Serum prealbumin is higher in peritoneal dialysis than in hemodialysis: A meta-analysis

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Background. Although not widely appreciated, the reported markers in both hemodialysis (HD) and peritoneal dialysis (PD) strongly correlate with the serum level of albumin, and correlates at least as well as albumin does with other nutrition markers in both hemodialysis (HD) and peritoneal dialysis (PD) [abstract; Koomen et al, Perit Dial Int 14(Suppl 1): S32, 1994] [1–9]. Serum prealbumin also predicts survival at least as well as does serum albumin in HD [1, 2, 5, 9], although not quite as well as serum albumin in PD [10, 11].

K/DOQI clinical outcome goals have been set for the serum levels of both prealbumin (≥30 mg/dL) and albumin (≥4.0 g/dL) [12]. It is well known that serum albumin concentration tends to be lower in PD than in HD [13, 14], probably due to the substantial peritoneal loss of albumin [15–19]. It is not surprising, therefore, that a serum albumin level of 4.0 g/dL or greater was achieved by 32% of HD patients but only 17% of PD patients in a recent large national survey [20]. Although not widely appreciated, PD also alters the serum level of prealbumin. However, serum prealbumin, like serum cholesterol, tends to be higher in PD than in HD [1, 9, 13, 14, 21], despite the loss of prealbumin and lipoproteins during PD [19, 22–24]. If PD induces a higher serum prealbumin level and lower serum albumin level compared to HD, clinical targets specific to PD for these proteins may be required.

The purpose of this study was to quantify the mean difference in serum prealbumin between PD and HD by performing a pooled analysis of mean serum prealbumin values in two sets of published reports. Set 1 comprised articles or abstracts that reported serum prealbumin in cohorts containing both PD and HD patients, and set 2, articles that measured prealbumin in unselected dialysis patients on a single modality. For comparison, the mean difference in serum albumin between PD and HD also was estimated in each of these data sets.

METHODS

Literature

Two literature sets were defined for meta-analysis. Articles or abstracts reporting mean serum prealbumin in
cohort with both PD and HD patients were included in set 1, and articles reporting mean serum prealbumin in cohorts of unselected dialysis patients on a single modality were included in set 2. Published articles that reported serum prealbumin in dialysis patients were located by searching PUBMED using “prealbumin” as the search word. Additional set 1 studies published as abstracts were identified by a manual search of the abstract publications of the American Society of Nephrology (1982 to 2001), and those of the International Society for Peritoneal Dialysis and the Annual CAPD Conference published in PD International between 1989 and 2001. The analysis was limited to publications located through the end of August 2001, reporting prealbumin concentration in units of mg/dL; when multiple follow-up reports were available on the same cohort, the earliest publication was chosen. Assay methods for prealbumin and albumin were recorded when available.

Six cohorts were selected for set 1 comprising 198 patients on PD and 441 patients on HD. In the first cohort, the PD and HD experiences were reported in separate publications [1, 21]; the second [14], third [9], and fourth [25] cohorts were each reported in single articles, and the fifth and sixth were reported as abstracts (abstracts; Koomen et al, op. cit.; Fassinger et al, Perit Dial Int 12(Suppl 1): 116, 1992) Three set 1 cohorts reported the prealbumin assay used (nephelometry [1, 9, 21]; immunodiffusion [24]); serum albumin data were available in four cohorts (abstract; Koomen et al, op. cit.) [1, 14, 21, 25], and the method used in one (bromcresol green [1, 21]). Twenty-three cohorts were selected for set 2, including nine PD cohorts comprising 490 patients (range 8 to 147) [11, 19, 24, 26–31], and fourteen HD cohorts comprising 11,766 patients (range 17 to 7123) [2–7, 32–39]. The prealbumin assays used were reported in eighteen studies and did not significantly differ between PD and HD (PD, immunodiffusion 3, immunoprecipitation 1, immunonephelometry 3; and HD, immunodiffusion 3, immunoprecipitation 2; immunonephelometry 4; antigen-antibody complex 2; P > 0.64 by chi-square). Twenty-two set 2 studies (all except reference 24) reported albumin data, and the method was available in eleven (PD, bromcresol green 2, immunochemical 1; HD, bromcresol green 6, immunodiffusion 2).

