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Low Protein Nitrogen Appearance as a Surrogate of Low Dietary Protein Intake Is Associated with Higher All-Cause Mortality in Maintenance Hemodialysis Patients[1–3]

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Abstract

To determine the association between all-cause mortality and dietary protein intake in patients with chronic kidney disease, we performed a large-scale, 8-y prospective cohort study in 98,489 maintenance hemodialysis patients from a multicenter dialysis care provider. Compared with the reference level (60 to <70 g/d), low protein nitrogen appearance (PNA) levels [<30 g/d, HR: 1.40 (95% CI: 1.30, 1.50); 30 to <40 g/d, HR: 1.33 (95% CI: 1.28, 1.39)] was associated with higher all-cause mortality, and high PNA levels [≥110 g/d, HR: 0.92 (95% CI: 0.88, 0.97); 100 to <110 g/d, HR: 0.87 (95% CI: 0.82, 0.91)] were associated with lower all-cause mortality in all analyses. This association was also found in subanalyses performed among racial and hypoalbuminemic groups. Hence, using PNA as a surrogate for protein intake, a low daily dietary protein intake is associated with increased risk of death in all hemodialysis patients. Whether the association between dietary protein intake and survival is causal or a consequence of anorexia secondary to protein-energy-wasting/inflammation or other factors should be explored in interventional trials. J. Nutr. 143: 1084–1092, 2013.

Introduction

In individuals with chronic renal failure, decreased dietary protein intake may be associated with poor survival (1,2). The malnutrition-inflammation complex syndrome (MICS)[14] is related to decreased appetite (3), inadequate protein and energy intake (4), and hypercatabolism as well as other causes such as acidemia and antianabolic states (4,5). Thus, maintenance hemodialysis (MHD) patients presenting with this constellation of features may suffer from protein-energy malnutrition, which may provoke, exacerbate, or be enhanced by inflammation (6). MICS and concomitant inadequate protein-energy intake have been implicated as possible causes of adverse clinical outcomes in maintenance dialysis patients.

Because MHD patients excrete little or no urine, the change in serum urea nitrogen between and during hemodialysis sessions becomes a reliable indicator of dietary nitrogen intake, provided the patient is in a steady state. Although indirect, this measure of protein intake is referred to as the urea kinetic-based protein nitrogen appearance (PNA) or the protein catabolic rate, which is usually normalized for body weight [normalized protein nitrogen appearance (nPNA)]. Although the association between nPNA and survival has been examined at baseline and time-dependent PNA levels measured quarterly (1), to more fully understand the direct relationships and potential confounders that can better inform more precise prospective studies, there

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[3] Supplemental Figure 1 and Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[14] Abbreviations used: CKD, chronic kidney disease; Kt/V, dialysis dose; LDO, large dialysis organization; MHD, maintenance hemodialysis; MICS, malnutrition-inflammation complex syndrome; nPNA, normalized protein nitrogen appearance; PNA, protein nitrogen appearance; SUN, serum urea nitrogen; TIBC, total iron-binding capacity; UKM, urea kinetic modeling; WBC, white blood cell.
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remains a need for additonal observational studies to examine the effects of PNA over time on mortality in a time-averaged analysis with or without multivariate adjustment for other elements of MICS, which also may vary over time.

Hypoalbuminemia is strongly associated with increased mortality in MHD and chronic peritoneal dialysis patients (7,8). Evidence indicates that both malnutrition and inflammation are major causes of severe hypoalbuminemia in MHD patients (4). Nutritional support has been shown to improve hypoalbuminemia and clinical outcome in patients with chronic kidney disease (CKD) (5,7,9,10). Indeed, several randomized and nonrandomized prospective trials in hypoalbuminemic MHD patients indicate that nutritional support may increase serum albumin (11), but it has not affected hard outcomes (12–14). Increased dietary protein in hypoalbuminemic patients thus might confer a survival advantage compared with those patients with lower dietary protein intakes. Moreover, race is an effect modifier in association between clinical outcomes and different nutritional markers in MHD patients, and it might explain the survival advantage of African American MHD patients compared with their white counterparts (15,16).

In a large, prospective cohort study in MHD patients from a multicenter dialysis care provider, we examined the hypothesis that survival would increase across the higher PNA groups independent of case-mix characteristics, comorbidity, dialysis dose, and other covariates. We also hypothesized that increases in PNA in hypoalbuminemic MHD patients would be associated with an improvement in survival in the same linear fashion, as would increased protein intake in blacks, whites, and Hispanics.

Participants and Methods

Patients. We examined the national database of large dialysis organization (LDOs) in the United States. Database creation has been described elsewhere (17). An 8-y cohort was created by using data collected from patients with stage 5 CKD undergoing MHD treatment between July 1, 2001, and September 30, 2009, among 966 LDO outpatient dialysis facilities in the US. The study was approved by the institutional review committees of Harbor-UCLA Medical Center and DaVita, Inc.

Patients' postdialysis weight from each treatment was averaged over each 13-wk quarter, and their BMI (weight in kg, divided by height squared in m^2) was calculated. Age was estimated by using date of birth and the first day of the entry quarter. Three race/ethnic groups were defined: whites (including non-Hispanic whites and Middle Easterners), self-described blacks (including African Americans and sub-Saharan Africans), and Hispanics.

History of tobacco smoking and preexisting cardiovascular and noncardiovascular comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the U.S. Renal Data System (18) and categorized into 5 comorbid conditions: *1*) congestive heart failure, *2*) peripheral vascular disease, *3*) inability to ambulate, *4*) hypertension, and *5*) alcohol dependency. Cohort time included the number of days that a patient participated in the cohort and was a number between 1 and 2920 d. Dialysis vintage was defined as the interval of time between the first day of dialysis treatment and the first day that the patient entered the cohort. Four categories of vintage were created: *1*) the first 6 mo, *2*) between 6 and 24 mo, *3*) between 2 and 5 y, and *4*) >5 y on dialysis. The entry quarter was defined as the first quarter in which the patient's dialysis vintage was >3 mo for at least half the duration of the quarter as in our previous studies (15,16,19–24).

Laboratory methods. All laboratory measurements were performed by LDO Laboratories in Deland, FL, by using standardized and automated methods. For each laboratory measure, the average of all available values obtained within any given calendar quarter were used in all analyses. The nPNA and dialysis dose (Kt/V) (single pool) were calculated by using urea kinetic modeling (UKM) formulas. The commonly used alternate formulas, representing simplified UKM equations, are as follows (25,26):

$$Kt/V = -\ln(R - 0.008 \times t) + [(4 - 3.5 \text{æ} R) \times UF/W)]$$

$$nPNA = C_0/[25.8 + (1.15/[Kt/V]) + 56.4/(Kt/V)] + 0.168$$

where R is the ratio of postdialysis to predialysis serum urea nitrogen (SUN), t is time of dialysis in hours, UF is the amount of ultrafiltration (in L), W is the postdialysis weight (in kg), and C_0 is the predialysis concentration of SUN. The nPNA unit is grams of net protein degradation per kilogram of body weight per day [g/(kg · d)]. However, the UKM formulas used in DaVita laboratories to calculate Kt/V and nPNA are more complex, and computational software programs are routinely used. In general, in all of the foregoing calculations, the PNA is a function of the urea nitrogen appearance [i.e., the urea generation rate (G)] and the calculated total body water (TBW), both of which are estimated during the UKM computations:

$$PNA = (5.423 \times G)/(0.001 \times TBW) + 0.168$$

All calculated PNA values are normalized (nPNA) to take into account the body weight based on the postdialysis dry weight of the patients, and other anthropometric and demographic variables entered into the UKM software program.

