Dietary Phosphorus Intake Tertiles			*P* for trend
	Tertile 1 ($n = 74$)	Tertile 2 ($n = 74$)	Tertile 3 ($n = 76$)	
Unadjusted	1.00	1.49 (0.84, 2.64) [0.16]	1.84 (1.07, 3.19) [0.02]	0.02
Case-mix[a] adjusted	1.00	1.66 (0.91, 3.02) [0.09]	1.89 (1.04, 3.43) [0.03]	0.02
Case-mix + diet[b] + 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[c] + inflammation[d] adjusted	1.00	1.88 (0.89, 3.95) [0.09]	2.37 (1.01, 6.32) [0.04]	0.04

[a]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.
[b]Diet includes calorie, protein, and potassium intakes.
[c]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.
[d]Inflammatory markers include CRP, IL-6, and TNF-α.

ments of <12, 12 to <14 (reference), 14 to <16 and ≥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 promineralizing milieu and actual bone tissue (9). Supersaturation of extracellular calcium and phosphorus may accelerate the development of medial wall vascular calcification, leading

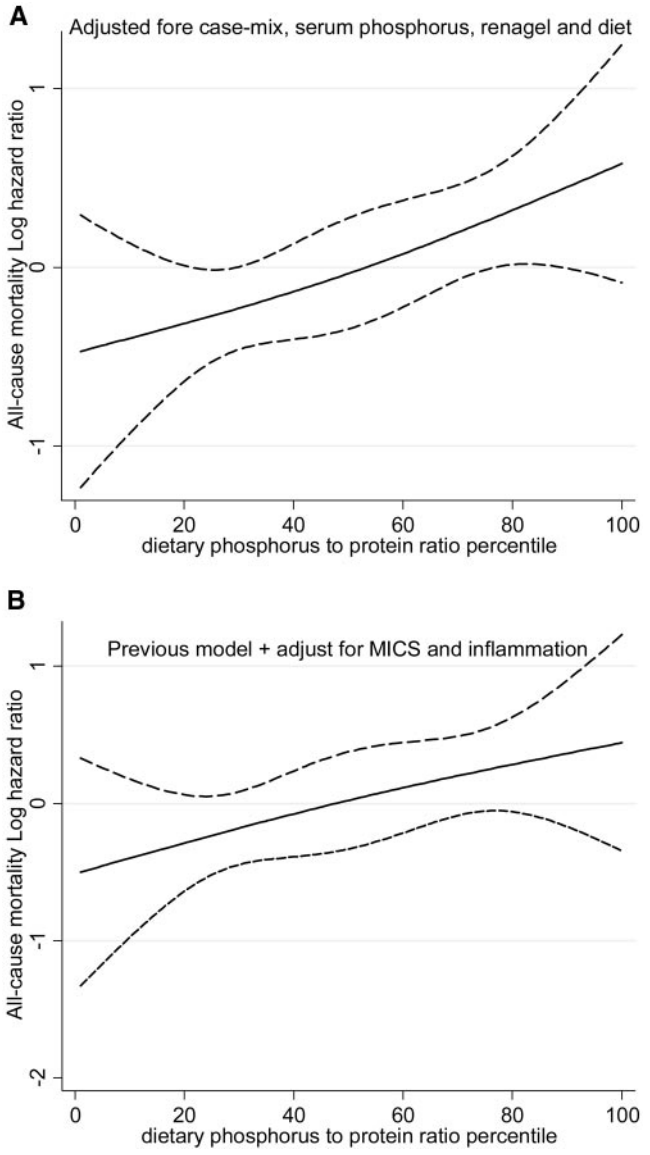

Figure 3. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality predictability (with 95% CI) according to the percentile of the patient's dietary phosphorus to protein ratio in the entire cohort of 224 MHD patients over 5 years (from October 2001 to January 2007). 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-α.

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[a] 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[b] + 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[c] + inflammation[d] 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

[a]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.
[b]Diet includes calorie, protein, and potassium intakes.
[c]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.
[d]Inflammatory markers include CRP, IL-6, and TNF-α.

