Prescribed Dietary Phosphate Restriction and Survival among Hemodialysis Patients

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Summary

Background and objectives Hyperphosphatemia is common among hemodialysis patients. Although prescribed dietary phosphate restriction is a recommended therapy, little is known about the long-term effects on survival.

Design, setting, participants, & measurements We conducted a *post hoc* analysis of data from the Hemodialysis Study (n = 1751). Prescribed dietary phosphate was recorded at baseline and annually thereafter. Marginal structural proportional hazard models were fit to estimate the adjusted association between dietary phosphate restriction and mortality in the setting of time-dependent confounding.

Results At baseline, prescribed daily phosphate was restricted to levels ≤870, 871 to 999, 1000, 1001 to 2000 mg, and not restricted in 300, 314, 307, 297, and 533 participants, respectively. More restrictive prescribed dietary phosphate was associated with poorer indices of nutritional status on baseline analyses and a persistently greater need for nutritional supplementation but not longitudinal changes in caloric or protein intake. On marginal structural analysis, there was a stepwise trend toward greater survival with more liberal phosphate prescription, which reached statistical significance among subjects prescribed 1001 to 2000 mg/d and those with no specified phosphate restriction: hazard ratios (95% CIs) 0.73 (0.54 to 0.97) and 0.71 (0.55 to 0.92), respectively. Subgroup analysis suggested a more pronounced survival benefit of liberal dietary phosphate prescription among nonblacks, participants without hyperphosphatemia, and those not receiving activated vitamin D.

Conclusions Prescribed dietary phosphate restriction is not associated with improved survival among prevalent hemodialysis patients, and increased level of restriction may be associated with greater mortality particularly in some subgroups.

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Introduction

Hyperphosphatemia is common among patients with end-stage renal disease. At any time, approximately half of patients on conventional hemodialysis (HD) have serum phosphate above the recommended level (1–4), and nearly all receive additional therapies (beyond HD) to lower phosphate (5). Elevated phosphate contributes to secondary hyperparathyroidism (6,7), elevated FGF23 levels (8,9), and vascular calcification (10–12), which in turn predispose to mortality in this population (13–15). Observational studies have consistently demonstrated a potent and dose-dependent association between higher serum phosphate levels and mortality (1,3,16–18), cardiovascular mortality and morbidity (3,4), and increased rates of hospitalization (14).

Current Kidney Disease Improving Global Outcomes guidelines recommend limiting dietary phosphate intake as a first-line therapy (with or without phosphate binders) for treatment of hyperphosphatemia and secondary hyperparathyroidism (19). However, there has been relatively little study of the effects of long-term dietary phosphate restriction among hemodialysis patients. Prior studies have been of short duration and conducted in highly selected patients and have considered effects only on surrogate end points (*e.g.* serum phosphate levels), not hard outcomes (20–24). Considering that phosphate-rich foods tend to be good sources of dietary protein (25,26) concern exists that long-term phosphate restriction may exacerbate protein energy malnutrition (27–30), which is both common and potently associated with mortality among hemodialysis patients (31–34).

To add clarity, we conducted a *post hoc* analysis of the Hemodialysis (HEMO) Study (35), in which we examined the associations between prescribed dietary phosphate (PDP) intake and mortality. The HEMO Study was selected because it is one of the few large-scale, prospective studies among dialysis patients in which dietary prescription was recorded.

Materials and Methods

Study Design

This study was deemed exempt by the Partners Health Care and Beth Israel Deaconess Medical Cen-

ter Institutional Review Boards. Data for these analyses were taken from the HEMO Study (35) and were made available through the National Institute of Diabetes and Digestive and Kidney Diseases Data Repository. Details of the parent trial have been previously published (36). Briefly, the HEMO study was a randomized controlled trial conducted among 1846 adult patients undergoing thrice-weekly in-center hemodialysis in one of 15 participating centers in the United States and was designed to test the effects of dialysis dose and dialytic membrane flux on clinical outcomes. Patients were enrolled between March 1995 and October 2000, and follow-up continued through December 31, 2001. Notable exclusion criteria included age >80 years, residual urea clearance >1.5 ml/min per 35 L of volume of urea distribution, serum albumin <2.6 g/dl, or serious comorbid medical conditions (end-stage cardiac, pulmonary, or hepatic disease, malignancy, active infection, or unstable angina). We further excluded participants who did not have any dietary prescription recorded at baseline ($n = 31$) and those who did not survive until the start of at-risk time ($n = 64$).