Blood samples were collected predialysis with the exception of the postdialysis SUN to calculate urea kinetics. Blood samples were drawn by using uniform techniques in all LDO dialysis clinics across the nation and were transported to the LDO Laboratory in Deland, FL. Most laboratory values, including complete blood cell counts and serum concentrations of urea nitrogen, albumin, creatinine, ferritin, and total iron-binding capacity (TIBC), were measured monthly. Both nPNA and Kt/V were estimated monthly. Serum ferritin was measured quarterly. Hemoglobin was measured weekly to biweekly in most patients. Patients with missing PNA values in all 33 quarters were excluded from the analysis.

The following 10 time-varying (quarterly changing) laboratory variables with up to 33 repeated measures per patient over the 8-y cohort time were also included in the time-averaged models as potential confounders: *1*) serum ferritin, *2*) serum albumin, *3*) serum TIBC, *4*) serum creatinine, *5*) serum phosphorus, *6*) serum calcium, *7*) serum bicarbonate, *8*) blood hemoglobin, *9*) peripheral white blood cell count (WBC), and *10*) lymphocyte percentage. These measures are related to MICS and have been associated in other studies with important outcomes in dialysis patients as described elsewhere (15,16,19–24).

Statistical and epidemiologic methods. Cox proportional hazard regressions with time-averaged measures were examined to determine whether 8-y survival rates were associated with PNA. Variables were averaged across quarters to form a cohort including all existing MHD patients of the first quarter (quarter 1) and all new MHD patients of subsequent quarters (quarters 2–33). Sixteen quarterly data sets were merged using unique patient identifiers, and a baseline value was created for each measure by left-truncating the first available value of the entry quarter for each patient. Models were analyzed within 10 categories of PNA: <30 g/d to ≥110 g/d, with eight 10-g/d incremental categories in between. The reference PNA category for all Cox analyses was ≥60 and <70 g/d. This category was chosen for its clinical relevance according to Kidney Disease Outcomes Quality Initiative recommendations and because it had the highest number of death cases.

Three types of models were examined on the basis of the level of multivariate adjustment: *1*) unadjusted models included only PNA category, entry quarter, and mortality data; *2*) case-mix–adjusted models included age, gender, race/ethnicity, diabetes mellitus, vintage category, primary insurance (Medicare, Medicaid, private, other), marital status (married, single, divorced, widowed, other), Kt/V (single pool), residual renal function at entry quarter (i.e., urinary urea clearance), iron saturation ratio, serum intact parathyroid hormone, and alkaline phosphatase levels history of smoking, and 5 preexisting comorbid conditions (see above); and *3*) case-mix– and MICS-adjusted models

TABLE 1 Demographic, clinical, and laboratory characteristics of MHD patients across base-quarter levels of protein catabolic rate (PNA)[1]

		Protein catabolic rate (PNA), *g/d*									
	Total (*n* = 98,489)	<30 (*n* = 2072)	30 to <40 (*n* = 6649)	40 to <50 (*n* = 12,356)	50 to <60 (*n* = 16,145)	60 to <70 (*n* = 16,503)	70 to <80 (*n* = 13,751)	80 to <90 (*n* = 10,494)	90 to <100 (*n* = 7393)	100 to <110 (*n* = 4737)	≥110 (*n* = 8389)
Age, *y*	64 ± 15	68 ± 16	69 ± 16	67 ± 16	66 ± 15.4	65 ± 15	64 ± 15	63 ± 14	62 ± 14	61 ± 14	58 ± 13
Gender, *% female*	45	79	68	58	49	43	39	37	35	64	31
Diabetes mellitus, *%*	59	43	49	53	55	59	61	64	65	66	69
Mortality, *%*	56	75	70	64	59	55	52	50	48	45	41
Race, *%*											
White	42	45	43	43	42	41	41	41	41	42	44
Asian	3	4	4	4	3	3	3	3	2	2	2
Black	32	31	32	32	32	32	31	62	32	33	35
Hispanic	15	11	13	15	15	17	17	17	17	17	13
Other	7	7	7	6	7	7	7	7	7	7	6
Vintage (time on dialysis),%											
0–<6 mo	14	27	21	16	14	12	11	11	11	11	11
6–<24 mo	32	37	36	36	34	32	30	29	28	28	28
2–<5 y	34	24	29	32	33	35	36	37	37	37	37
≥5 y	20	13	14	16	19	21	22	23	24	24	24
Primary insurance, *%*											
Medicare	62	61	65	63	63	63	62	61	61	61	58
Medicaid	6	7	6	7	6	6	6	5	5	5	5
Other	24	19	19	21	22	23	24	26	26	26	30
Marital status, *%*											
Married	39	28	31	33	36	39	41	43	42	43	43
Divorced	7	6	6	6	7	7	7	7	7	7	8
Single	22	22	21	22	22	22	22	22	23	23	25
Widowed	14	26	23	18	16	13	12	10	10	9	6
Kt/V (dialysis dose)	1.53 ± 0.35	1.54 ± 0.35	1.54 ± 0.35	1.53 ± 0.34	1.53 ± 0.34	1.52 ± 0.34	1.52 ± 0.34	1.52 ± 0.34	1.51 ± 0.35	1.52 ± 0.38	1.53 ± 0.43
KRU, *%*	0.62 ± 1.63	0.30 ± 1.19	0.34 ± 1.25	0.37 ± 1.69	0.43 ± 1.22	0.49 ± 1.35	0.61 ± 1.56	0.72 ± 1.66	0.81 ± 1.79	0.97 ± 2.05	1.49 ± 2.82
Comorbid states, *%*											
Hypertension	80	76	78	78	79	79	81	81	80	81	82
Alcoholism	1	3	2	2	1	1	1	1	1	< 1	< 1
Heart failure	29	29	30	29	29	28	28	29	29	28	29
Inability to ambulate	3	6	5	4	3	3	3	2	3	2	3
Tobacco use	5	7	6	6	5	5	4	4	4	4	4
PVD	12	14	14	13	12	12	12	11	11	10	10
Serum concentrations											
Albumin, *g/dL*	3.7 ± 0.46	3.1 ± 0.62	3.4 ± 0.54	3.5 ± 0.49	3.6 ± 0.45	3.7 ± 0.42	3.8 ± 0.40	3.8 ± 0.38	3.8 ± 0.38	3.8 ± 0.36	3.8 ± 0.35
Creatinine, *mg/dL*	7.9 ± 3.2	5.0 ± 2.3	5.8 ± 2.4	6.6 ± 2.6	7.3 ± 2.8	7.9 ± 3.0	8.4 ± 3.1	8.8 ± 3.2	9.1 ± 3.3	9.4 ± 3.5	9.7 ± 3.6
TIBC, *mg/dL*	209 ± 46	167 ± 54	188 ± 49	198 ± 47	205 ± 45	210 ± 43	213 ± 43	216 ± 42	219 ± 42	222 ± 42	226 ± 43
Carbon dioxide, *mg/dL*	22 ± 3.0	24 ± 3.4	23 ± 3.1	23 ± 3.0	23 ± 2.9	22 ± 2.9	22. ± 2.9	22 ± 2.9	22. ± 2.9	22 ± 2.9	21 ± 2.8
Calcium, *mg/dL*	9.2 ± 0.70	8.9 ± 0.81	9.1 ± 0.73	9.3 ± 0.72	9.2 ± 0.69	9.2 ± 0.69	9.2 ± 0.69	9.2 ± 0.68	9.2 ± 0.69	9.2 ± 0.70	9.2 ± 0.70

