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Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis

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Abstract

Purpose Serum albumin is one of the strongest mortality predictors in maintenance hemodialysis (MHD) patients. Yet, the degree to which serum albumin represents dietary protein intake or an inflammatory state, among others, is not clear. We hypothesize that these inadequate protein intake and inflammation contribute somewhat equally to hypoalbuminemia.

Methods In a cross-sectional analysis, we examined correlates of low serum albumin, <3.8 g/dL, in 812 MHD patients in whom interleukin-6 (IL-6) and normalized protein nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), were also measured. Logistic regression estimated odds ratios were employed, and spline models were plotted to examine the likelihood of relatively low serum albumin <3.8 g/dL.

Results Mean age (±SD) of patients was 54 ± 15 years; 53 % of patients were men, 50 % Hispanic, 31 % African–American, and 55 % diabetic. The mean dialysis vintage was 31 ± 34 months (median: 19, inter-quartile range: 7–44 months). The baseline serum albumin, averaged over a 3-month period (mean ± SD), was 3.88 ± 0.38 g/mL. The unadjusted correlation coefficients of l IL-6 and nPNA with serum albumin were −0.36 and +0.20,

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respectively ($p < 0.001$ for each comparison). The likelihood for an albumin <3.8 gr/dL increased linearly with decreasing nPNA and rising serum IL-6. This trend was steeper with increasing serum IL-6 up to a concentration of 30 ng/mL.

Conclusions Both low protein intakes and a high state of inflammation are associated with low serum albumin in MHD patients.

Introduction

Many individuals with advanced chronic kidney disease (CKD) who receive chronic hemodialysis (HD) treatment suffer from various degrees of protein-energy wasting (PEW) [1–3]. The *International Society of Renal Nutrition and Metabolism* (ISRNM) Expert Panel recently proposed a set of criteria for the detection of PEW, among which low serum albumin is one of the key diagnostic criteria [2].

Since maintenance hemodialysis (MHD) patients have little or no glomerular filtration rate (GFR), the change in serum urea nitrogen between and during hemodialysis sessions becomes a reliable indicator of dietary nitrogen intake, provided the patient is in a steady state. Although indirect, this measure of protein intake is referred to as the urea kinetic-based *protein nitrogen appearance* (PNA) or *protein catabolic rate* (PCR), which is usually *normalized* (*n*) to a typical body weight, hence, the *nPNA*. It was previously showed that the nPNA is a strong and independent predictor of mortality in MHD patients [4].

Protein-energy wasting (PEW) and inflammation are closely associated in MHD patients [5, 6]. Chronic inflammation is common in uremia, in part because of factors related to the GFR and to the standard dialysis procedure itself [7, 8], but also because of a genetic predisposition [9, 10]. Measures of inflammation and PEW are important predictors of mortality in patients with end-stage renal failure [11, 12].

In maintenance dialysis patients, a low serum albumin level is an indicator of more severe comorbidity, worse general health status, and protein-energy wasting (PEW) [13]. Hypoalbuminemia is a strong predictor of both cardiovascular [14] and all-cause mortality [15] and post-transplant mortality [16] in patients with different stages of CKD including those undergoing chronic dialysis treatments [17]. Although the serum albumin is a strong and clinically important predictor of adverse outcomes, it is not entirely known, which clinical markers are associated with serum albumin.

Although previous studies have shown that both dietary protein intake and inflammatory markers [18–20] are associated with serum albumin in MHD patients, to our knowledge, no study in the last 10 years has examined the association between protein intake and inflammatory markers and serum albumin level in MHD patients. We hypothesized that low serum albumin is associated with higher level of inflammatory markers and lower protein intake.

Methods

Patient population

We studied MHD patients who were participating in the *Nutritional and Inflammatory Evaluation in Dialysis* (NIED) Study [21]. The original patient cohort was derived from a pool of over 3,000 MHD outpatients over 5 years in eight DaVita Inc. chronic dialysis facilities in the South Bay Los Angeles area [see NIED Study Web site at http://www.NIEDStudy.org for more details]. Inclusion criteria were outpatients who had been undergoing MHD for at least 8 weeks, were 18 years or older, and who signed the Institutional Review Board approved consent form. Patients with an anticipated life expectancy of less than 6 months (for example, due to a metastatic malignancy or advanced HIV/AIDS disease) were excluded. From October 1, 2001 through December 31, 2006, 893 MHD patients from eight DaVita dialysis facilities in the Los Angeles South Bay area signed the informed consent form and underwent the periodic evaluations of the NIED Study. For this study, data including baseline serum albumin were available in 812 MHD patients.

The medical chart of each MHD patient was reviewed by a collaborating physician, and data pertaining to underlying kidney disease, cardiovascular history, and other comorbid conditions were extracted. A modified version of the Charlson Comorbidity Index, that is, without the age and kidney

disease components, was used to assess the severity of comorbidities [22].

Anthropometric measures

Body weight was measured immediately after a hemodialysis treatment. Other anthropometric measurements were taken while patients were undergoing a hemodialysis treatment or within 5–20 min after termination of the treatment. Biceps skinfold and triceps skinfold thicknesses were measured with a conventional skinfold caliper using standard techniques as previously described [23, 24].