Exposures, Outcomes, and Covariates

The primary exposure of interest was PDP, which was recorded at baseline and annually thereafter. Dietary prescriptions were determined by dietitians from the clinical dialysis centers (not study dietitians), except in certain situations (none of which related to phosphate or metabolic bone disease): normalized protein catabolic rate <1 g/kg/d, caloric intake <28 kcal/kg/d, declining serum albumin, or undesired weight loss. In these instances, HEMO Study dietitians initiated dietary counseling to increase protein intake ≥1 g/kg/d and caloric intake to ≥28 kcal/kg/d); if there was no improvement in 1 month, dietary supplements were then recommended.

The outcome considered was all-cause mortality. Each death was reported by the clinical center staff to HEMO investigators, who confirmed the event through review of hospital records, autopsy report, and a narrative summary of events leading up to death.

Demographic covariates included age, sex, race, and dialysis vintage, which were recorded at baseline (age and vintage were time-updated in marginal structural models). All of the remaining covariates were recorded at baseline; parentheses are used to indicate the frequency with which they were assessed during follow-up. Comorbid diseases of interest included diabetes, arterial disease (ischemic heart disease, cerebral vascular disease, and/or peripheral vascular disease), and congestive heart failure (annually). Dialysis-related covariates included access type (quarterly), equilibrated Kt/V (every 6 weeks), and activated vitamin D use (biannually). Equilibrated Kt/V was calculated using the Daugirdas formula using blood urea nitrogen concentrations before and 20 minutes after dialysis (37). Laboratory covariates of interest included serum albumin, creatinine, phosphate, corrected calcium (38), and parathyroid hormone (biannually).

Anthropometric data included estimated dry weight (every 6 weeks), midarm muscle circumference, and triceps skin-fold thickness (annually). Midarm muscle circumference was calculated as arm circumference − (π*(triceps skinfold thickness)) (both in cm) (39). Other nutritional covariates considered were normalized protein catabolic rate (every 6 weeks), appetite assessment (annually), and use of enteral nutritional supplements (annually); parenteral supplement use was too infrequent to enable meaningful analysis. The normalized protein catabolic rate was calculated as 0.0136*([Kt/V]*[(predialysisBUN − 20 minutes postdialysisBUN)/2] + 0.251 (40).

Measured caloric and protein intake corrected for body weight were also considered as potential covariates (annually). These were assessed by a certified HEMO Study dietitian via two-day (one dialysis and one nondialysis, in most instances on consecutive days) dietary recall. All food, drink, and oral/enteral supplements were included in the dietary recall. The Nutritionist IV (version 3.5) program was used to convert the dietary recall diaries into dietary intake data.

Statistical Analyses

The subjects were considered at-risk beginning on day 90 after randomization (to enable capture of baseline dietary data that was not complete at the time of randomization) and remained at risk until death, transplant, or the end of the study. Baseline variables were considered as the latest observed value preceding the start of at-risk time. In longitudinal and time-updated analyses, time-varying variables were updated to reflect the most proximate value observed before the anniversary of the start of at-risk time.

Continuous and categorical variables were compared across categories of PDP by the Kruskal Wallis and χ^2 tests, respectively. Longitudinal changes in continuous variables were examined by mixed effects linear regression; models contained the main-effects terms for PDP group and time, as well as PDP-by-time interaction terms (which represent the difference in slope over time according to PDP category); these models included a random-effects intercept term for patients to allow for inherent subject-specific differences and to minimize the effects of censoring on observed longitudinal trends. Changes in variables in the year after an alteration in PDP were compared between patients changed to more and less restrictive PDP by the paired t test.

The association between baseline PDP and subsequent survival was examined by Kaplan Meier methods and by unadjusted proportional hazards regression. Because of the number of potential confounders, multivariable adjustment was made by inverse probability of treatment weighting the proportional hazards model rather than by the introduction of individual covariate terms (41). Weights were estimated by a multinomial logistic regression model in which probability of observed PDP was the response variable, and covariates of interest were the predictor variables. Survival models were stratified on clinical center to minimize any potential center effect; the proportionality assumption was tested graphically and by examination of Schoenfeld residuals.

Marginal structural analysis was conducted through estimation of a pooled logistic regression model (42,43). In these analyses, follow-up time was divided into yearly intervals (to coincide with assessment of dietary intake variables); nonstatic covariates were time-updated. Multi-

variable adjustment for all covariates of interest in the original multivariable model was made by application of stabilized probability of exposure-times–stabilized probability of censoring weights as described previously (43–46). Sensitivity analyses were conducted among *a priori* specified subgroups to investigate for potential effect modification of the PDP mortality association on the basis of sex, race, baseline serum phosphate, and baseline activated vitamin D use.

