

## Is Decline in Serum Albumin an Ominous Sign for Subsequent Peritonitis in Peritoneal Dialysis Patients?

Savas Ozturk,<sup>1</sup> Ozlem Soyluk,<sup>2</sup> Dilek Karakaya,<sup>2</sup> Halil Yazici,<sup>3</sup> Yasar Kerem Caliskan,<sup>3</sup> Alaattin Yildiz,<sup>3</sup> Semra Bozfakioglu<sup>3</sup>

*Serum albumin levels have been used as a representative marker for morbidity and mortality in the dialysis population. We evaluated the significance of various biochemical values in peritoneal dialysis (PD) patients with a history of peritonitis.*

*In 51 patients [27 women, 24 men; mean age: 42.6 years (range: 19–70 years); average duration of PD: 28.26 ± 23.1 months] with history of peritonitis, we recorded serum albumin and cholesterol levels at the beginning of PD, at the last visit (1 month) before the peritonitis episode, and at months 1, 6, and 12 after the peritonitis episode. Routine data from peritoneal equilibration tests were also obtained.*

*Serum albumin showed a significant decline from the basal measurement at the measurements 1 month before and after the peritonitis episode ( $p = 0.026$  and  $0.025$  respectively). Serum cholesterol levels and dialysate-to-plasma creatinine at hours 2 and 4 revealed no significant alterations at the same time points.*

*The decline in serum albumin relative to the first visit (basal level) may be a factor showing the likelihood of peritonitis. A decline in serum albumin during follow-up may be an indicator for subsequent peritonitis. The absence of a similar decline in serum cholesterol levels (mimicking albumin) may rule out low dietary intake or malnutrition. Pathophysiologic explanations for these relationships are not obvious.*

*If the leading complication of PD is peritonitis, efforts should be focused on improving the factors that influence serum albumin levels.*

### Key words

Peritonitis, serum albumin, uremia

### Introduction

Peritoneal dialysis (PD) is a dialysis modality that permits patients to lead a higher quality life; however, the technique has some potential risk factors such as peritonitis, which is one of the main problems and the leading cause of hospitalization in PD patients (1). Peritonitis is reported to be directly responsible for 1%–6% of deaths in PD patients (2,3).

As in the nonuremic population, serum albumin levels have been used in the hemodialysis population as a representative marker for morbidity and mortality, and in that population, low serum albumin levels are known to be associated with an increased risk of death and morbidity (4–6). On the other hand, extension of these observations to PD patients has provoked controversy (7). Some publications have shown an association of low serum albumin with an increased risk of morbidity and mortality in PD patients (8–11).

The introduction of potential biochemical predictors of peritonitis arising during patient follow-up would be an important convenience in the routine management of PD patients. To examine parameters that are likely to lead to peritonitis, we studied the relationships of various biochemical values in PD patients with their history of peritonitis.

### Patients and methods

Patients from our PD unit who had experienced peritonitis for the first time and who had been on PD for at least 6 months, with a peritoneal equilibration test (PET) performed both before and after the peritonitis episode, constituted the study group. Data were analyzed retrospectively, with age, sex, PD period, and peritoneal leukocyte count being obtained from patient records. The patients with sterile peritonitis related to icodextrin use and those with a polymicrobial infection were excluded. We included in the study patients who experienced catheter loss or who died during the peritonitis episode regardless of the absence of a

From: <sup>1</sup>Haseki Training and Research Hospital, Division of Nephrology; <sup>2</sup>Istanbul University, Istanbul Medical Faculty, Internal Medicine; and <sup>3</sup>Istanbul University, Istanbul Medical Faculty, Internal Medicine, Division of Nephrology, Istanbul, Turkey.

post-peritonitis PET. Only patients with peritonitis showing an increased peritoneal leukocyte count were included in the study. Peritonitis was diagnosed if one of the following two criteria were present in addition to an effluent white blood cell count above 100 cells/mL with at least 50% polymorphonuclear neutrophil cells:

- Clinical findings (abdominal tenderness, fever, cloudy dialysate)
- Positive effluent culture

Serum albumin and cholesterol levels were obtained from hospital records at the start of PD and at the last follow-up (1 month) before peritonitis and at months 1, 3, 6, and 12 after peritonitis. The dialysate-to-plasma (D/P) ratio of creatinine at hours 2 and 4 of a routine scheduled PET, weekly total dialysate and urinary creatinine clearances, and total dialysate and urinary Kt/V urea before and after the peritonitis episode were also obtained.

