

Table 1. Clinical and biochemical parameters of all the 6 subjects

S No.	Primary IST	Indication	Baseline		Second month completion		Fourth month completion		Sixth month completion		F/U (mo)	Last follow-up		aPLA ₂ R (RU/ml)		RTX	
			UP (g/d)	Sr Alb (g/dl)	UP (g/d)	Sr Alb (g/dl)	UP (g/d)	Sr Alb (g/dl)	UP (g/d)	Sr Alb (g/dl)		UP (g/d)	Sr Alb (g/dl)	Pre-RTX	Post-RTX	Additional doses	Time (mo)
1	cCTX/GC	Relapse	8.98	3.10	3.88	3.10	3.60	3.20	1.03	3.60	14	0.701	3.70	73.11	4.528	02	03, 08
2	cCTX/GC	Resistant	6.20	1.40	1.20	5.50	1.25	5.20	3.00	2.10	12	3.20	3.10	121.59	93.99	03	01, 04, 05
3	TAC	Intolerant	2.30	1.30	2.90	3.13	2.86	3.42	1.92	4.32	15	0.29	4.32	28.87	2.00	04	04, 09, 12, 15
4	cCTX/GC	Resistant	5.50	3.50	2.90	3.90	3.10	3.20	3.20	4.40	13	1.13	4.34	111.87	2.00	02	02, 06
5	cCTX/GC	Resistant	31.00	1.68	16.220	1.59	3.80	1.98	19.60	1.83	10	8.80	3.50	27.13	79.76	02	01, 04
6	cCTX/GC ^a	Resistant	18.41	1.60	15.03	1.30	9.58	2.63	8.00	2.00	14	3.13	3.30	59.89	56.79	03	02, 05, 06

Mean time to CD19 repletion was 2.17 ± 1.17 (range 1–4) mo and all the subjects received further therapy (median doses 2.5, range 2–4).

aPLA₂R, m-type phospholipase A2 receptor antibody; cCTX/GC, cyclical cyclophosphamide and steroids; F/U, follow-up; IST, immunosuppressive therapy; RTX, rituximab; Sr Alb, serum albumin; TAC, tacrolimus; UP, urine protein.

^aPatient developed upper respiratory tract infection, which was successfully managed with oral antibiotics.

to <20 RU/ml, whereas none of the nonresponders achieved similar titer. Our results support the incorporation of aPLA₂R monitoring in the management of difficult to treat PMN.

To conclude, in cost-restrained setting, low-dose RTX targeting CD19 depletion can be used in the management of PMN refractory to standard immunosuppressive therapies with the acceptable side effect profile.

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DISCLOSURE

All the authors declared no competing interests.

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How Well Does Serum Albumin Correlate With Dietary Protein Intake in Dialysis Patients?



To the Editor: Serum albumin is a useful screening tool for recognizing protein energy wasting (PEW) in dialysis patients. However, there are many nonnutritional conditions that are far more important determinants of serum albumin levels than a patient's nutritional state.^{1,2} Nevertheless, we have observed that it is not unusual for caregivers to make a reflex connection between serum albumin and dietary protein intake and to act on an unfounded belief that protein

intake is problematic when serum albumin levels are low or declining. This may be done in the absence of other evidence of PEW or without further nutritional assessment.

The recognized limitations in serum albumin as a marker for dietary protein intake deserve further emphasis.³ We therefore examined the correlation between serum albumin levels and dietary protein intake (estimated by the normalized protein equivalent of nitrogen appearance [nPNA]) in a large group of end-stage renal disease (ESRD) patients on chronic peritoneal dialysis (PD). We did so with the expectation that the correlation would be poor, given the known determinants of albumin levels. Nevertheless, we proceeded because of the ready availability of accurate nPNA data in PD patients, the surprising absence of prior documentation of this albumin–nPNA relationship and the value of reemphasizing it.