Statistics and data analysis

For each cohort, in set 1 (where i = cohort identification number, ranging from 1 to 6), we tabulated the mean values of serum prealbumin (or albumin), the standard deviation (SD), and the number of subjects (N) separately for PD and HD, and computed the absolute difference of the means (diff.) and tested its significance by the t-test, and, lastly, computed the weighted mean of the six diff. values and the 95% confidence interval (CI), weighing each diff. by the inverse of its variance (weight), using a method based on a fixed-effects model [40]. The homogeneity of the distribution of the differences about the grand mean was tested with a chi-square test [Q = \sum weight_i \times (diff_i - grand mean)^2].

The set 2 study means were examined using a mixed model, with dialysis modality as a fixed factor, study as a random factor, and the inverse of the variance of the mean (N ÷ SD^2) as study weight. For any set 2 study that reported the mean values of prealbumin (or albumin) for subgroups only, we computed a single value for mean and a single pooled SD value by combining the subgroup data. The results of the meta-analysis presented are the estimates of the mean (±SE) in the PD and HD studies and of the mean difference. Sensitivity analyses were performed in order to test the robustness of the results relative to exclusion of potential outliers defined by a t statistic >3.5. Computations were performed using SAS version 8 (SAS Institute, Cary, NC, USA).

RESULTS

Prealbumin

In set 1, the mean concentration of serum prealbumin was higher in PD than in HD in each of the six cohorts, the difference ranging from 3.6 to 14.7 mg/dL (P < 0.05 in 5 of the cohorts; Table 1 and Fig. 1). There was a direct correlation between the HD and PD study means (Spearman correlation coefficient = 0.81 P < 0.05), which suggests that the calibration of the assays varied between the studies. The weighted mean difference between PD and HD was 5.4 mg/dL (95% CI, 3.8 to 7.0 mg/dL).

The set 2 study means also showed a clear trend to increased values in PD (Fig. 2), which was highly signifi-
Table 1. Mean serum prealbumin in set 1 cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>PD Mean ± SD (N)</th>
<th>HD Mean ± SD (N)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30.4 ± 8.0 (33)</td>
<td>26.5 ± 6.4 (125)</td>
<td>3.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>2</td>
<td>32.2 ± 9.5 (71)</td>
<td>28.6 ± 9.3 (53)</td>
<td>3.6</td>
<td>&lt;0.038</td>
</tr>
<tr>
<td>3</td>
<td>37 ± 9.9 (55)</td>
<td>31 ± 10 (192)</td>
<td>6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>46 ± 7.5 (3)</td>
<td>31.3 ± 8.9 (21)</td>
<td>14.7</td>
<td>&lt;0.013</td>
</tr>
<tr>
<td>5</td>
<td>44 ± 12 (28)</td>
<td>35 ± 10 (41)</td>
<td>9</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>6</td>
<td>40 ± 9.9 (8)</td>
<td>35 ± 2.6 (9)</td>
<td>5.8</td>
<td>&lt;0.12</td>
</tr>
</tbody>
</table>

*a mg/dL  
*b t test

Table 2. Weighted estimates of mean serum prealbumin in PD and HD and of the difference in set 2 studies

<table>
<thead>
<tr>
<th>PD (N)</th>
<th>HD (N)</th>
<th>PD-HD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.7 ± 1.2 (9)</td>
<td>32.7 ± 0.8 (14)</td>
<td>8.1 ± 1.4 mg/dL</td>
<td>&lt;10^-4</td>
</tr>
<tr>
<td>40.7 ± 1.0 (9)</td>
<td>33.1 ± 0.7 (13)</td>
<td>7.6 ± 1.2 mg/dL</td>
<td>&lt;10^-4</td>
</tr>
<tr>
<td>40.8 ± 0.9 (9)</td>
<td>33.9 ± 0.1 (12)</td>
<td>6.9 ± 0.9 mg/dL</td>
<td>&lt;10^-4</td>
</tr>
</tbody>
</table>

N denotes the number of studies. Data are mean ± SE.

*a Sensitivity analysis, excluding the largest outlier (see text)
*b Sensitivity analysis, excluding the two largest outliers (see text)

Significant on meta-analysis (Table 2). The estimate of the prealbumin difference was 8.1 mg/dL (95% CI, 5.2 to 10.9 mg/dL) in the analysis of all twenty-three studies. Sensitivity analyses also were performed excluding one or both of the most extreme outlying values, derived from two HD studies that were large and, hence, heavily weighted, that is, studies 1 (N = 1618 [38]) and 3 (N = 1053 [34]) in Figure 2. Eliminating both these studies yielded a conservative, lower estimate of the mean prealbumin difference (6.9 mg/dL; 95% CI, 5.2 to 8.6 mg/dL).

