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Is Controlling Phosphorus by Decreasing Dietary Protein Intake Beneficial or Harmful in Individuals with Chronic Kidney Disease?

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Abstract

Background—Dietary restrictions to control serum phosphorus, recommended routinely to individuals with chronic kidney disease, are usually associated with a reduction in protein intake. This may lead to protein-energy wasting and poor survival. We hypothesized that decline in serum phosphorus with concomitant decline in protein intake is associated with increased death risk.

Methods—In a 3-year (7/2001–6/2004) cohort 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 months and subsequent...
mortality. Four groups of MHD patients were defined based on 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 to MHD patients whose serum phosphorus and nPNA both rose over 6 months, those whose serum phosphorus decreased but nPNA increased had the greatest survival with a case-mix adjusted death risk ratio (RR) of 0.90 (95% confidence limits: 0.86, 0.95, p<0.001), whereas those whose phosphorus increased but nPNA decreased or those whose phosphorus and nPNA both decreased had worse mortality with RR of 1.11 (1.05,1.17) and 1.06 (1.01,1.12), respectively (P <0.001 and 0.02).

**Conclusions**—The risk of controlling serum phosphorus by restricting dietary protein intake may outweigh its benefit and lead to increased mortality. Additional studies including randomized controlled trials need to examine whether non-dietary control of phosphorus or restricting non-protein sources of phosphorus is safer and more effective.

**Keywords**

Hyperphosphatemia; dietary protein intake; protein-energy wasting; hemodialysis; malnutrition-inflammation-complex syndrome (MICS); survival; chronic kidney disease (CKD)

**Introduction**

Hyperphosphatemia is a common problem in individuals with advanced chronic kidney disease (CKD). (1, 2) Gradual decline in renal phosphorus clearance during the progression of CKD leads to increased serum phosphorus concentrations. (3) This development may result in additional mineral and bone disorders, such as the inhibition of 1-alpha hydroxylation of 25-hydroxycholecalciferol via the hyperphosphatemia induced fibroblast growth factor-23 (FGF-23) pathway. (4, 5) Both hyperphosphatemia and calcitriol deficiency may result in hyperparathyroidism and renal osteodystrophy. (6) Hyperphosphatemia may also contribute to worsening vascular calcification and increased risk of cardiovascular morbidity. (7, 8) Indeed, hyperphosphatemia is a known death risk in both the general population (9) and in those with CKD (10, 11) including maintenance dialysis patients, (12–14) and 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 by both administering phosphorus binders and restricting dietary phosphorus intake. (18–20)

Since 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, which are strong risk factors for increased death risk 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 levels in individuals 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 associated with a concomitant decline in protein intake
increases death risk, whereas controlling serum phosphorus without restricting dietary protein intake is associated with improved survival in established MHD patients.

**Methods**

**Patients**

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

**Clinical and Demographic Measures**

The study cohort has been described previously. 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 age 18 years or older and were required to have a dialysis vintage of 90 days or longer during at least half of the baseline calendar quarters.

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

History of diabetes mellitus was available in the database, while histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to Medical Evidence Form 2728. The latter were categorized into ten comorbid conditions: (1) ischemic heart disease, (2) congestive heart failure, (3) status post (s/p) cardiac arrest, (4) s/p 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 using uniform techniques in all of the DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, typically within 24 hrs. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, iron and total iron
binding capacity (TIBC), were measured monthly. Serum ferritin and intact parathyroid hormone (PTH) were usually measured quarterly. The conventional urea-kinetic measure known as Kt/V (single pool) was used to estimate dialysis dose. Normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), was assessed monthly as a measure of protein intake. Most blood samples were collected pre-dialysis; post-dialysis serum urea nitrogen was obtained to calculate urea kinetics.