METHODS

Medical records at the Dialysis Clinic, Inc. PD unit in North Brunswick, NJ from 1 January 2010 to 1 January 2015 were reviewed. A total of 104 patients were identified who had at least two 24-hour dialysate and urine collections for urea kinetic modeling and a serum albumin level measured on same day as the modeling. All patients were treated with continuous cyclic PD. All laboratory measurements were performed by Spectra Laboratories (Rockleigh, NJ). Over- and undercollections of urine were avoided by verbal and written instructions on proper collection techniques. Data from patients who had peritonitis within 8 weeks prior to testing were excluded. Demographic and clinical data were collected, including age, race, gender, time of initiation of dialysis, and cause of ESRD. Serum albumin levels were measured using the bromocresol green method.⁴ The PNA was determined from the total dialysate and urine urea content using the Randerson II formula⁵:

$$\text{PNA (g/kg/day)} = [10.76 \times (0.01 \times \text{urea generation rate} + 1.46)] / \text{weight}$$

The urea generation rate was calculated from the urea content of the 24-hour urine and spent dialysate collections.

All calculated PNA values were normalized (n) to ideal weight:

$$\text{nPNA} = [\text{PNA(g/d)}] / (\text{urea distribution volume}/0.58)]$$

Notably, we made no attempt to collect data on the many variables that might alter the relationship

between albumin and dietary protein. The only exception to this was our exclusion of patients with recent peritonitis. We did this because, in our experience, we believe that clinicians are quite cognizant that this condition will lower albumin levels and are unlikely to draw conclusions regarding protein intake from the results.

Statistical Analysis

Standard descriptive statistics were used for data analysis. Mean values were calculated for the multiple nPNA and serum albumin levels for individual patients, and results are expressed as mean \pm SD. Pearson correlation and regression analysis were used to assess the relationship between serum albumin and nPNA levels. A 2-sided *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA).

RESULTS

A total of 672 nPNA and serum albumin pairs in 104 patients were analyzed (mean, 6 values per patient; range, 2–22 values). Of the 104 patients, 62 were male (60%), with a mean age of 62 years (range, 21–93 years). The major causes of ESRD were diabetes (34%) and hypertension (20%). Patients' self-reported race was predominately white (51%, 20% black, 10% Asian, and 7% Hispanic).

The relationship observed between serum albumin and nPNA is shown in Figure 1. The correlation coefficient was low at 0.42 (*P* < 0.001), with an *r*² value of 0.177, indicating that only 18% of the variation in serum albumin was accounted for by variations in the level of nPNA.

The majority (91%) of the patients had serum albumin levels ≥ 3 g/dl. Those with albumin levels of 3 to 3.4 g/dl had an average nPNA of 0.93 g/kg/d, whereas those with albumin levels of 3.5–3.9 g/dl had a mean nPNA of 0.99 g/kg/d (Table 1). Thus, in this range of serum albumin, average nPNA declined by about 0.01 g/kg/d for a decline of 0.1 g/dl in albumin, or <1 g of dietary protein for a 70-kg patient. The correlation coefficient between nPNA and serum albumin for these patients was 0.30, with the level of nPNA accounting for only 9% of the variation in serum albumin. However, a serum albumin <3 g/dl was associated with a substantially depressed nPNA.

DISCUSSION

Dietary protein intake is clearly a significant factor in determining serum albumin, but its importance is

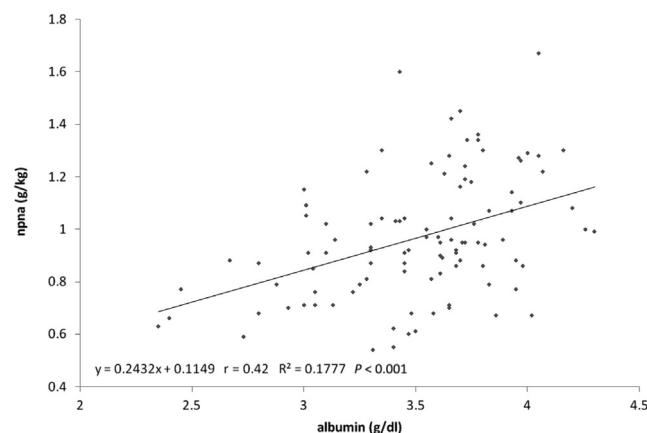


Figure 1. Relationship of normalized protein equivalent of nitrogen appearance (nPNA) with serum albumin, with regression line and equations. r , correlation coefficient; R^2 , square of correlation coefficient; x , albumin; y , nPNA.