(Continued)

TABLE 1 *Continued*

	Total	Protein catabolic rate (PNA), *g/d*								
		<30	30 to <40	40 to <50	50 to <60	60 to <70	70 to <80	80 to <90	90 to <100	100 to <110	≥110
	(*n* = 98,489)	(*n* = 2072)	(*n* = 6649)	(*n* = 12,356)	(*n* = 16,145)	(*n* = 16,503)	(*n* = 13,751)	(*n* = 10,494)	(*n* = 7393)	(*n* = 4737)	(*n* = 8389)
Phosphorus, *mg/dL*	5.6 ± 1.5	4.5 ± 1.3	4.8 ± 1.3	5.1 ± 1.3	5.3 ± 1.4	5.5 ± 1.4	5.7 ± 1.4	5.6 ± 1.4	6.0 ± 1.5	6.1 ± 1.5	6.4 ± 1.5
Alkaline phosphatase, *U/L*	118 ± 87	140 ± 110	131 ± 109	126 ± 95	123 ± 96	119 ± 87	115 ± 77	112 ± 73	109 ± 69	110 ± 80	106 ± 66
Intact PTH, *pg/mL*	343 ± 357	259 ± 299	284 ± 326	303 ± 332	322 ± 339	336 ± 363	340 ± 337	362 ± 381	369 ± 357	383 ± 374	423 ± 400
Protein catabolic rate, *g/d*	0.95 ± 0.26	0.52 ± 0.12	0.66 ± 0.13	0.76 ± 0.14	0.85 ± 0.16	0.93 ± 0.17	1.01 ± 0.19	1.07 ± 0.20	1.12 ± 0.21	1.17 ± 0.22	1.27 ± 0.27
Blood hemoglobin, *g/dL*	12.1 ± 1.4	11.7 ± 1.5	11.9 ± 1.	12.0 ± 1.	12.0 ± 1.4	12.1 ± 1.4	12.2 ± 1.3	12.1 ± 1.3	12.2 ± 1.3	12.2 ± 1.3	12.1 ± 1.3
WBCs, $x10^3/\mu L$	7.45 ± 2.5	7.60 ± 2.8	7.52 ± 2.7	7.44 ± 2.6	7.39 ± 2.5	7.37 ± 2.4	7.40 ± 2.5	7.41 ± 2.3	7.44 ± 2.3	7.57 ± 2.5	7.66 ± 2.3
Lymphocytes, *% of total WBCs*	20.5 ± 7.8	20.1 ± 8.6	19.8 ± 8.0	20.0 ± 7.8	20.3 ± 7.9	20.5 ± 7.8	20.7 ± 7.8	20.8 ± 7.7	20.8 ± 7.7	21.0 ± 7.7	20.7 ± 7.5
ISAT, *%*	28.3 ± 11.5	30.5 ± 14.2	27.4 ± 12.0	27.6 ± 11.8	27.6 ± 11.5	28.1 ± 11.3	28.8 ± 11.7	28.8 ± 11.4	28.9 ± 11.3	29.0 ± 10.8	28.6 ± 10.9
BMI, kg/m^2	26.8 ± 6.96	19.8 ± 4.09	21.6 ± 4.33	23.0 ± 4.52	24.3 ± 4.55	25.7 ± 4.95	27.0 ± 5.15	28.6 ± 5.71	30.1 ± 6.35	31.6 ± 6.46	36.3 ± 10.1

[1] Values are percentages or means ± SDs, as appropriate; *n* = 98,489. ISAT, iron saturation ratio; KRU, residual renal urea clearance; KtV, dialysis dose; MHD, maintenance hemodialysis; PNA, protein nitrogen appearance; PTH, parathyroid hormone; PVD, peripheral vascular disease; TIBC, total iron-binding capacity; WBC, white blood cell.

included all of the aforementioned covariates as well as BMI plus the 10 MICS-associated laboratory values (serum albumin, TIBC, ferritin, creatinine, calcium, phosphorus, bicarbonate, blood hemoglobin, WBCs, and lymphocyte percentage).

Standard descriptive statistics were also performed to obtain baseline demographic, clinical, and laboratory characteristics stratified by PNA category, and multiple linear regression models were fitted to construct Pearson's and partial correlations. To obtain ORs and 95% CIs for PNA values ≤70 g/d versus PNA values >70 g/d, we used logistic regression models after a check of variance inflation factors for each variable affirmed that there was no multicollinearity. Due to the large sample size, most associations and interactions we examined had very low *P* values. Values in the text are means ± SDs, and analyses were performed at the $\alpha = 0.05$ level of significance. All statistical analyses were performed by using SAS, version 9.2 (SAS Institute).

Results

There were 164,789 MHD patients in the LDO database during the 8-y study (**Supplemental Fig. 1**). After excluding patients receiving peritoneal dialysis or those who had undergone modality switches between hemodialysis and peritoneal dialysis (*n* = 33,495), participants younger than 19 y or within an outlier of age (*n* = 722), those missing nPNA measurements during the base quarter (*n* = 29,998), those missing base-quarter laboratory and demographic data (*n* = 8), and those missing follow-up data (*n* = 478) and PNA level (*n* = 1599), the final cohort consisted of 98,489 participants. All of these participants had the required data for time-averaged analyses.

The 98,489 observed MHD patients had a mean follow-up time of 1006 d, and there were 54,848 deaths (56%). The mean ± SD patient age was 64 ± 15 y, 45% were female, and 59% had diabetes mellitus (**Table 1**). MHD patients who had lower protein intakes, as determined by their PNA, included more women. All-cause mortality exhibited decreasing rates across increasing PNA values. **Supplemental Table 1** shows the basic characteristics of our population using nPNA categories.

