Serum Albumin in Patients on Continuous Ambulatory Peritoneal Dialysis—Predictors and Correlations With Outcomes

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ABSTRACT
Serum albumin (SA) is a powerful predictor of patient morbidity and mortality in hemodialysis, but data are limited for continuous ambulatory peritoneal dialysis (CAPD). SA was monitored in 76 new CAPD patients over 222 6-month periods and mean SA was correlated with morbidity and mortality during those periods. The influence of initial SA on duration of technique survival was also investigated. To determine which factors best predict SA, correlations with patient demographics and with 6-month measurements of dialytic dose, protein intake, and peritoneal transport were sought. Mean SA overall was 34.1 ± 3.3 g/L, and mean initial SA was 33.4 ± 3.1 g/L. Mean SA was lower in diabetics and in those aged 65 or over. Mean SA tended to increase during the first year on CAPD, and this increase was maintained, except in patients aged 65 or over, where it tended to revert to initial values. SA correlated with hospital days (r = −0.20; P < 0.005), fatigue index (r = −0.20; P < 0.005), nerve conduction (P < 0.001), and a variety of laboratory values, and lower SA was associated with technique failure (P < 0.03) and death (P < 0.07). Initial, as well as ongoing, SA was predictive of technique failure (P < 0.05) and Cox proportional hazards regression showed that this predictive power was independent of age, sex, diabetes, and other factors (P = 0.05). The strongest predictors of low SA by stepwise multiple regression were diabetes, a higher dialysate-to-plasma creatinine equilibration ratio, older age, lower body weight, and shorter time on CAPD. Neither protein catabolic rate nor dialytic dose was predictive of SA. SA correlates with morbidity and mortality in CAPD and is primarily influenced by factors that are difficult to alter. Strategies to correct low SA require investigation.

Key Words: Serum albumin, continuous ambulatory peritoneal dialysis, morbidity, mortality, nutrition, peritoneal equilibration test

The use of serum albumin (SA) as a prognostic indicator in ESRD patients on hemodialysis (HD) has recently received much attention. Lowrie and Lew have shown in a study of more than 12,000 HD patients monitored over the course of 1 year that SA was the most powerful predictor of death. In particular, they found that the mortality rate was twice as high for patients with SA between 35 and 40 g/L and almost five times as high for those with SA between 30 and 35 g/L, as compared with those with SA between 40 and 45 g/L (1). More recently, Churchill et al. have shown a correlation between SA and morbidity in the multicenter Canadian Hemodialysis Morbidity Study (2).

SA is potentially more compromised in continuous ambulatory peritoneal dialysis (CAPD) patients because of their large obligatory dialysate protein losses and their lower protein intake relative to their HD counterparts (3,4). However, the prognostic value of SA in CAPD has been less extensively investigated. Young et al. have shown that, in a group of 15 patients, low SA was associated with both peritonitis and number of days spent in the hospital (5). More recently, Teehan et al., in a study on the adequacy of dialysis, have found that SA was a more powerful predictor of mortality and of days hospitalized than were age and urea kinetic indices (6).

In this article, we have reviewed data on SA collected during a recent urea kinetics study involving follow-up of 76 new CAPD patients (7). In particular, we have investigated how SA alters with time on CAPD in our patient population as a whole and in subgroups such as the elderly and those with diabetes. We have asked how SA correlates with patient outcomes and whether the initial, as distinct from

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the ongoing, SA is predictive of long-term success or failure on CAPD, independent of other factors such as age, sex, and diabetes. In addition to looking at SA as a predictor, we have looked at SA as an outcome in itself, by seeking to identify, with stepwise multiple regression, those factors that are most predictive of SA.

MATERIALS AND METHODS

Seventy-six adult patients were monitored from the time of starting CAPD. There were 52 men and 24 women. This sex ratio is not unusual in our center and is consistent with the approximately 1.4:1 male-to-female ratio among new dialysis patients in Canada (8). The mean age when starting CAPD was 56.9 yr (range, 18 to 81). Twenty-two patients (29%) were diabetic.