sometimes overstated. Residual albuminuria and inflammation are much more important determinants of serum albumin levels.^{1,3} When used as part of a broader nutritional screening approach, serum albumin is valuable. However, it is not unusual for caregivers to equate low levels of this serum protein (albumin) to low levels of dietary protein. This, together with the ready availability of albumin levels, probably accounts, at least in part, for the widespread use of serum albumin as a nutritional marker in dialysis patients. Unfortunately, when more thorough evaluations are not performed, serum albumin may be perceived as the determinant of success or failure of nutritional interventions.

Serum albumin levels have long been recognized as very strong predictors of outcomes in dialysis patients.⁶ Furthermore, nutritional supplements may well be beneficial in patients with low serum albumin levels and may improve their outcomes.⁷ However, the basis for such improvement should not be ascribed to correction of inadequate protein intake, given the almost negligible relationship of albumin levels to protein intake, at least for patients with levels ≥ 3 g/dl.

Although nPNA determined from 24-hour urea excretion is considered an accurate means of estimating protein intake, there are some points to consider that preclude complete confidence in it. It is based on the assumption that patients are in the

steady state with respect to nitrogen balance. If they are catabolic (as with an infection or high-dose steroids), urea generation will suggest a protein intake that is greater than the actual value. However, this is much more likely to be a clinically important issue in patients in settings other than the outpatients used in this study.

The back calculation from urea to protein assumes a conversion factor of 6.25 based on the Kjeldahl nitrogen analysis. Although it is almost universally applied, it has nevertheless been questioned.⁸ However, an incorrect conversion factor would only shift the urea–nPNA curve, not alter our observation of its low R value.

Serum albumin also changes very slowly in response to diet and other influences as a result of its long (20-day) half-life. A poor correlation between serum albumin and nPNA could reflect, at least in part, the snapshot that nPNA reflects—analogue to a blood glucose compared to an HbA1c level. However, our analysis used an average of 6 pairs of nPNA–albumin results per patient, thereby abrogating much of this consideration.

The use of nPNA in a peritoneal dialysis setting is much less problematic than its use in hemodialysis. The problems in the latter include its nonsteady state, the rebound in blood urea nitrogen after dialysis, the typical absence of urine collections, and the calculation of urea generation from changes in the blood urea nitrogen and estimates of urea distribution volume. The nonsteady state issue also applies to a much lesser extent in our population, as CCPD provides more dialysis in the nocturnal period. This will generally make the daytime values that we obtained slightly different from the time-averaged blood urea nitrogen; values were usually measured in the morning when the blood urea nitrogen would be less than the time-averaged urea, leading to an overestimate of nPNA and dietary protein. However, this effect is likely to be minor.

This report of the poor correlation between nPNA and serum albumin is not a ground-breaking observation and is fully consistent with a large body of other data in this area. However, it serves to highlight a recognized concern in the interpretation of serum albumin levels and adds a quantitative dimension to the relationship between dietary protein and serum

Table 1. Serum albumin ranges and nPNA levels

Serum albumin (g/dl)	2.5–2.9 \pm 0.16	3–3.4 \pm 0.15	3.5–3.9 \pm 0.13	4–4.4 \pm 0.17
Subjects (n)	7	30	50	15
nPNA (g/kg/d)	0.75 \pm 0.11	0.93 \pm 0.23	0.99 \pm 0.22	1.1 \pm 0.26

nPNA, normalized protein equivalent of nitrogen appearance.

albumin. Clearly, serum albumin is not a surrogate for dietary protein intake, nor can it serve as an independent measure suitable for assessing a patient's nutritional state.

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DISCLOSURE

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