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Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients

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Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients.

Background. Cross-sectional studies have shown an inverse correlation between serum C-reactive protein (CRP) and serum albumin concentration in hemodialysis patients. The net effects of inflammation and dietary protein intake on nutritional markers over time are unknown.

Methods. To explore the effects of CRP and normalized protein catabolic rate (nPCR) on serum albumin and creatinine, we analyzed six consecutive months of laboratory data from 364 hemodialysis patients, using a multivariable Mixed model with conservative biases.

Results. The overall trend over time in serum albumin was slightly positive (0.039 g/dL/month) and in serum creatinine slightly negative (−0.052 mg/dL/month). With increasing CRP, serum albumin declined significantly (−0.124 g/dL/month per unit increase in log CRP, adjusted for age, gender, race, diabetes, and nPCR, $P < 0.0001$). Serum albumin increased with increasing nPCR (0.021 g/dL/month per 0.1 g/kg/day, $P < 0.0001$). The effect of CRP on albumin was attenuated in African Americans and at a higher nPCR. Corresponding values for creatinine mirrored those for albumin. With increasing CRP, creatinine declined significantly [−0.142 mg/dL/month per unit increase in log CRP, adjusted for age, gender, race, diabetes (time since initiation of dialysis; vintage), Kt/V, and nPCR, $P = 0.002$]. Serum creatinine increased with increasing nPCR (0.183 mg/dL/month per g/kg/day, $P < 0.0001$).

Conclusions. Proxies of inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. These data provide a rationale for prospective testing of dietary protein supplementation in hemodialysis patients with biochemical evidence of ongoing inflammation and "malnutrition."

Key words: malnutrition, C-reactive protein, nutritional markers, normalized protein catabolic rate, protein energy malnutrition, acute phase response, hypoalbuminemia.

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Laboratory abnormalities associated with the syndrome known as "protein energy malnutrition" are potent predictors of mortality and morbidity in hemodialysis patients [1]. These include the serum concentration of visceral proteins, such as albumin and prealbumin (transthyretin), and markers of somatic protein mass, including changes in body weight, Quetelet's index, midarm muscle circumference, and serum creatinine [2–6]. While the levels of serum albumin have been thought for decades to correlate directly and strongly with dietary protein intake, only recently have investigators and clinicians appreciated the influence of inflammation on the serum albumin concentration.

The presence and intensity of the inflammatory response have been classified by levels of proteins of the acute phase response, such as C-reactive protein (CRP) or serum amyloid A (SAA) or the cytokines that regulate them [for example, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6] [7, 8]. Large cross-sectional studies have identified these markers of inflammation as powerful predictors of coronary and cerebrovascular disease in the general population [9–11], and we [12] and others [13, 14] have shown a direct relationship between CRP concentration and all-cause and cardiovascular mortality in hemodialysis patients.

While we now have a better understanding of the relationship between inflammation and proxies of nutritional status, several critical questions remain. What is the effect of inflammation on serum albumin over time? How does nutrition modulate the effect of inflammation on albumin levels? What is the combined effect of inflammation and nutrition on nonvisceral proteins over time? Is there a meaningful effect of dietary protein intake on serum albumin or creatinine concentration in this population? If so, how do the effects of inflammation and dietary protein intake interrelate? Finally, do the effects of either inflammation or dietary intake differ among

Table 1. Patient characteristics

Age *years*	58.3 ± 16.2
Gender % *female*	47.5
Race % *African American*	39.5
Diabetes %	35.0
Vintage *years*	2.6 ± 3.4 (median 1.3, range 0–26.0 years)
Albumin *g/dL*	3.93 ± 0.45
Creatinine *mg/dL*	9.82 ± 3.32
Kt/V	1.54 ± 0.43
nPCR *g/kg/day*	1.00 ± 0.27
C-reactive protein	19.2 ± 20.8 (median 11.7, range 6.9–255.6)

The average value for each variable for months 6 to 12.

individuals by age, sex, or race? To explore these questions, we conducted a detailed analysis of longitudinal data from a relatively large cohort of hemodialysis patients. While observational, these data provide compelling evidence for the dual control of nutritional status by intake and inflammation, and raise additional critical questions regarding the optimal management of nutritionally compromised patients with end-stage renal disease (ESRD).

