

## A Comparative Study of C-Reactive Protein Plasma Levels in Patients on Hemodialysis and Peritoneal Dialysis

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**I**n dialysis patients, C-reactive protein (CRP), a well-recognized marker of inflammation, predicts mortality. Higher levels have been described in hemodialysis (HD) patients as compared with peritoneal dialysis (PD) patients. Our aim was to determine, based on CRP plasma levels, the degree of inflammation in HD patients using low-permeability polysulfone membranes and relatively pure dialysate, and that in PD patients. A secondary objective was to study factors associated with hypoalbuminemia and inflammation in both populations.

We studied 69 stable patients on dialysis (32 on HD and 37 on PD). The mean age was  $69.9 \pm 8.2$  years, and the mean time on dialysis was 27 months. The two populations were comparable for overall and cardiovascular comorbidities. Nephelometry was used to measure CRP plasma levels (normal levels  $< 0.6$  mg/dL). The  $Kt/V_{\text{urea}}$  corrected for residual renal clearance, and the equivalent of protein nitrogen appearance (PNA) were also calculated.

Of the patients studied, 53% showed CRP plasma levels higher than 0.6 mg/dL; in 36%, the levels were higher than 1 mg/dL. No significant differences in these percentages were noted between the two dialysis groups. Patients with CRP levels higher than 1 mg/dL showed lower serum albumin, iron, hemoglobin, and transferrin levels, and higher ferritin values and leukocyte counts. Under logistic regression analysis, CRP levels higher and lower than 1 mg/dL were significantly associated with serum albumin [ $p = 0.01$ ; odds ratio (OR): 0.15], iron ( $p = 0.006$ ; OR: 0.96), transferrin ( $p = 0.004$ ; OR: 0.97), and hemoglobin ( $p = 0.02$ ; OR: 0.67). Serum albumin levels were significantly lower in PD patients. Under regression analysis, serum albumin levels correlated with cholesterol ( $r: 0.25$ ;  $p = 0.04$ ), serum iron ( $r: 0.5$ ;  $p = 0.0001$ ), transferrin ( $r: 0.3$ ;  $p = 0.015$ ), ultrafiltration capacity ( $r: 0.42$ ;  $p = 0.008$ ), and CRP values above 0.6 mg/dL ( $r: -0.65$ ;  $p = 0.001$ ).

In conclusion, the frequent elevation of CRP plasma levels observed in both HD and PD patients suggests the pres-

ence of a silent inflammatory state. Hemodialysis performed with biocompatible, low-permeability membranes is not associated with higher CRP plasma levels than those seen in PD. In both groups, hypoalbuminemia is related to CRP level. Levels of serum albumin, slightly lower in PD patients, are also related to peritoneal ultrafiltration capacity.

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### Key words

C-Reactive protein, mortality, inflammation, peritoneal dialysis

### Introduction

Serum albumin is a remarkable predictor of morbidity and mortality in dialysis patients [1]. Some data suggest, however, that hypoalbuminemia may be secondary to non nutritional factors, specifically inflammation [2,3]. Bergström *et al.* [2] showed that serum albumin levels are predicted by C-reactive protein (CRP), and that CRP levels are better predictors of mortality than are albumin levels. Moreover, some authors found an independent association between CRP levels and morbidity and mortality in both hemodialysis (HD) [4–7] and peritoneal dialysis (PD) patients [8].

Although the relationships among CRP level, serum albumin, and morbidity and mortality in dialysis patients have been accepted, the cause for CRP elevation and the inflammatory mechanism causing the increase in mortality remain to be determined. End-stage renal disease (ESRD) patients have higher CRP plasma levels than does a healthy population [9], and HD patients have even higher levels than do PD or pre-dialysis patients [9,10]. This difference has been attributed to the HD process as a stimulus for inflammation. In addition, the use of “less biocompatible” membranes [9,11] and techniques associated with retrofiltration [12] cause a chronic inflammatory response.

The goal of this study was to determine, based on CRP plasma levels, the degree of inflammation in HD patients using low-permeability polysulfone membranes, and that in PD patients. A secondary objective was to study factors associated with hypoalbuminemia and inflammation in both populations.

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## Material and methods

We studied 69 stable dialysis patients, 32 on HD and 37 on PD; age range, 50 – 80 years; mean age,  $69.9 \pm 8.2$  years. Of the 69 patients, 56% were men, and 17% had diabetes. The study patients had been treated with dialysis for a mean of 27 months (range: 1 – 122 months). At the time of inclusion in the study, the patients showed no signs or symptoms of acute inflammatory disease.

All HD patients were treated three times per week with bicarbonate dialysate. The dialysate flow was 500 mL/min and the blood flow ranged between 300 mL/min and 350 mL/min. The duration of each HD session was adjusted to obtain Kt/V values higher than 1.2. All patients were treated with low-permeability polysulfone membranes: F8HPS and F10HPS (Fresenius Medical Care, Bad Homburg, Germany), with ultrafiltration coefficients of 11.1 mL/h/mmHg and 18 mL/h/mmHg respectively. The water analyses during the study period and the previous year found dialysate bacteria < 10 CFU/mL and endotoxin levels < 0.25 IU/mL. Of the patients on PD, 27 were on continuous ambulatory peritoneal dialysis (CAPD), and 10 were on automated peritoneal dialysis (APD).

