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The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients

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The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients.

Background. Cross sectional studies have established that the serum albumin level is dependent on serum levels of acute-phase proteins (APPs) or cytokine levels in hemodialysis patients. While the acute-phase response is generally associated with acute inflammatory events, a cross sectional analysis relating laboratory values to outcomes assumes these values to be unchanging. The longitudinal relationship among laboratory measurements and how they vary over time in a population of patients are unknown.

Methods. Patients who were enrolled in the HEMO Study were recruited into an ancillary longitudinal study to establish the predictive effect of temporal variation in the levels of APPs and of temporal variation in normalized protein catabolic rate (nPCR) on the serum albumin concentration. nPCR was measured monthly using a double-pool method. The positive APPs—C-reactive protein (CRP), α1 acid glycoprotein (α1-AG), and ceruloplasmin—and the negative APP—transferrin (Trf)—were measured in serum obtained before each dialysis session for six weeks and then monthly in 37 hemodialysis patients. A random coefficient regression analysis was used to assess the association of serum albumin with other measured parameters at each time point, as well as fixed patient characteristics.

Results. The within-subject coefficients of variation of albumin (median, range of 25th to 75th percentiles; median, 0.0614; range, 0.0485 to 0.0690) were significantly less than that of APPs (CRP, median, 0.878; range, 0.595 to 1.314, $P < 0.05$; and α1 AG, median, 0.173; range, 0.116 to 0.247, $P < 0.05$). The levels of APPs and albumin varied considerably over time. The primary predictor of current albumin was the current CRP level ($P = 0.0014$). nPCR also was a significant predictor for albumin levels ($P = 0.0440$) after controlling for the effect of APPs, suggesting an effect of nPCR on serum albumin concentration irrespective of the acute-phase response. Age and the presence of an arteriovenous graft were significant predictors that were associated with reduced albumin.

Conclusions. The acute-phase response is intermittent and is not a continuous feature in individual dialysis patients. Levels of APPs are the most powerful predictors for the levels of albumin concentration in hemodialysis in a longitudinal setting. Since variations in albumin are small, measurement of variations in APPs may provide greater insight into the dynamics of clinically relevant processes.

Key words: C-reactive protein, inflammation, transferrin, α1 acid glycoprotein, vascular access, nPCR albumin.

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Hypoalbuminemia is a powerful predictor of death [1] and has been associated with as much as a 20-fold increase in the relative risk of death [2]. It has been suggested that malnutrition, evidenced by hypoalbuminemia, plays a role in mortality. While hypoalbuminemia and malnutrition have been used nearly synonymously [3], there is strong evidence that inflammation also plays a role in determining the level of serum albumin in hemodialysis patients [4–6]. Both C-reactive protein (CRP) levels [4, 5] and cytokine levels [6] are predictive of temporal variation in albumin concentration in cross sectional studies, and they also predict survival [6, 7]. We previously reported that the levels of acute-phase proteins were increased in only about 30% of hemodialysis patients [4]. Others have found a similar proportion of dialysis patients exhibiting evidence of inflammation [7, 8].

Both CRP and cytokine levels also predict cardiovascular disease in patients without renal failure [9–12], as well as mortality from vascular disease [9–13]. Among patients with renal failure, those with elevations in CRP or those with hypoalbuminemia also have a significant increase in vascular disease [8], as well as an increase in cardiovascular death [7]. It has been postulated that inflammation is either a cause or a consequence of endothelial dysfunction and/or vascular disease [14]. Approximately 30% of hemodialysis patients have increased levels of CRP [4, 7, 8], consistent with the increased prevalence of vascular disease in this population [15].

Furthermore, the serum albumin concentration also correlated with normalized protein catabolic rate (nPCR), independently of CRP, in our cross sectional analysis [4]. Clearly, inflammation may affect appetite and thus cause both a direct suppression of albumin synthesis and a decrease in nPCR, presuming that the latter reflects protein ingestion.