Near-infrared interactance

To estimate the percentage of body fat and fat-free body mass, near-infrared (NIR) interactance was measured at the same time as the anthropometric measurements [25]. A commercial near-infrared interactance sensor with a coefficient of variation of 0.5 % for total body fat measurement (portable Futrex 6100®, Gaithersburg, Maryland, http://www.futrex.com) was used. NIR measurements were taken by placing, for several seconds on the upper aspect of the arm without a vascular access, a Futrex® sensor, and entering the required data (date of birth, gender, weight, and height) of each patient. NIR measurements of body fat appear to correlate significantly with other nutritional measures in MHD patients.

Laboratory tests

Pre-dialysis blood samples and post-dialysis serum urea nitrogen were obtained on a mid-week day, which coincided chronologically with the drawing of quarterly blood tests in the DaVita facilities. The single-pool Kt/V was used to represent the weekly dialysis dose. All routine laboratory measurements were taken by DaVita® Laboratories (Deland, FL) using automated methods.

Serum high-sensitivity C-reactive protein (CRP) was measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with antihuman CRP antibodies forming an insoluble aggregate (manufacturer: WPCI, Osaka, Japan, unit: mg/L, normal range: <3.0 mg/L) [26, 27]. Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) were measured by immunoassay kits based on a solid-phase sandwich ELISA using recombinant human IL-6 and TNF-α (manufacturer: R&D Systems, Minneapolis, MN; units: pg/mL; normal range: IL-6: <9.9 pg/mL, TNF-α: <4.7 pg/mL) [28, 29]. CRP and the cytokines were measured in the General Clinical Research Center Laboratories of Harbor-UCLA Medical Center. Serum transthyretin (prealbumin) was measured using immunoprecipitation analysis. Plasma total homocysteine concentrations were determined by high-performance liquid chromatography in the Harbor-UCLA Clinical Laboratories.

Statistical methods

Chi-square test and independent sample t test were employed to examine the differences between the two groups of patients with serum albumin <3.8 g/dL and ≥3.8 g/dL. Pearson's correlation coefficient (r) was used for the analyses of linear associations. CRP and IL-6 both were log-transformed because of the severe skewness. Multivariate regression analyses and analysis of covariance were performed to obtain adjusted p values controlled for case-mix and other covariates. Multivariate logistic regression analysis was utilized to examine the strength of association between case-mix and other variables of nutrition and inflammation with the presence of hypoalbuminemia (i.e., serum albumin <3.8 g/dL).

To express and compare the ability of the two inflammatory markers of interest (i.e., IL-6 and CRP) and the two nutritional markers of interest (i.e., nPNA and serum creatinine) and their mutual combinations in predicting serum albumin level <3.8 g/dL, we constructed receiver operating characteristic (ROC) curves each of the aforementioned predictors and serum albumin <3.8 g/dL as the reference variable. Then, the differences between the areas under ROC curves were examined using "roccomp" command in Stata. In a ROC curve, sensitivity (y-axis) is plotted versus one minus specificity (x-axis) for each possible cutoff value of IL-6, CRP, nPNA, creatinine, or probability function obtained from the logistic regression models containing one marker of inflammation and one marker of nutrition and serum albumin <3.8 g/dL as dependent (reference) variable [30]. Values are expected to be between 0.5 (indicating no discriminative ability) and 1.0 (indicating highest detection accuracy).

Case-mix and comorbidity covariates included gender, age, race, and ethnicity (Hispanics, Blacks, Asians, and others), diabetes mellitus, the modified Charlson Comorbidity Index, dialysis vintage (number of months on MHD treatment), and clinical and laboratory measures of MICS. Unadjusted and case mix-adjusted non-linear associations between IL-6 and CRP with the presence of serum albumin <3.8 g/dL were also examined using restricted cubic splines as an alternative to inappropriate linearity assumptions [31]. Fiducial limits are given as mean ± SD (standard deviation) or median and inter-quartile range; odds ratios include 95 % confidence interval (CI) levels. A p value <0.05 or a 95 % CI that did not span 1.0 was considered to be statistically significant. Descriptive and multivariate statistics were carried out with the statistical software "Stata version 10.0" (Stata Corporation, College Station, Texas).

Results

Baseline characteristics

Mean age (±SD) of patients was 54 ± 15 years; 53 % of patients (n = 430) were men, 50 % (n = 410) were Hispanic, 32 % (n = 258) were African–American, and 56 % (n = 455) were diabetic. The mean dialysis vintage was 31 ± 34 months (median: 19, inter-quartile range: 7–44 months). The average (mean ± SD) baseline serum albumin in the 812 MHD patients was 3.88 ± 0.38 ng/mL.

Table 1 shows baseline demographic, clinical, and laboratory variables according to the 6 a priori-selected groups of albumin in 812 maintenance hemodialysis patients. Hypoalbuminemic patients were older, more likely to be diabetic, and had more comorbidities. The inflammatory profile also shows that hypoalbuminemic patients had higher serum concentrations of CRP and IL-6, higher WBC levels, and a lower percentage of lymphocytes. Moreover, hypoalbuminemic patients had a lower nPNA and serum creatinine level. However, the differences between variables such as ethnicity, primary insurance, erythropoietin dose, serum ferritin, phosphorus, bicarbonate, and TNF-α were not significant in different albumin subgroups.

Table 2 shows the correlation coefficients of relevant clinical, nutritional, and inflammatory measures

with serum albumin levels in 812 MHD patients. Serum albumin was negatively correlated with age, MIS score, IL-6, CRP, white blood cell count, and erythropoietin dose. Furthermore, serum albumin was positively correlated with blood hemoglobin, serum nPNA, prealbumin, creatinine, and TIBC.

