Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease?1–4


ABSTRACT

Background: Dietary restrictions to control serum phosphorus, which are routinely recommended to persons with chronic kidney disease, are usually associated with a reduction in protein intake. This may lead to protein-energy wasting and poor survival.

Objective: We aimed to ascertain whether a decline in serum phosphorus and a concomitant decline in protein intake are associated with an increase in the risk of death.

Design: In a 3-y study (7/2001–6/2004) of 30 075 prevalent maintenance hemodialysis (MHD) patients, we examined changes in serum phosphorus and in normalized protein nitrogen appearance (nPNA), a surrogate of dietary protein intake, during the first 6 mo and the subsequent mortality. Four groups of MHD patients were defined on the basis of the direction of the changes in serum phosphorus and nPNA.

Results: Baseline phosphorus had a J-shaped association with mortality, whereas higher baseline nPNA was linearly associated with greater survival. Compared with MHD patients whose serum phosphorus and nPNA both rose over 6 mo, those whose serum phosphorus decreased but whose nPNA increased had greater survival, with a case-mix–adjusted death risk ratio of 0.90 (95% confidence limits: 0.86, 0.95; P < 0.001), whereas those whose phosphorus increased but whose nPNA decreased or those whose phosphorus and nPNA both decreased had worse mortality with a risk ratio of 1.11 (1.05,1.17; P < 0.001) and 1.06 (1.01,1.12; P = 0.02), respectively.

Conclusions: The risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled phosphorus and may lead to greater mortality. Additional studies including randomized controlled trials should examine whether non-dietary control of phosphorus or restriction of nonprotein sources of phosphorus is safer and more effective.


INTRODUCTION

Hyperphosphatemia is a common disorder in persons with advanced chronic kidney disease (CKD) (1, 2). Gradual decline in renal phosphorus clearance during the progression of CKD leads to increases in serum phosphorus concentrations (3). This development may result in additional mineral and bone disorders, such as the inhibition of 1-α-hydroxylation of 25-hydroxyvitamin D via the hyperphosphatemia-induced fibroblast growth factor-23 pathway (4, 5). Both hyperphosphatemia and calcitriol deficiency may result in hyperparathyroidism and renal osteodystrophy (6). Hyperphosphatemia also may contribute to worsening vascular calcification and greater risk of cardiovascular morbidity (7, 8). Indeed, hyperphosphatemia is a known death risk in both the general population (9) and CKD patients (10, 11), including maintenance dialysis patients (12–14), and it may worsen the rate of CKD progression (15–17). Hence, correction and prevention of hyperphosphatemia is a main component of the management of CKD. This goal is usually approached both by administering phosphorus binders and by restricting dietary phosphorus intake (18–20).

Because foods high in protein are a main source of dietary phosphorus, imposing dietary phosphorus restriction is often associated with a reduction in dietary protein intake. The latter can lead to malnutrition and protein-energy wasting (PEW), which are strong risk factors for greater risk of death in maintenance dialysis patients (21, 22). It is thus important to examine the risks or benefits of restricting dietary protein intake to control serum phosphorus concentrations in persons with renal insufficiency who undergo maintenance hemodialysis (MHD) treatment. It is not clear whether a reduction in serum phosphorus by virtue of a concurrent fall in protein intake is associated with better or worse survival. We hypothesized that a decline in serum phosphorus had a J-shaped association with mortality, whereas higher baseline nPNA was linearly associated with greater survival. Compared with MHD patients whose serum phosphorus and nPNA both rose over 6 mo, those whose serum phosphorus decreased but whose nPNA increased had greater survival, with a case-mix–adjusted death risk ratio of 0.90 (95% confidence limits: 0.86, 0.95; P < 0.001), whereas those whose phosphorus increased but whose nPNA decreased or those whose phosphorus and nPNA both decreased had worse mortality with a risk ratio of 1.11 (1.05,1.17; P < 0.001) and 1.06 (1.01,1.12; P = 0.02), respectively.

Conclusions: The risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled phosphorus and may lead to greater mortality. Additional studies including randomized controlled trials should examine whether non-dietary control of phosphorus or restriction of nonprotein sources of phosphorus is safer and more effective.
phosphorus associated with a concomitant decline in protein intake increases the risk of death, whereas controlling serum phosphorus without restricting dietary protein intake is associated with improved survival in established MHD patients.