For each patient, follow-up was divided into 6-month periods. At the beginning of each 6-month period, the following parameters were measured: normalized protein catabolic rate (PCRN), body weight and surface area, KT/V, total creatinine clearance (TCC), residual renal function, dialysate protein losses, and dialysate-to-plasma ratio for creatinine (D/P Cr). During each 6-month period, laboratory values and clinical outcomes were recorded. SA was measured monthly, and the mean value for each 6-month period was calculated. If the patient did not complete the 6-month follow-up, the mean monthly value for the shorter period was calculated. We chose to monitor mean 6-month SA values in order to avoid giving undue weight to transient changes in SA and because nutritional parameters and dialytic dose were also measured every 6 months. Differences between SA in subgroups were investigated by the two-sample t test. Changes in SA over time were examined by means of the paired t test.

Six-month means were calculated for blood urea, serum creatinine, electrolytes, calcium and phosphate, alkaline phosphatase and hemoglobin. Parathyroid hormone levels (intact molecule assay) and serum cholesterol and triglycerides were measured once every 6 months.

Clinical outcomes monitored were death, technique failure (which was defined as death or transfer to HD or automated PD), days hospitalized, peritonitis rate, blood transfusions, and patients' subjective scoring on a 0 to 3 scale of fatigue, pruritis, and insomnia. The latter were estimated monthly and averaged over each 6-month period. Nerve conduction velocity was measured in the lateral peroneal nerve every 6 to 12 months.

Correlations were sought, by calculating Pearson correlation coefficients, between the mean 6-month SA and other biochemical values as well as clinical outcomes, KT/V, TCC, PCRN, D/P Cr values, dialysate protein losses, body weight, body surface area, and residual renal function.

To determine if initial SA, as distinct from ongoing SA, was predictive of technique survival, patients were divided into two groups on the basis of whether initial SA was above or below the median value. The log rank test was then used to compare technique survival in the two groups. Initial SA was defined as the mean monthly SA over the first 6 months on CAPD. To determine whether the prognostic value of initial SA was independent of other factors, a Cox proportional hazards regression was performed. The other factors tested were age, sex, diabetic status, initial KT/V, TCC, PCRN, and D/P Cr. In both of these analyses, one-sided P values were calculated, because the initial hypothesis, on the basis of the HD data (1,2), was that the patients with the higher initial SA would do better than those with the lower initial SA.

SA was measured with an SMA 12/60 Auto-Analyzer located at Toronto Western Hospital. Dialysate protein losses were measured by a Biuret method (9). KT/V was calculated, using the sum of daily dialysate drainage volume plus residual urea clearance as KT and 55% of body weight (for women) or 60% (for men) as an estimate of V (7). For comparative purposes, V was also calculated by the method of Watson et al. on the basis of sex, height, weight, and age (10,11). PCR was calculated by the method of Teehan et al. and was normalized for body weight to give PCRN (12). As an alternative estimation, the V value calculated by the method of Watson et al. was divided by 0.55 (for women) or 0.6 (for men) to give an idealized body weight, which was then used to normalize PCR. TCC was measured by adding dialysate creatinine clearance (corrected for dialysate glucose content) to residual renal creatinine clearance and adjusting for 1.73 m² body surface area (13). Residual renal function was calculated as the mean of residual renal urea and creatinine clearance corrected for surface area. D/P Cr was measured after a 4-h, 2-L, 4.25% Dianeal dwell with appropriate correction for dialysate glucose (13). Surface area was calculated by the Du Bois method on the basis of height and weight (14). In all cases, means are expressed ± the standard deviation.

RESULTS

Patient Follow-Up

The 76 patients were monitored over 222 6-month periods. Overall, follow-up per patient averaged 19.9 months (range, 1 to 57 months). As is inevitable in long-term studies in CAPD patients (15), drop out was high. Twenty-five patients experienced technique failure (including 13 deaths), 21 underwent transplantation, 4 transferred to other centers, 1 recovered renal function, and 7 refused to continue
Mean SA over the whole study period was 34.1 ± 3.3 g/L (range, 23.8 to 41.6 g/L), and median SA was 34.0. Mean initial SA was 33.4 ± 3.1 g/L (range, 24.3 to 39 g/L), and median initial SA was also 33.4 g/L. There was no significant change in SA with time on CAPD when all patients were considered (Figure 1). However, when a paired analysis was done on only those 49 patients having follow-up for at least 12 months, there was a significant increase from a mean of 34.7 ± 3.0 in the first 6 months to a mean of 35.0 ± 3.0 in the second 6 months (two-sided \( P < 0.0001 \); paired \( t \) test). Similarly, for 32 patients having at least 18 months of follow-up, paired analysis showed an increase from a mean of 35.5 ± 2.4 g/L in the first 6 months to a mean of 35.9 ± 2.6 g/L in the third 6 months \( (P < 0.05) \). There was no significant change in the mean value between the second and third 6-month periods (Table 1).