Non-linear associations

Figure 1 illustrates the cubic spline curves depicting non-linear association between serum albumin concentrations and nPNA and serum creatinine. Figure 1a shows that the serum albumin concentration increases with increasing nPNA up to around 1.4 g/kg/day. Figure 1b shows a rather linear positive association between serum albumin concentrations and serum creatinine up to a serum creatinine concentration of about 14 mg/dL. Figure 2 also shows the non-linear associations between serum albumin and measures of inflammation. It shows that the declining concentrations of serum albumin with the severity of inflammatory measures is more prominent with regard to serum IL-6 than with CRP; however, decline in serum albumin with increasing serum CRP shows a more linear and consistent trend.

Table 3 shows the unadjusted and multivariate adjusted odds ratios (OR) for the occurrence of a serum albumin concentration <3.8 g/dL among the study population. It shows that women had more than twice the risk of being hypoalbuminemic even after adjustment for case-mix and other markers of PEW. Even though there was no unadjusted association between hypoalbuminemia and race/ethnicity, African/American patients had an OR of 2.36 of hypoalbuminemia after adjustment for other relevant confounders. Higher concentrations of serum prealbumin, creatinine, and TIBC were associated with a lower likelihood of hypoalbuminemia even after multivariate adjustments. Table 3 also shows that each 1-unit increment in the logarithm of serum IL-6 or CRP was associated, respectively, with a 24 and 16 % increase in the odds of having serum albumin <3.8 g/dL. Figure 3 indicates the unadjusted and case mix-adjusted associations of IL-6 and CRP with the probability of a serum albumin <3.8 g/dL. In general, the higher concentrations of IL-6 and CRP were associated with greater odds of a serum albumin <3.8 g/dL.

Table 1 Baseline demographic, clinical, and laboratory variables according to the 6 a priori-selected groups of albumin in 812 maintenance hemodialysis patients

	<3.4 (n = 70)	3.4–<3.6 (n = 97)	3.6–<3.8 (n = 155)	3.8–<4.0 (n = 159)	4.0–<4.2 (n = 192)	≥4.2 (n = 139)	p value[a]
Demographics							
Age (years)	60 ± 13	59 ± 14	57 ± 15	55 ± 14	51 ± 14	46 ± 14	<0.001
Men (%)	51	37	41	50	57	75	<0.001
Race: % African–American	26	37	39	36	32	18	0.002
Diabetes mellitus (%)	69	69	59	57	47	38	<0.0001
Charlson comorbidity score	2.8 ± 1.7	2.3 ± 1.5	2.0 ± 1.4	2.1 ± 1.7	1.5 ± 1.4	1.5 ± 1.6	<0.0001
Nutritional status and body composition							
Malnutrition-inflammation score	11.0 ± 4.3	6.6 ± 3.8	5.1 ± 2.9	5.2 ± 2.8	3.5 ± 2.5	3.1 ± 2.5	<0.0001
Body mass index (kg/m^2)	26.6 ± 8.8	26.7 ± 5.6	28.2 ± 7.4	26.5 ± 5.1	26.0 ± 5.8	25.2 ± 4.7	0.003
Triceps skinfold (mm)	17.2 ± 10.9	18.8 ± 10.3	20.3 ± 10.8	17.8 ± 10.0	16.9 ± 9.5	14.9 ± 7.9	<0.001
Biceps skinfold (mm)	8.4 ± 7.4	10.6 ± 8.6	12.8 ± 10.5	10.3 ± 7.2	9.3 ± 6.6	7.6 ± 5.6	<0.0001
Mid-arm muscle circumference (cm)	30.5 ± 7.0	31.7 ± 5.9	33.1 ± 6.7	31.5 ± 5.7	31.1 ± 5.7	30.2 ± 4.0	0.0016
Near-infrared-measured body fat (%)	27.4 ± 11.0	29.6 ± 10.3	29.9 ± 10.9	27.6 ± 10.4	25.4 ± 10.8	21.6 ± 9.5	<0.0001
nPNA or nPCR (g kg^{-1} day^{-1})	0.98 ± 0.29	1.02 ± 0.23	1.04 ± 0.25	1.05 ± 0.21	1.07 ± 0.24	1.16 ± 0.21	<0.0001
Hemodialysis treatment measures							
Dialysis vintage <6 months (%)	48	23	24	18	17	19	<0.0001
Dialysis vintage (months)	22.1 ± 31.8	25.4 ± 25.7	30.0 ± 34.9	35.8 ± 58.5	33.6 ± 33.8	30.3 ± 30.6	0.047
Dialysis dose (Kt/V single pool)	1.57 ± 0.33	1.56 ± 0.28	1.59 ± 0.34	1.59 ± 0.28	1.62 ± 0.30	1.67 ± 0.31	0.09
Biochemical measurements							
Serum							
Transthyretin (prealbumin) (mg/dL)	20.1 ± 7.6	22.2 ± 6.7	26.7 ± 8.2	28.3 ± 8.6	30.6 ± 9.3	33.3 ± 10.6	<0.0001
Creatinine (mg/dL)	7.5 ± 2.4	8.9 ± 2.9	10.1 ± 3.3	10.5 ± 3.4	10.9 ± 3.2	11.4 ± 2.9	<0.0001
TIBC (mg/dL)	181.9 ± 47.5	200.2 ± 37.9	206.3 ± 37.7	203.0 ± 37.6	216.9 ± 37.9	220.1 ± 35.5	<0.0001
Iron saturation ratio (%)	30.2 ± 13.3	30.0 ± 11.7	30.9 ± 10.3	30.8 ± 10.3	32.9 ± 11.2	34.9 ± 10.7	0.0016
Iron (mg/dL)	55.9 ± 34.3	61.6 ± 28.9	64.2 ± 25.7	61.7 ± 21.8	70.7 ± 24.2	77.9 ± 27.3	<0.0001
Calcium (mg/dL)	8.8 ± 0.5	9.2 ± 0.7	9.2 ± 0.7	9.4 ± 0.6	9.6 ± 0.7	9.6 ± 0.6	<0.0001
iPTH (pg/mL)	215.5 ± 203.7	290.9 ± 343.5	350.4 ± 380.6	366.3 ± 418.4	319.1 ± 293.7	297.6 ± 289.0	0.058
Total homocysteine (μmol/L)	19.3 ± 10.4	21.3 ± 6.9	25.1 ± 10.7	24.0 ± 10.3	25.1 ± 14.3	24.1 ± 8.5	0.0016
C-reactive protein (mg/L)	7.5 ± 7.6	7.8 ± 6.4	6.5 ± 9.0	5.8 ± 6.0	4.7 ± 6.6	4.0 ± 4.7	0.0001
IL-6 (pg/mL)	32.1 ± 46.9	24.4 ± 72.5	24.2 ± 62.8	19.6 ± 62.3	12.8 ± 32.9	7.8 ± 10.0	0.0081
Blood							
Hemoglobin (g/dL)	11.5 ± 1.6	11.9 ± 1.1	12.0 ± 1.0	12.1 ± 0.9	12.3 ± 0.8	12.3 ± 0.8	<0.0001