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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References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296-1305, 2004
2. Berl T, Henrich W: Kidney-heart interactions: Epidemiol-

ogy, pathogenesis, and treatment. *Clin J Am Soc Nephrol* 1: 8-18, 2006
3. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL: Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. *Kidney Int* 71: 31-38, 2007
4. Brenner BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249: F324–F337, 1985
5. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD: Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 70: 771-780, 2006
6. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16: 520-528, 2005
7. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G: Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 112: 2627-2633, 2005
8. Shinaberger CS, Greenland S, Kopple JD, Van Wyck D, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K: Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr* 88: 1511-1518, 2008
9. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15: 2208-2218, 2004
10. Reynolds JT, Homel P, Cantey L, Evans E, Harding P, Gotch F, Wuerth D, Finkelstein S, Levin N, Kliger A, Simon DB, Finkelstein FO: A one-year trial of in-center daily hemodialysis with an emphasis on quality of life. *Blood Purif* 22: 320-328, 2004
11. Nishizawa Y, Jono S, Ishimura E, Shioi A: Hyperphosphatemia and vascular calcification in end-stage renal disease. *J Ren Nutr* 15: 178-182, 2005
12. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA: The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J Am Soc Nephrol* 19: 1092-1105, 2008
13. Uribarri J: Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. *Semin Dial* 20: 295-301, 2007
14. Block G, Uribarri J, Coladonato JA, Fan SL, Cunningham J, Nolan CR, Qunibi WY, Lindberg JS: How should hyperphosphatemia be managed in dialysis patients? *Semin Dial* 15: 315-328, 2002
15. Nolan CR, Qunibi WY: Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis. *Kidney Int Suppl* (95): S13–S20, 2005
16. Sullivan C, Sayre SS, Leon JB, Machekano R, Love TE, Porter D, Marbury M, Sehgal AR: Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: A randomized controlled trial. *JAMA* 301: 629-635, 2009
17. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 73: 391-398, 2008
18. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson A, Kopple JD: Understanding sources of dietary phosphorus in the management of chronic kidney disease patients. *Clin J Am Soc Nephrol* January 21, 2010 [epub ahead of print]
19. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42: S1–S202, 2003
20. Bross R, Zitterkoph J, Pithia J, Benner D, Rambod M, Kovesdy CP, Kopple JD, Kalantar-Zadeh K: Association of serum total iron-binding capacity and its changes over time with nutritional and clinical outcomes in hemodialysis patients. *Am J Nephrol* 29: 571-581, 2009
21. Colman S, Bross R, Benner D, Chow J, Braglia A, Arzaghi J, Dennis J, Martinez L, Baldo DB, Agarwal V, Trundnowski T, Zitterkoph J, Martinez B, Khawar OS, Kalantar-Zadeh K: The Nutritional and Inflammatory Evaluation in Dialysis patients (NIED) study: Overview of the NIED study and the role of dietitians. *J Ren Nutr* 15: 231-243, 2005
22. Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, Kovesdy CP, Kopple JD, Kalantar-Zadeh K: Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: A 5-year prospective cohort study. *Am J Kidney Dis* 53: 298-309, 2009
23. Shantouf R, Rambod M, Kovesdy CP, Ahmadi N, Nissenson AR, Budoff MJ, Kalantar-Zadeh K: Association of serum alkaline phosphatase and coronary artery calcification in hemodialysis patients. *Am J Kidney Dis* 53: A70–A70, Meeting Abstract 190, 2009
24. Bross RCG, Kovesdy C, Oreopoulos A, Noori N, Golden S, Benner D, Kopple J, Kalantar-Zadeh K: Comparing body composition assessment tests in long-term hemodialysis patients *Am J Kidney Dis* 2010, in press
25. Mehrotra R, Kermah D, Fried L, Kalantar-Zadeh K, Khawar O, Norris K, Nissenson A: Chronic peritoneal dialysis in the United States: Declining utilization despite improving outcomes. *J Am Soc Nephrol* 18: 2781-2788, 2007
26. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML: A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 108: 609-613, 2000
27. Nelson EE, Hong CD, Pesce AL, Peterson DW, Singh S, Pollak VE: Anthropometric norms for the dialysis population. *Am J Kidney Dis* 16: 32-37, 1990
28. Williams AJ, McArley A: Body composition, treatment time, and outcome in hemodialysis patients. *J Ren Nutr* 9: 157-162, 1999
29. Kalantar-Zadeh K, Dunne E, Nixon K, Kahn K, Lee GH, Kleiner M, Luft FC: Near infra-red interactance for nutritional assessment of dialysis patients. *Nephrol Dial Transplant* 14: 169-175, 1999
30. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, Block G, Kopple JD: Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr* 83: 202-210, 2006
31. Miller JE, Kovesdy CP, Nissenson AR, Mehrotra R, Streja E, Van Wyck D, Greenland S, Kalantar-Zadeh, K: Association of hemodialysis treatment time and dose with mortality and the role of race and sex. *Am J Kidney Dis* 55: 100-112, 2010
32. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Compar-