For all survival analyses, we examined for and excluded potential effect modification on the basis of membrane type (high/low flux) and dose assignment (high/standard) through inclusion of two-way PDP-by-treatment group cross product terms. In addition, we introduced treatment group assignment indicator variables into all multivariable models and observed no appreciable effect on estimates (data not shown), indicating that there was no confounding on the basis of membrane type or dose assignment. All of the analyses were completed using STATA, versions 9.0 and 10.0MP (College Station, TX).

Results

Of the 1846 participants randomized in the HEMO study, 1751 had sufficient data for inclusion in the study cohort. At baseline, the mean age was 57.7 ± 14.0 years, 56.5% were female, 63.0% were black, 44.7% were diabetic, mean serum albumin was 3.6 ± 0.4 mg/dl, mean serum phosphate level was 5.8 ± 1.9 mg/dl, mean corrected serum calcium was 9.6 ± 1.0 mg/dl, 54.2% were using activated vitamin D, and 22.2% were using nutritional supplements.

The distribution of PDP at baseline is shown in Figure 1. On the basis of the staccato pattern observed, PDP was characterized by observed quartile with another category used to represent subjects with no prescribed restriction in dietary phosphate.

Predictors and Metabolic Consequences of PDP

Baseline cross-sectional comparison of participant characteristics across categories of PDP is shown in Table 1. In general, participants with more restrictive PDP were more likely to be female, black, and dialyze via a graft. These participants tended to have evidence of poorer nutritional status (lower serum albumin, creatinine, body weight, midarm muscle circumference, and triceps skin-fold thickness; poorer appetite; and greater use of nutritional supplements) despite having greater caloric and protein intake. (To further explore whether differences in consumed calories and protein derived from differences in aggregate macronutrient intake or from lower body weight in more restrictive PDP groups, we alternatively examined protein and caloric intake as indexed to height: there were no significant differences in height-indexed protein intake [g/cm/d] across PDP groups [quartile (Q) 1, 0.38 ± 0.13; Q2, 0.37 ± 0.14; Q3, 0.39 ± 0.14; Q4, 0.40 ± 0.15; no prescription, 0.37 ± 0.13; global P value = 0.06]; height-indexed caloric intake [kcal/cm/d] was significantly different in at least one PDP group [global P value = 0.001], but there was no obvious trend with respect to the severity of prescribed dietary phosphate restriction [Q1, 9.4 ± 3.2; Q2, 9.0 ± 3.3; Q3, 9.1 ± 3.1; Q4, 9.9 ± 3.3; no prescription, 9.0 ± 3.0].)

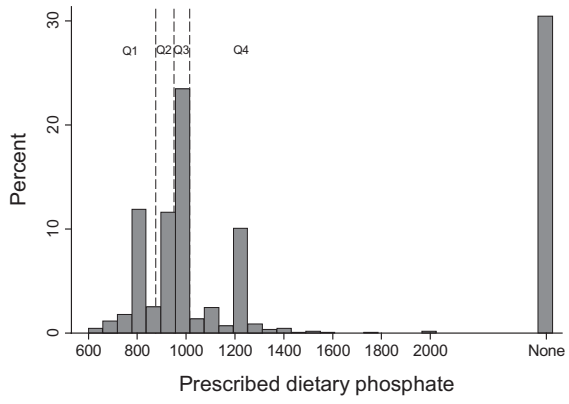

Figure 1. | Distribution of PDP among the study cohort. On the basis of the empiric distribution, PDP was categorized according to observed quartile (indicated by dashed lines), with a separate category used to represent subjects with no prescribed restriction of dietary phosphate.

There was no consistent trend in serum phosphate or corrected calcium levels across PDP categories, but more restrictive PDP tended to cosegregate with high parathyroid hormone levels. Observed phosphate intake tended to track with PDP (except for the group with no specified phosphate prescription), but differences across groups were modest.

Mixed-effect linear models were used to examine post-baseline longitudinal trends in indices of nutritional status and metabolic bone disease control on the basis of baseline PDP. Serum phosphate tended to remain stable over time, and there was no consistent trend in longitudinal changes in serum phosphate across baseline PDP groups: serum phosphate tended to rise more among patients with baseline PDP 1000 and 1001 to 2000, but these differences in slope did not achieve statistical significance, and this trend did not extend to patients with the most permissive PDP (Figure 2A). Parathyroid hormone levels tended to rise overall, more so among patients with more liberal PDP (Figure 2B). There were no consistent trends across PDP groups in longitudinal change in corrected serum calcium, serum albumin, creatinine, normalized protein catabolic rate, body weight, midarm muscle circumference, triceps skin-fold thickness, or intake of calories, protein, or phosphate (data not shown). On time-updated cross-sectional analysis, more restrictive PDP was associated with a greater use of enteral nutritional supplements at all times between years 0 and 3 (Figure 3); data were too scant to provide for meaningful inference at later time points.