All of the published studies have been based on cross sectional analysis following a single measurement. It is unknown whether this evidence of inflammation represents a chronic condition or instead an indicator for single or multiple acute processes. Indeed, it is unknown whether activation of the acute-phase response, as measured by increased CRP levels, is a consequence of chronic infection or of chronic inflammation as might result from underlying endothelial dysfunction, or instead represent an acute time-limited process. We address the temporal variability of the acute-phase response and the nPCR, as well as its relationship to albumin concentration at each point in time in a group of dialysis patients.

METHODS

Patient selection

Patients enrolled in the HEMO study sponsored by the National Institutes of Health in two of the participating centers, one at the University of California Davis (Sacramento, CA, USA), and the other at Beth Israel Medical Center (New York, NY, USA), were recruited to participate in this ancillary longitudinal study. During the first six weeks of observations, albumin, transferrin (Trf), CRP, α1-acid glycoprotein (α1-AG), and ceruloplasmin (Cer) were each measured weekly. Following that period, each protein was measured monthly on serum obtained from predialysis samples. nPCR was measured monthly using a double-pool method [16].

Two patients were dialyzed using a CA210 dialyzer, and four were dialyzed using a CT190G dialyzer (Baxter Healthcare Corporation, Deerfield, IL, USA). All of these were subjected to reuse with bleach/formaldehyde. Ten patients were dialyzed with F8 dialyzers (Fresenius Medical Care AG, Bad Homburg, Germany) reused with bleach/formaldehyde, four with F8 dialyzers reused with citric acid, and one with an F6 dialyzer without reuse. Seven patients were dialyzed with a F80B dialyzer reused with bleach/formaldehyde and nine with an F80A dialyzer reused with citric acid.

All dialysis was performed using a bicarbonate-based dialysate at a delivered bicarbonate concentration of 39 mEq/L.

Nine patients had glomerulonephritis as the cause for renal failure. Of these, one had heroin nephropathy. Four patients had renal failure caused by hypertension. Two patients had hereditary nephritis. Two had polycystic kidney disease, and one had analgesic nephropathy. One patient had end-stage renal disease (ESRD) of unknown (unassigned) etiology, and the remainder (10) were diabetic and were presumed to have diabetic renal disease.

Kt/V was measured monthly, but we were not permitted to analyze any outcome using that variable, since it was part of the randomization scheme of the HEMO study and the investigators were blinded to that parameter.

All of the patients were anuric, so urinary protein losses did not perturb serum protein concentrations.

Laboratory methods

Albumin was measured in duplicate using bromcresol green. All other proteins were measured with rate nephelometry using a Beckman Array automated nephelometer [17]. All nephelometric measurements were made in duplicate in each of two optical systems. The average of these values was used for calculations.

Plasma volume measurements

Plasma volume was determined at the time of the first measurement of acute-phase proteins (APPs) by an intravenous injection of [^{125}I] human serum albumin as described previously [18]. A 10 μCi bolus of [^{125}I] human albumin was injected, and blood samples were drawn at 5, 15, 30, and 60 minutes. The serum was separated and counted in a γ counter. The plasma was counted in triplicate. Plasma volume was calculated by regression to zero time. Weight at the time of measurement in kilograms was used to calculate plasma volume in percent.

The mean value for each protein and for nPCR was calculated for each patient. The median and range of each parameter were calculated from the mean for each parameter for each patient.

Statistical methods

From longitudinal measurements of albumin, CRP, α1-AG, Cer, Trf, and nPCR on 37 dialysis patients, we conducted a random coefficient regression analysis [19] in an attempt to determine how well the albumin concentration at each point in time could be established by the other measures. This method assumed that each subject had his/her own set of regression coefficients that were random variables all following the same joint population distribution. Considering the random coefficients to be nuisance parameters, our interest was in generating the fixed effects coefficients and determining the contribution of the fixed effects in describing the association of serum albumin with concurrently measured predictor variables. We also wanted to determine whether any of a set of fixed demographic and medical variables included at the start of the study played a role in describing albumin concentration. These variables included patient

gender, ethnicity, age, and vascular access at the time of entry, presence or absence of diabetes, and body mass index (BMI). Additional details are given in the **Appendix**.