ison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347: 1557-1565, 2002
33. Erbagci AB, Tarakcioglu M, Aksoy M, Kocabas R, Nacak M, Aynacioglu AS, Sivrikoz, C: Diagnostic value of CRP and Lp(a) in coronary heart disease. *Acta Cardiol* 57: 197-204, 2002
34. Pecoits-Filho R, Barany P, Lindholm B, Heimburger O, Stenvinkel P: Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol Dial Transplant* 17: 1684-1688, 2002
35. Beutler B, Cerami A: The biology of cachectin/TNF–a primary mediator of the host response. *Annu Rev Immunol* 7: 625-655, 1989
36. Block G, Thompson FE, Hartman AM, Larkin FA, Guire KE: Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. *J Am Diet Assoc* 92: 686-693, 1992
37. Block G, Woods M, Potosky A, Clifford C: Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol* 43: 1327-1335, 1990
38. Mares-Perlman JA, Klein BE, Klein R, Ritter LL, Fisher MR, Freudenheim JL: A diet history questionnaire ranks nutrient intakes in middle-aged and older men and women similarly to multiple food records. *J Nutr* 123: 489-501, 1993
39. Block G, Hartman AM, Naughton D: A reduced dietary questionnaire: development and validation. *Epidemiology* 1: 58-64, 1990
40. Block G, Wakimoto P, Jensen C, Mandel S, Green RR: Validation of a food frequency questionnaire for Hispanics. *Prev Chronic Dis* 3: A77, 2006
41. Day N, McKeown N, Wong M, Welch A, Bingham S: Epidemiological assessment of diet: A comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. *Int J Epidemiol* 30: 309-317, 2001
42. Durrleman S, Simon R: Flexible regression models with cubic splines. *Stat Med* 8: 551-561, 1989
43. Kalantar-Zadeh K, Mehrotra R, Regidor DL, McAllister CJ, Kopple JD: Should serum phosphorus be controlled by decreasing dietary protein in CKD [Abstract]? Presented at the American Society of Nephrology annual conference, San Diego, CA, 2006
44. Kovesdy CP, Anderson JE, Kalantar-Zadeh K: Outcomes associated with serum phosphorus level in males with non-dialysis dependent CKD. *Clin Nephrol* 2010, in press
45. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ: Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. *Am J Kidney Dis* 46: 455-463, 2005
46. Kalantar-Zadeh K, Kopple JD, Deepak S, Block D, Block G: Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. *J Ren Nutr* 12: 17-31, 2002
47. Kooienga L: Phosphorus balance with daily dialysis. *Semin Dial* 20: 342-345, 2007
48. Kovesdy CP, Kalantar-Zadeh K: Bone and mineral disorders in pre-dialysis CKD. *Int Urol Nephrol* 40: 427-440, 2008
49. Slinin Y, Foley RN, Collins AJ: Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol* 16: 1788-1793, 2005
50. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12: 2131-2138, 2001
51. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM: Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 39: 695-701, 2002
52. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342: 1478-1483, 2000
53. Amann K, Ritz E, Wiest G, Klaus G, Mall G: A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. *J Am Soc Nephrol* 4: 1814-1819, 1994
54. Qing DP, Ding H, Vadgama J, Wu YY, Kopple JD: Elevated myocardial cytosolic calcium impairs insulin-like growth factor-1-stimulated protein synthesis in chronic renal failure. *J Am Soc Nephrol* 10: 84-92, 1999
55. Massry SG, Fadda GZ: Chronic renal failure is a state of cellular calcium toxicity. *Am J Kidney Dis* 21: 81-86, 1993
56. Stack AG, Saran R: Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. *Am J Kidney Dis* 40: 1202-1210, 2002
57. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL: Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 96: 1755-1760, 1997
58. Loghman-Adham M: Adaptation to changes in dietary phosphorus intake in health and in renal failure. *J Lab Clin Med* 129: 176-188, 1997
59. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, MacDonald PN, Brown AJ: Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. *J Clin Invest* 97: 2534-2540, 1996
60. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359: 584-592, 2008
61. Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, Grimm, R, Liu J, Louis T, Manning W, Matas A, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li S, Li S, Roberts T, Snyder J, Solid C, Wang C, Weinhandl E, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Johnson R, Sheets D, Forrest B, Berrini D, Constantini E, Everson S, Frederick P, Eggers P, Agodoa L; United States Renal Data System. Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 45(1 Suppl 1): A5–A7, S1–S280, 2005
62. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, Thadhani R, Wolf M: Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 20: 388-396, 2009
63. Kloppenburg WD, Stegeman CA, Hooyschuur M, van der Ven J, de Jong PE, Huisman RM: Assessing dialysis adequacy and dietary intake in the individual hemodialysis patient. *Kidney Int* 55: 1961-1969, 1999
64. Calvo MS, Carpenter TO: The influence of phosphorus on the skelton. In: *Nutritional Aspects of Bone Health*, 5th Ed., edited by New SA, Bonjour JP, Cambridge UK, The Royal Society of Chemistry, 2003, p 253