**Analysis**

Analysis of variance (ANOVA) was used to compare differences across groups. The change in serum phosphorus and protein intake, represented by nPNA (nPCR), was defined as the difference between the 13-week (3-month) averaged values of the baseline calendar quarter (Q2 2001) and its subsequent quarter (Q3 2001). We used Cox proportional-hazard models with three levels of regression adjustment: (I) 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; (II) Case-mix adjusted models that included all of the above plus diabetes mellitus and the 10 pre-existing comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 mos, 6 mos to 2 yrs, 2–5 yrs and ≥5 yrs), primary insurance (Medicare, Medicaid, private and others), 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), presence or absence of a dialysis catheter, and residual renal function during the entry quarter; and (III) Malnutrition-inflammation-complex syndrome (MICS) adjusted models, which included all of the covariates in the case-mix model as well as up to 12 surrogates of nutritional status and inflammation, including the average doses of rHuEPO, calcitriol, and paricalcitol, and up to 9 laboratory variables as surrogates of the nutritional state or inflammation with known association with clinical outcomes in MHD patients: serum albumin, creatinine, TIBC, ferritin, calcium, and bicarbonate; peripheral white blood cell count (WBC); lymphocyte percentage; and hemoglobin. In our view results from the minimally adjusted models are likely to be underadjusted due to omission of potential confounders, while results from the MICS adjusted models may be overadjusted due to possible inclusion of biological intermediates. We thus prefer to base inferences on the case-mix adjusted models. Because we cannot be certain of the best model, however, we have performed three 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 (albumin, creatinine, TIBC and lymphocyte) which may be in the etiologic pathway. We also excluded Kt/V due to its mathematical correlation with nPNA. 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 two measures and analyzed the mortality predictability of the created “joint” scores. In an attempt to mitigate the impact 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 also examined with restricted cubic splines. 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 to 2.5% of the values of the given variable.

Missing covariate data (under 2% for most laboratory and demographic variables and under 3% for any of the 10 comorbid conditions) were imputed by the mean of the existing values, except for ferritin and PTH where the median was used. All analyses were carried out with Stata version 10.0 (Stata Corporation, College Station, Texas).

Results

The original 6-month (July to Dec, 2001) national database of all DaVita MHD patients included 47,156 subjects. After deleting those patients who did not continue hemodialysis treatment for more than 90 days by the middle of each calendar quarter, 41,093 MHD patients remained for analysis. After excluding 306 patients without core data such as age or gender, 9,644 subjects without electronic records of phosphorus and nPNA (nPCR) measurements in both Q3 and Q4 of 2001, and 1,068 patients (0.2%) whose second calendar quarter data were the same as the first quarter (since the first quarter value may have been 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 four categories based on the concurrent fall or rise in their serum phosphorus and nPNA from the first (Q3) to the second (Q4 of 2001) calendar quarter. Concordant (same direction) change in both serum phosphorus and nPNA occurred in 61% of patients, whereas 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 to 0.14 g/kg/day lower in those whose nPNA rose, whereas other variables did not differ considerably across the four groups. Since baseline serum phosphorus and baseline nPNA were related to subsequent changes in serum phosphorus and nPNA, respectively, they were accordingly included in all multivariate models. Figure 1 illustrates the association between nPNA and serum phosphorus at baseline, indicating that patients with higher protein intake tended to have higher serum phosphorus levels.

Figure 2 (upper left panel) shows that mortality rate progressively decreased with increasing levels of nPNA up to a threshold value of approximately 1.4 g/kg/day, above which there was no further decline. By contrast, mortality increased both below serum phosphorus levels of 4.0 mg/dL and above levels of 5.0 g/dL, leading to a J-shaped phenomenon (Figure 2, upper right panel). In 54% of the MHD patients (n=16,213) the 13-week averaged nPNA rose over 6 months, whereas in 45% it fell. As shown in the left lower panel of Figure 2, a fall in nPNA was incrementally associated with higher mortality with a calculated death risk ratio of 1.18 (95% CL: 1.13, 1.22) for each 0.1 g/kg/day fall in nPNA. Even though a slight rise in nPNA up to +0.1 g/kg/day 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
months was noted in 50% of MHD patients (n=15,112) and was associated with increased death risk, as depicted in the right lower panel of Figure 2; each 1 mg/dL increase in serum phosphorus was associated with the death risk ratio of 1.13 (95% CL: 1.07,1.20). Although a slight fall in serum phosphorus showed a trend towards improved survival, absolute change in serum phosphorus > 1.0 mg/dL in 6 months, whether rise or fall, were associated with increased death risk.