The modeling was performed in two stages. First, we tried to find the best model for predicting the measured albumin concentration at each time point using only the longitudinally measured physiological variables (that is, CRP, α1-AG, Cer, Trf, and nPCR) as predictors. Here, we used stepwise forward variable selection using the Akaike Information Criterion (AIC Criterion), which is a commonly used model selection criterion that penalizes models for containing too many predictors. In a second step, after obtaining the best model based on the physiological variables, the demographic variables and other patient characteristics were considered as additional predictors. These variables were considered for inclusion in the model as fixed effects. Ethnicity was divided into white, black, and Hispanic. Asian patients formed the baseline group for ethnicity against which the other ethnicities were compared.

Finally, coefficient of variations (CVs) for each protein and nPCR were measured. Differences between CVs were assessed by pair-wise *t*-tests for dependent data.

RESULTS

The patients ranged in age from 19 to 81 years, with a median of 59 years. The 25th and 75th percentiles were 49.5 and 69 years, respectively. The BMIs of the patients ranged from 16.6 to 33.3 kg/m^2, with a median value of 24.5 kg/m^2. The 25th and 75th percentiles were 21.1 and 27.2 kg/m^2, respectively. There were no significant differences in these values in the patients enrolled in the two study centers.

Plasma volume was 4.95 ± 1.16%, with a range of 2.93 to 8.05% body weight. There was no correlation between plasma volume and plasma albumin concentration (r^2 = 0.00355, P = 0.726; Fig. 1).

There was a total of 20 patients who had arteriovenous (AV) grafts, 12 with AV fistulas and 5 with transcutaneous access (catheters). Fifteen patients had diabetes mellitus, and 22 did not. The mean time that patients had been on hemodialysis at the initiation of this study (measurement of plasma volume followed by subsequent determination of serum proteins) was 57.8 months, with a range of 117.3 months (minimum 10.3 months, maximum 127.6 months, 75th percentile 76.2 months, 25th percentile 41.3 months). There was no difference in the time of initial of dialysis and the start of this study between the patient population at Beth Israel Medical Center and the population at UC Davis Medical Center. Ethnic and gender demographic data are presented in Table 1.

The median and range (25th and 75th percentile) for the concentration of each protein and for nPCR are presented in Table 2.

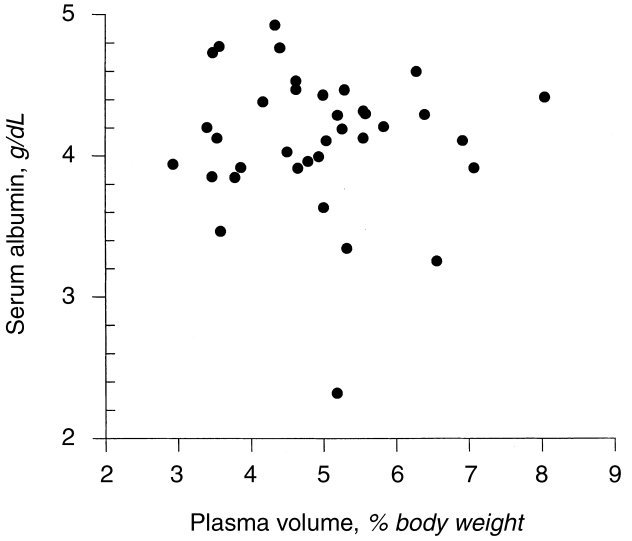

Fig. 1. Relationship between initial plasma volume measured by isotope dilution ([^{125}I] human serum albumin) and initial serum albumin concentration (R2 = 0.00355; P = NS).

Neither the serum albumin concentration nor that of APPs was constant. The levels of APPs varied considerably over time (Fig. 2). Variances in CRP were two orders greater than that of albumin or Trf, and variances in α1-AG were one order of magnitude greater than that of albumin (Fig. 2). The acute-phase response was usually of limited duration (Fig. 3). Figure 3 shows the temporal relationships between albumin and CRP levels in 12 consecutive patients in whom CRP values varied by a minimum of one order of magnitude. At each point in time, the concentration of serum albumin was associate with the current levels of the APPs and nPCR. Of these, CRP was the strongest predictor of serum albumin.