No difference was seen between the mean SA in men (34.2 ± 3.3 g/L) and women (34.1 ± 3.2 g/L), but the mean SA in diabetics (31.9 ± 2.8 g/L) was significantly lower than that in nondiabetics (35.2 ± 3.2 g/L) \( (P < 0.0001) \). Also, the mean SA in patients aged 65 or over (33.2 ± 3.2 g/L) was significantly lower than that in those under 65 yr of age (35.0 ± 2.3 g/L) \( (P < 0.0001) \).

These differences were also apparent for the initial SA with the mean initial value in the 22 diabetics (31.4 ± 2.7 g/L) being lower than that in the 54 nondiabetics (34.2 ± 2.9 g/L) \( (P < 0.0005) \). Similarly, initial SA was no different between men (33.5 ± 3.1 g/L) and women (33.3 ± 3.2 g/L) but was significantly lower in the 29 patients aged 65 or over (32.4 ± 3.0 g/L) than in the 47 patients under 65 yr of age (34.0 ± 3.1 g/L) \( (P < 0.03) \).

An analysis of changes in SA with time in the different subgroups was done with only the 32 patients with 18 months or longer of follow-up. A significant increase in SA between the first and second 6-month periods was seen for both diabetics and nondiabetics and for patients above and below age 65 (Table 2). This increase was maintained into the third 6-month period in diabetics, nondiabetics, and those aged under 65 but, in those aged 65 or over, there was a significant decline in SA back towards initial levels \( (P < 0.05) \), suggesting that, among patients on long-term CAPD, the elderly are the most at risk for a declining SA (Table 2).

In individual patients, SA sometimes varied markedly so that, in 19 of 49 patients with 12 or more months of follow-up, the 6-month mean SA altered by more than 3.3 g/L relative to the initial SA (equivalent to 1 SD in terms of the population as a whole). In 15 of these 19 cases, the SA increased, and in 4, it decreased. However, in patients with very low or
very high initial SA values, subsequent changes in SA were less marked. Thus, none of the six patients with an initial SA less than 30 g/L subsequently achieved an SA above 32.4 g/L, and none of the five patients with initial SA above 37 g/L subsequently dropped below 34 g/L.

Correlations of SA With Clinical Outcomes

SA correlated inversely with the number of days hospitalized \((r = -0.20; P < 0.005)\) and with patients' subjective estimate of fatigue \((r = -0.20; P < 0.005)\). Although these correlation coefficients are low, statistical significance was achieved because of the large number of observations. SA did not correlate significantly with the overall peritonitis rate or with the number of peritonitis episodes caused by *Staphylococcus aureus* or by gram-negative bacteria. SA did not correlate significantly with the number of transfusions received or with estimates of pruritus or insomnia. SA showed a strong positive correlation with nerve conduction velocity \((r = 0.34; P < 0.001)\).

SA values were significantly lower in 6-month periods preceding technique failure than in those not preceding technique failure \([32.7 \pm 3.4 \text{ g/L} (25 \text{ values}) \text{ versus } 34.3 \pm 3.2 \text{ g/L} (196 \text{ values}); P < 0.03]\). SA values were also lower in 6-month periods preceding death than in those not preceding death, but this did not quite reach significance, probably because of the relatively small number of deaths \([32.5 \pm 3.4 \text{ g/L} (13 \text{ values}) \text{ versus } 34.2 \pm 3.2 \text{ g/L} (208 \text{ values}); P < 0.07]\).

Correlations of SA With Laboratory Values

SA showed a positive correlation with serum creatinine \((r = 0.49; P < 0.0001)\), blood urea \((r = 0.31; P < 0.0001)\), serum potassium \((r = 0.27; P < 0.001)\), phosphate \((r = 0.25; P < 0.001)\), and parathyroid hormone \((r = 0.27; P < 0.001)\) and, more weakly, with hemoglobin \((r = 0.15; P < 0.05)\) and serum triglycerides \((r = 0.18; P < 0.05)\). There was a significant inverse correlation with serum bicarbonate \((r = -0.27; P < 0.001)\). There was no significant correlation with serum sodium, calcium, or cholesterol levels.

Does Initial SA Predict Technique Survival?