Table 1 continued

	<3.4 (n = 70)	3.4—<3.6 (n = 97)	3.6—<3.8 (n = 155)	3.8—<4.0 (n = 159)	4.0—<4.2 (n = 192)	≥4.2 (n = 139)	p value[a]
WBC (×1,000 cell/µl)	8.3 ± 2.7	7.5 ± 1.9	7.4 ± 3.1	7.1 ± 1.9	7.1 ± 2.0	6.7 ± 1.6	0.0001
Lymphocyte (% of total WBC)	19.0 ± 7.1	20.0 ± 6.5	22.8 ± 8.6	23.1 ± 7.6	23.9 ± 8.4	24.2 ± 6.7	<0.0001

All values are presented as Mean ± SD or percentages

Kt/V dialysis dose, *TIBC* Total iron-binding capacity, *nPNA* normalized protein catabolic rate, *IL-6* Interleukin 6, *TNF-α* Tumor necrosis factor-α

[a] p values are based on *ANOVA* or Chi-square test where indicated

Table 4 shows the death hazard ratios according to the progressive integers of serum albumin concentrations in the 812 MHD patients. The association was linear, and lower serum albumin levels were associated with higher risks of death.

Figure 4 illustrates the combined (three-dimensional) association of serum IL-6 and nPNA with the odds of a serum albumin <3.8 g/dL. As shown in Fig. 4, the odds of a serum albumin <3.8 g/dL increases linearly with decreasing nPNA, and there is an increasing trend toward hypoalbuminemia with increment of serum IL-6. This trend is steeper with increasing serum IL-6 concentrations up to about 30 ng/mL.

Discussion

In this cross-sectional study in the twenty-first century, we showed that both low protein intake and high level of inflammatory markers are associated with low serum albumin concentrations in MHD patients. This finding has important clinical implications, since physicians commonly employ the serum albumin level to evaluate the nutritional status and overall health of a MHD patient. It is important to know that each 1-unit increment in the logarithm of serum IL-6 or CRP was associated, respectively, with a 24 and 16 % increase in the odds of the serum albumin being <3.8 g/dL.

Many previous epidemiological studies have shown a strong association between serum albumin and prospective mortality in chronic dialysis patients, including CV death, and post-transplant mortality in dialysis patients [13, 16, 32]. Evidence indicates that both malnutrition and inflammation are the major causes of severe hypoalbuminemia in MHD patients [33]. Nutritional support has been shown to improve hypoalbuminemia and different outcomes in patients with CKD [16, 32, 34, 35]. Indeed, several randomized and nonrandomized prospective trials in hypoalbuminemic MHD patients indicate that nutritional support may increase serum albumin [36], but it has not effect on clinical outcomes [37–39]. Increased dietary protein in hypoalbuminemic patients thus might confer a survival advantage compared to hypoalbuminemic patients with lower dietary protein intakes.

We found that each 1-unit increment in the logarithm of the serum IL-6 or CRP was associated,

Table 2 Unadjusted and multivariate adjusted correlation coefficients of serum albumin and selected continuous variables in 812 maintenance hemodialysis patients