SUBJECTS AND METHODS

Patients

We examined data from all stage 5 CKD patients who underwent MHD treatment from July 1, 2001, to December 31, 2001, in any of the 560 outpatient dialysis facilities of a large dialysis organization in the United States (DaVita, Inc; El Segundo, CA), and we followed those patients until death, censoring, or June 30, 2004. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, the requirement for written informed consent was waived. The study was approved by the Institutional Review Committees of both Los Angeles Biomedical Research Institute at Harbor–UCLA and DaVita Clinical Research.

Clinical and demographic measures

The study cohort was described previously (14, 21, 23, 24). To minimize measurement variability, all repeated measures for each patient during the baseline calendar quarters (Q3 and Q4 2001) were averaged, and this average was used in all models. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. MHD patients for this study were ≥18 y old and were required to have a dialysis vintage of ≥90 d during ≥1 of the baseline calendar quarters.

The dose of the injectable medications administered in the dialysis clinics, including the 2 vitamin D receptor activators paricalcitol (Zemplar; Abbott, Abbott Park, IL) and calcitriol (Calcijex; Abbott) and recombinant human erythropoietin (rHuEPO, EPOGEN; Amgen, Inc, Thousand Oaks, CA), were calculated for each baseline calendar quarter. The dates of death or censoring events such as kidney transplantation or moving abroad were obtained for all patients who did not survive to June 30, 2004 or who were lost before that date.

A history of diabetes mellitus was available in the database, whereas histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to Medical Evidence Form 2728 (25). The preexisting comorbid conditions were categorized into 10 conditions: 1) ischemic heart disease, 2) congestive heart failure, 3) the patient’s status after cardiac arrest, 4) the patient’s status after myocardial infarction, 5) pericarditis, 6) cardiac dysrhythmia, 7) cerebrovascular events, 8) peripheral vascular disease, 9) chronic obstructive pulmonary disease, and 10) cancer.

Laboratory measures

Blood samples were drawn by using uniform techniques in all of the DaVita dialysis clinics, and they were transported to the DaVita Laboratory (DeLand, FL), typically within 24 h. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum concentrations of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, iron, and total iron–binding capacity (TIBC), were measured monthly. Serum ferritin and intact parathyroid hormone usually were measured quarterly. The conventional urea-kinetic measure known as $Kt/V$ (single pool) (a term in which $K = \text{rate of clearance}$; $t = \text{the amount of time of the session}$; and $V = \text{the area distribution volume after hemolysis}$) was used to estimate the dialysis dose. The normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (21), was assessed monthly as a measure of protein intake. Most blood samples were collected before dialysis; post-dialysis serum urea nitrogen was obtained to calculate urea kinetics.

Statistical analysis

Analysis of variance was used to compare differences across groups. The change in serum phosphorus and protein intake, represented by nPNA, was defined as the difference between the 13-wk (3-mo) averaged values of the baseline calendar quarter (Q2 2001) and its subsequent quarter (Q3 2001). We used Cox proportional hazard models with 3 levels of regression adjustment. The first level comprised a minimally adjusted model that included mortality as the outcome measure, a defined predictor such as baseline serum phosphorus or its change over time, and the entry calendar quarter. The second level comprised case mix–adjusted models that included all of the above plus diabetes mellitus and the 10 preexisting comorbid conditions, history of tobacco smoking, categories of dialysis vintage (<6 mo, 6 mo–2 y, 2–5 y, or ≥5 y), primary insurance (Medicare, Medicaid, private, or other), marital status (married, single, divorced, widowed and other, or unknown), the standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by $Kt/V$ (single pool), the presence or absence of a dialysis catheter, and residual renal function during the entry quarter. The third level comprised malnutrition-inflammation complex syndrome (MICS)–adjusted models that included all of the covariates in the case-mix model and ≤12 surrogates of nutritional status and inflammation: the average doses of rHuEPO, calcitriol, and paricalcitol and ≤9 laboratory variables with known association with clinical outcomes in MHD patients—serum albumin, creatinine, TIBC, ferritin, calcium, and bicarbonate; peripheral white blood cell count; lymphocyte percentage; and hemoglobin. In our view, results from the minimally adjusted models are likely to be underadjusted as a result of the omission of potential confounders, whereas results from the MICS-adjusted models may be overadjusted as a result of the possible inclusion of biological intermediates. We thus prefer to base inferences on the case-mix–adjusted models. Because we cannot be certain which model is the best, however, we have performed 3 levels of adjustments to provide the full spectrum of the results.