Table 2 shows the bivariate (unadjusted) and multivariate-adjusted correlation coefficients between PNA and some clinically relevant variables in the baseline quarter of the cohort. Serum creatinine, phosphorus, albumin, and TIBC concentrations displayed the strongest unadjusted correlations with PNA.

Figure 1*A* shows death HRs of different PNA values using the time-averaged models in all 98,489 MHD patients studied. Adjusting for case-mix covariates, increased PNA confers a survival advantage among all patients. Compared with the reference level (60 to <70 g/d), patients with low PNA levels [<30 g/d, HR: 1.40 (95% CI: 1.30, 1.50); 30 to <40 g/d, HR: 1.33 (95% CI: 1.28, 1.39)] were associated with higher all-cause mortality and patients with high PNA levels [≥110 g/d, HR: 0.92 (95% CI: 0.88, 0.97); 100 to <110 g/d, HR: 0.87 (95% CI: 0.82,0.91)] were associated with lower all-cause mortality in all levels of analysis (**Supplemental Table 2**). In all patients, the relationship between protein intake and mortality was reverse J-shaped when nPNA (normalized to body weight) was examined (Fig. 1*B*). We found similar results in our sensitivity analysis when we excluded patients with <6 or 12 mo dialysis vintage (data not shown). These analyses were repeated for the hypoalbuminemic subgroup (serum albumin <3.5 mg/dL), and similar trends were observed (**Fig. 2**).

Similar relationships were also observed in a race-based subanalysis of 3 mutually exclusive subgroups: black, Hispanic, and white. We found similar reverse linear associations between PNA and mortality in black, Hispanic, and white patients (**Fig. 3**).

TABLE 2 Bivariate (unadjusted) and multivariate correlation coefficients between PNA and selected clinical and laboratory variables at base quarter[1]

Variable	Unadjusted (Pearson) correlation	*P*	Adjusted (partial) correlation[2]	*P*
BMI	0.67	<0.001	0.68	<0.001
Dialysis vintage	0.10	<0.001	0.02	<0.001
Serum albumin	0.27	<0.001	0.07	<0.001
Bicarbonate	−0.16	<0.001	−0.09	<0.001
Creatinine	0.34	<0.001	0.26	<0.001
Intact PTH	0.10	<0.001	−0.01	0.001
TIBC	0.26	<0.001	0.10	<0.001
Phosphorus	0.28	<0.001	0.11	<0.001

[1] *n* = 98,489 MHD patients. MHD, maintenance hemodialysis; PNA, protein nitrogen appearance; PTH, parathyroid hormone; TIBC, total iron-binding capacity.
[2] Adjusted for case-mix features (age, sex, race, diabetic status), dialysis vintage, dialysis dose, comorbid states, and malnutrition-inflammation complex syndrome variables (serum albumin, TIBC, ferritin, creatinine, calcium, phosphorus, bicarbonate, blood hemoglobin, white blood cell count, and lymphocyte percentage).

To identify the predictors of low protein intake (i.e., PNA ≤70 g/d), we performed logistic regression analysis. Results from the multivariate model are shown in **Table 3**. After adjusting for case-mix and MICS covariates, we found that the odds of experiencing low PNA were 46% higher for blacks than for whites and 257% higher for females compared with males, and that a 0.1-g/dL decrease in serum albumin increased the odds of experiencing low protein intake by 5%.

Discussion

With the use of time-adjusted analyses in a contemporary cohort of 98,489 adult dialysis patients, we found that low PNA level, as a surrogate of dietary intake, was associated with mortality even after controlling for such demographic and laboratory variables as age, gender, diabetes, and albumin.

Almost two-thirds of all MHD patients in the US die within 5 y of initiation of chronic dialysis treatment, mostly due to cardiovascular disease (27). Survival in dialysis patients has not improved substantially in the past 2 decades (27). Recent randomized clinical trials have shown no survival benefit of cholesterol-lowering interventions using rosuvastatin (28), atorvastatin (29), simvastatin/ezetimibe (30), or high-dose folic acid to treat hyperhomocysteinemia (31). Although a study on high-flux membrane hemodialysis showed survival benefits for cardiovascular mortality, there were no such results for all-cause mortality (32), and additional efforts in the form of several multicenter clinical trials have also failed to show any survival advantage of increasing dialysis dose above a double pool Kt/V urea of ~1.05 in these patients (33,34). Hence, there appear to be other prevailing conditions that contribute to this substantial mortality rate and that need to be identified and better studied. Our study reiterates that protein intake may be an important nontraditional risk factor in these patients.

Higher PNA was associated with better survival in our case-mix model. A notable finding was the mitigation, but not complete removal, of the protective effect of PNA on survival upon further adjustment for MICS surrogates, leading to an almost horizontal line for the >80-g/d PNA range. This may reflect an overadjustment bias (35,36), especially because the MICS may be a causal intermediate in the etiologic pathway between protein intake and survival. If so, additional multivariate adjustment for MICS may be inappropriate. Nonetheless, the observed residual association between protein intake and survival supports the presence of an effect.

We found that an nPNA ≥1.3 g · kg^{-1} · d^{-1} was not associated with improved survival, but rather with increased mortality. This reverse J-shaped association is consistent with previous findings (1) and was also found in our study in subanalyses of hypoalbuminemic patients and in all 3 racial/ethnic groups analyzed separately. The reverse J-shaped upward trend in all-cause mortality may be a consequence of toxic effects of a very-high-protein diet, a hypercatabolic state due to inflammation, the outcome-associated confounding effect of body weight in smaller patients, or a reflection of a behavior pattern due to poor compliance to medical prescription, any of which may be acting singly or in concert to produce this increase in mortality risk. It is considered unlikely that inflammation by itself could be a sole cause of a chronically increased nPNA, because a substantially increased protein catabolism from inflammation is generally a rather self-limited phenomenon. Furthermore, normalizing PNA to body weight is a matter of