Variable	Unadjusted	Case mix[a] adjusted	Case mix + inflammatory markers (full model)[b] adjusted
Demographics			
Age	**−0.30*****	**−0.17****	**−0.15*****
Charlson comorbidity score	**−0.24*****	**−0.14****	−0.02
Dialysis vintage	0.07*	0.06	−0.07*
Nutritional status and body composition			
Malnutrition–inflammation score	**−0.54*****	**−0.49*****	**−0.47*****
Body mass index	**−0.10****	−0.04	−0.02
Triceps skinfold	−0.09*	0.02	0.03
Biceps skinfold	−0.09*	−0.02	−0.01
Mid-arm muscle circumference	−0.06^Δ	−0.02	−0.01
Near-infrared-measured body fat	−0.21***	−0.01	0.01
Hemodialysis treatment measures			
Dialysis dose	**0.10****	**0.14*****	**0.12****
nPNA	**0.20*****	**0.17*****	**0.17*****
Erythropoietin dose	**−0.27*****	**−0.28*****	**−0.26*****
Vitamin D dose	0.08^Δ	0.08^Δ	0.09*
Biochemical measurements			
Transthyretin (prealbumin)	**0.41*****	**0.38*****	**0.36*****
Creatinine	**0.33*****	**0.21*****	**0.20*****
Ferritin	−0.05	−0.00	0.00
TIBC	**0.28*****	**0.27*****	**0.26*****
Iron saturation ratio	**0.16*****	**0.12****	**0.10****
Iron	**0.26*****	**0.24*****	**0.22*****
Calcium	**0.32*****	**0.35*****	**0.35*****
Phosphorus	0.05	−0.04	−0.02
Bicarbonate	−0.06^Δ	−0.02	−0.03
Total homocysteine	**0.14*****	**0.14*****	**0.13*****
Log C-reactive protein	**−0.23*****	**−0.19*****	**−0.12****
Log IL-6	**−0.36*****	**−0.31*****	**−0.29*****
Log TNF-α	−0.02	−0.03	−0.02
Hemoglobin (g/dL)	**0.23*****	**0.24*****	**0.23*****
Hemoglobin A1c (%)	**−0.11***	**−0.13***	**−0.11***
White blood cell count (×1,000 cell/μl)	**−0.18*****	**−0.16*****	**−0.14*****
Lymphocyte (% of total WBC)	**0.20*****	**0.16*****	**0.16*****

nPNA, normalized protein catabolic rate; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor-α

Correlation coefficients indicated in bold are statistically significant. ^{Δ} $0.05 \le p < 0.20$; * $0.01 \le p < 0.05$; ** $0.001 \le p < 0.01$; *** $p < 0.001$

[a] Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, primary insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b] Full model consists of case-mix variables and three inflammatory markers: C-reactive protein, Interleukin-6, and Tumor necrosis factor-α

respectively, with a 24 and 16 % increase the odds of having a serum albumin <3.8 g/dL. Kaysen et al. [40] reported that in MHD patients, the serum albumin concentration changes with inflammation and poor nutritional intake due to their effects on albumin catabolism and synthesis, respectively. These authors
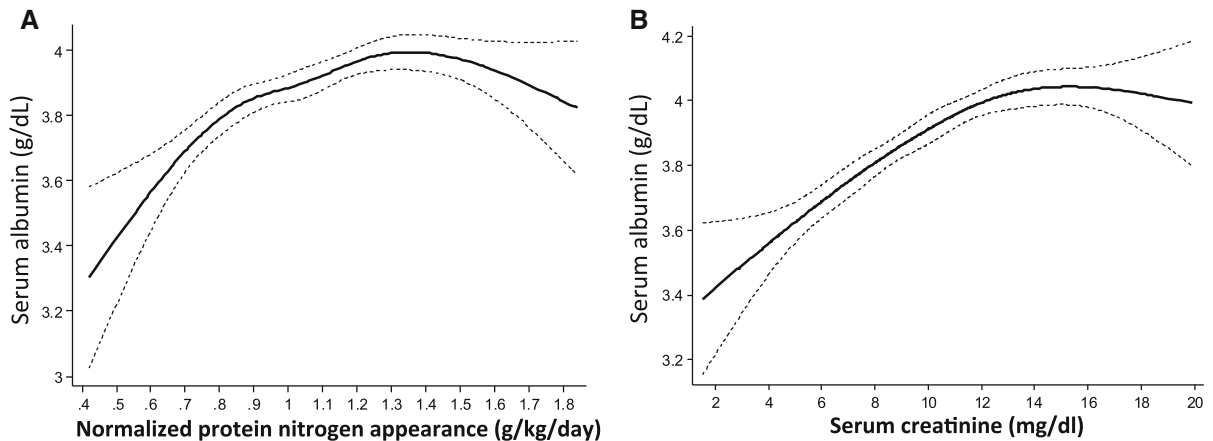
Fig. 1 *Cubic spline curves* illustrating non-linear association of serum albumin concentrations with normalized protein nitrogen appearance (nPNA) (**a**) and with serum creatinine (**b**)
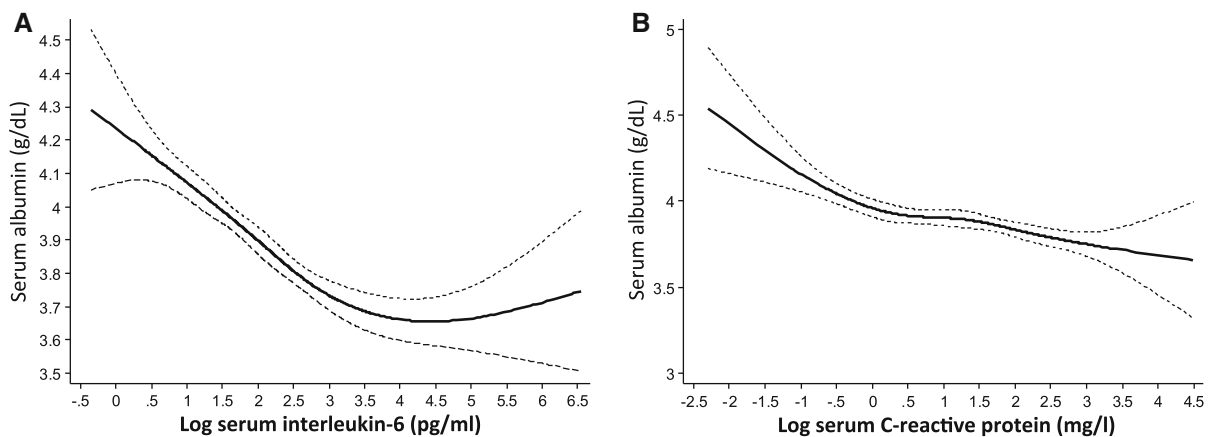
Fig. 2 *Cubic spline curves* illustrating non-linear association of serum albumin concentrations with serum interleukin-6 (**a**) and with serum C-reactive protein (**b**)