Serum albumin was measured using the bromocresol green method on a Roche P Module (Roche Professional Diagnostics, Nutley, NJ, U.S.A.) and an Abbott Architect 1600 clinical chemistry auto-analyzer (Abbott Diagnostics, Abbott Park, IL, U.S.A.). Blood urea was measured by the urease method on the same analyzers. The remaining biochemical tests were also performed on the same chemistry analyzers.

The PETs were performed by instilling 2 L PD solution (2.27% or 2.30% glucose) into the peritoneum after a routine overnight exchange. To achieve the appropriate fluid distribution, the patient was requested to turn from side to side after instillation of each 400 mL fluid. Dialysate samples were analyzed for urea, creatinine, glucose, and sodium concentrations at hours 0, 2, and 4 of the dwell. A serum sample was taken at hour 2, and the drain volume was measured at hour 4. At the same time points, D/P ratios were calculated for urea and creatinine. The ratio of the dialysate glucose concentration at drain time to the initial glucose concentration ( $D/D_0$ ) was also calculated. The PET results were then assessed using the Renal Soft software application, version 2.0 (Baxter Healthcare Corporation, Deerfield, IL, U.S.A.).

#### *Statistical analyses*

The study results were analyzed statistically using the SPSS pocket program (SPSS, Chicago, IL, U.S.A.), and mean values  $\pm$  standard deviation were determined.

Values of  $p$  less than 0.05 were accepted as statistically significant. We applied the Student  $t$ -test to differences between the means of two groups when variables were continuous and the chi-square test to differences between frequencies when the variables were categorical. The correlation analyses used the Pearson or Spearman correlation test.

#### **Results**

A total of 51 patients (27 women, 24 men; mean age:  $42.6 \pm 14.3$  years; average duration of PD before peritonitis:  $28.26 \pm 23.1$  months) were included in the study. Of these 51 patients, 39 (76.5%) were undergoing continuous ambulatory PD (CAPD), 10 (19.6%) were on continuous cycling PD, and 2 (3.9%) were on nocturnal intermittent PD. The causes of end-stage renal disease were chronic glomerulonephritis in 16 patients (31.4%), unknown in 15 patients (29.4%), hypertensive nephrosclerosis in 8 patients (15.7%), diabetic nephropathy in 5 patients (9.8%), and others in 7 patients (13.7%). All of the patients were performing self-PD.

The mean peritoneal leukocyte count was  $3538 \pm 4713$  cells/mL (polymorphonuclear cells:  $3346 \pm 4500$  cells/mL). The mean time required for a decline in the peritoneal leukocyte count to less than 100 cells/mL was  $10.5 \pm 6.0$  days. Three patients (5.9%) died during peritonitis, and the peritoneal catheters of 7 patients (13.7%) were removed. Figures 1 and 2 present serum albumin and total cholesterol levels in the study patients. Table I presents the peritoneal clearances and permeability test results throughout the study.

Statistical analyses showed that serum albumin significantly declined from the basal value 1 month before and 1 month after a peritonitis episode ( $p = 0.026$  and  $0.025$  respectively, Table I). However, the other albumin measurements showed no differences (Figure 1). Although the daily dialysate exchange volumes were considerably increased after peritonitis ( $8.9 \pm 0.23$  L before peritonitis vs.  $10.2 \pm 0.27$  L after peritonitis;  $p < 0.001$ ), basal weekly total creatinine clearances declined significantly at the measurements before and after peritonitis ( $p = 0.007$  and  $0.022$  respectively). Furthermore, serum cholesterol levels and D/P creatinine (hours 2 and 4) revealed no significant alterations at the same time points (Table I). However, the last D/P creatinine measured at hours 2 and 4 of a PET before the peritonitis episode