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 two 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 two percentile scores yielded a rank score for each patient between 0.02 and 1.98 (Figure 3, left panel). The difference between the two percentile scores (nPNA score minus serum phosphorus score) yielded a rank number between −1 and +1 (Figure 3, right panel). Mortality was highest at both extremes of the sum of the percentiles (left panel of Figure 3) but declined progressively with increasing values of the differences between percentiles.

We then calculated the death-risk ratios for the four combinations of the changes in serum phosphorus and nPNA. As shown in Table 2 and Figure 4, compared to the simultaneous rise in nPNA and serum phosphorus (reference), rise in nPNA with fall in serum phosphorus was associated with lowest risk, whereas the opposite difference (rise in phosphorus but fall in nPNA) and concordant fall in both nPNA and phosphorus had the highest risk. Additional analyses using changes in serum albumin as a surrogate of the nutritional status yielded similar death risk ratios as shown in Table 2. Figure 5 shows additional stratified analyses of the risk of the baseline nPNA ≥ 0.0 g/kg/day (vs.<1.0 g/kg/day) across the increments of serum phosphorus changes, indicating that, even though a drop in nPNA was somewhat consistently associated with a higher risk, the death risk was even stronger with simultaneous fall in serum phosphorus or with larger magnitude of phosphorus drop.

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 and found that a fall in the serum phosphorus should prompt an evaluation of dietary protein intake, and if nPNA has also fallen during the same period, the patient may be at increased 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 presents a possible 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 individuals with CKD, both disorders of minerals and bone metabolism (MBD) (3, 28) and protein-energy wasting (PEW) (22, 29) are common and may be related to exceptionally high mortality in this patient population.(13, 14, 21, 30, 31) While both are associated with
poor clinical outcomes, these two seemingly separate disorders are usually assumed to have
distinct and unrelated etiologies and to act through different clinical pathways.

MBD is believed to develop with worsening hyperphosphatemia as a result of inadequate
renal phosphorus clearance, leading to increased activation of FGF-23 and subsequent
inhibition of 1-alpha hydroxylation of 25-hydroxy vitamin D, secondary hyperparathyroidism
(SHPT) 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 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 individuals with
advanced CKD, especially those undergoing MHD.

Nonetheless, the resulting prevention of MBD may be at the expense of worsening PEW,
and vice versa, since higher protein intake may lead to increased serum phosphorus
concentrations (Figure 1). This therapeutic conundrum is encountered frequently during the
medical care of MHD patients.(35) Many nephrologists and dietitians are not sure whether
they should reinforce dietary restrictions in their MHD patients (which often includes
significant protein restriction, in order to achieve a serum phosphorus within the
recommended target zone)(35) or whether they should liberalize or encourage protein intake
in order to improve nutritional status and prevent hypoalbuminemia (which is associated
with elevated death risk). Indeed, the lower mortality in African American maintenance
dialysis 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 its benefit.
However, reduced protein intake may be the result of poor appetite that happens commonly
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 2, right upper panel) is consistent with several previous studies.(12–14)
Whereas the increased death risk observed with higher phosphorus levels has biologic
support (such as worsening SHPT and vascular calcification), the association of low
phosphorus and death risk is more poorly understood. The latter association may be due to
the decline in protein intake and worsening PEW in individuals with exceptionally low
phosphorus. In a recent study,(14) low serum phosphorus showed a much stronger
unadjusted association with death risk than 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 the right lower panel of Figure 2 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 2, left
upper panel), consistent with our previous study.(21) The nPNA, also known as nPCR, is a
urea kinetic-based estimate of dietary protein intake in MHD patients assuming minimal or
no residual renal function. (38, 39) However, the nPNA is collinear with Kt/V, since both nPNA and Kt/V are calculated using the same urea nitrogen levels. (38, 39) Higher protein intakes may indeed lead to lower mortality by virtue of improving nutritional status; this is why we did not adjust for additional nutritional markers in models presented in Figures 2. While a moderate rise in nPNA was associated with reduced mortality, more drastic rise in nPNA exhibited a paradoxical trend towards higher mortality, as shown in the left lower panel of Figure 2. The latter association may result from worsening hyperphosphatemia from higher protein intake, hence, once again illustrating the countervailing risks and benefits of high protein intake.