Biochemical and hematologic parameters were measured by routine methodologies and included urea, albumin, total protein, cholesterol, serum iron, transferrin, ferritin, hemoglobin, and leukocytes. Plasma levels of CRP were measured by nephelometry, considering non quantifiable normal levels lower than 0.6 mg/dL. A higher level was interpreted as indicative of inflammation, and CRP was quantified.

Upon entrance into the study, an Overall Comorbidity Index (OCI) was scored for each patient. This index includes 24 pathologic conditions defined by specific criteria and scored from 0 – 4: 0 for absence, 1 for presence without repercussion, and 2 – 4 for a presence that causes mild (score 2), moderate (score 3), or severe (score 4) physical limitation. From the OCI, and including angina, arrhythmia, congestive cardiac failure, hypertension, and peripheral vascular or cerebral diseases, a cardiovascular comorbidity index (CCI) was also calculated [13].

Dialysis dose was established by the mean Kt/V<sub>urea</sub> corrected for residual renal clearance. Daily protein intake was estimated from the normalized equivalent of protein nitrogen appearance (nPNA). Both parameters were calculated for current and for ideal body weight. Peritoneal membrane characteristics were determined by the usual methods using a 4-hour, 2.27% dextrose exchange for calculation of ultrafiltration and dialysate-to-plasma (D/P) solute ratio.

Statistical analysis was performed using the SPSS 6.12 software program (SPSS Inc., Chicago, IL, U.S.A.). The Student *t*-test was used for comparison of unpaired data, and the Mann–Whitney test was used for nonparametric data comparison. The Fisher exact test and the chi-square test were used to estimate associations among qualitative variables. A

linear regression analysis was also performed using Pearson or Spearman coefficients, depending on normal or non normal distribution. A logistic regression analysis was performed to determine possible influences of multiple variables on CRP (at values higher and lower than 1 mg/dL). Values of *p* less than 0.05 were considered significant.

## Results

Table I shows the demographic and clinical characteristics of the two groups. Patients on PD had a slightly lower mean age; the two populations were similar for other demographic parameters. Data on comorbidity and the percentage of patients with diabetes were also similar. Aggregate weekly Kt/V<sub>urea</sub> was  $2.2 \pm 0.4$  in PD patients and  $4.1 \pm 0.8$  in HD patients. The mean duration of HD treatment was  $10 \pm 0.9$  hours per week.

### C-Reactive protein

Of the patients studied, 53% showed CRP plasma levels higher than 0.6 mg/dL; in 36% of the patients, the levels were higher than 1 mg/dL (Table I). No significant differences were seen between the dialysis groups in regard to these percentages. In fact, mean values of CRP higher than 0.6 mg/dL were not different between the HD and PD patients ( $2 \pm 1.3$  mg/dL for HD vs  $1.8 \pm 1.3$  mg/dL for PD).

Table II shows the principal differences between patients with CRP levels higher and lower than 1 mg/dL. Comorbidity indices, protein intake, and erythropoietin (EPO) dose were similar. Nonetheless, patients with CRP levels higher than 1 mg/dL showed lower serum albumin, iron, hemoglobin, and transferrin levels, and higher ferritin values and leukocyte counts.

Logistic regression analysis found that CRP levels higher and lower than 1 mg/dL were significantly associated with serum albumin [*p* = 0.01; odds ratio (OR): 0.15], serum iron (*p* = 0.006; OR: 0.96), transferrin (*p* = 0.004; OR: 0.97), and hemoglobin (*p* = 0.02; OR: 0.67). The other quantitative and qualitative variables were not significantly related to CRP values.

TABLE I Patient characteristics and laboratory data.

	HD (n=32)	PD (n=37)	<i>p</i> Value
Age (years)	70.3±7.2	64.0±8.0	<0.01
Sex (M/F)	18/14	21/16	NS
Diabetes (yes/no)	9/23	10/27	NS
Time on dialysis (months)	34±5	21±26	NS
Overall comorbidity	7.4±4.3	6.9±3.8	NS
CRP > 1 mg/dL (yes/no)	14/18	11/26	NS
CRP > 0.6 mg/dL (yes/no)	18/14	19/18	NS
Albumin (g/dL)	3.9±0.33	3.7±0.38	<0.05
Total protein (g/dL)	7.5±0.5	6.7±0.5	<0.05
nPNA (g/kg/day)	1.05±0.31	1.02±0.24	NS

HD = hemodialysis; PD = peritoneal dialysis; NS = nonsignificant; CRP = C-reactive protein; nPNA = normalized equivalent of protein nitrogen appearance, calculated for ideal weight.

TABLE II Characteristics of, and laboratory values for, patients with plasma levels of C-reactive protein (CRP) higher and lower than 1 mg/dL.