Baseline PDP was not necessarily instituted concurrently with study start but instead represented the level of the subjects' prevalent dietary phosphate prescription. Therefore, nutritional and metabolic bone parameters may have already achieved (or neared) steady-state before study start on the basis of prestanding PDP. To further explore the potential effect of PDP on these parameters, we examined their change over 1 year after a change in PDP (Table 2). Change to a more restrictive PDP tended toward greater reduction in serum phosphate, attenuated fall in corrected serum calcium, and more pronounced rise in triceps skin

Table 1. Baseline comparison of demographic, anthropometric, comorbidity, biochemical, and nutritional characteristics across categories of prescribed dietary phosphate

	First Quartile (n = 300)[a]	Second Quartile (n = 314)[a]	Third Quartile (n = 307)[a]	Fourth Quartile (n = 297)[a]	No Phosphate Prescription (n = 533)[a]	Global P Value for Differences among Groups[b]
PDP (mg/d)	800 (600 to 870)	900 (871 to 999)	1000 (1000 to 1000)	1200 (1001 to 2000)	NA	NA
Age (years)	57.3 ± 14.8	59.1 ± 13.4	58.6 ± 13.5	56.8 ± 13.2	57.2 ± 14.6	0.14
Female gender[c]	79.7%	57.0%	54.4%	36.4%	55.7%	<0.001
Black race[c]	69.7%	76.4%	65.8%	54.2%	54.6%	<0.001
Vintage						0.008
≤1 year	24.3%	25.8%	22.5%	21.9%	18.6%	
1 to 2 years	19%	25.2%	22.2%	27.6%	20.6%	
2 to 4 years	23.3%	17.8%	26.1%	25.3%	29.1%	
>4 years	33.3%	31.2%	29.3%	25.3%	31.7%	
Access[c]						<0.001
graft	68.7%	63.7%	65.2%	52.5%	53.9%	
fistula	23.7%	27.7%	28.7%	41.8%	40.5%	
catheter	7.7%	8.6%	6.2%	5.7%	5.6%	
Diabetes	42.7%	47.1%	45.0%	43.1%	45.0%	0.81
Arterial disease[c]	53.3%	58.0%	57.7%	58.3%	52.7%	0.34
CHF[c]	42.7%	40.8%	37.5%	41.4%	35.8%	0.25
EDW (kg)						
female[c]	60.4 ± 12.4	70.6 ± 13.6	68.9 ± 15.2	71.7 ± 15.6	68.0 ± 16.0	<0.001
male[c]	65.2 ± 12.5	71.2 ± 12.2	73.8 ± 15.4	77.0 ± 13.6	70.5 ± 12.8	<0.001
MAMC (cm)						
female[c]	22.9 ± 3.5	24.3 ± 4.3	24.3 ± 4.0	25.3 ± 4.7	23.6 ± 4.7	0.001
male	24.4 ± 3.3	25.6 ± 2.8	25.6 ± 3.9	26.2 ± 3.4	25.2 ± 4.1	0.02
TSF (mm)						
female[c]	18.7 ± 10.0	22.7 ± 13.4	21.7 ± 10.9	21.7 ± 9.2	23.5 ± 15.2	<0.001
male	12.5 ± 8.5	11.3 ± 6.7	13.8 ± 8.7	14.2 ± 8.3	14.4 ± 11.8	0.004
Alb (g/dl)[c]	3.59 ± 0.36	3.61 ± 0.37	3.59 ± 0.33	3.65 ± 0.35	3.67 ± 0.36	0.006
Cr (mg/dl)[c]	9.69 ± 2.84	10.76 ± 3.04	10.44 ± 3.10	10.63 ± 2.80	10.05 ± 2.69	0.001
eKt/V	1.50 ± 0.27	1.49 ± 0.31	1.49 ± 0.31	1.46 ± 0.30	1.49 ± 0.31	0.21
Corrected Ca (mg/dl)	9.62 ± 1.05	9.51 ± 1.02 (n = 313)	9.62 ± 0.95	9.52 ± 0.97	9.70 ± 0.89	0.004
Phos (mg/dl)	5.90 ± 1.99	5.73 ± 1.89 (n = 313)	5.63 ± 1.82	6.01 ± 1.90	5.72 ± 1.88	0.05

Table 1. (Continued)