Life table analyses were carried out to examine the effect of initial SA on technique survival. The log rank test showed that the high albumin group had a lower rate of failure, compared with that of the low albumin group \((P < 0.05; \text{one-sided test})\) (Figure 2). Thus, the median technique survival for the high albumin group was 46 months compared with 32 months for the low albumin group.

A Cox proportional hazards analysis was done to determine which factors were independently related to technique survival time. The covariates examined were initial SA, age at commencement on CAPD, sex, diabetic status, and initial measurements, made at the end of the CAPD training period, of TCC, KT/V (urea), and PCRN. Of all these factors, only the initial SA was a significant independent predictor \((P = 0.05; \text{one-sided test})\).

Predictors of SA

Mean values of a number of possible predictors of SA are shown in Table 3. SA was not significantly correlated with KT/V (by either method) or with TCC or with dialysate KT/V or creatinine clearance taken alone or with PCRN (by either method). There was, however, a weak but significant positive correlation with the PCR before normalization for body weight \((r = 0.23; P < 0.001)\). SA was correlated positively with body weight \((r = 0.32; P < 0.0001)\) and surface area \((r = 0.23; P < 0.001)\) and negatively with dialysate protein losses \((r = -0.20; P < 0.005)\) and with D/P Cr \((r = -0.35; P < 0.0001)\).

Stepwise multiple regression was performed to determine which factors were independently predictive of SA. Independent variables tested were age, sex, diabetic status, time on CAPD, body weight, surface area, dialysate protein losses, D/P Cr, KT/V, TCC, PCRN, PCR, and residual renal function. The most powerful predictors were diabetic status, D/P Cr, weight, age, and time on CAPD, which together gave a model accounting for almost 40% of total variation in SA (Table 4). Factors such as PCR, PCRN, and KT/V made no significant additional contribution. The addition of TCC would have increased the adjusted \(r^2\) value by only 0.9% and therefore was not considered to be warranted.
TABLE 3. Parameters measured every 6-months—222 measurements in 76 patients

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>KT/V</td>
<td>0.68 ± 0.21</td>
<td>0.32–1.77</td>
</tr>
<tr>
<td>KT/V (V by Watson)</td>
<td>0.72 ± 0.19</td>
<td>0.40–1.60</td>
</tr>
<tr>
<td>TCC</td>
<td>73.6 ± 32.1 L/wk</td>
<td>32.8–218.5</td>
</tr>
<tr>
<td>PCR</td>
<td>61.9 ± 12.4 g/day</td>
<td>37.4–111.0</td>
</tr>
<tr>
<td>PCRN</td>
<td>0.97 ± 0.22 g/kg/day</td>
<td>0.50–1.73</td>
</tr>
<tr>
<td>PCRN (Weight by Watson)</td>
<td>1.02 ± 0.21 g/kg/day</td>
<td>0.58–1.90</td>
</tr>
<tr>
<td>Residual Renal Function</td>
<td>17.3 ± 23.1 L/wk</td>
<td>0–132.5</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>0.66 ± 0.10</td>
<td>0.35–0.97</td>
</tr>
<tr>
<td>Dialysate Protein</td>
<td>8.3 ± 3.2 g/day</td>
<td>1.0–21.2</td>
</tr>
<tr>
<td>Losses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>65.6 ± 14.2 kg</td>
<td>41.6–101.0</td>
</tr>
<tr>
<td>Body Surface Area</td>
<td>1.71 ± 0.21 m²</td>
<td>1.34–2.16</td>
</tr>
</tbody>
</table>

* Corrected for 1.73.

TABLE 4. Predictors of SA (grams/liter)—stepwise multiple regression modela

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>39.18</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>−9.39</td>
</tr>
<tr>
<td>Diabetesb</td>
<td>−2.42</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.254</td>
</tr>
<tr>
<td>Time (months on CAPD)</td>
<td>0.062</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>−0.04</td>
</tr>
</tbody>
</table>

a S, 2.55; r², 39.7; r² (adj) = 38.3; P < 0.0001.
b +1, diabetes; 0, no diabetes.

DISCUSSION

Our finding that SA is a good predictor of adverse clinical outcomes in CAPD patients is in line with similar findings in large numbers of patients on maintenance HD (1,2) and in hospital patients in general (16). It also supports previous, less-detailed reports on smaller numbers of patients, suggesting such a relationship (5,6). However, we did not detect the correlation between low SA and peritonitis reported by Young et al. (5). We also showed, using the log rank test and Cox proportional hazards regression, that the initial, as distinct from the ongoing, SA is independently predictive of technique failure.