	CRP < 1 mg/dL	CRP > 1 mg/dL	p Value
Men	56.8%	56%	NS
Diabetic patients	31.8%	20%	NS
Overall comorbidity index	6.7±3.7	7.8±4.4	NS
CV comorbidity index	3.1±2.8	3.2±2.1	NS
Age (years)	65.4±8.5	69.4±7.2	0.055
Time on dialysis (months)	23.6±29	33.8±29	NS
nPNA (g/kg/day)	1.06±0.29	0.97±0.22	0.08
Albumin (g/dL)	3.9±0.3	3.7±0.4	0.014
Hemoglobin (g/dL)	12.2±1.8	11.1±1.6	0.016
Serum iron (µg/dL)	89.4±35	63±22	0.002
Ferritin (ng/mL)	520±411	743±484	0.056
Transferrin (mg/dL)	215±44	180±28	0.001
Leukocytes (cells/mL)	6686±2669	7990±2645	0.055
EPO dose (U/kg/week)	100±60	115±44	NS

NS = nonsignificant; CV = cardiovascular; nPNA = normalized equivalent of protein nitrogen appearance, calculated by ideal weight; EPO = erythropoietin.

For CRP values higher than 0.6 mg/dL, the correlation between CRP and serum albumin was negative and significant ( $r = -0.65$ ;  $p < 0.001$ ).

#### Serum albumin

Serum albumin levels were significantly lower in PD patients (Table I). In regression analysis, the variables significantly associated with serum albumin levels were these: cholesterol ( $r = 0.25$ ,  $p = 0.04$ ), serum iron ( $r = 0.5$ ,  $p = 0.0001$ ), transferrin ( $r = 0.3$ ,  $p = 0.015$ ), ultrafiltration capacity with 2.27% glucose (UF 2.27%:  $r = 0.42$ ,  $p = 0.008$ ), and CRP values above 0.6 mg/dL ( $r = -0.65$ ,  $p = 0.001$ ). In multiple regression analysis, serum albumin was independently related to serum iron ( $r = 0.56$ ,  $r^2$  adjusted = 0.29,  $p = 0.001$ ) and UF 2.27% ( $r = 0.62$ ,  $r^2$  adjusted = 0.35,  $p = 0.004$ ).

#### Discussion

In dialysis patients, CRP has become one of the best predictors of morbidity and mortality [2,4–6]. Cardiovascular disease continues to be the principal cause of death in these patients. Evidence is growing for an inflammatory component in the atherosclerosis process. Elevated CRP has been confirmed as an independent cardiovascular risk factor in healthy people [14] and in ESRD patients [6,15]. Owing to the important repercussions of these factors on dialysis survival, any measure designed to estimate and control the process should be considered important.

Levels of CRP in renal patients are possibly higher than in the general population. The reasons have not been identified, but the uremic state or the renal disease itself may be the cause [9]. Haubitz *et al.* [9] found that these high levels are even higher among HD patients relative to PD or pre-dialysis patients. The elevation was confirmed by the increased levels after HD was initiated in 8 patients. The group concluded that PD represents a lower degree of inflammation than does HD.

However, that study was performed on HD patients using cuprophane membranes. The same authors had previously demonstrated CRP elevation with the use of cuprophane membranes [16].

McIntyre *et al.* [10] also found higher CRP levels in HD patients than in PD patients, although the HD process with modified cellulose did not increase such levels. The researchers suggest that the use of dialysate with non pure water may be related to the phenomenon of chronic inflammation. Other authors suggest that the acquisition of endotoxins via retrofiltration from dialysate prepared using non pure water may be the inflammatory stimulus [12].

The patients included in the present study were treated with biocompatible membranes (polysulfone) with a low degree of permeability to avoid retrofiltration, and the water used was relatively pure. Possibly as a consequence of these precautions, we found no differences in CRP plasma levels between our HD and PD patients.

The fact that most patients under either dialysis modality had elevated CRP values requires another explanation. The inflammation represented by these values may be due to the associated uremic status, or to pathologic conditions, or to both. Nonetheless, the two indices of comorbidity did not vary between patients with CRP values higher than 1 mg/dL (Table II). Libetta *et al.* [17] demonstrated that interleukin-6 (IL-6) and  $\beta_2$ -microglobulin in blood mononuclear cells are elevated in all renal patients relative to healthy people, with no differences by the type of dialysis.

Several studies have demonstrated a relationship between serum albumin and CRP levels in both PD and HD [2,3,7,8]. Patients on PD show serum albumin levels that are lower than those in patients on HD. This difference could be explained by over-hydration [18] and high peritoneal permeability [19,20]. The association observed between ultrafiltration capacity and serum albumin corroborates this hypothesis.

#### Conclusion

The frequent elevation of CRP plasma levels observed in HD and PD patients suggests the presence of silent inflammatory states in the two populations. Hemodialysis performed with biocompatible, low-permeability membranes is not associated with CRP plasma levels higher than those seen in PD. Hypoalbuminemia is related with CRP levels in both groups. Levels of serum albumin, slightly lower in PD patients, are also associated with diminished peritoneal ultrafiltration capacity.

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