The between-assay CV for the CRP assay was less than 2% and for that of the albumin assay was less than 3%.

The fixed effects parameter estimates and P values for tests of significance are reported in Table 3. Note that the model fitting included both fixed and random effects. The predictors listed in Table 2 resulted in the best overall model fit only from the longitudinal predictors (after incorporating a penalty for including too many variables in the model via AIC). The CRP coefficient estimate was negative and highly significant, indicating a strong inverse relationship between albumin and CRP. Additionally, the nPCR coefficient estimate was significantly positive. The Cer and α1-AG coefficient estimates were small and insignificant.

Concerning fixed parameters, ethnicity, gender, the presence of diabetes, and BMI failed to achieve significance. Both age and the presence of an AV graft were

Table 1. Demographic characteristics of patients by ethnicity, gender and hemodialysis center

Location	Ethnicity	Female	Male	Subtotal	Total
University of California Davis	African American	5	6	11	
	Asian	1	2	3	
	Hispanic		3	3	
	White	2	5	7	24
Beth Israel	African American	5	3	8	
	Hispanic		3	3	
	White	1	1	2	13

A total of 37 hemodialysis patients who had been entered into the HEMO study were entered into an ancillary study in which the concentration of a group of acute phase proteins were measured longitudinally over time.

Table 2. Median values and range for each parameter

	Range of means of the parameters		Means of the parameters
Parameter	25th	75th	Median of the means
Albumin	3.91 g/dL	4.29 g/dL	4.08 g/dL
CRP	0.364 mg/dL	2.05 mg/dL	0.991 mg/dL
α1-AG	93 mg/dL	149 mg/dL	117 mg/dL
Ceruloplasmin	33.9 mg/dL	48.6 mg/dL	37.7 mg/dL
Transferrin	169 mg/dL	207 mg/dL	186 mg/dL
nPCR	0.801	1.04	0.897

The mean value for each protein and for nPCR was calculated for each patient. The median and range of each parameter was calculated from the mean for each parameter for each patient. The 25th and 75th percentile and median for the concentrations of the proteins and for nPCR (parameters) are presented.

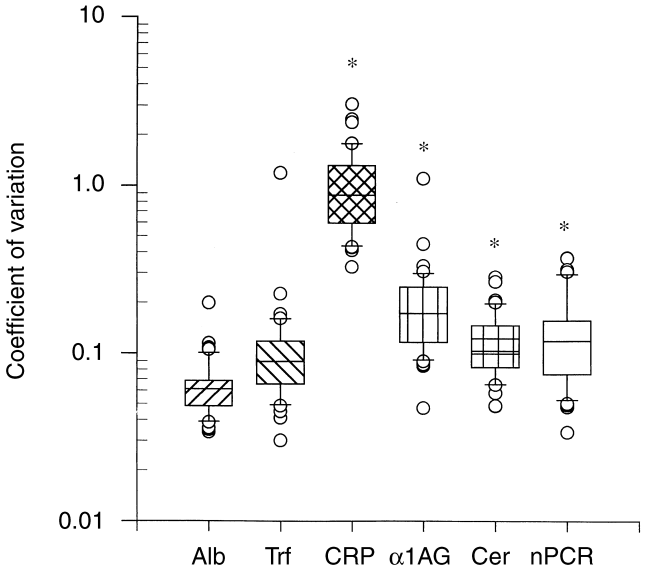

Fig. 2. Coefficients of variation of albumin (Alb), transferrin (Trf), C-reactive protein (CRP), α1-acid glycoprotein (α1-AG), ceruloplasmin (Cer), and normalized protein catabolic rate (nPCR) during sequential measurements in 37 patient on hemodialysis. Results are presented as means and standard deviations; $*P < 0.05$ vs. albumin.