showed that the markers of nutritional status primarily affected albumin synthesis, whereas inflammation caused hypoalbuminaemia by increasing the albumin fractional catabolic rate [40]. In another study, Kaysen et al. showed that increasing inflammation and higher dietary protein intake exerted competing effects on serum albumin in MHD patients [18]. In our study using a patients' population from twenty-first century, we found similar results. However, all of these previous studies were performed before 2000 when the dialysis practice and pattern were different than nowadays.

Serum albumin levels decrease with inflammation due to several causes, including reduced synthesis, increased catabolism, and translocation of albumin to extravascular pools [41, 42]. TNF-α and IL-1 directly suppress appetite [43, 44]. 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 [45]. Administering IL-6 receptor antibodies prevented these effects in mice transgenic for IL-6 [46]. Therefore, the inflammatory response may induce protein-energy malnutrition by decreased intake, in addition to increased catabolism.

Our study should be qualified for several potential limitations. Like all observational studies, the present study cannot prove causality. Another limitation is that dietary intake was not measured. The nPNA is

Table 3 Odds ratios (and 95 % CI) of a low serum albumin level (<3.8 vs. ≥3.8 g/dL) in 812 MHD patients

| Variable	Unadjusted	Case mix adjusted[a]	Case mix + Mics adjusted[b]
Demographics			
Age (each 10 year increase)	1.04 (1.02–1.05)***	1.03 (1.01–1.04)**	1.03 (1.01–1.04)**
Men (vs. women)	0.49 (0.37–0.66)***	0.61 (0.41–0.90)*	0.53 (0.28–1.01)
Race/ethnicity			
African–American versus others	1.31 (0.97–1.77)	2.93 (1.59–.5.41)**	2.36 (1.30–4.29)**
Hispanic versus others	1.01 (0.76–1.34)	2.11 (1.19–3.74)*	1.69 (1.00–2.86)*
Primary insurance			
Medicare versus others	1.35 (0.96–1.90)	1.31 (0.89–1.94)	1.35 (0.87–2.11)
Diabetes mellitus (vs. no DM)	1.95 (1.46–2.61)***	1.06 (0.64–1.77)	0.88 (0.54–1.44)
Charlson comorbidity score (each 1 unit ↑)	1.24 (1.13–1.36)***	1.20 (1.03–1.41)*	0.94 (0.80–1.09)
Dialysis vintage (vs. 6 ≤ vintage < 12 months)			
vintage < 6 months	1.29 (0.80–2.09)	1.02 (0.50–2.10)	1.54 (0.82–2.90)
12 months ≤ vintage < 2 years	0.79 (0.49–1.29)	0.56 (0.29–1.09)	0.78 (0.42–1.45)
2 years ≤ vintage < 5 years	0.44 (0.27–0.71)**	0.40 (0.21–0.75)**	0.64 (0.35–1.18)
5 years ≤ vintage	0.81 (0.48–1.37)	0.64 (0.32–1.30)	1.05 (0.51–2.14)
Nutritional status and body composition			
Malnutrition–inflammation score (each 5 ↑)	1.28 (1.22–1.35)***	1.26 (1.29–1.33)***	1.20 (1.12–1.29)***
Body mass index (each 1 kg/m^2 increase)	1.04 (1.01–1.07)**	1.03 (1.00–1.05)	1.02 (0.95–1.09)
Triceps skinfold (each 1 mm ↑)	1.03 (1.01–1.04)**	1.0 (0.99–1.03)	0.99 (0.96–1.03)
Biceps skinfold (each 1 mm ↑)	1.03 (1.01–1.05)**	1.02 (1.00–1.04)*	1.02 (0.98–1.05)
Mid-arm muscle circumference (each 1 cm ↑)	1.03 (1.01–1.06)**	1.03 (1.00–1.06)*	1.05 (0.99–1.11)
Near-infrared-measured body fat (each 1 % ↑)	1.04 (1.02–1.05)***	1.01 (0.99–1.03)	0.99 (0.95–1.04)
Hemodialysis treatment measures			
Dialysis dose (each 1 unit Kt/V sp increase)	0.62 (0.38–0.99)*	0.42 (0.24–0.72)**	0.78 (0.38–1.64)
nPNA or nPCR (each 0.1 g kg^{-1} day^{-1} incr.)	0.31 (0.17–0.58)* **	0.37 (0.19–0.71)* *	0.56 (0.22–0.39)
Erythropoietin dose (each 1,000 u/wk up)	1.07 (1.04–1.10)***	1.08 (1.04–1.11)** *	1.00 (0.99–1.00)
Vitamin D dose (each 10 unit increase)	1.00 (0.99–1.00)*	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Biochemical measurements			
Transthyretin (prealbumin) (each 10 mg/dL)	0.92 (0.90–0.94)***	0.92 (0.90–0.94)***	0.95 (0.93–0.97)***
Creatinine (each 1 mg/dL)	0.84 (0.80–0.88)***	0.90 (0.85–0.96)**	0.91 (0.84–0.99)*
Ferritin (each 100 ng/mL)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
TIBC (each 10 mg/dL)	0.99 (0.98–0.99)***	0.99 (0.98–0.99)***	0.99 (0.98–1.00)
Iron saturation ratio (each 10 %)	0.98 (0.97–0.99)**	0.99 (0.97–1.00)	0.97 (0.93–1.01)
Iron (each 10 mg/dL)	0.99 (0.98–0.99)***	0.99 (0.98–1.00)**	1.02 (1.00–1.04)
Calcium (each 1 mg/dL)	0.38 (0.30–0.49)***	0.33 (0.25–0.44)***	0.39 (0.29–0.54)***
Phosphorus (each 1 mg/dL)	0.98 (0.89–1.08)	1.10 (0.99–1.23)	1.07 (0.93–1.24)
Bicarbonate (each 1 mg/dL)	1.01 (0.96–1.07)	0.98 (0.93–1.04)	0.97 (0.91–1.05)
Total homocysteine (each 1 μmol/L)	0.99 (0.97–1.00)*	0.99 (0.97–1.01)	1.00 (0.99–1.02)
C-reactive protein (each 1 mg/L)	1.05 (1.03–1.08)***	1.05 (1.03–1.08)***	1.02 (0.99–1.05)