Our study is limited insofar as it is observational and record-based, thus limiting 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-year period of the cohort, although this period is crucial because almost half of MHD patients die within 3 years of dialysis initiation. Analyses over longer periods would have to control for changes in practice patterns. The strengths of our study include uniform laboratory measurements with all laboratory data obtained from one single facility, large sample size; and availability of 3-month averaged laboratory data.

In conclusion, it is plausible that the risk of controlling serum phosphorus by imposing dietary protein restriction may outweigh its benefit 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 non-protein sources of phosphorus such as food additives or highly processed convenience foods is warranted. (18) Because increased protein intake with a concurrent decline in serum phosphorus appears to be associated with the lowest mortality, diligent use of potent phosphorus binders may be helpful, especially binders that do not lead to increased 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 which treatment protocols offer the greatest survival advantage for MHD patients and whether non-dietary control of phosphorus or restricting non-protein sources of phosphorus is safer and more effective.

Acknowledgments

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References


Figure 1.
The association between the baseline dietary protein intake, represented by 13-week averaged nPNA (nPCR), and 13-week averaged serum phosphorus in 30,075 MHD patients in the baseline calendar quarter of the cohort. Error bars represent standard deviation. P for trend <0.001
Figure 2.
Comparing the 3-year mortality predictabilities of the baseline dietary protein intake, represented by nPNA (nPCR), and serum phosphorus concentration, as well as their changes over time using Cox regression models in 30,075 MHD patients. The Y-axis shows the logarithm of the risk ratio of all-cause mortality over 3 years of observation, i.e., July 2001 to June 2004. The multivariable regression spline models are adjusted for case-mix and MICS. Dashed lines are 95% pointwise confidence levels. Upper Right Panel: Baseline, 13-week averaged nPNA. Upper Left Panel: Baseline, 13-week averaged serum phosphorus concentration. Lower Right Panel: Changes in the 13-week averaged nPNA over two consecutive calendar quarters. Lower Left Panel: Changes in the 13-week averaged serum phosphorus concentration over two consecutive calendar quarters.
Mortality predictability of the combinations of the percentiles of the changes in dietary protein intake, represented by nPNA (nPCR), and serum phosphorus (PO₄) concentration in 30,075 MHD patients. The Y-axis shows the logarithm of the risk ratio of all-cause mortality over 3 years based on a multivariable Cox regression spline model, adjusted for case-mix and MICS. Dashed lines are 95% pointwise confidence levels. Each patient received a percentile score between 0.01 and 0.99 according to the percentile rank of the change in nPNA or serum phosphorus. The sum of the two percentile scores for each patient resulted in a number between 0.02 and 1.98 (Right Panel), whereas the difference between nPNA and serum phosphorus concentration in each patient resulted in a number between −0.98 and +0.98 (Left Panel).
Figure 4.
The 3-year death risk ratios of the four combinations of the changes in serum phosphorus (PO$_4$) concentration and dietary protein intake, measured via nPNA (nPCR), over two consecutive calendar quarters in 30,075 MHD patients using Cox regression model.
Risk of death for nPNA ≥1.0 (vs. <1.0) g/kg/day

Figure 5.
The 3-year death risk ratio of the baseline dietary protein intake (nPNA or nPCR) ≥1.0 g/kg/day (vs. <1.0 g/kg/day) across the increments of changes in serum phosphorus concentration over two consecutive calendar quarters in 30,075 MHD patients using Cox regression model.
Table 1