significant in predicting albumin concentration and were included in the final model (Table 4). Specifically, the included nonlongitudinal predictors, age and vascular access, were instrumental in predicting the base level of albumin. In the fitted model, this predicted baseline was then added to the time-varying effects on albumin by the longitudinal predictors. With age and access added as predictors, the model fit improved on the model that contained only the longitudinal predictors, CRP, nPCR, Cer, and α1-AG, according to the AIC criterion. Other variables considered did not improve on this new model. It should be noted that at this point, it cannot be excluded that once the sample size grew, some of the variables that were omitted in the current model, such as ethnicity or BMI, and especially the presence of a transcutaneous access (catheter), could eventually reach statistical significance.

As a final note, we looked at the possibility of lagged predictors in the random coefficient regression model. For example, do changes in CRP temporally precede changes in albumin? We found that none of the lagged predictors were of additional predictive value for albumin change. The absence of an influence of previous levels of CRP on current albumin levels may have been a consequence of the time interval between measurements (up to 1 month) in the study and also reflected the positive correlation of adjacent measurements.

DISCUSSION

Several groups have reported evidence that inflammation is responsible for establishing serum albumin concentration in patients on hemodialysis in cross sectional studies [4–6, 8]. To our knowledge this is the first longitudinal observation of the acute-phase response, as measured by APPs, in this patient population in which the of the relationship between albumin concentration and that of APPs and of nPCR at each time point has been made. It has been proposed that the dialysis process is directly responsible for inflammation in hemodialysis patients [20–22]. Our data would instead suggest that transient processes are responsible for activation of the acute-phase response in the cohort of patients examined here. The acute-phase response generally spanned a period of several dialysis treatments, a finding that is inconsistent with an intradialytic cause of inflammation. CRP has recently been associated with vascular disease in