METHODS

This study was approved by the institutional review board of the institution where the patients received treatment and were studied. Dialyzers used were either F80s or F8s (Fresenius Medical Care AG, Bad Homburg, Germany). Dialyzers were subject to reuse with citric acid and heat. Baseline and interdialytic body weights were not recorded. No patients received interdialytic parenteral nutrition (IDPN).

Patient cohort

All prevalent hemodialysis patients in two hemodialysis units at Beth Israel Medical Center (New York, NY, USA) as of January 1998 were included in the cohort, as were incident patients who arrived during the calendar year. Data on age, sex, race, primary renal disease (diabetes, hypertension, other), vintage (time since initiation), and vascular access (fistula, graft, catheter) were recorded and, with the exception of vascular access, are presented in Table 1. The following laboratory studies were collected during the months of January, May, and July through December inclusive: CRP, albumin, creatinine, hematocrit, ferritin, intact parathyroid hormone (PTH), single-pool Kt/V and normalized protein catabolic rate (nPCR). Albumin was measured using the bromocresol green method. CRP was measured using a rate nephelometer, with a minimum value of 6.9 mg/L. All deaths and hospitalizations were recorded. Deaths were classified as being caused by cardiovascular disease or other causes; hospitalizations were classified as being caused by cardiovascular disease, infection, or other causes. The dialysis and general medical care provided in the units were based on published clinical practice guidelines (NKF-DOQI) [15].

Statistical analysis

Continuous variables were described as mean ± SD or median where appropriate and analyzed using the Student *t* test, analysis of variance, or the Wilcoxon rank sum test where appropriate. The correlation was described with the Pearson product moment correlation coefficient. Categorical variables were described using proportions and analyzed using the χ^2 test. CRP was log transformed to attenuate the influence of very high values on inference testing. Overall survival was calculated using the Kaplan-Meier product limit estimate [16]. Proportional hazards ("Cox") regression was used for all survival analyses (that is, time to death, time to death or hospitalization) [17]. We fit unadjusted, case mix-adjusted, and multivariable-adjusted survival models, with the latter, including albumin, creatinine, nPCR, hematocrit, ferritin, PTH, and Kt/V as candidate variables. Plots of log [−log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption [18]. All prevalent patients as of January 1998 (month 1) were used for the survival analysis, providing up to 12 months of follow-up. Linear regression was used for the cross-sectional analyses examining the relationships among CRP and serum albumin and creatinine. Linear model performance was assessed using total and partial R^2 and Mallow's Cp. The May 1998 cohort (month 5) was arbitrarily chosen for these analyses. The analysis of repeated measures of albumin and creatinine was performed using the Mixed model with an unstructured covariance matrix [19]. The Mixed procedure was chosen for its flexibility, as it allowed the incorporation of all available data without restriction on the number of observations or the presence of missing data. We applied an unstructured variance–covariance matrix to obviate assumptions of a particular data structure that might otherwise have been required and to ensure that *P* values were conservatively estimated. Model fitness was assessed using the Aikaike's information criteria. The July to December cohort (months 7 through 12) was used for these analyses to provide a sufficiently long follow-up time and efficient use of data points. Only patients with two or more values for serum albumin or creatinine were included in the analyses.

For all regression analyses, variables were selected using backward elimination, with the exit criterion based on $P < 0.05$. For face validity, age, sex, and race were included in all models; the inclusion of other variables depended on the level of statistical significance. The effect modification was evaluated by the inclusion of multiplicative interaction terms for selected variables. All analyses were conducted using SAS 7.0 (SAS Institute, Cary, NC, USA).

To exclude an effect of the initiation of dialysis on clinical outcome variables (albumin), we also analyzed the data following the exclusion of 25 patients who started dialysis during the period of observation. Additionally, any patient who started dialysis within three months of the first of six months was removed and the data reanalyzed.

RESULTS

A total of 426 patients were cared for in the two dialysis units over the 12-month study period. The mean age was 58.3 ± 16.2 years. Forty-seven percent were women. Thirty-nine percent were African American. Twenty-seven percent were white, and 33% were of other races or ethnicities. The primary renal diagnosis was roughly evenly split among diabetes (35%), hypertension (31%), and other causes (34%). The mean dialysis vintage was 31 ± 41 months (range <1 to 312 months). Among the initial (month 1) cohort ($N = 292$), the most common vascular access was an arteriovenous (AV) fistula (43%), followed by an AV graft (34%) and a permanent or temporary central venous catheter (23%). There was no significant difference in the types of vascular access when cataloged during month 5 or months 7 through 12.