Baseline data of 30,152 MHD patients (July through December 2001), categorized into 4 groups based on the changes in dietary protein intake, represented by nPNA (nPCR), and serum phosphorus over two consecutive calendar quarters.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Both increased</th>
<th>nPNA↑ but phosphorus ↓</th>
<th>nPNA↓ but phosphorus ↑</th>
<th>Both decreased</th>
<th>p-value*</th>
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<td>Number of patients (%)</td>
<td>30,152 (100%)</td>
<td>9,788 (32%)</td>
<td>6,425 (21%)</td>
<td>5,322 (18%)</td>
<td>8,617 (29%)</td>
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<td>age (years)</td>
<td>60.7±15.2</td>
<td>60.4±15.2</td>
<td>60.1±15.4</td>
<td>60.8±15.0</td>
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<td>Gender: women%</td>
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<td>47%</td>
<td>45%</td>
<td>47%</td>
<td>48%</td>
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<td>Race: Black%</td>
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<td>36%</td>
<td>35%</td>
<td>37%</td>
<td>35%</td>
<td>0.02</td>
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<tr>
<td>Race: 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>
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<tr>
<td>Dialysis vintage (months)</td>
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<td>59.6±0.3</td>
<td>60.7±42.3</td>
<td>63.4±42.6</td>
<td>62.1±41.3</td>
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<td>69%</td>
<td>69%</td>
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<td>Marital status: married%</td>
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<td>43%</td>
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<td>History of comorbid states:</td>
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<tr>
<td>AIDS</td>
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<td>1%</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>heart failure</td>
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<tr>
<td>PVD</td>
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<tr>
<td>Tobacco smoking</td>
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<td>5%</td>
<td>0.8</td>
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<tr>
<td>Body mass index (kg/m2)</td>
<td>26.2±6.2</td>
<td>26.1±6.3</td>
<td>26.0±6.1</td>
<td>26.2±6.3</td>
<td>26.3±6.2</td>
<td>&lt;0.001</td>
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<td>Kt/V single dose</td>
<td>1.56±0.30</td>
<td>1.53±0.30</td>
<td>1.52±0.30</td>
<td>1.60±0.31</td>
<td>1.59±0.30</td>
<td>&lt;0.001</td>
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<tr>
<td>nPNA (nPCR) [g/kg/day]</td>
<td>1.04±0.24</td>
<td>0.94±0.22</td>
<td>0.96±0.22</td>
<td>1.06±0.24</td>
<td>1.08±0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in nPNA (g/kg/d)</td>
<td>+0.02±0.20</td>
<td>+0.17±0.15</td>
<td>+0.14±0.12</td>
<td>−0.12±0.11</td>
<td>−0.16±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>5.8±1.5</td>
<td>5.4±1.4</td>
<td>6.1±1.5</td>
<td>5.4±1.4</td>
<td>6.1±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in phosphorus (mg/dL)</td>
<td>+0.2±0.8</td>
<td>+1.0±0.8</td>
<td>−0.7±0.7</td>
<td>+0.7±0.6</td>
<td>−0.9±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.83±0.34</td>
<td>3.80±0.36</td>
<td>3.84±0.34</td>
<td>3.84±0.34</td>
<td>3.85±0.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value* for comparison with other groups.
2×2 grouping based on the change in nPNA and phosphorus