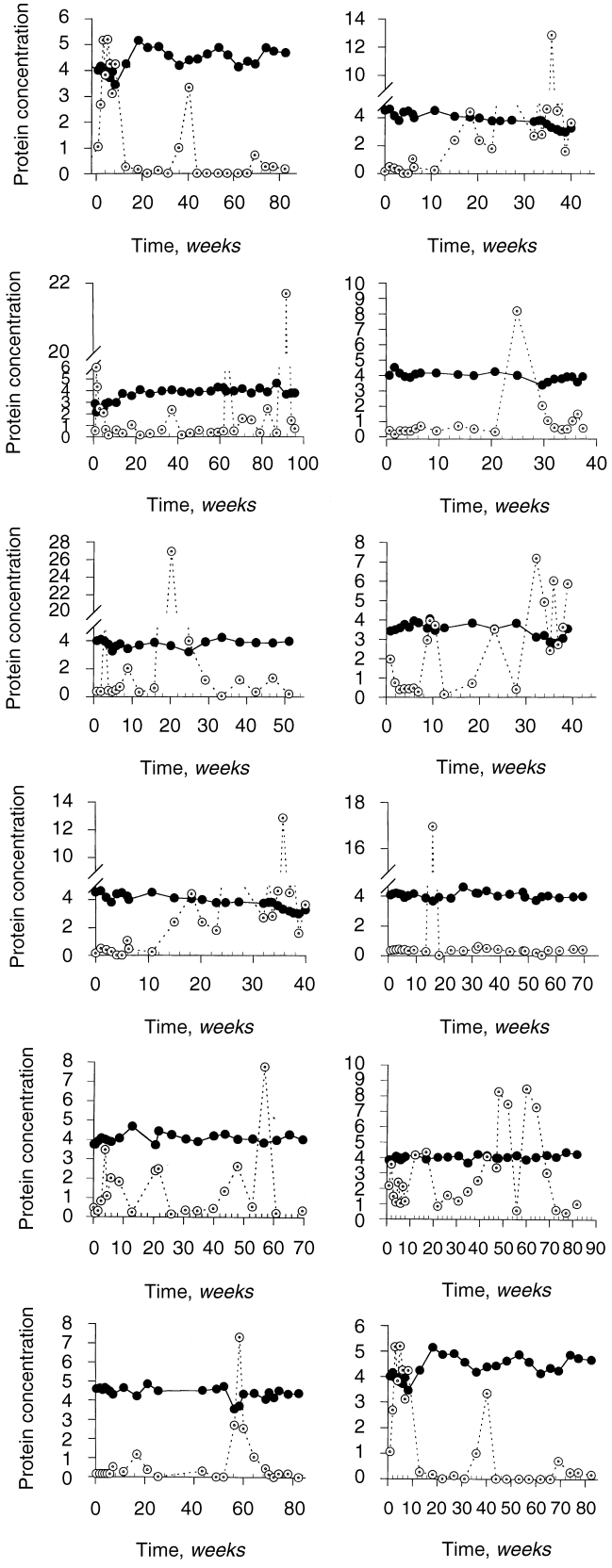

Table 3. Fixed effect parameter estimates

	Value	Approximate standard error	Z ratio	*P* value
Intercept	3.964	0.2003	19.796	
CRP	−0.036	0.0122	−2.956	0.0031
nPCR	0.230	0.1031	2.227	0.0259
Ceruloplasmin	0.00203	0.0042	0.477	0.6334
α1-AG	−0.00056	0.0011	−0.487	0.6263

The results of a random coefficient regression analysis based solely on the longitudinal measurements to determine how well albumin levels over time were determined by changes in the other measures. This method assumed that each subject had his/her own set of regression coefficients that were random variables all following the same joint population distribution. We utilized a stepwise forward variable selection, resulting in a model that contained CRP, nPCR, ceruloplasmin, and α1-AG as predictors. The model fitting techniques factor in both the fitting of the fixed and random effects. So, even though two of the above four fixed effect estimates are not considered statistically significant, this particular group of variables resulted in the best overall model fit.

Table 4. The final model for explaining the variation in albumin concentration over time

	Estimates			
Fixed effects	Value	Standard error	Z ratio	*P* value
(Intercept)	4.4053	0.2418	18.222	
CRP	−0.0390	0.0122	−3.196	0.0014
nPCR	0.2115	0.1050	2.014	0.0440
Cer	0.0041	0.0039	1.066	0.2866
α1-AG	−0.0007	0.0011	−0.621	0.5347
Age per year	−0.0057	0.0026	−2.224	0.0261
Graft $N = 20$	−0.2388	0.0833	−2.869	0.0041
Catheter $N = 5$	−0.1994	0.1234	−1.616	0.1060

After obtaining the best model based on the longitudinal physiological variables, a variety of demographic variables and other patient characteristics were considered as additional fixed effects predictors. The only variables that remained in the final model were age and type of vascular access.

patients without renal failure [9–11]. Cardiovascular mortality predictions have been based on a single measurement, suggesting that a single episode of inflammation either is reflective of underlying vascular disease that only intermittently expresses itself by overt activation of the acute phase response or that intermittent inflammation leads to pathologic vascular change that subsequently leads to mortality. Stenvinkel et al established that CRP levels correlated with carotid artery structure, as assessed by ultrasonography in dialysis patients [8]. This finding would suggest either that vascular disease predisposes patients to both episodic increases in CRP levels and also separately to subsequent morbidity from that vascular disease or, if inflammation in their population occurs in a pattern that is similar to what we report

Fig. 3. Temporal variation in serum albumin concentration (●, g/dL) and CRP concentration (○, mg/dL) in 12 consecutive hemodialysis patients in whom CRP changed by at least one order of magnitude during the period of observation.

here, that transient inflammatory processes lead to demonstrable vascular disease quite quickly.