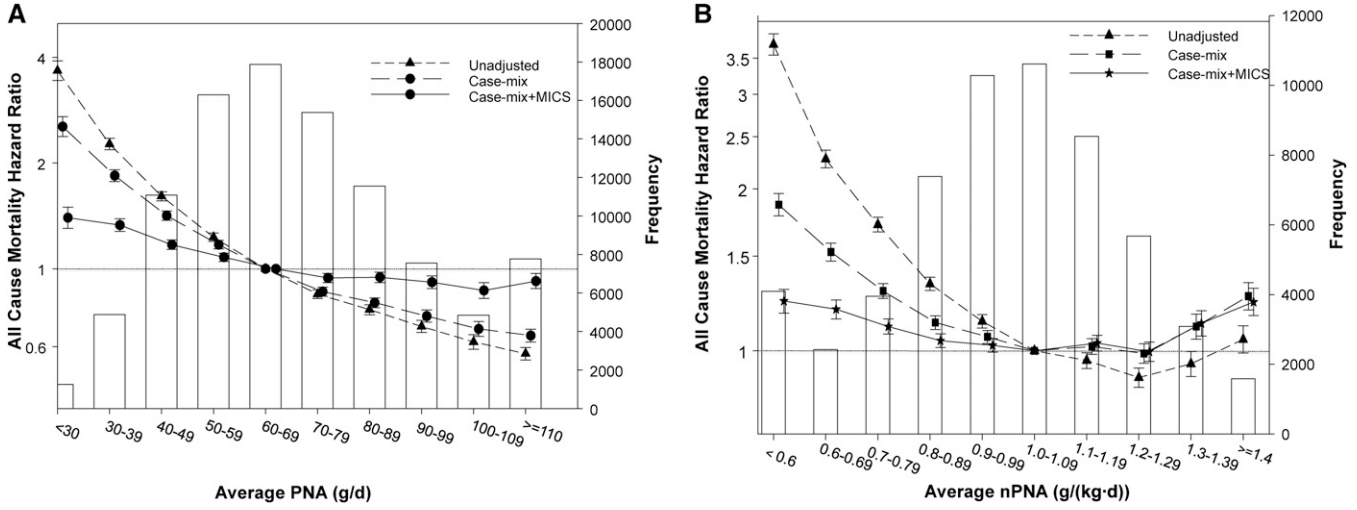

FIGURE 1 Associations between PNA (*A*) (*n* = 98,489) and nPNA (*B*) (*n* = 100,088) and 8-y mortality in all MHD patients based on time-averaged models using averaged quarterly measures. MHD, maintenance hemodialysis; MICS, malnutrition-inflammation complex syndrome; nPNA, normalized protein nitrogen appearance; PNA, protein nitrogen appearance.

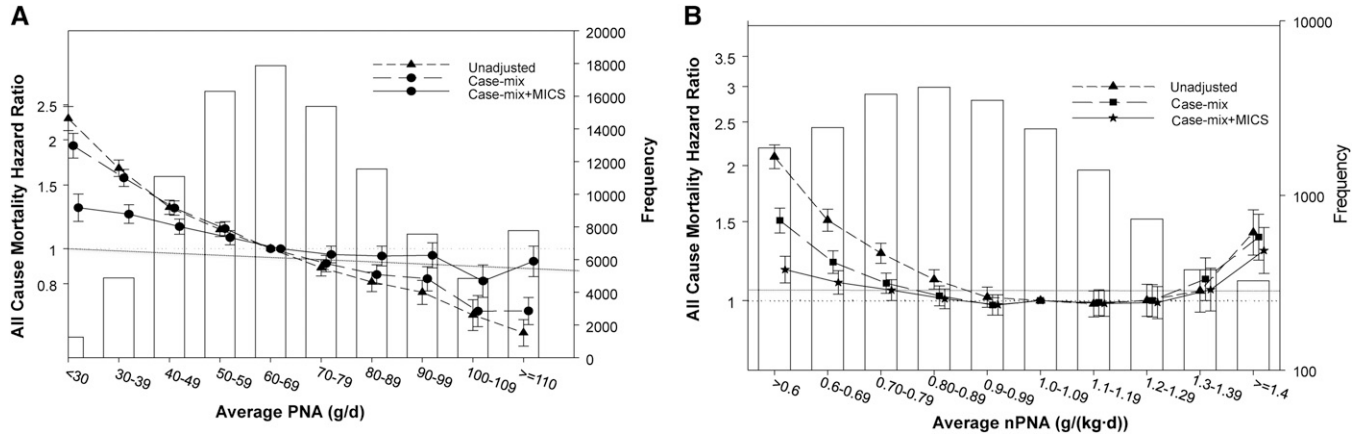

FIGURE 2 Time-averaged associations between PNA (*A*) and nPNA (*B*) and 8-y mortality among 26,433 MHD patients with serum albumin <3.5 mg/dL. MHD, maintenance hemodialysis; MICS, malnutrition-inflammation complex syndrome; nPNA, normalized protein nitrogen appearance; PNA, protein nitrogen appearance.

controversy in the literature, as it can be misleading in obese, malnourished, and edematous individuals (37). In reality, one does not need to account for patient size in order to calculate a prescribed protein intake; such adjustments have actually proven to mathematically bias results against seemingly well-nourished or obese patients (38). In our study, the reverse J-shaped association was eliminated when nPNA was multiplied by dry body weight to obtain PNA, and when categories were plotted against all-cause mortality, suggesting that PNA may be a more reliable surrogate than nPNA for dietary protein intake. It is important to note that nPNA, according to the equations, underestimates dietary protein intake by ~6–8 g protein/d and more accurately reflects "measured" net protein degradation as determined by the urea nitrogen appearance.

FFQs (39,40) or dietary interviews represent a more direct approach to the assessment of protein intake in MHD patients, and although vulnerable to imprecision and bias, future studies using these methods may help to elucidate the etiology of these reverse J-shaped associations.

The PNA-mortality associations were the same in all races. However, there was a difference in mortality risk trends among blacks, whites, and Hispanics across categories of nPNA. We found similar reverse J-shaped associations between nPNA and mortality in black and white patients. However, in Hispanic patients only low nPNA was associated with higher mortality risk. These results have added a new perspective to our previous findings (15,41), which reveal a racial survival difference whereby Hispanic and black MHD patients experience lower mortality than their non-Hispanic white counterparts, perhaps due to differences in nutritional and inflammatory status.

There are some potential pitfalls of our study. One of them is our lack of explicit laboratory markers of inflammation such as