In models that examined the mortality predictability of baseline protein intake (nPNA) or its change over time, we did not adjust for other nutritional variables (eg, albumin, creatinine, TIBC, or lymphocyte) that may be in the etiologic pathway. We also excluded $Kt/V$ because of its mathematical correlation with nPNA (21, 26). To examine the combined association of the changes in serum phosphorus and nPNA with death, we added and subtracted the percentiles of the changes in these 2 measures and analyzed the mortality predictability of the created “joint” scores. In an attempt to mitigate the effect of the regression to the mean, all case mix– and MICS-adjusted models that examined the “change” as a mortality predictor were also controlled for the baseline serum phosphorus and nPNA.
Nonlinear associations for continuous mortality predictors were examined with the use of restricted cubic splines (27). To limit the instability of such models at extreme predictor levels, fitting was usually restricted to 95% of the predictor values by excluding the upper and lower 1–2.5% of the values of the given variable.

Missing covariate data (<2% for most laboratory and demographic variables and <3% for any of the 10 comorbid conditions) were imputed by the mean of the existing values, except for ferritin and parathyroid hormone, for which the median was used. All analyses were carried out with STATA software (version 10.0; Stata Corporation, College Station, TX).

### RESULTS

The original 6-mo (July through December 2001) national database of all DaVita MHD patients included 47 156 subjects. After deletion of those patients who did not continue hemodialysis treatment for >90 d by the middle of the each calendar quarter, 41 093 MHD patients remained for analysis. After exclusion of 306 patients without core data such as age or sex, 9644 subjects without electronic records of phosphorus and nPNA measurements in both Q3 and Q4 of 2001, and 1068 patients (0.2%) whose data from the second and first calendar quarters were the same (because the first quarter value may have been

### TABLE 1

Baseline data for 30 152 maintenance hemodialysis patients (July through December 2001), categorized into 4 groups according to the changes in dietary protein intake [represented by normalized protein equivalent of total nitrogen appearance (nPNA)] and serum phosphorus over 2 consecutive calendar quarters divided by the middle of the each calendar quarter.

<table>
<thead>
<tr>
<th>Patients [n (%)]</th>
<th>All patients</th>
<th>9788 (32)</th>
<th>6425 (21)</th>
<th>5322 (18)</th>
<th>8617 (29)</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60.4 ± 15.2‡</td>
<td>60.1 ± 15.4</td>
<td>60.8 ± 15.0</td>
<td>61.5 ± 14.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Women (%)</td>
<td>47</td>
<td>47</td>
<td>45</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Black (%)</td>
<td>36</td>
<td>36</td>
<td>35</td>
<td>37</td>
<td>35</td>
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<tr>
<td>Hispanic (%)</td>
<td>16</td>
<td>15</td>
<td>17</td>
<td>15</td>
<td>17</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>46</td>
<td>48</td>
<td>44</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Dialysis vintage (mo)</td>
<td>61.2 ± 41.4</td>
<td>59.6 ± 40.3</td>
<td>60.7 ± 42.3</td>
<td>63.4 ± 42.6</td>
<td>62.1 ± 41.3</td>
</tr>
<tr>
<td>Medicare as primary insurance (%)</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>Married (%)</td>
<td>42</td>
<td>43</td>
<td>43</td>
<td>41</td>
<td>42</td>
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<tr>
<td>History of comorbid states</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Heart failure (%)</td>
<td>26</td>
<td>27</td>
<td>26</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Ischemic heart disease (%)</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Acute myocardial infarction (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Chronic pulmonary disease (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tobacco smoking (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

1 TIBC, total iron–binding capacity; PTH, parathyroid hormone; WBC, white blood cell; EPO, erythropoietin. nPNA is also known as normalized protein catabolized rate (nPCR).

2 $P$ values among those who received paricalcitol (ANOVA).

3 & represents SD (all such values).
carried forward into the second quarter rather than measured again), the final cohort included 30 075 prevalent MHD patients. Analysis of the follow-up time started from the first day of the calendar quarter in which the patient met inclusion criteria.