The correlation between low SA and both older age and diabetes is no surprise (17,18), but the stability of the SA with time and its tendency actually to increase in patients staying on CAPD for 1 to 2 yr conflicts with earlier observations suggesting that SA may fall or, at best, stay steady in these patients (19,20). Our findings suggest that a rising SA during the first year on CAPD is associated with technique survival and, conversely, that those about to fail experience a declining SA. The relative stability of SA in the various subgroups suggests that diabetic and elderly patients not only start off with a lower SA than their nondiabetic and younger counterparts but also tend to stay at a lower value, long term. Although numbers were small, there was a tendency, not seen in the other subgroups, for SA in patients ages 65 or over to decline during the second year on CAPD. Although mean values in these subgroups were relatively stable, there were many individual patients who showed substantial variation in SA so that, for example, over a third of patients with 12 or more months of follow-up had an alteration of more than 3.3 g/L in their mean 6-month SA, with this alteration involving an increase in the majority of cases. This individual SA variation applied less to patients with initial SA under 30 g/L, none of whom subsequently achieved an SA greater than 32.3 g/L.

The strongest single determinant of SA, other than diabetic status, in our patient cohort was the D/P Cr as measured in a 4-h peritoneal equilibration test. This was unexpected, but since our initial preliminary report of this inverse relationship (21), a similar finding has been reported by other investigators (22). This relationship cannot be attributed solely to the correlation of both SA and D/P Cr with dialysate protein losses because the latter is not an independent predictor of SA. Similarly, the recognized association of high D/P Cr with diabetes, old age, and time on CAPD (23) is not the explanation because these factors were included in the multiple regression model. A possible explanation is that high D/P Cr values are associated with rapid glucose transport across the peritoneum, which leads to ultrafiltration problems and consequent overhydration, which may in turn predispose to malnutrition and low SA. Also, it may be that the overhydration associated with a high D/P Cr has a dilutional effect on SA. The fact that less than 40% of variation in SA is accounted for by the factors included in the regression model is not unexpected in view of the large number of poorly defined factors related to general health and nutrition that are likely to determine SA.

The practical significance of the correlation of low SA and adverse outcomes in dialysis patients is unclear. It is likely that low SA is a marker rather than a direct cause of susceptibility to morbid events and that the underlying problem is one of malnutrition. It is also likely that the morbidity events in themselves predispose to further malnutrition and consequent lower SA values, so instigating a "vicious circle" of deterioration. However, the fact that the initial, as well as the ongoing, SA is predictive of morbidity suggests that low SA is not just a consequence of that morbidity. The relationship between low SA and malnutrition is not a simple one, as indicated by the
absence, both in this study and in others (24), of close correlation between SA and PCRN, the most frequently monitored index of protein intake in dialysis patients. Also, low SA is not a simple consequence of inadequate dialysis, as indicated by the lack of correlation with either KT/V urea or creatinine clearance. Rather, factors that are not easily modified, such as age, diabetes, weight, and peritoneal membrane characteristics, appear to be important in determining SA. A critical question is whether nutritional and medical intervention can lead to a sustained increase in SA in patients with low values and, if so, whether this in turn would be associated with a consequent decrease in morbidity and mortality. Investigation of these issues is important if low SA is to be more than a marker of adverse prognosis in CAPD patients.

The correlation of low SA with low levels of urea, creatinine, phosphate, potassium, and triglycerides in serum likely reflects the common association of all of these with poor nutritional status. Similarly, the association of low serum bicarbonate with high SA is probably due to the common association with good nutritional status and the consequent higher dietary acid load. This does not contradict the reported association between acidosis and protein malnutrition in uremic patients (25), because the relatively greater acidosis in the patients with higher SA values in this study is probably more related to their better protein intake than to poorer control of their uremia.

In conclusion, our study suggests that SA values tend to increase somewhat with time on CAPD, that both ongoing and initial SA values are predictive of adverse outcomes in patients, and that, in addition to diabetes and older age, high D/P Cr is a strong predictor of low SA. Protein malnutrition is an important problem in CAPD patients (26), and SA may be a more useful indicator of it than are measurements of PCRN. Future research should look at interventions aimed at correcting low SA to see if they can modify the associated morbidity and mortality.

REFERENCES