Albumin

Mean serum albumin was significantly higher in HD than in PD in each data set on meta-analysis. The weighted mean difference was 0.25 g/dL (95% CI, 0.14 to 0.36 g/dL) in set 1, and 0.28 ± 0.07 g/dL (P ≤ 0.001) in set 2. Prealbumin and albumin serum levels are known to correlate directly within a group of dialysis patients treated with a single modality. However, when the albumin and prealbumin study means were plotted together, an inverse trend was evident between the dialysis modalities in each data set (Figs. 3 and 4).
DISCUSSION

Meta-analysis of two sets of publications yielded similar estimates of the effect of dialysis modality on serum prealbumin level. The mean concentration difference between PD and HD was 5.4 mg/dL in set 1 and 6.9–8.1 mg/dL in set 2. The mean effect of dialysis on serum albumin concentration was also similar in both study sets: 0.25 to 0.28 g/dL higher in HD.

The meta-analytic models accounted for the variation in study means caused by sampling error and dialysis modality, but it is important to consider how the results might be affected by other factors, such as publication bias, confounding, and study artifacts [41]. It is unlikely that publication bias affects the present analysis because the included studies were neither conducted nor published for reasons related to whether dialysis affects prealbumin concentration. Some of the variation between studies may be the result of confounding by differences in patient characteristics. For example, sex, diabetes, and proteinuria may influence serum prealbumin (abstract; Maru et al, J Am Soc Nephrol 8:72A, 1997) [1, 42, 43]. To minimize this problem, set 2 included no cohorts that had been assembled based on any of these characteristics (for example, all non-diabetics). Given the specificity of immunoassays, it is unlikely that an interferent exists in the serum having differing activities in PD and HD. However, assay calibration differences will inevitably exist between studies [44]. They result in a spurious increase in the variation among the study means, and presumably explain the direct correlation observed between HD means and PD means in set 1. Since the assay methods for PD and HD were identical within each set 1 study, the impact of calibration on the estimate of the concentration difference between PD and HD should be minimized. In set 2, the similarity of the assays used in the PD and HD studies also should reduce the impact of calibration on the estimate of the difference, unless, by chance, a large weight were assigned to an outlying value, which in fact occurs in this data set. This problem was addressed in the sensitivity analysis that excluded the two most extreme such outliers, producing a result (6.9 mg/dL) close to that of the set 1 analysis. Finally, any inflation of the variance, due to interstudy differences in either patient or assay characteristics, widens the confidence intervals of the estimated difference.

One implication of these concentration differences is that the use a single value for either serum prealbumin (≥30 mg/dL) or albumin (≥4.0 g/dL) as a clinical target [12, 20] is confounded by dialysis modality. A single target value would not be expected to perform consistently in both PD and HD. For example, using these targets to classify the prognosis and nutritional state of the cohorts contained in sets 1 and 2 combined (Table 3) might lead one to conclude that PD therapy is both optimal and suboptimal (each PD cohort mean satisfied the prealbumin target but none satisfied the albumin target), and, similarly, that PD therapy is both better (higher prealbumin) and worse (lower albumin) than HD. On the other hand, if these differences are regarded as intrinsic to PD, as we suggest below, then the laboratory reference ranges and clinical target values should be set accordingly. To be consistent in both HD and PD, the respective targets should be set approximately 6 mg/dL higher for prealbumin and approximately 0.3 g/dL lower for albumin in PD, with the exact target values varying by laboratory.