Table 3 continued

Variable	Unadjusted	Case mix adjusted[a]	Case mix + Mics adjusted[b]
Log C-reactive protein (each 1 unit)	1.49 (1.29–1.72)[***]	1.49 (1.27–1.74)[***]	1.16 (0.94–1.42)
Log IL-6 (each 1 unit)	1.79 (1.53–2.10)[***]	1.69 (1.01–1.04)[***]	1.24 (1.00–1.54)*
TNF-α (each 10 pg/mL)	1.00 (0.98–1.01)	1.00 (0.98–1.00)	0.99 (0.98–1.00)
Log TNF-α (each 1 unit)	0.99 (0.82–1.20)	1.03 (0.84–1.26)	0.93 (0.73–1.19)
Hemoglobin (g/dL)	0.70 (0.60–0.81)[***]	0.64 (0.55–0.76)[***]	0.76 (0.63–0.93)[**]
Hemoglobin A1c (%)	1.08 (0.95–1.24)	1.12 (0.97–1.31)	1.03 (0.87–1.22)
WBC (×1,000 cell/μl)	1.15 (1.07–1.23)[***]	1.13 (1.04–1.22)[**]	1.03 (0.93–1.14)
Lymphocyte (% of total WBC)	0.96 (0.94–0.98)[***]	0.96 (0.94–0.98)[***]	0.98 (0.95–1.00)