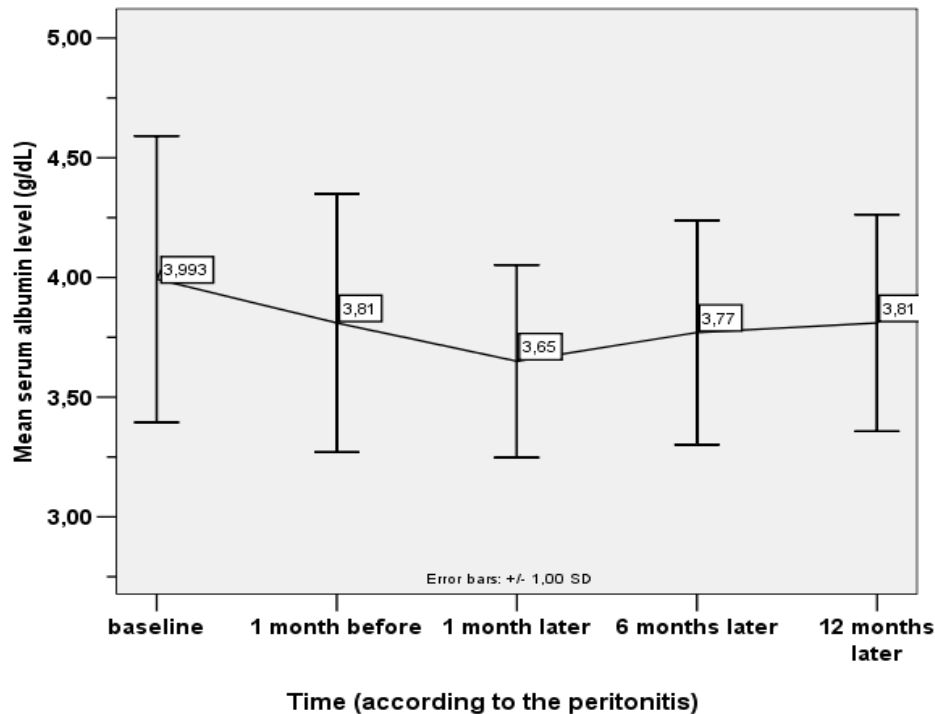


FIGURE 1 Serum albumin level according to time from a peritonitis episode. The serum albumin level at baseline was significantly higher than the levels 1 month before and 1 month after a peritonitis episode ( $p < 0.05$ ).

showed a significant negative correlation with serum albumin levels 1 month before the peritonitis episode ( $r = -0.385$ ;  $p = 0.039$  and  $0.446$ ;  $p = 0.029$ ). No such correlation between D/P creatinine and other albumin measurements was observed.

The daily antihypertensive drug requirement per patient was 0.89 drugs (range: 0 – 4 drugs) before peritonitis; after peritonitis, it was 1.04 drugs (range: 0 – 5 drugs;  $p =$  nonsignificant).

The diagnostic peritoneal leukocyte counts showed no correlation with age, sex, or serum albumin level. No correlations were observed for age, sex, duration of PD before the peritonitis episode, or serum albumin and total cholesterol levels (Figure 1 and 2) with peritoneal leukocyte count at the time of the peritonitis diagnosis.

### Discussion

Peritoneal dialysis is a patient-dependent treatment option. The most important complication associated with this treatment is peritonitis. Although many factors contribute to the incidence of peritonitis, some

specific factors arising during the follow-up period may have a significant influence. Our study retrospectively examined patients at a single center who had experienced peritonitis. We analyzed the relationships between peritonitis and some important biochemical parameters during a period surrounding the first episode of peritonitis in these patients.

The study noted a reduction in serum albumin as compared with the first visit (basal level) as a factor preceding the peritonitis episode (Figure 1). Although the study population was a selective group with a history of peritonitis, and the low albumin level might be a result of multiple causes such as poor intake, subclinical inflammation, or protein loss with dialysate, the decline in serum albumin during follow-up may be an indicator for the subsequent peritonitis. The absence of a similar decline in serum cholesterol level parallel with the decline in albumin level may rule out low dietary intake or malnutrition—a well-known cause of hypoalbuminemia and a risk factor for peritonitis (12,13)—as a factor here (Figures 1 and 2).