The half-lives of cytokines and of the APPs are quite short, and their total body masses are quite small in comparison to that of albumin [23–26], and in the cases of CRP and serum amyloid A (SAA), the biological range in values varies by up to 1000-fold [27]. For that reason, changes in the albumin fractional catabolic rate or in the rate of albumin synthesis require considerable time to be seen. Furthermore, the biological range of albumin synthetic rates, fractional catabolic rates, and serum values are much smaller than those of either CRP or cytokines. This we believe is the reason for the contrast in variances between albumin and Trf on one hand and the positive APPs we measured on the other. Clearly, a measurement of CRP not only correlates with low albumin levels [4, 5, 7, 8], but because the variability in CRP is far greater than that in albumin, it is easier to detect events that may lead to morbidity by measuring this parameter. The greater range of CRP values with similar precision in the two assays may make it a more sensitive clinical indicator of morbidity than is albumin. It should be noted that measurement of limitations of our study design could not enable us to use CRP levels to predict future albumin concentrations, since measurements of both proteins were made at one month intervals.

Normalized protein catabolic rate, a marker of nitrogen intake at steady state, also has described albumin concentration at each time point, consistent with our previous single cross sectional study [4]. However, we found no evidence for an interaction of the effects of nPCR and CRP. Thus, two separate processes, inflammation and reduced protein catabolism, most likely reflect the reduced protein intake, each separately contributing to cause a decrease in serum albumin concentration.

The use of intensive nutritional support, including intradialytic parenteral nutrition (IDPN), remains controversial [28–30]. One problem with analysis of the effect of purely nutritional-directed therapy on outcomes resulting primarily from a non-nutritional cause, such as inflammation, could be resolved by evaluating separately patients with primarily nutritionally induced hypoalbuminemia, having low levels of both CRP and nPCR from those in whom CRP is elevated.

We were able to observe an effect of age and vascular access on predicting albumin concentration. However, we were unable to detect an effect of ethnicity, the presence of diabetes, or BMI on predicting changes in albumin concentration. It is possible that this lack of association between some of these variables and albumin change is a result of the moderate sample size, and other conclusions will be drawn by studies of greater power.

C-reactive protein and interleukin-6 have each been found to be powerful predictors of both serum albumin concentration and of mortality [9, 10]. All of these observations have been based on cross-sectional analysis of data. These previous observations suggest that even a single episode of activation of the acute-phase response has lethal potential that is easily identifiable in relatively small populations [9, 10] and that may occur even following the resolution of that acute episode. This is surprising considering the fact that CRP levels vary and are increased for only a fraction of time in any given dialysis patient.

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APPENDIX

The form of the random coefficients regression model is as follows:

$$y_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})\, x_{ij1} + (\beta_2 + b_{i2})x_{ij2} + \ldots + (\beta_{q-1} + b_{i,q-1})x_{ij,q-1} + \beta_q x_{ijq} + \ldots + \beta_{r-1}x_{ijr-1} + \varepsilon_{ij} \quad (1)$$

where y_{ij} represents the albumin concentration for patient i at time j; x_{ijk} represents the k^{th} predictor (for example, CRP) for patient i at time j; β_0 is the population average intercept. $\beta_1, \beta_2, \ldots, \beta_{q-1}$ are the population average slopes corresponding to longitudinal physiological measurements. $\beta_q, \beta_{q+1}, \ldots, \beta_{r-1}$ are the population average slopes for the fixed predictors (that is, demographic and other prestudy measurements). b_{i0} is the random effects intercept term for patient i, and $b_{i1}, b_{i2}, \ldots, b_{i,q-1}$ are the random effects slope terms for patient i. There are a total of q random effects and r fixed effects. Finally, ε_{ij} is the within-subject error term for patient i at time j. Assuming the ε_{ij} are independent of the $b_i = (b_{i0}, b_{i1}, \ldots, b_{i,q-1})^t \sim N(0, D)$, where D is the covariance matrix of the random effects. We assume $\varepsilon_i = (\varepsilon_{i1}, \varepsilon_{i2}, \ldots, \varepsilon_{ini})^t \sim N(0, \sigma^2\Lambda_i)$, where n_i = number of observed times for patient i. Since it is likely that a positive within-subject correlation exists and owing to the fact the designs varied from patient to patient, we found it appropriate to model the within-subject correlation, represented by Λ_i, with an AR1-continuous process.

Note that all analyses were performed using the linear mixed effects model function, lme(), in S-Plus, version 4.5 [31, 32].

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