Predictors of mortality and hospitalization in the initial cohort

To confirm findings previously described in smaller cohorts, the association between CRP and mortality and hospitalization were evaluated in the 292 patient cohort alive and on hemodialysis at the start of 1998. The annualized mortality rate was 12.2%. The median CRP was 9.85 mg/L, and the 10 and 90% limits were 6.9 and 39.9 mg/L, respectively. Stratified by tertiles of CRP, the mortality rates were 9.5, 12.7, and 23.7% in tertiles 1, 2, and 3, respectively ($P = 0.01$). In the unadjusted Cox model, the relative risk (RR) and 95% CI associated with a unit increase in log CRP was 1.96 (95% CI, 1.40 to 2.75). Adjusting for case mix, the RR was 1.76 (95% CI, 1.26 to 2.46). After an additional adjustment for serum albumin and dialysis dose, the RR associated with a unit increase in log CRP was 1.55 (95% CI, 1.08 to 2.25), despite colinearity between log CRP and albumin (Pearson $r = -0.30$, $P < 0.0001$). As expected, the RR of death increased with age and diabetes and decreased with increasing serum albumin (RR 0.42, 95% CI, 0.23 to 0.79 per g/dL increase). A negative coefficient for the linear Kt/V term and a positive coefficient for the quadratic Kt/V term confirmed the J-shaped relationship between Kt/V and mortality [20]. There was no association between nPCR and mortality.

To explore the effect of CRP variability on survival, the study sample was restricted to those patients who had CRP values in months 1, 5, and 7 ($N = 237$). Fifty-seven (24%) were consistently in the lowest tertile. One hundred forty-eight (62%) were in different tertiles at different time points, and 32 (14%) were consistently in the highest tertile of CRP. Six-month mortality rates were 3.5, 6.3, and 9.5% in these groups, corresponding to annualized rates of 7, 12.6, and 19.0%. Therefore, we have no evidence that a "high CRP phenotype" exists that does not suffer increased risk from the inflammatory response.

One hundred sixty-six (57%) patients were hospitalized at least once over the 12-month study period. There was a significant association between log CRP and all-cause hospitalization (RR 1.25, 95% CI, 1.03 to 1.52), even after adjusting for diabetes (RR 1.67, 95% CI, 1.22 to 2.29). However, with additional adjustment for serum albumin, the association between log CRP and hospitalization was no longer statistically significant ($P = 0.48$). There was no demonstrable association between log CRP and cause-specific hospitalization.

Cross-sectional analysis of albumin, creatinine, CRP, and protein catabolic rate

Kaysen, Stevenson, and Depner have previously shown an inverse correlation between log CRP and serum albumin and a direct correlation between nPCR and albumin [7]. The effects of log CRP and nPCR on albumin were independent. In the current study, we aimed to validate and extend these findings, simultaneously adjusting for additional factors that might influence the serum albumin concentration. The mean serum albumin was 3.88 ± 0.47 g/dL. The estimated multivariable effect of log CRP on serum albumin was −0.175 g/dL per unit increase in log CRP ($P < 0.0001$), and the estimated multivariable effect of nPCR on serum albumin was 0.044 g/dL per 0.1 g protein/kg/day increase in nPCR ($P < 0.0001$). Increased age ($P = 0.04$) and diabetes ($P = 0.02$) were associated with lower serum albumin, and male sex ($P = 0.0008$) was associated with higher serum albumin concentrations. Log CRP explained the largest fraction of the variance in albumin (partial $R^2 = 0.13$), and nPCR explained the next largest fraction (partial $R^2 = 0.07$). While the complex interplay among six variables cannot be graphically displayed, Figure 1 shows the log CRP, nPCR, and serum albumin in three dimensions, highlighting the "dual influence" of inflammation and dietary intake on serum albumin. Note the scarcity of data points in the right hand panel of Figure 1 corresponding to patients spontaneously having an nPCR ≥1.2 and a log CRP in the upper tertile.

