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Normalized Protein Nitrogen Appearance Is Correlated With Hospitalization and Mortality in Hemodialysis Patients With Kt/V Greater Than 1.20

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Objectives: Normalized protein nitrogen appearance (nPNA), also known as protein catabolic rate (nPCR), reflects the daily protein intake in maintenance hemodialysis (MHD) patients. Several studies indicate that nPNA and Kt/V correlate with clinical outcome and also with each other. Thus, the relationship between low nPNA and poor outcome could be due to uremia, low Kt/V or due to reported mathematical coupling between nPNA and Kt/V. We therefore investigated whether nPNA is associated with outcome in patients who have adequate or high Kt/V.

Design: Prospective cohort.

Settings: Outpatient dialysis unit affiliated with a tertiary-care community medical center.

Patients: From a pool of 135 MHD outpatients in one dialysis unit, 122 patients with a delivered, $Kt/V_{sp} > 1.20$, independent of their residual renal function, were evaluated. Patients (61 women, 61 men), aged from 23 to 89 years (53.4 ± 14.0 years) (\pm SD), had been undergoing MHD for one month to 17 years.

Intervention: Review of laboratory values and clinical outcome.

Main outcome measures: Twelve-month mortality and hospitalization.

Results: Delivered Kt/V_{sp} ranged from 1.23 to 2.71 (1.77 ± 0.34), nPNA from 0.5 to 2.15 (1.13 ± 0.29 g/kg/day), and serum albumin, from 1.9 to 4.6 (3.76 ± 0.37 g/dL). During the 12-month follow-up, 55 patients were hospitalized overnight at least once; 12 patients died; 5 patients underwent renal transplantation, and 6 patients left the study. The nPNA and Kt/V_{sp} did not correlate significantly ($r = .09$) except when analysis was limited to Kt/V values < 1.5 ($r = .54$). Serum nPNA and albumin were the only variables with statistically significant correlations with both mortality and 3 measures of hospitalization (H): total days of H (H_D), total number of H (H_F), and time to first H (H_T). The case-mix adjusted correlations for serum albumin and nPNA versus total days (r_{HD}) and frequency of H (r_{HF}) were significant, and Cox analysis based on H_T and time to death resulted in significant odds ratios for each standard deviation decrement for both serum albumin and nPNA. Serum total iron binding capacity (TIBC) and

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creatinine concentrations also correlated with some but not all outcome measures: lower serum concentrations of these values were each significantly associated with poor clinical outcomes.

Conclusions: Both nPNA and serum albumin predict prospective hospitalization and mortality in MHD patients with $Kt/V > 1.20$. Serum TIBC and creatinine concentrations appear to have association with some outcome measures as well. These data are consistent with the possibility that protein intake affects the clinical course even in the setting of an adequate to high hemodialysis dose. Studies based on randomized assignments to different protein intakes would be helpful to confirm these conclusions.

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PROTEIN-ENERGY malnutrition (PEM) occurs commonly in maintenance hemodialysis (MHD) patients and is associated with inflammation, risk of cardiovascular disease, and poor outcome.¹⁻³ The term “malnutrition-inflammation complex syndrome” (MICS) has been used to refer to the close interplay between these 2 important, outcome-predicting conditions.^{4,5} However, the degree to which PEM is secondary to inflammation or vice versa is not clear.⁴ It has been argued that in maintenance hemodialysis (MHD) patients, inflammation by itself and without the contribution of PEM is a strong and adequate predictor of poor outcome, including higher rates of hospitalization and mortality.⁶⁻⁹ Some studies maintain that hypoalbuminemia has a strong association with dialysis outcome essentially because serum albumin is an inflammatory marker and not a reflection of protein intake. However, other reports suggest that protein intake by itself may be an independent outcome predictor.^{6,10} Normalized protein (equivalent of total) nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), is a mathematical representation of the amount of daily protein intake in MHD patients, and is usually routinely calculated and monitored on a monthly basis in MHD patients in North America and many other parts of the world.¹¹⁻¹³ Therefore, it would be helpful to know whether nPNA is associated with morbidity and mortality in MHD patients and whether its outcome-predicting value is comparable to that of serum albumin.