As shown in Table 1, patients were divided into 4 categories according to the concurrent fall or rise in their serum phosphorus and nPNA from the first (Q3) to the second (Q4) calendar (2001) quarter. Concordant (same-direction) change in both serum phosphorus and nPNA occurred in 61% of patients, and discordant (opposite-direction) change occurred in the remaining 39%. The baseline serum phosphorus was 0.7 mg/dL lower in those whose serum phosphorus rose, and the baseline nPNA was 0.12–0.14 g·kg\textsuperscript{-1}·d\textsuperscript{-1} lower in those whose nPNA rose, whereas other variables did not differ considerably across the 4 groups. Because baseline serum phosphorus and baseline nPNA were related to subsequent changes in serum phosphorus and nPNA, respectively, they were included in all multivariate models. The association between nPNA and serum phosphorus at baseline, which indicates that patients with higher protein intake tended to have higher serum phosphorus concentrations, is shown in Figure 1.

The mortality rate progressively decreased with increasing concentrations of nPNA up to a threshold value of $1.4$ g·kg\textsuperscript{-1}·d\textsuperscript{-1}, above which there was no further decline (Figure 2A). In contrast, mortality increased below serum phosphorus concentrations of 3.5 mg/dL and above concentrations of 4.5 mg/dL, which led to a J-shaped phenomenon (Figure 2B). In 54% of the MHD patients ($n = 16213$), the 13-wk averaged nPNA concentration rose over 6 mo, whereas in 45% it fell. As shown in Figure 2C, a fall in nPNA was incrementally associated with higher mortality, with a calculated death risk ratio (RR) of 1.18 (95% CL: 1.13, 1.22) for each 0.1 g·kg\textsuperscript{-1}·d\textsuperscript{-1} fall in nPNA. Even though a slight rise in nPNA up to 0.1 g·kg\textsuperscript{-1}·d\textsuperscript{-1} appeared to be associated with greater survival, further increase in nPNA did not exhibit this trend. A rise in the averaged serum phosphorus over 6 mo was noted in 50% of MHD patients ($n = 15112$) and was associated with increased death risk, as depicted in Figure 2D; each 1 mg/dL increase in serum phosphorus was associated with a death RR of 1.13 (95% CL: 1.07, 1.20). Although a slight fall in serum phosphorus showed a trend toward improved survival, an extreme change—whether rise or fall—in serum phosphorus of $>1.0$ mg/dL in 6 mo was associated with an increase in the risk of death.

To evaluate the combined effect of the changes in serum phosphorus and nPNA and their competing risks of death, we examined the sum and the difference of percentile changes in these 2 measures. For this analysis, each patient received a ranking score between 0.01 and 0.99 corresponding to the percentile rank of the change in phosphorus and a second ranking score corresponding to the change in nPNA. The sum of the 2 percentile scores yielded a rank number between $-0.98$ and $+0.98$ (Figure 3A). The difference between the 2 percentile scores (nPNA score minus serum phosphorus score) yielded a rank number between $-0.98$ and $+0.98$ (Figure 3B). Mortality was highest at both extremes of the sum of the percentiles (Figure 3A), but it declined progressively with increasing differences between percentiles.

We then calculated the death RR for the 4 combinations of the changes in serum phosphorus and nPNA. As shown in Table 2 and Figure 4, compared with the simultaneous rise in nPNA and serum phosphorus (reference), the rise in nPNA with a fall in serum phosphorus was associated with a lower risk, whereas the opposite difference (a rise in phosphorus with a fall in nPNA) and a concordant fall in both nPNA and phosphorus had a higher risk. Additional analyses using changes in serum albumin as a surrogate of the nutritional status yielded similar death RR, as shown in Table 2. Additional stratified analyses of the risk of a baseline nPNA of $\geq 1.0$ g·kg\textsuperscript{-1}·d\textsuperscript{-1} (compared with $<1.0$ g·kg\textsuperscript{-1}·d\textsuperscript{-1}) across the increments of serum phosphorus changes are shown in Figure 5; they indicate that, even though a rise in nPNA was somewhat consistently associated with greater survival, the survival advantage was even stronger with simultaneous fall in serum phosphorus or with a drop in phosphorus of a larger magnitude.

**DISCUSSION**

We examined the ability of changes in serum phosphorus and nPNA, a surrogate of dietary protein intake, to predict death in 30 075 MHD patients in a large dialysis organization. We found that a fall in the serum phosphorus concentration should prompt an evaluation of dietary protein intake, and, if nPNA has also fallen during the same period, the patient may be at greater risk of death. Another finding was that lowering serum phosphorus in an MHD patient, if it requires protein restriction, may be effective in achieving the surrogate outcome but may present a risk of death. These findings are most consistent with the hypothesis that controlling serum phosphorus by restricting dietary protein intake may indeed cause more harm than good in MHD patients.