Strikingly similar results were observed for the serum creatinine concentration. The mean serum creatinine was 9.69 ± 3.11 mg/dL. The estimated multivariable effect of log CRP on serum creatinine was −0.472 mg/dL per unit increase in log CRP ($P = 0.002$), indicating an association between inflammation and muscle mass,

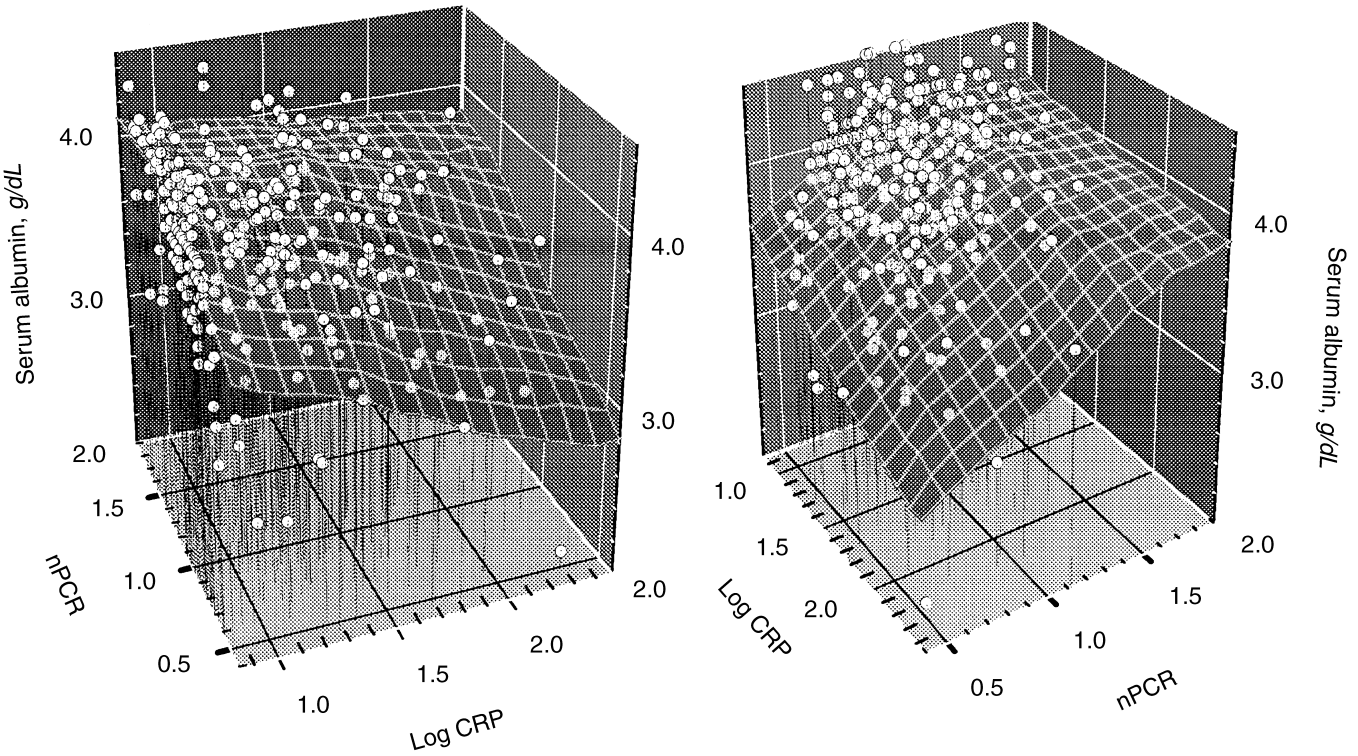

Fig. 1. Relationship between the dependent variable, serum albumin and normalized protein catabolic rate (nPCR), a representative of protein catabolism, and log transformed C-reactive protein (CRP) is represented as a plane. These variables are statistically independent. The individual data points are represented as open symbols. As CRP increases, albumin decreases, but this effect is modulated by nPCR. If the data array are rotated around the axis describing serum albumin concentration (right panel), it is evident that very few patients have a value for nPCR greater than 1.2 g/kg/day when log CRP is greater than 1.5. Data are presented from month 5, randomly selected. Creatinine = 9.597 − (1.761 * log CRP) + (2.070 * nPCR). $N = 288$; $R = 0.307$; log CRP < 0.001; nPCR < 0.001.