Since both nPNA and Kt/V , a measure of dialysis treatment dose, are calculated on the basis of predialysis and postdialysis serum urea nitrogen (SUN), it has been suggested that there is a mathematical coupling between these 2 measures.^{14,15} This may lead to confounding and lack of utility of nPNA if its magnitude is indeed

influenced by Kt/V variation. Moreover, individuals with low Kt/V values may be uremic, and this also could engender a low protein intake and reduce nPNA. Thus, because the Kt/V is an independent outcome predictor in MHD patients, the association between a low nPNA and outcome could be attributable to the adverse effects of reduced Kt/V . Indeed, if one examines the published associations between nPNA and Kt/V , the lower Kt/V values (ie, $<1.00-1.10$) appear particularly important for generating the statistically significant relationships. The National Kidney Foundation Kidney Disease and Dialysis Outcome Quality Initiative (K/DOQI) guidelines have proposed a target dose of 1.20 or higher for MHD patients.¹³ It is not known whether morbidity and mortality in MHD patients are independently associated with protein intake, as reflected by nPNA, when the dialysis dose meets the published guidelines. The purpose of this study was to determine the association between nPNA and 12-month prospective hospitalization and mortality in a group of MHD patients with a more adequate Kt/V_{sp} (ie, >1.20) and to re-examine the relationship between nPNA and Kt/V at these higher Kt/V levels.

Methods

Patients

There were 135 patients undergoing MHD in our Harbor-UCLA Medical Foundation, Inc/DaVita Dialysis Unit, located in Torrance, CA, at the commencement of this study (April, 2000). Criteria for acceptance into this study were outpatients who were undergoing MHD for at least 8 weeks, who were 18 years or older, and who had Kt/V_{sp} values greater than 1.20 on 2 or 3 separate occasions: at the time of onset of the study, the month prior to the study (March, 2000, only if a patient had been on dialysis for

more than 1 month), and the first month after initiation of the study (May, 2000). This dialysis unit routinely aims for a dialysis dose Kt/V_{sp} of 1.40 or higher. Hence, out of 135 MHD patients, 123 patients met all 3 inclusion criteria, including the Kt/V_{sp} values of 1.20 or higher during the above-mentioned 2 or 3 consecutive months. However, in 1 patient, the average of the 2 available Kt/V measures was >2.8 , and this patient was excluded as an outlier; therefore, 122 MHD patients remained in the study. These patients (61 men, 61 women) were followed for up to 12 months (April, 2000 through March, 2001).

Mortality and Hospitalization

Mortality was determined irrespective of the cause of death during the 12-month period of the cohort study. Hospitalization data during the 12-month follow-up were studied by assessing the frequency of hospitalization and its total duration in days, as defined by the United States Renal Data System report.¹⁶ The hospitalization data were obtained on all 122 MHD patients. Hospitalization was defined as any hospital admission that included at least 1 overnight stay in the hospital.² The admission day was counted as 1 full hospitalization day, but the discharge day was not. Therefore, the minimum duration of hospitalization per admission was 1 day. No exclusion criteria for determining hospitalizations were used except for renal transplantation. Thus, all hospital admissions except for renal transplantation were counted. However, because the vast majority of dialysis access-related hospitalizations did not require overnight admission, essentially only those access-related hospitalizations were included that were associated with other comorbid conditions such as infection or cardiovascular events. For those few patients in the hospital at the start of this cohort study, that hospitalization was not counted. For patients who were still in the hospital at the end of the 1-year cohort study, all hospitalization days of the last admission were counted up to a maximum 30 days. For those patients who died and those who left the cohort during the prospective follow-up, the hospitalization rates during the survival time were standardized by use of the multiplication factor, 12/survival-time (in months).

Three methods were used to assess the 12-month prospective hospitalization: The annual

hospitalization frequency (H_F) was the total number of hospital admissions during the 12-month prospective cohort irrespective of the length of each admission. The annual hospitalization days (H_D) were the sum of all hospitalization days of a given patient during the same period. The number of days at risk from the start of the cohort until the first hospitalization event for each individual per year was assessed in a survival model (H_T). Accordingly, the risk time for each individual is defined as the days from study entry until the first hospitalization, a censoring event, or the study anniversary day occurs.