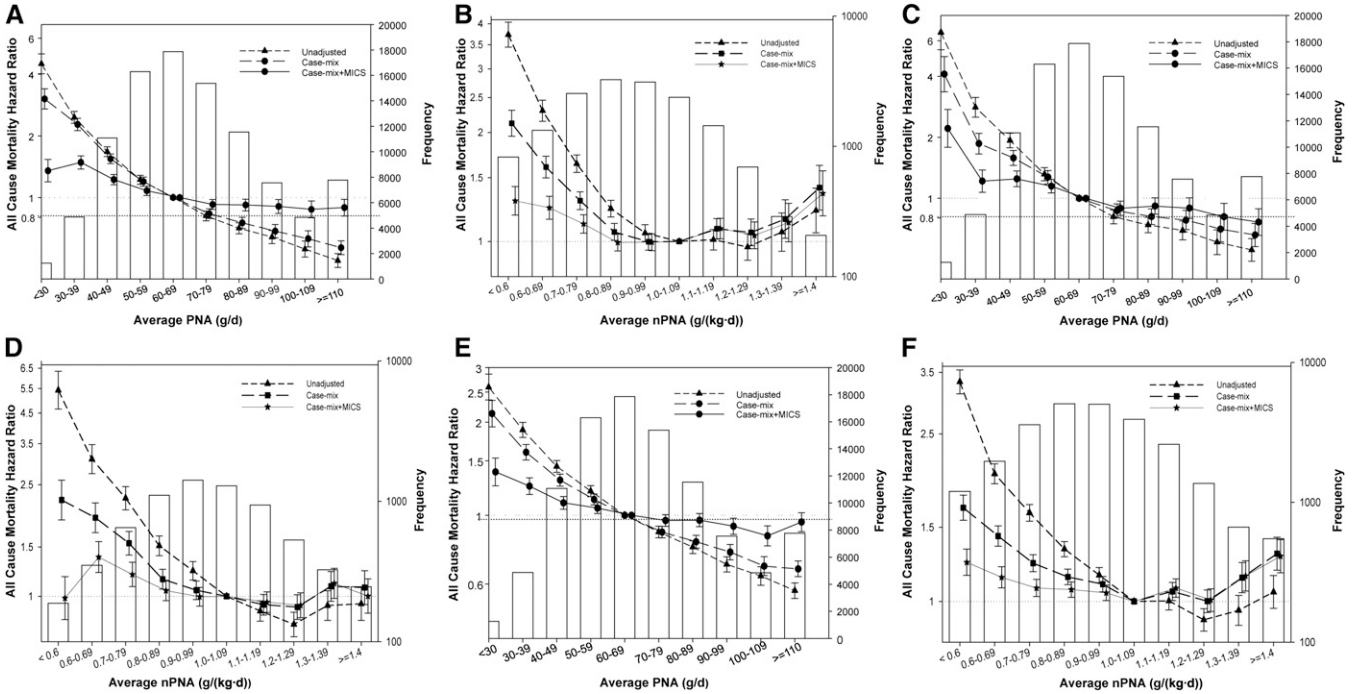

FIGURE 3 Time-averaged associations between PNA/nPNA and 8-y mortality among 32,046 black (*A*, *B*), 15,488 Hispanic (*C*, *D*), and 41,776 white (*E*, *F*) MHD patients. MHD, maintenance hemodialysis; MICS, malnutrition-inflammation complex syndrome; nPNA, normalized protein nitrogen appearance; PNA, protein nitrogen appearance.

TABLE 3 Multivariate logistic regression model predicting PNA of 970 g/d in 98,489 MHD patients, 2001–2009[1]

	Unadjusted		Case-mix adjusted		Fully adjusted	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (10-y increase)	1.28 (1.27, 1.29)	<0.001	1.31 (1.30, 1.32)	<0.001	0.93 (0.92, 0.95)	<0.001
Gender (female)	2.18 (2.12, 2.23)	<0.001	1.89 (1.83, 1.94)	<0.001	3.57 (3.42, 3.72)	<0.001
Diabetes mellitus	0.63 (0.61, 0.65)	<0.001	0.50 (1.42, 1.52)	<0.001	0.52 (0.50, 0.54)	<0.001
Race						
White (reference)	1.00	NA	1.00	NA	1.00	NA
Black	0.98 (0.95, 1.01)	0.12	1.22 (1.12, 1.27)	<0.001	1.46 (1.39, 1.53)	<0.001
Hispanic	0.90 (0.87, 0.93)	<0.001	1.10 (1.05, 1.14)	<0.001	1.26 (1.20, 1.33)	<0.001
Asian	1.49 (1.38, 1.61)	<0.001	1.66 (1.53, 1.80)	<0.001	1.49 (1.34, 1.65)	<0.001
Vintage (time on dialysis)						
0–<6 mo (reference)	1.00	NA	1.00	NA	1.00	NA
6–<24 mo	1.15 (1.12 1.18)	<0.001	0.65 (0.62, 0.68)	<0.001	0.78 (0.74, 0.83)	<0.001
2–<5 y	0.74 (0.72, 0.76)	<0.001	0.42 (0.40, 0.44)	<0.001	0.77 (0.73, 0.82)	<0.001
≥5 y	0.86 (0.858, 0.90)	<0.001	0.38 (0.36, 0.40)	<0.001	0.88 (0.82, 0.94)	<0.001
Primary insurance						
Medicare (reference)	1.00	NA	1.00	NA	1.00	NA
Medicaid	1.19 (1.13, 1.23)	<0.001	1.31 (1.23, 1.34)	<0.001	1.16 (1.07, 1.25)	<0.001
Other	0.73 (0.71, 0.75)	<0.001	0.90 (0.87, 0.94)	<0.001	0.94 (0.90, 0.98)	0.005
Marital status						
Married (reference)	1.00	NA	1.00	NA	1.00	NA
Divorced	0.95 (0.91, 1.00)	0.05	1.28 (1.22, 1.33)	0.08	1.06 (0.99, 1.14)	0.09
Single	0.94 (0.91, 0.97)	<0.001	1.20 (1.16, 1.24)	<0.001	1.12 (1.06, 1.17)	<0.001
Widowed	2.18 (2.10, 2.27)	<0.001	1.28 (1.22, 1.33)	<0.001	1.20 (1.13, 1.27)	<0.001
Other variables						
Kt/V (dialysis dose) (+1 increase)	1.90 (1.81, 1.99)	<0.001	1.98 (1.86, 2.10)	<0.001	0.41 (0.37, 0.44)	<0.001
Residual renal function	0.75 (0.74, 0.76)	<0.001	0.70 (0.69, 0.72)	<0.001	0.73 (0.71, 0.74)	<0.001
BMI (+1 kg/m^2)	0.78 (0.78, 0.79)	<0.001	0.76 (0.75, 0.76)	<0.001	0.75 (0.74, 0.75)	<0.001
Comorbid states (presence of)						
Congestive heart failure	1.03 (1.01, 1.06)	0.02	0.90 (0.87, 0.92)	<0.001	0.87 (0.83, 0.91)	<0.001
Hypertension	0.86 (0.83, 0.89)	<0.001	0.81 (0.78, 0.84)	<0.001	0.91 (0.94, 1.03)	0.40
Inability to ambulate	1.37 (1.27, 1.48)	<0.001	1.10 (1.01, 1.19)	0.02	0.85 (0.77, 0.95)	0.004
PVD	1.19 (1.15, 1.24)	<0.001	1.19 (1.14 1.25)	<0.001	1.02 (0.97, 1.08)	0.45
Tobacco use	1.42 (1.34, 1.51)	<0.001	1.75 (1.64, 1.87)	<0.001	1.52 (1.39, 1.66)	<0.001
Alcohol dependence	1.73 (1.54, 1.94)	<0.001	1.76 (1.55, 1.99)	<0.001	1.49 (1.27, 1.74)	<0.001
Serum concentrations						
Albumin (0.1-g/dL decrease)	1.14 (1.13, 1.14)	<0.001	1.11 (1.11, 1.12)	<0.001	1.05 (1.04, 1.06)	<0.001
Creatinine (1-mg/dL increase)	0.78 (0.79, 0.80)	<0.001	0.71 (0.71, 0.72)	<0.001	0.75 (0.74, 0.75)	<0.001
Phosphorus (1-mg/dL increase)	0.68 (0.67, 0.68)	<0.001	0.73 (0.72, 0.74)	<0.001	0.82 (0.81, 0.84)	<0.001
Total iron-binding capacity (10-mg/dL increase)	0.90 (0.89, 0.90)	<0.001	0.90 (0.89, 0.90)	<0.001	0.94 (0.93, 0.94)	<0.001
Carbon dioxide (1-mg/dL increase)	1.11 (1.11, 1.12)	<0.001	1.09(1.09, 1.10)	<0.001	1.07 (1.06, 1.08)	<0.001
Calcium (1-mg/dL increase)	0.83 (0.81, 0.85)	<0.001	0.83 (0.81, 0.85)	<0.001	0.95 (0.91, 0.98)	0.004
Iron saturation ratio (+1%)	1.00 (0.99, 1.00)	0.78	1.00 (0.99, 1.01)	0.27	0.99 (0.98, 0.99)	<0.001
Ferritin (100 μg/L increase)	1.03 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001	0.98 (0.983, 0.99)	<0.001
Alkaline phosphatase (10-U/L increase)	1.02 (1.02, 1.04)	<0.001	1.03 (1.03, 1.04)	<0.001	0.99 (0.99, 1.00)	0.56
Intact PTH (100-pg/mL increase)	0.95 (0.94, 0.95)	<0.001	0.94 (0.94, 0.95)	<0.001	1.00 (0.99, 1.01)	0.10
White blood cells ($\times 10^3/\mu$L)	1.00 (1.00, 1.01)	0.13	0.98 (0.97, 0.98)	<0.001	0.98 (0.97, 0.99)	<0.001
Lymphocytes (+1%)	0.99 (0.98, 0.99)	<0.001	0.99 (0.98, 0.99)	<0.001	1.01 (1.01, 1.01)	<0.001