since the association was present after adjusting for the effects of Kt/V on serum creatinine. The multivariable effect of nPCR on serum creatinine was 0.304 mg/dL per 0.1 g protein/kg/day increase in nPCR ($P < 0.0001$). Increased age ($P < 0.0001$), diabetes ($P < 0.0001$), and Kt/V ($P < 0.0001$) were associated with lower creatinine, and male sex ($P < 0.0001$) and African American race ($P < 0.0001$) were associated with higher serum creatinine concentrations. Overall, 52% of the variance in serum creatinine could be explained by these factors. It is noteworthy that the nPCR explained more variation in serum creatinine than either race or gender. Figure 2 shows the relationships among log CRP, nPCR, and serum creatinine.

Longitudinal analysis using Mixed models

Longitudinal models were conducted using repeated measures of serum albumin and creatinine as dependent variables, and we focused on the influence of a marker of inflammation (log CRP) and dietary protein intake (nPCR) on the time trends in albumin and creatinine. All models were adjusted for age, sex, race, and diabetes. In the case of creatinine, models were also adjusted for Kt/V given the effects of dialysis on serum creatinine concentration. We tested for effect modification of inflammation and dietary protein intake on albumin and creatinine by creating multiplicative interaction terms of log CRP (for example, log CRP × age, log CRP × sex) and nPCR (for example, nPCR × age, nPCR × sex).

There were 364 patients with at least two serum albumin determinations during the six-month period of study. The overall trend in serum albumin concentration was estimated at 0.039 g/dL/month. Log CRP was the most important determinant of serum albumin concentration over time. Averaged across all patients, the effect of log CRP on serum albumin was −0.124 g/dL/month ($P < 0.0001$, per unit increase in log CRP). nPCR was also a key determinant of serum albumin (influencing the albumin trend more so than age, sex, race, or diabetes). Per 0.1 g protein/kg/day increase in nPCR, the serum albumin increased 0.021 g/dL/month ($P < 0.0001$). Removal of the 25 incident patients yielded no significant difference in the albumin over time-parameter estimate (0.039 g/dL/month, $P < 0.0001$). Also, when patients who had started dialysis within three months of the initiation of this study were removed, there was still a significant difference in the trend of albumin over time (0.037 g/dL/month, $P < 0.0001$, $N = 271$, rather than