Laboratory Evaluation

All laboratory measurements were performed by DaVita Laboratories in Deland, FL, with automated methods. For each laboratory measure, the average of either 2 or 3 values obtained in consecutive months (March through May, 2000) were used in all analyses. The nPNA and Kt/V (single pool) were calculated using the following urea kinetic modeling formula^{17,18}:

$$Kt/V = -\ln(R - 0.008 \times t) + ((4 - 3.5 \times R) \times UF/W)$$

$$\begin{aligned} \text{nPNA} = C_0 / (25.8 + (1.15 / (Kt/V)) \\ + 56.4 / (Kt/V)) + 0.168 \end{aligned}$$

where R is the ratio of postdialysis to predialysis 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 (in mg/dL).

Statistical and Epidemiologic Methods

The initial cross-sectional study included 122 subjects, who were subsequently followed for 12 months as a prospective cohort. Hospitalization data were used as continuous outcome measures and mortality as a dichotomized outcome. To determine the significance and strength of associations, we used Pearson's correlation coefficient r for analyses of associations between continuous variables and Spearman rank for nonparametric variables. Multivariate regression analysis was performed to obtain partial (adjusted) correlations controlled for age, gender, race, and diabetes (case-mix adjustment). To calculate the relative risk of first hospitalization and death in the prospective cohort, study hazard ratios and their 95%

Table 1. Demographic and Laboratory Data in 122 Patients at the Start of the Cohort*

Variable	Mean	SD	Minimum	Maximum
Age (y)	53.4	14	23	89
Vintage (dialysis mo)	39.9	41.7	1	213.8
Time to death (mo)	11.1	2.4	1.3	12
Hospitalization frequency (annual)	1.453	2.773	0	18.461
Hospitalization days (annual)	10.3	26.6	0	188
Time to first hospitalization (mo)	8.3	4.4	0.1	12
Post-HD weight (kg)	68.6	19.3	33.4	152.7
BMI (kg/m ²)	25.6	5.2	16.3	46.1
nPNA (g/kg/d)	1.13	0.29	0.5	2.15
KtV _{sp}	1.77	0.34	1.23	2.71
Urea reduction ratio (%)	76.6	5.8	64	93
Serum Albumin (g/dL)	3.76	0.37	1.9	4.6
Total Iron Binding Capacity (mg/dL)	200.2	45.4	81	346
Hematocrit (%)	34.2	3.7	24	42.3
Hemoglobin (g/L)	11.4	1.2	8.1	14.6
Ferritin (μg/mL)	514	307	12	1,757
Iron (μg/mL)	63.1	28.9	13	150
Calcium (mg/dL)	9.46	0.75	7.1	11.3
Phosphorus (mg/dL)	5.53	1.68	1.6	9.7
Intact PTH (μ/mL)	269.7	243.4	6	1,233
Creatinine (mg/dL)	9.63	2.83	3.3	16.9
Urea Nitrogen (mg/dL)	57.6	16.1	21	100
CO ₂ (meq/L)	25.9	3.6	17	35

Note. Laboratory data for each patient are the average of up to 3 values during consecutive months (March through May, 2000).

*Blood specimens were obtained immediately before a midweek hemodialysis treatment.

confidence intervals (CIs) were obtained with Cox proportional hazard models to control for the above-mentioned demographic variables. Any 95% CI not including 1.00 was considered statistically significant. The Cox proportional hazard calculated R^2 (also known as pseudo- R^2) was used for comparison with other multivariate correlations. Plots of log (-log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption. The Poisson regression model was used to further evaluate the association between hospitalization data (H_D and H_F) and relevant predictors. Each multivariate model included 1 outcome (-dependent) variable and 5 predicting (independent) variables (ie, age, gender, race, diabetic status and the variable under study for that particular model [X]). Hence, the general multivariate model is a function of

$$b_1 \times \text{age} + b_2 \times \text{gender} + b_3 \times \text{race} + b_4 \\ \times \text{diabetes} + b_5 \times X$$

where b_1 through b_5 are coefficients of the model terms, and X is the predicting variable. Therefore, the association between each predicting

variable and the outcomes (first hospitalization or death) was studied via separate multivariate models but with uniform case-mix adjustment for each model. Descriptive and multivariate statistics were carried out with the statistical software Stata, version 7.0 (Stata Corporation, College Station, TX), and all results were verified using a second statistical software Statistica for Windows, Release 5.1 (Statsoft, Inc, Tulsa, OK). Fiducial limits are given as means \pm SD (standard deviation). A P -value of $< .05$ is considered to be statistically significant.