	First Quartile (n = 300)[a]	Second Quartile (n = 314)[a]	Third Quartile (n = 307)[a]	Fourth Quartile (n = 297)[a]	No Phosphate Prescription (n = 533)[a]	Global P Value for Differences among Groups[b]
PTH (pg/ml)[c]						<0.001
≤150	31.3%	30.6%	42.7%	39.4%	44.3%	
151 to 300	22.0%	20.4%	20.9%	21.9%	21.6%	
>300	38.0%	33.4%	27.7%	30.3%	28.0%	
missing	8.7%	15.6%	8.8%	8.4%	6.2%	
nPCR (g/kg/d)	1.01 ± 0.25	1.02 ± 0.25	1.05 ± 0.24	1.00 ± 0.27	1.04 ± 0.27	0.004
Vitamin D use	53.7% (n = 298)	54.1%	49.0% (n = 306)	58.3%	55.4% (n = 531)	0.23
Nutritional supplement use[c]	27.3%	33.1%	25.7%	15.5%	14.6%	<0.001
Appetite[c]						0.004
very good	21.3%	36.0%	26.4%	32.0%	32.3%	
good	41.0%	32.2%	43.7%	34.7%	37.7%	
fair	26.0%	21.7%	21.2%	25.6%	22.7%	
poor	8.3%	8.9%	6.2%	6.4%	6.4%	
very poor	3.3%	1.3%	2.6%	1.4%	0.9%	
Observed protein intake (g/kg/d)[c]	1.01 ± 0.42 (n = 287)	0.93 ± 0.44 (n = 309)	0.96 ± 0.40 (n = 304)	0.94 ± 0.40 (n = 293)	0.92 ± 0.42 (n = 528)	0.03
Observed caloric intake (kcal/kg/d)[c]	24.9 ± 9.7 (n = 287)	22.1 ± 9.3 (n = 309)	22.6 ± 9.1 (n = 304)	23.5 ± 9.8 (n = 293)	22.2 ± 9.5 (n = 528)	<0.001
Observed phosphate intake (mg/d)	820 ± 380 (n = 288)	810 ± 390 (n = 309)	840 ± 380 (n = 304)	910 ± 430 (n = 293)	830 ± 380 (n = 528)	0.02

The values are expressed as the means ± standard deviation or proportion, except for PDP, which is expressed as median (range). EDW, estimated dry weight; MAMC, midarm muscle circumference; TSF, triceps skin-fold thickness; CHF, congestive heart failure; Alb, serum albumin; Cr, serum creatinine; eKT/V, equilibrated Kt/V; Corrected Ca, corrected serum calcium; Phos, serum phosphate; nPCR, normalized protein catabolic rate; NA, not applicable.

[a]Except where indicated.

[b]P value for global comparisons among groups by Kruskal Wallis and χ^2 tests for continuous and categorical variables, respectively.

[c]$P < 0.05$ for two-way comparison between first quartile and no-prescription groups by Wilcoxon rank sum test.

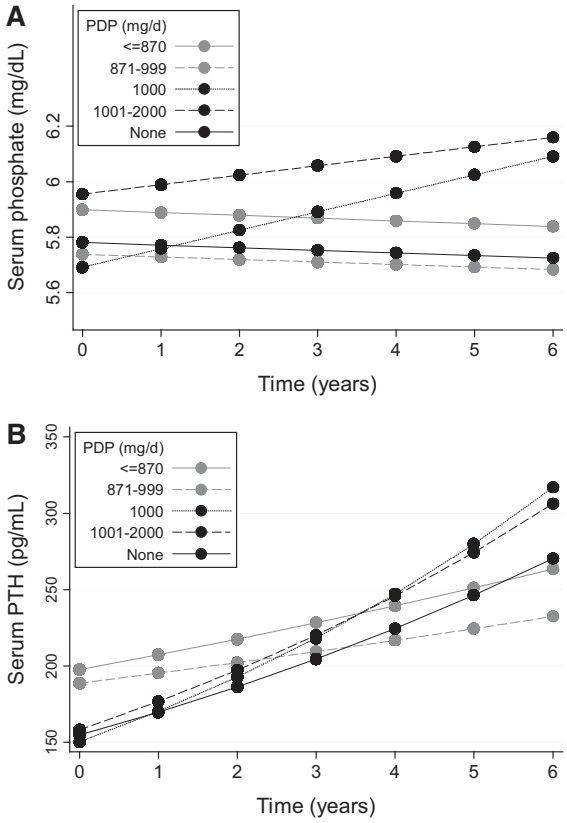

Figure 2. | Longitudinal changes in metabolic bone disease indices according to baseline PDP. (A) Overall, serum phosphate did not change over time ($P = 0.77$); although serum phosphate tended to rise more in quartiles 3 (PDP 1000 mg/d) and 4 (PDP 1001 to 2000 mg/d), these differences were not statistically significant from the referent group (PDP ≤870 mg/d): P for group-by-time interaction 0.12 and 0.38, respectively. (B) Overall, serum parathyroid hormone (PTH) tended to rise over time ($P = 0.03$), and this slope was greater among participants with more permissive PDP: P for group by time interaction 0.01, 0.05, and 0.11 for PDP 1000, 1001 to 2000, and no-restriction groups, respectively (referent PDP ≤870 mg/d). [Because of its highly skewed distribution, PTH was analyzed on the log scale and back transformed for this figure, accounting for the curvilinear appearance.]