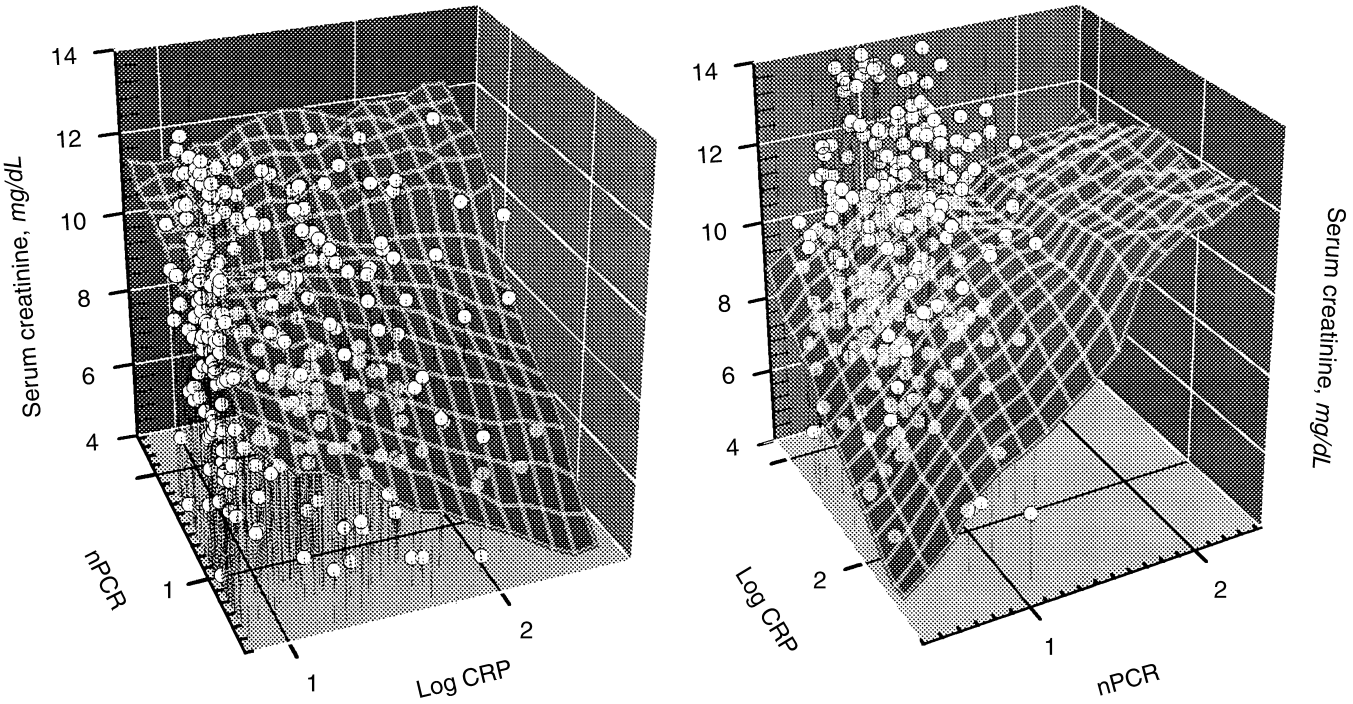

Fig. 2. Relationship between the dependent variable, creatinine and nPCR, and log-transformed CRP concentration is represented on a plane. The individual data points are represented as open symbols. Albumin = 3.877 − (0.409 * log CRP) + (0.481 * nPCR). $N = 287$; $R = 0.449$; log CRP < 0.001; nPCR < 0.001.

364). Thus, the increase in serum albumin over time was not due solely to changes among incident patients or patients starting dialysis 90 or fewer days earlier.

There was a significant interaction between log CRP and race ($P = 0.02$), with African-American race attenuating the (negative) effect of inflammation on serum albumin concentration. The effect of log CRP on serum albumin was −0.108 g/dL/month among African Americans, compared with −0.141 g/dL/month among the non-African Americans, corresponding to a 23% relative decrease in the effect. There was a highly significant interaction between log CRP and nPCR ($P < 0.0001$). Considering the trend in serum albumin over time, the overall effect of inflammation (log CRP) was negative, and the overall effect of dietary protein intake (nPCR) was positive. However, lower dietary protein intake tended to facilitate the adverse effects of inflammation, while higher dietary protein intake tended to defend against those effects. Finally, there was a minuscule effect of Kt/V on serum albumin (−0.005 g/dL/month per 0.1 increase in Kt/V) that did not reach statistical significance ($P = 0.053$).

There were 352 patients with at least two serum creatinine determinations during the six-month period of study. The overall trend in serum creatinine concentration over time was estimated at −0.052 mg/dL/month. nPCR was the most important determinant of serum creatinine concentration, with an effect of 0.183 mg/dL/month per 0.1 g protein/kg/day increase ($P < 0.0001$). In addition to age, sex, race, and diabetes, vintage and Kt/V were significantly associated with the serum creatinine trend.

The longitudinal analysis of serum creatinine confirmed the cross-sectional results, indicating a significant effect of inflammation on serum creatinine over time. Per unit increase in log CRP, there was a −0.142 mg/dL/month decrease in serum creatinine concentration. There were no significant interactions among nPCR or log CRP and other covariates on the trends in serum creatinine.

Two additional longitudinal analyses were conducted. The first was to confirm the validity of the Mixed model by examining the effect of log CRP on hematocrit, as inflammation is well known to promote erythropoietin resistance, and to decrease erythrocyte production. Indeed, there was a significant effect of log CRP on hematocrit (−1.0% hematocrit per month per unit increase in log CRP, $P < 0.0001$), with or without adjusting for case mix and other laboratory variables. We then explored whether there was an effect of inflammation on dietary intake, using nPCR as the dependent variable in another Mixed analysis. This model showed a small effect of log CRP on serial nPCR (−0.032 g/kg/day per unit increase in log CRP, $P = 0.0002$).