* $0.01 \le p < 0.05$; ** $0.001 \le p < 0.01$; *** $p < 0.001$

[a] Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, primary insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b] Full model consists of case-mix variables and three inflammatory markers: C-reactive protein, Interleukin-6, and Tumor necrosis factor-α
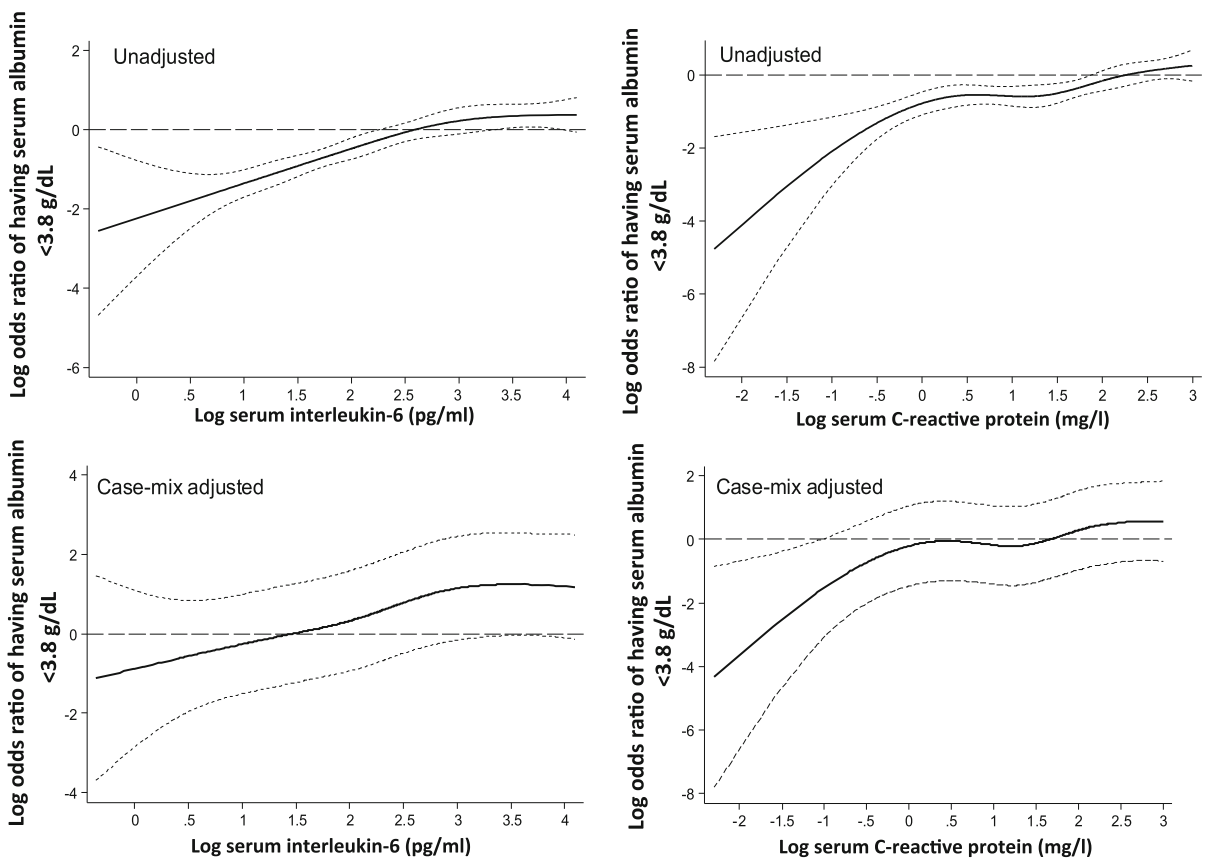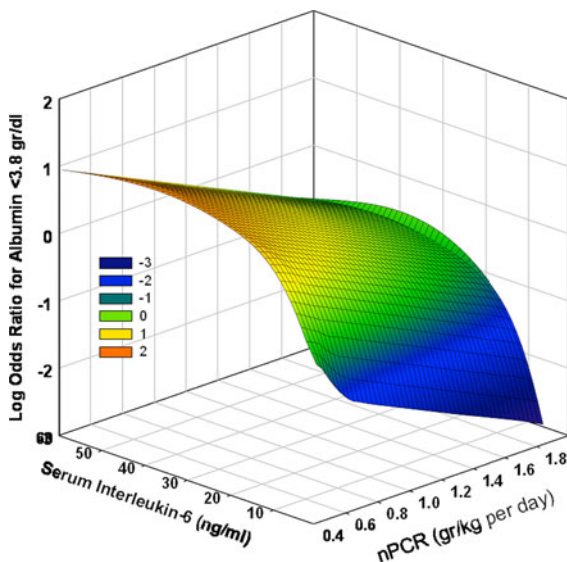

Fig. 3 Log odds ratio of having serum albumin <3.8 g/dL across spectrum of serum interleukin-6 (*left*) and C-reactive protein (*right*) before and after multivariate adjustment for case-mix variables in 812 maintenance hemodialysis patients

Table 4 Death hazard ratios according to the 6 groups of serum albumin in 812 maintenance hemodialysis patients

Albumin categories (mg/dL)	Unadjusted		Case mix[a] adjusted		Case mix + inflammatory markers[b] adjusted	
	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
<3.4 (n = 70)	2.67 (1.75–4.09)	<0.001	2.45 (1.59–3.78)	<0.001	2.39 (1.54–3.72)	<0.001
3.4–<3.6 (n = 97)	2.16 (1.45–3.23)	<0.001	2.00 (1.33–3.01)	0.001	1.97 (1.30–2.98)	0.001
3.6–<3.8 (n = 155)	1.29 (0.87–1.91)	0.21	1.33 (0.89–1.98)	0.17	1.32 (0.88–1.98)	0.18
3.8–<4.0 (n = 159)	1 (Reference)		1 (Reference)		1 (Reference)	
4.0–<4.2 (n = 192)	0.69 (0.45–1.04)	0.079	0.81 (0.53–1.25)	0.35	0.83 (0.54–1.27)	0.38
≥4.2 (n = 139)	0.53 (0.32–0.88)	0.015	0.85 (0.50–1.45)	0.56	0.86 (0.51–1.46)	0.57
Each 0.2 decrease in serum albumin	1.30 (1.22–1.37)	<0.001	1.24 (1.16–1.32)	<0.001	1.23 (1.15–1.31)	<0.001

[a] Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, primary insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b] Full model consists of case-mix variables and three inflammatory markers: C-reactive protein, Interleukin-6, and Tumor necrosis factor-α

Fig. 4 The relationship between the dependent variable, log odds ratio of serum albumin <3.8 g/dL and independent variables, IL-6, and normalized protein nitrogen appearance (nPNA)

considered a valid surrogate for dietary protein intake under steady-state conditions. However, particularly in the face of inflammation, the nPNA may overestimate dietary protein intake because of an increase in endogenous nitrogen breakdown. Furthermore, whether PNA should be normalized to body weight is a matter of controversy, as it can be misleading in obese, malnourished, and edematous individuals [47]. It is also important to note that nPNA, according to the

equations, underestimates dietary protein intake by roughly 6–8 g of protein per day and more accurately reflects "measured" net protein degradation as determined by the urea nitrogen appearance. Moreover, we do not have data from peritoneal dialysis patients; therefore, our findings cannot be extrapolated to patients undergoing chronic peritoneal dialysis.

The strengths of our study include the well-characterized cohort, the comprehensive clinical and laboratory evaluations including body composition measures, detailed evaluation of comorbid states by study physicians at baseline, and the measurements of pro-inflammatory cytokines and markers. In addition, the subjects were selected without having any prior knowledge of their inflammatory status.

Conclusions

We showed both measures of low protein intake and high levels of inflammatory markers are associated with low serum albumin in MHD patients.

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