[1] Kt/V, dialysis dose; MHD, maintenance hemodialysis; NA, not applicable; PNA, protein nitrogen appearance; PTH, parathyroid hormone; PVD, peripheral vascular disease.

C-reactive protein or proinflammatory cytokines. However, we did have data for serum albumin, ferritin, TIBC, and WBCs and lymphocytes, which are all associated with inflammation (42–46). Furthermore, whereas serum C-reactive protein may be a more sensitive inflammatory marker, it may also be a more short-term marker, whereas albumin is a longer-term indicator of MICS. In addition, we did not have data about dietary and lifestyle factors, which can have an effect on PNA level. The included patients were older, more likely diabetic, and more likely Hispanic or black (**Supplemental Table 3**), differences which might affect the generalizability of our results.

One of the reported limitations of nPNA is its mathematical coupling with the dialysis dose (Kt/V) (26). Indeed, in our study, the correlation coefficient between Kt/V and nPNA was 0.309. However, an alternative explanation is that the change in the measured nPNA may be a consequence of a better dialysis dose and subsequently improved appetite with greater nutrient intake, leading to improved survival (3). In a recent study, a significant association between Kt/V and nPNA was found only for Kt/V values <1.2 (26). All multivariate models in our study were adjusted for Kt/V; hence, it is unlikely that the mathematical or clinical association between these 2 measures had a

bearing on the multivariate-adjusted association between the nPNA and mortality. Another potential limitation of nPNA is that the metabolic status of any given patient cannot be estimated by it; patients may be in negative or positive nitrogen balance for a variety of reasons (47). However, MHD patients are rarely in negative or, particularly, in positive nitrogen balance (>1.0 to 1.5 g/d) for more than a very few days (26,47). Thus, except for those exceptional times when an MHD patient is in strongly negative or positive nitrogen balance, the nPNA should rather closely reflect the dietary protein intake (e.g., within ±10–15%). Moreover, the extremely large size of our study and the use of the 13-wk averaged nPNA in lieu of 1 single measurement mitigate the effect of nitrogen balance status on our examined associations.

Among the strengths of our study is the use of time-averaged models to examine the relation of PNA groups to all-cause mortality while controlling for other nutritional and inflammatory indices and the dialysis dose. Furthermore, our data are based on an 8-y cohort period. Hence, our results are reflective of long-term survival rates. Our time-averaged findings are supported by the observed relations of different rates of PNA gain and loss over time to survival. The data originate from 1 dialysis care provider that has uniform patient management practices; all laboratory measurements were performed in 1 facility, and most data were means of several measures. Hence, measurement variability was minimized.

In conclusion, in a contemporary cohort from one of the largest dialysis facilities, we found that PNA as a surrogate of protein intake shows a inverse association with mortality, but the survival advantage of high PNA levels was not robust. It is possible that the association between protein intake and survival is secondary to protein-energy-wasting or additional factors, and it would be worthwhile to further investigate this possibility through interventional trials. Our effect estimates are subject to various potential biases, not all of which are addressable with the observational database available to us. Nonetheless, if causal, the time-averaged association of PNA with survival would have major clinical and public health implications. Clinical trials based on dietary interventions in MHD patients including nutritional supplements with or without antiinflammatory or antioxidant properties could provide valuable information on the cause of the association between PNA and mortality (48). Such interventions may also include appetite-stimulating agents (49), because a poor appetite is associated with MICS and poor outcome (3). Until randomized, prospective controlled trials are conducted, special caution should be exercised in interpreting observational data such as ours.