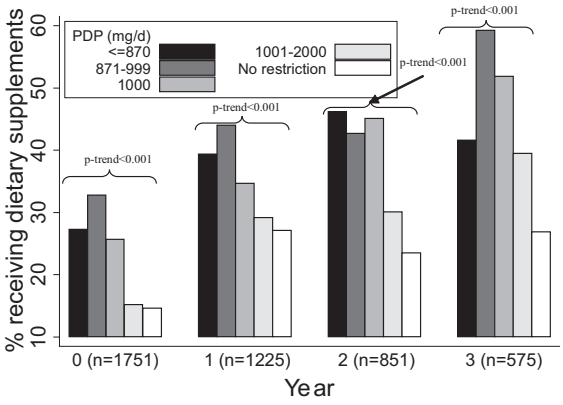

Figure 3. | Use of dietary supplements over time among the categories of PDP. In these analyses, PDP was time updated to reflect the current year's prescription. P trend across PDP groups <0.001 within each year.

fold and body weight but also attenuated rise in caloric intake and greater reduction in midarm muscle circumference than change to a more permissive PDP; none of these trends achieved conventional levels of statistical significance. Of note, 17.1% of participants changed to more restrictive PDP *versus* 11.1% of those changes to more permissive PDP died in the year after the change (P difference was 0.02).

Association between PDP and Survival

Overall, participants contributed a total of 4690 patient years of at-risk time during which 817 died; median follow-up time was 2.3 years. On unadjusted baseline analysis, PDP was not associated with mortality: compared with subjects with the most restrictive PDP, the hazard ratios (HRs) (95% confidence intervals [CIs]) for all-cause mortality were 0.91 (0.71 to 1.17), 0.90 (0.70 to 1.16), 0.92 (0.69 to 1.22), and 0.90 (0.68 to 1.18), for participants with PDP 871 to 999, 1000, 1001 to 2000 mg/d, and no restriction, respectively (Figure 4). Upon multivariable adjustment to correct for baseline differences between groups, the no-restriction group tended toward improved survival (HR (95% CI) 0.86 (0.61 to 1.22)), but this association did not achieve statistical significance. Results were largely unchanged upon further adjustment for protein and caloric intake.

Overall, 29.1% of subjects had a change in PDP after baseline. To minimize exposure misclassification on this basis and to account for potential time-dependent confounding, we used marginal structural analysis to better estimate the association between PDP and survival. On marginal structural analysis, there was a stepwise trend toward greater survival with more liberal PDP (Figure 5A). Compared with the referent group with PDP ≤870 mg/d, the PDP 1001 to 2000 mg/d and no-restriction groups were associated with significant reductions in all-cause mortality: HRs (95% CIs) 0.73 (0.54 to 0.97) and 0.71 (0.55 to 0.92), respectively. Upon further adjustment for caloric and protein intake, the trend was quite similar. Although formal testing for interaction was not possible, the association between more permissive PDP and better survival seemed to be accentuated among nonblacks, participants with serum phosphate <5.5 mg/dl, and those who were not taking vitamin D on prespecified subgroup analyses (Figure 5B).

Discussion

Although phosphate restriction is a recommended first-line therapy for hyperphosphatemia, there has been no prior study of its long-term effects on mortality. Our primary finding was that prescribed dietary phosphate restriction was not associated with survival benefit and in fact may have been harmful.

One potential explanation for our findings is that prescribed phosphate restriction results in unintended reductions in intake of other beneficial macronutrients (29). Consistent with this hypothesis, more restrictive PDP cosegregated with poorer nutritional indices on baseline analysis. We were unable to demonstrate consistent trends

Table 2. Changes in indices of metabolic bone disease control, nutritional status, and body composition in the year after a change in prescribed dietary phosphate