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Both increased</th>
<th>nPNA↑ but phosphorus↓</th>
<th>nPNA↓ but phosphorus↑</th>
<th>Both decreased</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in albumin (mg/dL)</td>
<td>+0.01±0.21</td>
<td>+0.06±0.21</td>
<td>+0.01±0.19</td>
<td>-0.01±0.20</td>
<td>-0.04±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>9.7±3.2</td>
<td>9.3±3.1</td>
<td>9.8±3.3</td>
<td>9.8±3.2</td>
<td>9.9±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIBC (mg/dL)</td>
<td>200±41</td>
<td>197±41</td>
<td>201±41</td>
<td>200±40</td>
<td>202±41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ferritin (ng/ml)</td>
<td>691±498</td>
<td>691±495</td>
<td>663±478</td>
<td>714±517</td>
<td>699±505</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>calcium (mg/dL)</td>
<td>9.3±0.7</td>
<td>9.3±0.7</td>
<td>9.3±0.7</td>
<td>9.3±0.7</td>
<td>9.3±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>intact PTH (pg/ml)</td>
<td>346±374</td>
<td>317±341</td>
<td>359±404</td>
<td>351±369</td>
<td>366±386</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>bicarbonate (mg/dL)</td>
<td>21.9±2.6</td>
<td>22.3±2.6</td>
<td>21.8±2.6</td>
<td>22.0±2.6</td>
<td>21.5±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood hemoglobin (g/dL)</td>
<td>12.0±1.1</td>
<td>11.9±1.2</td>
<td>12.1±1.1</td>
<td>11.9±1.2</td>
<td>12.1±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC count (X1,000)</td>
<td>7.1±2.2</td>
<td>7.1±2.1</td>
<td>7.0±2.1</td>
<td>7.2±2.2</td>
<td>7.1±2.2</td>
<td>0.006</td>
</tr>
<tr>
<td>lymphocyte %</td>
<td>21±8</td>
<td>21±8</td>
<td>22±8</td>
<td>22±8</td>
<td>22±8</td>
<td>0.4</td>
</tr>
<tr>
<td>Proportion receiving Paricalcitol</td>
<td>69%</td>
<td>68%</td>
<td>70%</td>
<td>69%</td>
<td>68%</td>
<td>0.05</td>
</tr>
<tr>
<td>Proportion receiving calcitrol</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td>5%</td>
<td>0.03</td>
</tr>
<tr>
<td>Paricalcitol dose (mcg/week)*</td>
<td>14.1±10.8</td>
<td>14.1±10.9</td>
<td>14.1±10.0</td>
<td>14.5±10.0</td>
<td>14.0±10.6</td>
<td>0.09</td>
</tr>
<tr>
<td>EPO dose (units/week)</td>
<td>18.8±16.7</td>
<td>19.9±17.1</td>
<td>19.1±16.5</td>
<td>18.1±16.7</td>
<td>17.8±16.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P-values are based on ANOVA.

Abbreviations: MHD: maintenance hemodialysis, PVD: peripheral vascular disease, PTH: parathyroid hormone, nPNA: normalized protein nitrogen appearance, nPCR: normalized protein catabolic rate, TIBC: total iron binding capacity, EPO: erythropoietin.

* Among those who received paricalcitol.
Table 2

Death rate ratios (RR) and 95% confidence level (CL) based on Cox regression models across the four different combinations of changes in nutritional status and serum phosphorus over two consecutive calendar quarters in 30,152 MHD patients. In the upper section, the nutritional status is represented by the dietary protein intake, measured indirectly via nPNA (nPCR); and in the lower section by serum albumin concentration.

<table>
<thead>
<tr>
<th>Combinations of changes</th>
<th>Case-mix adjusted*</th>
<th></th>
<th>Case-mix &amp; MICS adjusted**</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CL)</td>
<td>P-value</td>
<td>RR (95% CL)</td>
<td>P-value</td>
</tr>
<tr>
<td>Changes in nPNA and phosphorus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>both increased</td>
<td>1.0</td>
<td>n/a</td>
<td>1.0</td>
<td>n/a</td>
</tr>
<tr>
<td>nPNA↑ but phosphorus↓</td>
<td>0.90 (0.86–0.95)</td>
<td>&lt;0.001</td>
<td>0.93 (0.88–0.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>nPNA↓ but phosphorus↑</td>
<td>1.11 (1.05–1.17)</td>
<td>&lt;0.001</td>
<td>1.10 (1.04–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>both decreased</td>
<td>1.06 (1.01–1.12)</td>
<td>0.02</td>
<td>1.09 (1.04–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Changes in albumin and phosphorus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>both increased</td>
<td>1.0</td>
<td>n/a</td>
<td>1.0</td>
<td>n/a</td>
</tr>
<tr>
<td>albumin↑ but phosphorus↓</td>
<td>0.91 (0.86–0.96)</td>
<td>0.002</td>
<td>0.92 (0.87–0.98)</td>
<td>0.008</td>
</tr>
<tr>
<td>albumin↓ but phosphorus↑</td>
<td>1.28 (1.22–1.37)</td>
<td>&lt;0.001</td>
<td>1.28 (1.21–1.35)</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>
<td>1.26 (1.19–1.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* case-mix adjusted models include adjustment for age, gender, diabetes mellitus, standardized mortality ratio, race, vintage, primary insurance, marital status, dialysis dose, dialysis catheter, and baseline comorbid states

** Malnutrition-inflammation complex syndrome (MICS) model covariates include all case-mix covariates plus surrogates of malnutrition and inflammation (see text).