Results

Basic descriptive statistics for pertinent variables are presented in Tables 1 and 2. Table 1 summarizes pertinent continuous variables. Age of the patients averaged 53.4 ± 14 years, and the mean vintage (duration of chronic intermittent dialysis therapy) was 39.9 ± 41.7 months. The average dose of delivered Kt/V was 1.77 ± 0.34 , with a range between 1.23 and 2.71. The mean measured nPNA was 1.13 ± 0.29 g/kg/d. The patients were hospitalized for 10.3 ± 26.6 days during the 12-month period of follow-up. Male

Table 2. Nonparametric Data of the Cohort of 122 MHD Patients

Variable	%	n
Gender (female)	50.0%	61
Diabetes mellitus	45.1%	55
Hospitalized at least once	45.1%	55
Death rate	9.8%	12
Renal transplantation rate	4.1%	5
Left the study alive prior to the twelfth month	4.9%	6

and female patients were equal in number. Forty-five percent of patients were hospitalized at least once during the 12 months. The annual death rate was 9.8%.

Table 2 shows some non-parametric data of the cohort. Approximately 45% of the patients were diagnosed with diabetic nephropathy as their underlying kidney disease. During the 12-month follow-up, 55 patients were hospitalized overnight at least once, 12 patients died, 5 patients underwent renal transplantation, and 6 patients left the study because they changed their dialysis unit locations.

Table 3 shows the case-mix (multivariate) adjusted correlations controlled for age, race, gender, and diabetes. Among pertinent variables, nPNA and serum albumin and total iron binding capacity (TIBC) were the only values with statistically significant correlations with both hospitalization days and frequency. Correlation coefficients for albumin were generally stronger than for nPNA. There was no significant correlation between nPNA and Kt/V_{sp} ($r = 0.09$, Fig. 1). By dividing the patients into 2 distinct groups based on a Kt/V_{sp} cutoff of 1.50, there was a strong, significant correlation between Kt/V and nPNA for lower Kt/V_{sp} values < 1.50 ($r = 0.54$, $P < .001$), whereas no significant correlation was seen for higher Kt/V_{sp} values ($r = 0.03$, $P > .20$) (Fig. 1).

Table 4 summarizes hospitalization rate ratios based on Poisson regression for all variables shown previously in Table 3. Because the hospitalization data are not normally distributed because of zero values for the many patients who were never hospitalized during the 12-month cohort, Poisson regression models based on logarithmic conversion of the hospitalization indices were studied. All ratios were statistically significant, although the strength of the association, shown by the magnitude of R^2 , varied widely, and the observed trend was consistent with that seen in the correlation coefficient analyses.

Table 5 describes the hazard ratios and 95% CIs of the time to H_T with Cox proportional hazard models based on the initial values at the start of the prospective cohort study. The model controls for age, gender, race, and diabetes status to estimate the relative risks. Serum albumin and nPNA exhibited the strongest association with H_T . The relative risk of first hospital admission for each SD decrement in serum albumin was 1.54 (95% CI, 1.16 to 2.24; $P = .003$) and for nPNA 1.43 (95% CI, 1.06-1.93; $P = .019$). None of the other clinical, laboratory, and demographic measures showed a statistically significant association with H_T based on the Cox proportional hazard model.

Table 6 lists the hazard ratios and 95% CI of death with Cox proportional hazard models in a similar approach as described previously for H_T . The relative risk of death for nPNA was 3.29 (95% CI, 1.57 to 6.91; $P = .002$) and for serum albumin was 2.47 (95% CI, 1.62-3.76; $P < .001$). Serum TIBC, hemoglobin, urea, and creatinine also exhibited statistically significant associations with the relative risk of death.