	Change over 1 Year after Conversion to More Restrictive PDP (n = 232)[a]	Change over 1 Year after No Change in PDP (n = 1553)[a]	Change over 1 Year after Conversion to More Liberal PDP (n = 236)[a]	P Value for Difference between Groups with Change to More Restrictive *versus* More Liberal PDP
Serum phosphorus (mg/dl)	−0.3 ± 1.9	0.1 ± 1.9	0.0 ± 1.9	0.11
Corrected calcium (mg/dl)	0.0 ± 0.9	0.1 ± 1.1	−0.1 ± 1.1	0.22
Serum PTH (pg/ml)	20.4 ± 383 (n = 209)	24.3 ± 362 (n = 1474)	31.0 ± 336 (n = 225)	0.76
Serum albumin (g/dl)	−0.1 ± 0.3	0.0 ± 0.3	0.0 ± 0.4	0.11
Serum creatinine (mg/dl)	−0.2 ± 2.0	−0.2 ± 1.9	−0.2 ± 1.9	0.85
Normalized PCR (g/kg/d)	0.0 ± 0.3	0.0 ± 0.3 (n = 1554)	0.0 ± 0.2 (n = 235)	0.94
EDW (kg)	−0.8 ± 4.5	−0.7 ± 4.6 (n = 1554)	−1.3 ± 3.9 (n = 235)	0.24
Triceps skinfold thickness (mm)	0.5 ± 10.8 (n = 216)	−0.7 ± 7.7 (n = 1385)	−1.0 ± 7.6 (n = 220)	0.11
Mid-arm muscle circumference (cm)	−0.5 ± 3.5 (n = 216)	0.0 ± 2.8 (n = 1385)	−0.1 ± 3.0 (n = 220)	0.25
Observed caloric intake (kcal/kg/d)	0.3 ± 10.9 (n = 213)	0.0 ± 10.5 (n = 1403)	1.3 ± 10.0 (n = 214)	0.35
Observed protein intake (g/kg/d)	0.0 ± 0.5 (n = 213)	0.0 ± 0.5 (n = 1403)	0.0 ± 0.5 (n = 214)	0.99

PCR, protein catabolic rate; EDW, estimated dry weight.
[a]Except where indicated.

Figure 4. | Association between PDP and all-cause mortality on baseline analyses. For each model, the referent group is PDP ≤870 mg/d. Multivariable models were adjusted, through application of inverse probability of treatment weights, for age, sex, race, dialysis vintage, access type, eKt/V, diabetes, congestive heart failure, arterial disease, serum albumin, serum creatinine, corrected serum calcium, serum phosphorus, serum parathyroid hormone, vitamin D use, estimated dry weight, triceps skin-fold thickness, midarm muscle circumference, normalized protein catabolic ratio, appetite assessment, and nutritional supplement use (each specified as per Table 1); two-way interaction terms with sex were included for estimated dry weight, triceps skin-fold thickness, and midarm muscle circumference to account for sex-specific differences in the prognostic significance of these variables. In addition, an expanded model (multivariable + intake) was fit that included all of the above covariates as well as observed caloric and protein intake (each normalized to body weight).

in longitudinal changes in nutritional parameters on the basis of baseline PDP overall, perhaps because of participants having already achieved steady-state or because of informative censoring (*e.g.* selective death of subjects with worsening nutritional indices, which would attenuate observable difference among groups). However, changes to more restrictive PDP tended toward association with greater reductions in serum albumin, less robust rise in caloric intake, and replacement of lean body mass (midarm muscle circumference) with fat (triceps skin-fold) than changes to more permissive PDP.

The choice to consider prescribed phosphate restriction (as opposed to measured phosphate intake) as the exposure was premeditated and deliberate; our rationale was three-fold. First, dietary prescription is the point of potential intervention in clinical practice, and its consideration is consistent with intention-to-treat principles. Second, prescribed phosphate intake is less subject to confounding on the basis of comorbid conditions (*i.e.* those that predispose to both cachexia and death) than is measured phosphate intake. Finally, there have been no other studies that have specifically examined dietary phosphate prescription's association with mortality among HD patients. In fact, we are unaware of any study that has examined the association between any component of dietary prescription and survival among HD patients. Whether the prognostic significance of differences in spontaneous dietary intake across individuals is a valid surrogate for the efficacy of within-patient manipulations of dietary prescription remains un-