DISCUSSION

Hypoalbuminemia is a potent risk factor for mortality and morbidity in ESRD and in other populations, includ-

ing the older patients and individuals undergoing a variety of types of noncardiac surgery [21, 22]. While reduced dietary intake can lead to hypoalbuminemia, these effects are generally mild. In a prospective 24-week study in which healthy volunteers were subjected to semistarvation (1500 kcal/24 h), serum albumin decreased only moderately (from 4.28 to 3.86 g/dL) in spite of a 23% reduction in body weight and muscle mass [23]. Therefore, more significant reductions in serum albumin concentration reflect processes beyond nutrient deprivation, specifically external losses (as with peritoneal dialysis) and inflammation [24].

Serum albumin levels decrease with inflammation because of several factors, including reduced synthesis, increased catabolism, and translocation of albumin to extravascular pools [25]. It is unlikely that hypoalbuminemia per se directly causes events that precipitate mortality. Despite the important functions served by albumin, hereditary analbuminemia is compatible with normal life. Individuals with hereditary analbuminemia are essentially asymptomatic and present primarily with hyperlipidemia [26]. This observation suggests that the underlying processes associated with hypoalbuminemia are responsible for the increased risk of death in ESRD, rather than the low level of albumin itself.

While the link between hypoalbuminemia and mortality may be largely explained by albumin (or cholesterol or prealbumin) behaving as a negative acute phase reactant, this mechanism does not fully explain why predialysis serum urea nitrogen, serum creatinine, and nPCR have also been inversely correlated with mortality in several studies. TNF-α and IL-1 directly suppress appetite [27, 28]. Cytokines may also induce catabolism, leading to a wasting illness that is indistinguishable from prolonged starvation. In particular, IL-6 and TNF-α induce muscle breakdown in rats, and IL-6 appears to mediate experimental cancer cachexia [29]. Administering IL-6 receptor antibodies prevented these effects in mice transgenic for IL-6 [30]. Therefore, the inflammatory response may induce protein-energy malnutrition by decreased intake, in addition to increased catabolism. Of note, should infection cause negative nitrogen balance in the context of these studies, then nPCR should overestimate the effect of dietary protein. Thus, our statistical analysis of the effect of nPCR on outcome variables (creatinine and albumin) is weighted against us. Indeed, had we a direct measure of nitrogen intake, the associations may have been stronger.

We have recently established that inflammation in the hemodialysis patient population is also a dynamic process [31]. The levels of acute phase proteins vary widely, while serum albumin concentration varies on a far smaller scale. The reason for this is the much larger range in available values for the major acute phase proteins, such as CRP, and the much shorter half-lives [32] when compared with albumin [33]. Nevertheless, in cross-sectional studies, the concentrations of markers of inflammation vary in lock step with the concentration of albumin [31]. The cross-sectional and longitudinal results are consistent with what has been reported about the effects of inflammation both on albumin concentration and synthetic rate [34] as well as on muscle protein [35, 36]. The observation that higher protein intake may attenuate the effects of inflammation is consistent with results from prospectively controlled trials in which nutrient intake was intentionally controlled in patients following trauma [37, 38] and during recovery from trauma [39].

The individuals described herein were not asked to modify their diet for the purpose of this investigation. Interestingly, very few patients with high CRP values have nPCR in excess of 1.0 g protein/kg/day (Figs. 1 and 2, right panels). If one were to extrapolate the Mixed models, increases in nPCR above 1.0 g protein/kg/day might either slightly increase or attenuate the decrease in serum albumin and creatinine concentrations during episodes of inflammation.

Figures 1 and 2 are each three-dimensional plots representing a single cross section in time of the patient population. Even within this randomly selected cross-section, it is clear that at nPCR $\geq$1.2, the relationship between log CRP and both albumin and creatinine is relatively flat, in contrast to what is seen for nPCR $<$1.0. Thus, even within the range observed here, there is attenuation of the effect of increased CRP. While it is not possible to present graphically the interaction between these variables over time, if one dichotomizes to nPCR $\geq$1.0 vs. nPCR $<$1.0, we see a difference ($-$0.1157 vs. $-$0.1368 g/dL/month per log unit increase in CRP). Of note, there are very few patients who spontaneously have an nPCR $\geq$1.0 and high levels of CRP simultaneously. Our data suggest that this group, while small, suffer less of an effect of increased CRP on the outcome variables measured (albumin and creatinine). We think this is an important observation because it might be possible to modulate the effects of inflammation intentionally by increasing protein and calorie intake, and thus increasing nPCR by intent. Alternatively, the patients who continue to have a high nPCR during inflammation may have other significant differences than those who do not, and they may just reflect different populations. For example, since cytokines directly suppress appetite, those patients who continue to spontaneously eat adequately despite elevated CRP levels may have less systemic inflammation.