In summary, nPNA and serum albumin were the only two variables with statistically significant correlations with both mortality and all 3 measures of hospitalization, although serum TIBC

Table 3. Case-Mix (Multivariate) Adjusted Correlation Coefficients (Controlled for Age, Race, Gender and Diabetes)

	Hospitalization days (H_D)		Hospitalization frequency (H_F)	
	Correlation Coefficient (r)	P -value	Correlation Coefficient (r)	P -value
nPNA	-0.18	.045	-0.26	.005
Albumin	-0.29	.002	-0.43	<.001
TIBC	-0.18	.044	-0.20	.028
Creatinine	-0.14	.112	-0.20	.025
Urea	-0.10	.263	-0.14	.128
Hemoglobin	-0.09	.341	-0.17	.055
BMI	-0.03	.721	-0.03	.747

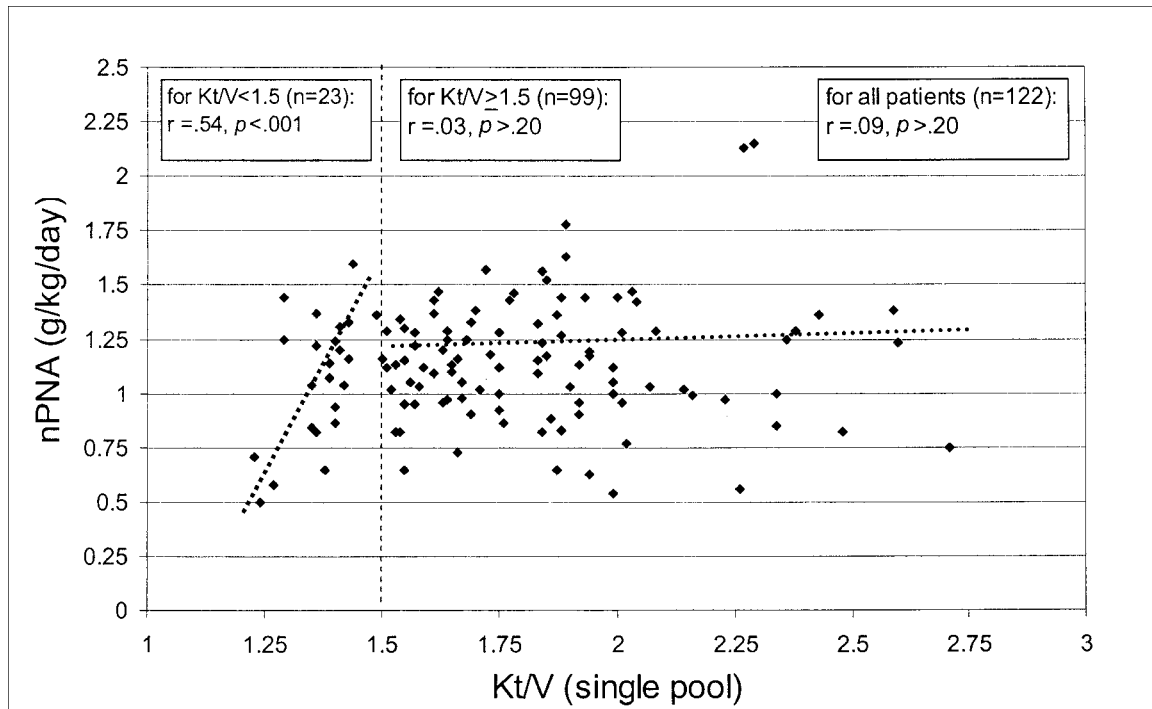


Figure 1. Exploring the association between nPNA and Kt/V_{sp} in 122 MHD patients with a Kt/V_{sp} value > 1.20 . No significant correlation existed between these 2 urea kinetic indices despite their known mathematical association ($r = .09$, $P > .20$). However, by dividing the patients into 2 distinct subgroups based on a Kt/V_{sp} cutoff of 1.50, there was a strong, significant correlation between Kt/V and nPNA for the lower Kt/V_{sp} values < 1.50 ($r = .54$, $P < .001$), whereas there was essentially no correlation at higher Kt/V_{sp} values ($r = .03$, $P > .20$).

and creatinine had some significant associations, which were occasionally even stronger than those for nPNA. However, serum TIBC and creatinine did not have a significant association with the time to first hospitalization (H_T), and serum creatinine did not correlate significantly with the number of hospitalization days.