In CKD patients, both disorders of minerals and bone metabolism (MBD) (3, 28) and PEW (22, 29) are common and may be related to exceptionally high mortality (13, 14, 21, 30, 31). Whereas both of these disorders are associated with poor clinical outcomes, these 2 seemingly separate disorders are usually assumed to have distinct and unrelated etiologies and to act through different clinical pathways.

Disorders of minerals and bone metabolism are believed to develop with worsening hyperphosphatemia as a result of an inadequate renal phosphorus clearance, which leads to increased activation of fibroblast growth factor-23 and subsequent inhibition of 1-$\alpha$-hydroxylation of 25-hydroxyvitamin D, secondary hyperparathyroidism, and renal osteodystrophy (1, 4, 5). PEW is
believed to result from inadequate protein intake (32) due to anorexia from the uremic state (33) and other conditions that restrict oral food ingestion in MHD patients, and it is usually associated with chronic inflammation, sarcopenia, hypoalbuminemia, and weight loss (22, 34). Hence, restricting dietary phosphorus intake and increasing dietary protein intake are recommended to most persons with advanced CKD, especially those undergoing MHD.

Nonetheless, the resulting prevention of disorders of minerals and bone metabolism may be at the expense of worsening PEW, and vice versa, because higher protein intake may lead to higher serum phosphorus concentrations (Figure 1). This therapeutic conundrum is encountered frequently during the medical care of MHD patients (35). Many physicians and dietitians are not sure whether they should reinforce dietary restrictions in their MHD patients (restrictions that often include significant protein restriction, which is intended to achieve a serum phosphorus concentration within the recommended target zone) (35), or whether they should liberalize or encourage protein intake to improve nutritional status and prevent hypoalbuminemia (which is associated with elevated risk of death). Indeed, the lower mortality in African American MHD patients may be related to higher protein intake at the expense of worsening hyperphosphatemia (36). Our findings further support the idea that the risk of controlling serum phosphorus by imposing dietary protein restriction may outweigh the benefit. However, reduced protein intake may be the result of the poor appetite that is common in these patients independent of restricting or liberalizing dietary intake (33, 37).

Our finding of a J-shaped association of baseline serum phosphorus concentrations with survival (Figure 2B) is consistent with the findings of several previous studies (12–14). Whereas the greater risk of death observed with higher phosphorus concentrations has biologic support (such as worsening secondary hyperparathyroidism and vascular calcification), the association of a low phosphorus concentration and death risk is more poorly understood. The latter association may be due to the decline in protein intake and worsening PEW in persons with exceptionally low phosphorus. In a recent study (14), low serum phosphorus concentrations showed a much

**FIGURE 2.** Comparisons of the 3-yr mortality predictabilities of the baseline dietary protein intake [represented by the normalized protein equivalent of total nitrogen appearance (nPNA)] and the serum phosphorus concentration and of their changes over time by using Cox regression models in 30,075 maintenance hemodialysis (MHD) patients. The y-axis shows the logarithm of the risk ratio of all-cause mortality over 3 yr of observation, ie, July 2001 through June 2004. The multivariable regression spline models are adjusted for case-mix and MICS. Dashed lines are 95% pointwise confidence levels. A: baseline, 13-wk averaged nPNA. B: baseline, 13-wk averaged serum phosphorus concentration. C: changes in the 13-wk averaged nPNA over 2 consecutive calendar quarters. D: changes in the 13-wk averaged serum phosphorus concentration over 2 consecutive calendar quarters.
stronger unadjusted association with death risk than did hyperphosphatemia, but, after extensive multivariate adjustment, the association weakened. The remaining association may be due to the exceptionally strong effect of PEW, which would act as a residual confounder. Similarly, the U-shaped association in Figure 2D indicates that a rise in serum phosphorus over time is associated with increasing mortality, whereas a major fall in serum phosphorus is also associated with death risk, perhaps because of its link to PEW and low protein intake.