The cause of the depression in serum albumin in PD is presumably the peritoneal loss of albumin (4 to 6 g/day) [17, 19, 22, 23, 45], a high proportion of the amount of albumin normally synthesized (10 to 15 g/day) [46, 47]. Consistent with this supposition, the rate of loss of albumin (or total protein) in PD correlates inversely with serum albumin [15–18]. However, the cause of the increase in prealbumin concentration in PD is unknown. In fact, PD might be expected to lower serum prealbumin because the rate of peritoneal loss of prealbumin (50 to 110 mg/day) [19, 24] represents a sizable fraction of the normal synthesis rate (500 to 650 mg/day) [47]. Therefore, the increased prealbumin level in PD must be due to some combination of reduced volume of distribution, increased rate of synthesis, and/or decreased rate of catabolic clearance in PD compared to HD. Prealbumin and albumin normally have similar volumes of distribution [47]. Even if there were systematic differences between PD and HD in the factors that influence distribution volume, that is, capillary permeability and state of hydration, they would be unlikely to selectively raise the concentration of prealbumin and not that of albumin because of the similarity of the two molecules in size and charge [48]. One plausible, though speculative mechanism for the increase in serum prealbumin in PD is a change in the metabolism of prealbumin (increased hepatic synthesis or reduced systemic catabolism) due to peritoneal loss of a regulatory molecule (such as, albumin), similar to the known alteration in cholesterol metabolism. Observations in PD patients that support a causal role for albumin in regulating hepatic metabolism of other proteins or lipoproteins include: (a) the peritoneal rate of loss of albumin (or total protein) correlates directly with the elevation in serum cholesterol [15, 45]; and (b) intravenous albumin infusion causes the serum levels of fibrinogen, factor 7, and lipoprotein(a) to fall [18]. Moreover, in nephrotic patients with normal renal function, it has been analogously found that the serum levels of prealbumin and cholesterol are both elevated, despite overt losses of prealbumin and lipoproteins, and it has been hypothesized that, like serum cholesterol, serum prealbumin is elevated as a result of the stimulation of hepatic synthesis by the large renal loss of albumin and/or the resultant hypoalbuminemia [43, 48, 49]. Fu-
ture studies are needed to directly examine whether alterations in metabolism or in volume of distribution explain the higher serum prealbumin in PD compared to HD.

The concentration of prealbumin correlates directly with that of serum albumin within a group of patients on a single form of dialysis (abstract; Koomen et al, op. cit.) [1–3, 6–8]. This probably reflects the similar effects on prealbumin and albumin of variations in the states of nutrition, inflammation, and hydration. However, if albumin and prealbumin serum levels reflect only these three factors, the inverse correlation observed between dialysis modalities in Figures 3 and 4 raises a question. How can PD patients simultaneously have lower albumin, implying poorer nutrition, more inflammation, and/or more overhydration than in HD patients, and have higher prealbumin, implying the opposite? This apparent paradox can be resolved by recognizing two additional PD-specific factors that influence the serum levels of prealbumin and albumin: the direct effect of PD losses, and a secondary alteration in prealbumin metabolism (for example, the hypothesized stimulation of the liver). This hypothesis could explain the “paradoxical” inverse correlation between groups as well as the known direct correlation within a modality, illustrated in Figure 5. Peritoneal albumin losses and increased hepatic prealbumin synthesis shift the within-group albumin vs. prealbumin regression line downward and rightward in PD, creating the inverse correlation between groups. Of note, the between-group and within-group correlations of serum albumin with serum cholesterol in dialysis patients follow the same pattern shown in Figure 5 [13].

We conclude that serum prealbumin level is approximately 6 mg/dL higher in PD than in HD, perhaps due to a stimulatory effect of peritoneal albumin loss on hepatic prealbumin synthesis, while serum albumin is approximately 0.3 g/dL lower in PD. Different prealbumin and albumin serum reference ranges and clinical targets should be set for PD and for HD, with the exact values varying by laboratory.

ACKNOWLEDGMENTS

This material is based upon work supported by the Department of Veterans Affairs (VA) and was presented at the World Congress of Nephrology in San Francisco, CA, USA, on October 15, 2001. The authors thank Ms. Francine Tidona, Chief Librarian, and Mr. Robert Hall, Health Sciences Librarian, at the VA NY Harbor Healthcare Center (Brooklyn, NY) for their invaluable assistance with this study.

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E-mail: Phillip.Goldwasser@med.va.gov

REFERENCES


Table 3. K/DOQI outcome goals for serum levels of prealbumin and albumin applied to mean values from sets 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prealbumin ≥30 mg/dL</td>
<td>100% (15/15)</td>
<td>75% (15/20)</td>
<td>&lt;0.048</td>
</tr>
<tr>
<td>Albumin ≥4 g/dL</td>
<td>0% (0/12)</td>
<td>39% (7/18)</td>
<td>&lt;0.016</td>
</tr>
</tbody>
</table>

a One-tailed Fisher’s exact test
b For the 18 HD cohorts that had serum albumin data, this rate is 72% (13/18)