Discussion

In this prospective study, we showed that the amount of daily protein intake, as measured by a

urea kinetic index and expressed as nPNA, also known as nPCR, has a bearing on hospitalization and mortality in MHD patients whose dialysis dose was considered to be at least adequate. Moreover, we have confirmed previous studies¹⁹⁻²⁵ indicating that serum albumin was a strong predictor of outcome, and that serum TIBC and creatinine were significantly correlated with mortality and most measures of hospitalization in this cohort of 122 MHD patients where Kt/V was greater than 1.20.

Table 4. Hospitalization Rate Ratios (for H_D and H_F) by Means of Poisson Regression Analysis, Adjusted for Age, Gender, Race and Diabetes, Based on 1 Decrement Amounting to the Standard Deviation of the Variable in Question

	Hospitalization Frequency (H_F)			Hospitalization Days (H_D)		
	Rate Ratio (95% CI)	P	R^2	Rate Ratio (95% CI)	P	R^2
nPNA	1.74 (1.63-1.86)	$<.001$	0.1610	1.74 (1.47-2.05)	$<.001$	0.1183
Albumin	1.71 (1.64-1.78)	$<.001$	0.2144	1.83 (1.63-2.05)	$<.001$	0.2010
TIBC	1.75 (1.64-1.86)	$<.001$	0.1835	1.57 (1.33-1.86)	$<.001$	0.0968
Creatinine	1.84 (1.73-1.97)	$<.001$	0.1636	2.08 (1.74-2.48)	$<.001$	0.1530
BUN	1.32 (1.24-1.40)	$<.001$	0.1077	1.40 (1.19-1.64)	$<.001$	0.0699
Hemoglobin	1.22 (1.16-1.29)	$<.001$	0.0994	1.34 (1.16-1.55)	$<.001$	0.0673

Table 5. Relative Risk (RR) of Time to First Hospitalization (H_T) for a Standard Deviation Decrement of Each Variable, Based on Cox Proportional Hazard Regression Analysis, Adjusted for Age, Gender, Race and Diabetes

	RR (95% CI)	P-Value	Pseudo-R ²
nPNA (for each l of one SD)	1.43 (1.06-1.93)	.019	0.0384
Albumin	1.54 (1.16-2.04)	.003	0.0418
Creatinine	1.37 (0.97-1.93)	.075	0.0326
Urea	1.29 (0.96-1.73)	.089	0.0323

Among the measures of protein intake in MHD patients, net urea generation measurements, as determined by the urea nitrogen appearance or nPNA are ones that are most often used because they are easily measurable and mathematically accurate. The nPNA conveniently can be used to study populations of MHD patients in almost all dialysis units in the United States, because it is one of the monthly screening measures.

There are limitations to the preciseness with which the nPNA indicates the daily protein intake. First, the nPNA is dependent on the manufacturer's estimates of the dialyzer permeability characteristics and also on the accuracy of the measured blood and dialysate flow rates. Second, there are fluctuations of nPNA from day to day caused by changes in daily protein intake.²⁶ Third, when daily protein intake is lower than 1.0 g/kg body weight (bw), it may be overestimated by nPNA.²⁷ Conversely, when daily protein intake is higher than 1.0 g/kg bw, it may be underestimated by nPNA.²⁷ Fourth, for the nPNA to accurately estimate the protein intake, the patient's protein metabolism should be at equilibrium or nearly so at the time of measurement.²⁸ Fifth, the volume of distribution of urea, a measurement necessary for the calculation of nPNA, may be difficult to estimate accurately, particularly in obese, malnourished, or edematous patients.²⁹ Finally, delayed equilibrium with subsequent urea rebound after dialysis, which can

vary according to the patient and the characteristics of the dialysis procedure, may lead to an overestimate of the nPNA.^{30,31}