We have previously reported an association between the administration of IDPN and survival in maintenance hemodialysis patients [40]. More than 1600 patients who had received IDPN were compared with $>$22,000 non-IDPN recipient controls, adjusting for age, sex, race, diabetes, serum creatinine, and dialysis dose. Among individuals with hypoalbuminemia, there was a signifi-

cant reduction in the odds of death at one year. Among individuals whose initial serum albumin concentration was <3.0 g/dL, the odds of death were 0.70, or 30% below expected. The increase in survival was accompanied by steady increases in the mean serum albumin and creatinine concentrations during the months after starting IDPN. Our present findings suggest that intentionally increasing protein and calorie intake within the population of dialysis patients who have increased CRP levels might improve serum albumin and survival. IDPN indeed may provide such a means. To establish a positive effect would require prospective trials.

This study has several important limitations. First, the CRP assay was insensitive in the lower range. The chosen assay resulted in some misclassification, in that the referent CRP group included patients with very low and low CRP values who could not be differentiated. This would have diminished the RR estimates of higher CRP concentrations. Using a more sensitive assay, we found a significantly increased risk when patients with CRP values between 2.6 and 5.2 μg/mL and patients with CRP values ≤2.6 μg/mL were compared [12]. More importantly, the "floor" induced by the assay may have resulted in slightly inaccurate effect estimates (on serum albumin and creatinine). However, the effects of CRP on albumin and creatinine are a function of the log of CRP and are thus amplified at very high levels, and quite small and indeed undetectable statistically when the levels are low. The insensitivity of the assay used for CRP is therefore unlikely to have affected the observed interactions significantly. While important to consider, this limitation would not have affected the qualitative results. Second, dietary intake was not measured. The nPCR is considered a valid surrogate for dietary protein intake under steady-state conditions. However, particularly in the face of inflammation, the nPCR may overestimate dietary protein intake because of endogenous nitrogen breakdown. Moreover, normalizing the PCR to body weight may introduce error since the somatic protein pool (that is, skeletal muscle) is not perfectly correlated with body weight. For example, normalization of PCR in an obese individual may result in an underestimate of dietary protein intake compared with the direct dietary assessment. While clearly imperfect, we do not believe that the qualitative results would have changed had data on dietary protein intake been available. Third, since all patients studied were on hemodialysis, our findings cannot be extrapolated to patients on peritoneal dialysis. In addition to the factors influencing albumin concentration described here, peritoneal transport characteristics and other factors additionally influence albumin metabolism in the peritoneal dialysis population. Finally, while the observational nature of this study enhances its generalizability, the associations described may not be causal. In other words, while a sustained increase in nPCR may directly increase serum albumin and creatinine, other factors confounding both nPCR and albumin may be operative. We believe that inflammation is one of these factors; if this is indeed true, we depend on CRP alone to fully adjust for the effects of inflammation. CRP levels change rapidly, and our measurements were made monthly, leaving potential gaps in our periods of observation. More long-lived acute phase proteins, such as α1 acid glycoprotein, fibrinogen, or ceruloplasmin, may provide additional information if available. We may also be able to develop a more comprehensive understanding of the inflammation-intake paradigm by consideration of cytokines (for example, IL-1, IL-6, TNF-α) or negative acute phase proteins (for example, prealbumin and transferrin) in future studies.

In summary, inflammation and dietary protein intake exert competing effects on serum albumin and creatinine over time that are statistically significant and clinically meaningful. Therapeutically, the model would predict that by increasing nPCR from 0.8 to 1.2 g/kg/day, one might expect an increase in albumin of approximately 0.5 g/dL and an increase in creatinine of approximately 4.4 mg/dL over a six-month period, all else being equal. The effects of increased dietary protein intake on albumin might be accentuated in the face of inflammation. While the aphorism of old may be "feed a cold, starve a fever" [41], at least among hemodialysis patients with biochemical evidence of inflammation, the opposite therapeutic strategy of protein–nutritional supplementation should be prospectively tested in clinical trials.

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