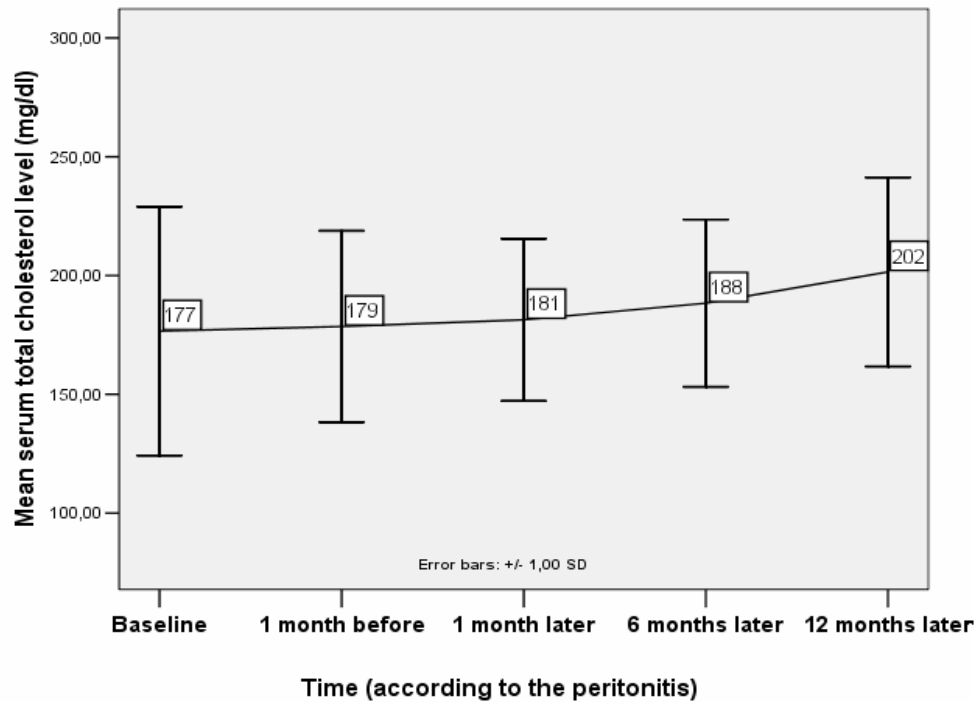


FIGURE 2 Serum total cholesterol levels according to time from a peritonitis episode. No significant changes were seen in the levels of total cholesterol.

The pathophysiologic explanation for these relationships is not obvious. Serum albumin concentration is related not only to production and catabolism, but also to inflammation and peritoneal losses (14,15). Peritoneal membrane transport status and the presence of comorbidities may also contribute.

Our results accord with the literature in this area. A retrospective analysis of 246 incident CAPD patients by Chow *et al.* (16) demonstrated that a lower serum albumin level at the start of CAPD was a significant predictor of peritonitis, with hazard ratio of 1.67 [95% confidence interval (CI): 1.08 to 2.60] for every decrease of 10 g/L in serum albumin ( $p = 0.021$ ). In addition, Sirivongs *et al.* (17) also demonstrated that increases in baseline serum albumin (1 g/dL) and hematocrit (1%) were associated with, respectively, a 27% and a 3% decrease in the risk of peritonitis [hazard ratios: 0.73 (95% CI: 0.59 to 0.91) and 0.97 (95% CI: 0.94 to 1.00) respectively].

Although low levels of serum albumin are known to be associated with an increased risk of death and

morbidity in the hemodialysis population, the results in PD patients are controversial (5,6). In the re-analysis of the CANUSA study (18), the relative risk of technique failure was found to be increased with a lower serum albumin concentration, which may implicate serum albumin in an increased risk for peritonitis. Clinically, it is common for PD patients to experience fluid retention during peritonitis. Compared with baseline, a PET during peritonitis reveals an increase in D/P creatinine and a decrease in D/D<sub>0</sub> glucose. Dialysate protein losses are also increased, and a significant decrease occurs in net ultrafiltration (19). These changes associated with peritonitis are usually reversible, and after recovery, membrane transport returns to baseline.