One of the reported limitations of nPNA is its mathematical coupling with Kt/V, which is another urea kinetic measure that is used to measure the dose of dialysis. One study³² showed that in a group of MHD patients when the Kt/V was increased from 0.82 to 1.33, there was an increase in nPNA from 0.83 to 1.00 g/kg/d, a rise in plasma albumin concentration from 3.5 to 3.9 g/dL, and a reduction in the gross annual mortality rate by over 50%. However, an alternative explanation is that the change in the measured nPNA may have been a consequence of a better dialysis dose and subsequently improved appetite with greater nutrient intake.³³⁻⁴⁰ This important feature of nPNA could be ascribed to a reduced uremic toxicity and a mathematic coupling with Kt/V. Nevertheless, not all studies found a strong association between nPNA and Kt/V.⁴¹⁻⁴³ In an attempt to minimize the possible effect of Kt/V or uremic toxicity on nPNA and, hence, calculated protein intake, we limited the patients in the present study to those with a Kt/V of greater than 1.20. We found no significant statistic association between nPNA and Kt/V in our study ($r = 0.09$) (Fig. 1). When we split our sample into 2 subgroups based on a Kt/V cutoff of 1.50, we found a strong and significant correlation between Kt/V and nPNA in the lower Kt/V group, but essentially none in the higher Kt/V group (Fig. 1). Therefore, it appears that for higher Kt/V values, the mathematic association between nPNA and Kt/V essentially disappears.

The nPNA has been shown to correlate with morbidity and mortality in MHD patients. In the National Cooperative Dialysis Study (NCDS), an nPNA greater than 1.0 g/kg/d and a timed average urea concentration of approximately 50 mg/dL were associated with low morbidity.⁴² Several studies indicate that nPNA predicted mortality or hospitalization.^{2,44-47} Our results are

Table 6. Relative Risk of Death (D) for a Standard Deviation Decrement of Each Variable, Based on Cox Proportional Hazard Regression Analysis, Adjusted for Age, Gender, Race and Diabetes

	RR (95% CI)	P-Value	Pseudo-R ²
nPNA	3.29 (1.57-6.91)	.002	0.1550
Albumin	2.47 (1.62-3.76)	<.001	0.1988
TIBC	5.65 (2.44-13.05)	<.001	0.3083
Creatinine	3.02 (1.54-5.92)	.001	0.1471
Urea	2.59 (1.31-5.12)	.006	0.1267
Hemoglobin	2.22 (1.29-3.81)	.004	0.1275

consistent with the above-mentioned findings, because we found that nPNA, along with serum albumin, was one of the only variables that had a significant association with both mortality and all 3 measures of hospitalization. However, it should be noted that the metabolic status of any given patient cannot be estimated by means of nPNA. It is not clear as to how many of our patients were in neutral nitrogen balance, catabolic, or anabolic. Other values such as simultaneous direct measurement of dietary nitrogen intake along with nPNA and their comparison would be required to evaluate the true metabolic status of an individual MHD patient.⁵¹ On the other hand, MHD patients are rarely in more than 1.0 to 1.5 g of negative or, particularly, positive nitrogen balance for more than a very few days.⁵¹ 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 (eg, within \pm 10%-15%).

A unique feature of the present study was that only rather well-dialyzed MHD patients were studied (ie, those with $Kt/V > 1.20$ during 2 to 3 consecutive months). As discussed above, some data provide evidence that protein intake in MHD patients may rise with an increase in the delivered dose of dialysis.^{31,48} Therefore, by studying only well dialyzed patients, we mitigated the confounding effect of the dose of dialysis or uremic status on the possible changes in appetite and nutritional intake.³¹ Moreover, we not only used the Kt/V value obtained during the initial month of this cohort study, but also ensured that the Kt/V during the month before and the month after the initiation of the study was greater than 1.20. Hence, all 122 patients in our cohort had indeed received an adequate dose of dialysis during the first 2 to 3 months of the beginning of the cohort study according to published clinical practice (K/DOQI) guidelines.¹³ Accordingly, we showed that even among those patients who received more than what is often believed to be an adequate dose of hemodialysis, the daily protein intake still had a strong and significant bearing on important clinical outcome measures.