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Literature Cited

1. Shinaberger CS, Kilpatrick RD, Regidor DL, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. Am J Kidney Dis. 2006;48:37–49.
2. Kopple JD. The National Kidney Foundation K/DOQI clinical practice guidelines for dietary protein intake for chronic dialysis patients. Am J Kidney Dis. 2001;38:S68–73.
3. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80:299–307.
4. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003;42:864–81.
5. Kalantar-Zadeh K, Cano NJ, Budde K, Chazot C, Kovesdy CP, Mak RH, Mehrotra R, Raj DS, Sehgal AR, Stenvinkel P, et al. Diets and enteral supplements for improving outcomes in chronic kidney disease. Nat Rev Nephrol. 2011;7:369–84.
6. Ling PR, Smith RJ, Kie S, Boyce P, Bistrian BR. Effects of protein malnutrition on IL-6-mediated signaling in the liver and the systemic acute-phase response in rats. Am J Physiol Regul Integr Comp Physiol. 2004;287:R801–8.
7. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, Kalantar-Zadeh K. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. Am J Kidney Dis. 2011;58:418–28.
8. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H Jr, Kopple JD, Greenland S. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant. 2005;20:1880–9.
9. Molnar MZ, Kovesdy CP, Bunnapradist S, Streja E, Mehrotra R, Krishnan M, Nissenson AR, Kalantar-Zadeh K. Associations of pretransplant serum albumin with post-transplant outcomes in kidney transplant recipients. Am J Transplant. 2011;11:1006–15.
10. Dezfuli A, Scholl D, Lindenfeld SM, Kovesdy CP, Kalantar-Zadeh K. Severity of hypoalbuminemia predicts response to intradialytic parenteral nutrition in hemodialysis patients. J Ren Nutr. 2009;19:291–7.
11. Cano N, Labastie-Coeyrehourq J, Lacombe P, Stroumza P, di Costanzo-Dufetel J, Durbec JP, Coudray-Lucas C, Cynober L. Perdialytic parenteral nutrition with lipids and amino acids in malnourished hemodialysis patients. Am J Clin Nutr. 1990;52:726–30.
12. Cano NJ, Fouque D, Roth H, Aparicio M, Azar R, Canaud B, Chauveau P, Combe C, Laville M, Leverve XM, et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. J Am Soc Nephrol. 2007;18:2583–91.
13. Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, El Nahas M, Feldt-Rasmussen B, Mitch WE, Wanner C, Gothberg M, Ikizler TA. Opportunity & trade: a large-scale randomized clinical trial of growth hormone in hemodialysis patients. Nephrol Dial Transplant. 2011;26:4095–103.
14. Wolfson M, Jones MR, Kopple JD. Amino acid losses during hemodialysis with infusion of amino acids and glucose. Kidney Int. 1982;21:500–6.
15. Streja E, Kovesdy CP, Molnar MZ, Norris KC, Greenland S, Nissenson AR, Kopple JD, Kalantar-Zadeh K. Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. Am J Kidney Dis. 2011;57:883–93.
16. Ricks J, Molnar MZ, Kovesdy CP, Kopple JD, Norris KC, Mehrotra R, Nissenson AR, Arah OA, Greenland S, Kalantar-Zadeh K. Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. Am J Kidney Dis. 2011;58:574–82.
17. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD. Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. Hypertension. 2005;45:811–7.
18. Longenecker JC, Coresh J, Klag MJ, Levey AS, Martin AA, Fink NE, Powe NR. Validation of comorbid conditions on the end-stage renal disease medical evidence report: the CHOICE study. Choices for Healthy Outcomes in Caring for ESRD. J Am Soc Nephrol. 2000;11:520–9.
19. Molnar MZ, Streja E, Kovesdy CP, Budoff MJ, Nissenson AR, Krishnan M, Anker SD, Norris KC, Fonarow GC, Kalantar-Zadeh K. High platelet count as a link between renal cachexia and cardiovascular mortality in end-stage renal disease patients. Am J Clin Nutr. 2011;94:945–54.
20. Molnar MZ, Lukowsky LR, Streja E, Dukkipati R, Jing J, Nissenson AR, Kovesdy CP, Kalantar-Zadeh K. Blood pressure and survival in

long-term hemodialysis patients with and without polycystic kidney disease. J Hypertens. 2010;28:2475–84.
21. Miller JE, Kovesdy CP, Nissenson AR, Mehrotra R, Streja E, Van Wyck D, Greenland S, Kalantar-Zadeh K. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis. 2010;55:100–12.
22. Miller JE, Kovesdy CP, Norris KC, Mehrotra R, Nissenson AR, Kopple JD, Kalantar-Zadeh K. Association of cumulatively low or high serum calcium levels with mortality in long-term hemodialysis patients. Am J Nephrol. 2010;32:403–13.
23. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, Nissenson AR, Krishnan M, Kopple JD, Mehrotra R, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc. 2010;85:991–1001.
24. Kalantar-Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowsky LR, Streja E, Ricks J, Jing J, Nissenson AR, Greenland S, et al. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. J Bone Miner Res. 2010;25:2724–34.
25. Daugirdas JT. The post:pre dialysis plasma urea nitrogen ratio to estimate K.t/V and NPCR: validation. Int J Artif Organs. 1989;12:420–7.
26. Kalantar-Zadeh K, Supasyndh O, Lehn RS, McAllister CJ, Kopple JD. Normalized protein nitrogen appearance is correlated with hospitalization and mortality in hemodialysis patients with Kt/V greater than 1.20. J Ren Nutr. 2003;13:15–25.
27. U.S. Renal Data System. USRDS 2011 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2011 [cited 12 Jan 2012]. Available from: http://www.usrds.org/adr.aspx.
28. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
29. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
30. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
31. Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP. Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. J Am Soc Nephrol. 2004;15:420–6.
32. Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G, Clark W, Levey AS, Leypoldt JK, Ornt DB, et al. Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. J Am Soc Nephrol. 2003;14:3251–63.
33. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–9.
34. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S; Mexican Nephrology Collaborative Study Group. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13:1307–20.
35. Leistikow B. Commentary: questionable premises, overadjustment, and a smoking/suicide association in younger adult men. Int J Epidemiol. 2003;32:1005–6.
36. Thompson WD. Overadjustment in case-control studies. Am J Epidemiol. 1982;115:797–801.
37. Canaud B, Leblanc M, Garred LJ, Bosc JY, Argiles A, Mion C. Protein catabolic rate over lean body mass ratio: a more rational approach to normalize the protein catabolic rate in dialysis patients. Am J Kidney Dis. 1997;30:672–9.
38. Harty JC, Boulton H, Curwell J, Heelis N, Uttley L, Venning MC, Gokal R. The normalized protein catabolic rate is a flawed marker of nutrition in CAPD patients. Kidney Int. 1994;45:103–9.
39. Kalantar-Zadeh K, Kovesdy CP, Bross R, Benner D, Noori N, Murali SB, Block T, Norris J, Kopple JD, Block G. Design and development of a dialysis food frequency questionnaire. J Ren Nutr. 2011;21:257–62.
40. Bross R, Noori N, Kovesdy CP, Murali SB, Benner D, Block G, Kopple JD, Kalantar-Zadeh K. Dietary assessment of individuals with chronic kidney disease. Semin Dial. 2010;23:359–64.
41. Noori N, Kovesdy CP, Dukkipati R, Feroze U, Molnar MZ, Bross R, Nissenson AR, Kopple JD, Norris KC, Kalantar-Zadeh K. Racial and ethnic differences in mortality of hemodialysis patients: role of dietary and nutritional status and inflammation. Am J Nephrol. 2011;33:157–67.
42. Reddan DN, Klassen PS, Szczech LA, Coladonato JA, O'Shea S, Owen WF Jr, Lowrie EG. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transplant. 2003;18:1167–73.
43. Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH. Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. Am J Kidney Dis. 2001;37:564–72.
44. Kalantar-Zadeh K, Kleiner M, Dunne E, Ahern K, Nelson M, Koslowe R, Luft FC. Total iron-binding capacity-estimated transferrin correlates with the nutritional subjective global assessment in hemodialysis patients. Am J Kidney Dis. 1998;31:263–72.
45. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. Nephrol Dial Transplant. 2004;19:141–9.
46. Kalender B, Mutlu B, Ersoz M, Kalkan A, Yilmaz A. The effects of acute phase proteins on serum albumin, transferrin and haemoglobin in haemodialysis patients. Int J Clin Pract. 2002;56:505–8.
47. Kopple JD, Gao XL, Qing DP. Dietary protein, urea nitrogen appearance and total nitrogen appearance in chronic renal failure and CAPD patients. Kidney Int. 1997;52:486–94.
48. Kalantar-Zadeh K, Braglia A, Chow J, Kwon O, Kuwae N, Colman S, Cockram DB, Kopple JD. An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: a pilot/feasibility study. J Ren Nutr. 2005;15:318–31.
49. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossein C. Megestrol acetate in a moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. J Ren Nutr. 2005;15:345–55.