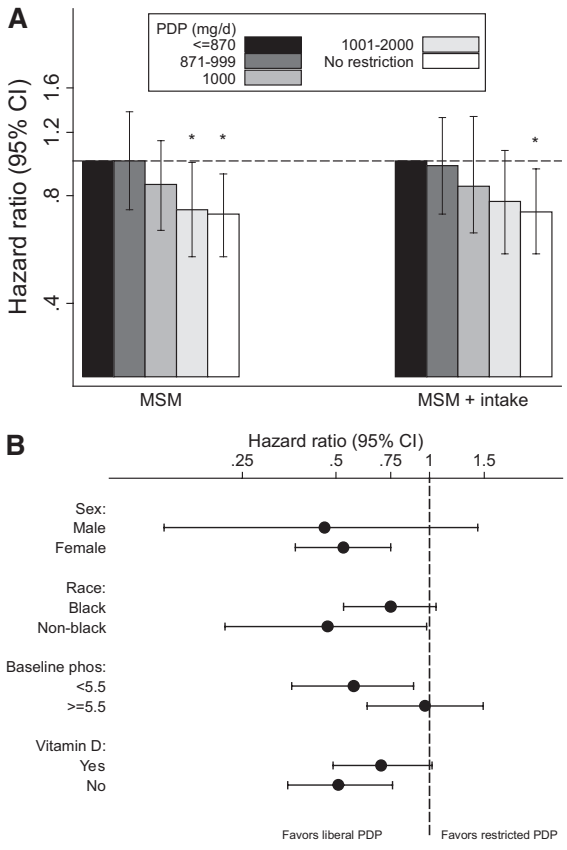

Figure 5. | Associations between PDP and survival using marginal structural models (MSM) to adjust for age, sex, race, dialysis vintage, access type, eKt/V, diabetes, congestive heart failure, arterial disease, serum albumin, serum creatinine, corrected serum calcium, serum phosphorus, serum parathyroid hormone, vitamin D use, estimated dry weight, triceps skin-fold thickness, midarm muscle circumference, normalized protein catabolic ratio, appetite assessment, nutritional supplement use, and two-way sex-interaction terms for estimated dry weight, triceps skin-fold thickness, and midarm muscle circumference using stabilized inverse probability of treatment and censoring weights. (A) Stratum-specific HRs (95% CIs) with and without additional inclusion of protein and caloric intake; the referent for each model is PDP ≤870 mg/d. (B) HRs (95% CIs) for no phosphate restriction (referent PDP ≤870 mg/d) among predefined subgroups (serum phosphate and vitamin D use categories are based on baseline values); stabilized weights were re-estimated within each group.

certain given the potential for residual confounding and issues of patient adherence.

Our findings challenge the long-held belief that prescribed dietary phosphate restriction is beneficial (38,47,48). Recently, Kidney Disease Improving Global Outcomes released guidelines regarding the management of hyperphosphatemia in patients with chronic kidney disease, which includes a recommendation for prescribing dietary phosphate restriction alone or in combination with oral phosphate binders (19). Dietary phosphate restriction was considered a 2d recommendation, which is to say "weak," with "very low" quality of evidence. The guidelines acknowledged the paucity of data to support this accepted practice and highlight the need for further studies. Our results suggest that there is little reason to favor the prescribed withholding of phosphate among hemodialysis patients, particularly in light of recent data suggesting that phosphate binders may improve survival in this population (49).

It bears great emphasis that these data pertain only to dietary phosphate restriction as is currently practiced. Although we are unaware of data regarding the precise nutritional advice given to patients regarding phosphate intake, our clinical experience dictates that most instruction centers on reducing intake of foods with intrinsically high phosphate levels; these foods (*e.g.* dairy, meats, legumes) tend to be nutrient dense. However, there has been growing awareness of the heavy use (and high bioavailability) of inorganic phosphates added to processed foods as preservatives. Given that these foods are not necessarily as nutritionally dense as those with naturally high phosphate content, it stands to reason that curtailment of processed food intake might result in less nutritional impairment and more favorable effects on survival. Dedicated study is warranted.

As with all observational studies, our results may be impacted by residual confounding. Although we attempted to adjust estimates for many factors that are associated with both PDP and survival, we acknowledge the possibility that other confounders exist. Most notably, we lacked data on (and therefore could not adjust for) phosphate binder use, which has recently been associated with improved survival in one observational study (49). However, national registry data from this era suggest that the vast majority of HD patients (80 to 88%) were receiving phosphate binders (50), which mitigates to some degree the likelihood that differences in use existed among PDP groups. Finally, considering that these data were obtained in the context of a clinical trial, it is likely that our participants were healthier than the general hemodialysis population. As such, further work is needed to examine the generalizability of our findings particularly to octagenarians, the obese, and patients with end-stage cardiac, hepatic, and pulmonary disease.

Conclusion

In conclusion, these data suggest that prescribed dietary phosphate restriction, as currently practiced, was not associated with improved survival among prevalent hemodialysis patients and may be associated with greater mortality, particularly in some patient subgroups. Further work is needed to confirm and generalize findings.

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Disclosures

Dr. Brunelli's spouse is an employee at Genzyme. He serves on medical advisory boards to C.B. Fleet Co. and Amgen.

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