One of the potential limitations of our study is the lack of follow-up of the initial values throughout the cohort, with the exception of the hospitalization and mortality data. However, cohort studies are not infrequently based on such an

approach, because they examine the impact of baseline values (exposure) on the prospective outcome measures. Moreover, our nPNA data were based on measurements in 3 consecutive months. Another limitation is that no other measure of protein intake was utilized in addition to nPNA. Nevertheless, other previous studies already have shown the validation of nPNA as a measure of protein intake (see previously in this article).^{12,49-51} Also, in our study, we did not use any specific measures of inflammation, such as C-reactive protein or cytokines, although it is generally believed that serum albumin and TIBC are negative acute phase reactants, as well as indicators of nutritional status. It is generally accepted that one of the mechanisms by which inflammation engenders adverse clinical events is by inducing anorexia and, hence, protein-energy malnutrition. Thus, the nPNA may itself be an indicator of inflammation. However, epidemiologic research as well as metabolic studies indicate that low protein intakes may, independently of the presence or absence of inflammation, be associated with poor clinical outcome.^{52,53} Ling and Bistran have observed that otherwise normal rats that were randomized to receive a diet low in protein and energy may experience a rise in serum acute phase proteins and cytokines which is not seen in control fed rats (Pei-Ra Ling, MD, and Bruce Bistran, MD, personal communication, July, 2002).

Our study population has certain characteristics that may restrict the generalization of our findings to the general MHD population. First, our patients are almost 10 years younger than the MHD population in the United States according to the USRDS data of 2000.⁵⁴ Second, over 30% of our patients are Hispanic compared to only 10.2% in the United States.⁵⁴ Third, our dialysis time is relatively high (ie, 4 to 5 hours), with Kt/V values > 1.20 in over 94% of our patients (123 out of 135 MHD patients). Taken altogether, it is not surprising to observe significantly lower mortality and hospitalization rates in our study population as compared with the USRDS. Such characteristics generally weaken the existing associations between risk factors (such as nPNA) and the outcome of interest. Therefore, our observed associations might have been even stronger if we had had older and sicker patients with higher mortality and hospitalization rates.

A secondary finding in our study was the significant association between both serum TIBC

and serum creatinine and most, but not all, of the clinical outcome measures. As indicated above, serum TIBC is a both nutritional marker^{55,56} and acute phase reactant,⁵⁷⁻⁶² and some previous studies have shown that it is an outcome predictor in ESRD patients.⁶³ In MHD patients, the predialysis serum creatinine reflects both their skeletal muscle mass and skeletal muscle (meat) intake as well, of course, as their dialysis treatment. A higher predialysis serum creatinine also has been shown to be paradoxically associated with a better outcome, a phenomenon that is referred to as reverse epidemiology of cardiovascular risk factors in ESRD patients.⁶⁴

In summary, the results reported in the present study provide evidence that even in MHD patients who receive adequate to high dialysis doses ($Kt/V > 1.20$), indicators of protein nutrition (nPNA and serum albumin) predict prospective hospitalization and mortality. Serum creatinine, TIBC (transferrin), urea nitrogen, and hemoglobin are also significant predictors of mortality, but they were not shown to have statistically significant correlations with all 3 of the hospitalization indices studied. The results of this study are consistent with the notion that nutritional intake and nutritional status influence morbidity and mortality in well-dialyzed MHD patients. As nPNA is only a surrogate measure of protein intake, it would be helpful if our findings were confirmed in studies where protein intake is measured more directly (eg, by means of dietary records or food frequency questionnaires).⁶⁵ Nevertheless, previous studies have shown the validity of the nPNA as a measure of protein intake in MHD patients, even though the validity of nPNA at high doses of dialysis still needs to be investigated more thoroughly. A definitive answer to the question of whether nutritional intake or malnutrition influences clinical outcome in MHD patients may be obtained only by studying MHD individuals who are randomly assigned to nutritional interventions. Until randomized clinical trials are performed, such epidemiologic studies as ours may help elucidate the associations between the measures of nutrition and outcome in the rapidly growing ESRD population.

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