We also found that higher baseline nPNA was associated with lower mortality (Figure 2A), which is consistent with our previous study (21). The nPNA, also known as normal protein catabolic rate (nPCR), is a urea kinetic-based estimate of dietary protein intake in MHD patients when minimal or no residual renal function is assumed (38, 39). However, nPNA is collinear with \( K_t/V \), because both nPNA and \( K_t/V \) are calculated by using the same urea nitrogen concentrations (38, 39). Higher protein intakes may indeed lead to lower mortality by virtue of improving nutritional status; that is why we did not adjust for additional nutritional markers in the models presented in Figure 2. Whereas a moderate rise in nPNA was associated with lower mortality, a more drastic rise in nPNA was associated with a paradoxical trend toward higher mortality, as shown in Figure 2C. The latter association may result from worsening hyperphosphatemia from higher protein intake, which once again may illustrate the countervailing risks and benefits of high protein intake.

### Table 2

Death rate ratios (RRs) and 95% confidence levels (CL) based on Cox regression models across the 4 different combinations of changes in nutritional status and serum phosphorus over 2 consecutive calendar quarters in 30,152 maintenance hemodialysis patients.

<table>
<thead>
<tr>
<th>Combinations of changes</th>
<th>Case mix–adjusted</th>
<th>Case mix– and MICS–adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>RR (95% CL) P</td>
<td>RR (95% CL) P</td>
</tr>
<tr>
<td>Changes in nPNA and phosphorus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both increased</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>nPNA ↑ but phosphorus ↓</td>
<td>0.90 (0.86–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nPNA ↓ but phosphorus ↑</td>
<td>1.11 (1.05–1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both decreased</td>
<td>1.06 (1.01–1.12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Changes in albumin and phosphorus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both increased</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Albumin ↑ but phosphorus ↓</td>
<td>0.91 (0.86–0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>Albumin ↓ but phosphorus ↑</td>
<td>1.28 (1.22–1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both decreased</td>
<td>1.24 (1.18–1.31)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1. MICS, malnutrition-inflammation complex syndrome; nPNA, normalized protein equivalent of total nitrogen appearance. In the upper section, the nutritional status is represented by the dietary protein intake, measured indirectly via nPNA [also known as normalized protein catabolic rate (nPCR) ]; in the lower section, the nutritional status is represented by the serum albumin concentration.
2. Case mix–adjusted models included adjustment for age, sex, diabetes mellitus, standardized mortality ratio, race, dialysis vintage, primary insurance, marital status, dialysis dose, dialysis catheter, and baseline comorbid states.
3. The MICS model covariates include all case-mix covariates plus surrogates of malnutrition and inflammation, as described in Statistical analysis.
The present study was limited insofar as it was observational and record-based, which limited direct inferences to associations among available measurements, rather than to effects of primary variables. In particular, we lacked direct measurements of dietary protein intake and had no data on oral medication, especially phosphorus binders, although data on injectable medications were available and adjusted for. Our analysis was further limited to a 3-y period, although this period is crucial because almost half of MHD patients die within 3 y of dialysis initiation. Analyses over longer periods would have to control for changes in practice patterns. The strengths of the present study included uniform laboratory measurements and the fact that all laboratory data were obtained from a single facility, the large sample size, and the availability of 3-mo averaged laboratory data.

In conclusion, it is plausible that the risk of controlling serum phosphorus by imposing dietary protein restriction may outweigh the benefit of phosphorus control in MHD patients. The persistent association between low protein intake and worse survival may indicate that methods other than restricting protein intake should be sought to restrict dietary phosphorus intake. More attention to nonprotein sources of phosphorus such as food additives or highly processed convenience foods is warranted (18). Because higher protein intake and a concurrent decline in serum phosphorus appear to be associated with the lowest mortality, diligent use of potent phosphorus binders may be helpful, especially if these binders do not lead to an excessive calcium load or pill burden, although binder choice remains a topic of debate (40–43). In any event, our results underscore the need for clinical trials to determine the treatment protocols that offer the greatest survival advantage for MHD patients and to ascertain whether nondietary control of phosphorus or restriction of nonprotein sources of phosphorus is safer and more effective.

The authors’ responsibilities were as follows—CSS: proposed the hypothesis and contributed to the design of the study, collation and analyses of data, and writing and revision of the manuscript; KK-Z (principal investigator on the supporting research grants): contributed to obtaining funding for the study, collation and partial analysis of data, and writing and revision of the manuscript; CPK: contributed to constructing the STATA codes for the cubic splines analyses and to manuscript preparation; JDK and SG: contributed to the analysis of the data and reviewed and approved the final manuscript; and DVW: contributed to the provision of data and final review and approval of the manuscript. KK-Z, CPK, RM, and JDK have received grants, honoraria,
REFERENCES