Microscopic findings in patients with acute peritonitis have revealed denudation of the mesothelial surface (20). These patients often need a temporary change in their standard dialysis prescription (shorter dwell times or increased tonicity) to maintain ultrafiltration. If alternative osmotic agents such as icodextrin

TABLE I Peritoneal clearance and permeability test results throughout the study

Measure	Baseline	Before peritonitis	After peritonitis	p Value
Weekly Kt/V urea	2.41±0.52	2.30±0.41	2.25±0.42	NS
D/P creatinine (hour 2)	0.49±0.10	0.46±0.09	0.45±0.07	NS
D/P creatinine (hour 4)	0.64±0.13	0.62±0.12	0.61±0.10	NS
Weekly CCr (L)	71.0±6.9 <sup>a,b</sup>	56.0±8.7 <sup>a</sup>	60.2±7.1 <sup>b</sup>	<sup>a</sup> 0.007 <sup>b</sup> 0.022

NS = nonsignificant; D/P = dialysate-to-plasma ratio; CCr = creatinine clearance.

are available, several studies have indicated that ultrafiltration can be maintained during an episode of peritonitis with those agents (21). In addition, dialysate levels of interleukins 1 and 6 have been shown to remain elevated more than 1 month after an episode of peritonitis (22), probably because of cytokine-mediated increases in vascularity (20,23,24).

All of these changes may explain the decline of serum albumin in our patients in the first month after a peritonitis episode. But why did mean serum albumin decline 1 month before the peritonitis episode?

Peritoneal host defenses (opsonization, chemotaxis, phagocytosis, and intracellular killing) are known to be very important in the prevention of peritonitis, especially peritonitis of bacterial origin (25). Hence, if the peritoneal immune defense is intact, peritonitis may not develop even after bacterial contamination of the peritoneal cavity. Betjes *et al.* (26) showed that macrophage-related phagocytosis declined in most patients 1–2 days before the onset of clinical peritonitis in the peritoneal cavity, suggesting that not only entry of bacteria into the peritoneal cavity, but also malfunction of the peritoneal immune function contributes to peritoneal infection.

In our study, D/P creatinine at hours 2 and 4 of a PET before peritonitis showed a significant negative correlation with serum albumin levels 1 month before the peritonitis episode ( $r = -0.385$  and  $-0.446$ , and  $p = 0.039$  and  $0.029$  respectively). It appears that, before peritonitis, peritoneal permeability to small solutes increases and serum albumin decreases, with peritonitis subsequently developing. As a result, a decrease in serum albumin before peritonitis may be a reflection of increased peritoneal permeability, perhaps not only for solutes and proteins, but also for microorganisms. However, our study could not show whether the decline in serum albumin was a result of increased catabolism or increased peritoneal macromolecular clearance. This point should be clarified with

studies analyzing peritoneal effluent during the time before a peritonitis episode.

The most important limitation of our study is its lack of a control group. A control group might reveal that the reduction in serum albumin before a peritonitis episode is present only in patients who develop that complication and that this reduction is not an effect of PD or another factor over time. Other limitations include the fact that residual renal function was not analyzed, and effluent albumin losses and peritonitis culture results were not obtained.

### Conclusions

If the most important complication of PD is peritonitis, and if a decline in serum albumin has been associated with an increased risk of peritonitis, then efforts should be focused on improving factors that influence serum albumin levels. Furthermore, clinicians should be aware of the risk of subsequent peritonitis if serum albumin in a PD patient declines.

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*Corresponding author:*

Savas Ozturk, MD, Haseki Training and Research Hospital, Department of Nephrology, Haseki Egitim ve Arastirma Hastanesi, Nefroloji Klinigi Haseki, Fatih, Istanbul, Turkey.

*E-mail:*

savasozturkdr@yahoo.com