Changes of Serum Albumin and C-Reactive Protein Are Related to Changes of Interleukin-6 Release by Peripheral Blood Mononuclear Cells in Hemodialysis Patients Treated With Different Membranes

Bruno Memoli, MD, Roberto Minutolo, MD, Vincenzo Bisesti, PhD, Loredana Postiglione, PhD, Angela Conti, PhD, Luigi Marzano, MD, Alfredo Capuano, MD, Michele Andreucci, MD, Mario M. Balletta, MD, Bruna Guida, MD, and Ciro Tetta, MD, for the Collaborative Study Group on SMC Membrane

- Protein malnutrition, a condition associated with an albumin concentration less than 3.5 g/dL, has been shown to be a major risk factor for increased mortality in hemodialysis patients. The aim of this cross-over study was to evaluate the relationship between the type of membrane adopted and serum albumin changes by measuring peripheral blood mononuclear cells (PBMC) interleukin-6 (IL-6) release, serum albumin, and plasma concentrations of C-reactive protein (CRP) in 18 patients dialyzed with different membranes. During the study, all patients were dialyzed with cuprophan (CU), synthetically modified cellulosic (SMC) membrane (a new cellulosic membrane with lesser complement activation), and cellulose diacetate (CD) membrane, and have served as their own controls. IL-6 spontaneous release by PBMC resulted after 3 months of SMC (436.2 ± 47.4 pg/mL) significantly (P < 0.05) reduced as compared with CU (569.3 ± 24.5 pg/mL). This effect was more evident after 6 months of dialysis with SMC (220 ± 35.3 pg/mL, P < 0.01 versus CU and versus 3 months of SMC). The passage to CD membrane was followed by a progressive new increase in the IL-6 PBMC release (332.3 ± 30.7 after 3 months, and 351.2 ± 35.8 pg/mL after 6 months, respectively) that, however, remained significantly (P < 0.05) lower than CU. The behavior of CRP plasma levels resembled that of IL-6 PBMC release (23.3 ± 4.7 in CU, 11.0 ± 2.1 after 3 months in SMC, and 7.9 ± 1.5 after 6 months in SMC, respectively). IL-6 release values were positively correlated with circulating levels of CRP (r = 0.3264, P < 0.002). Serum albumin increased after 6 months of dialysis with SMC membranes (3.25 ± 0.09 g/dL in CU and 3.64 ± 0.07 g/dL in SMC, P < 0.05). When the patients were switched to CD, serum albumin showed a slight, though not statistically significant, decrease. Serum albumin concentrations negatively correlated with both IL-6 release values (r = −0.247, P < 0.05) and CRP plasma levels (r = −0.433, P < 0.001). In conclusion, our data clearly show that a significant relationship exists between biocompatibility of the membranes and serum albumin changes; serum albumin levels, in fact, are negatively correlated with the PBMC spontaneous IL-6 release values and CRP circulating levels.

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INDEX WORDS: Serum albumin; biocompatibility; interleukin-6 (IL-6); C-reactive protein (CRP); dialysis membranes.

Mortality AND morbidity rates of end-stage renal disease patients undergoing chronic dialysis therapy still remain high (greater than 20%) despite the fact that the efficiency and quality of dialysis treatments have been considerably ameliorated. Many factors have been associated with this high mortality and morbidity; they include basic factors (age, sex, and so forth) and comorbid conditions (diabetes, cancer, history of myocardial infarction, and so forth).1

Dialysis treatment characteristics per se, however, including dialysis dose, choice of the dialytic membrane, and purity of dialysate, may also play a significant role.2,3 In particular, blood interaction with dialysis membranes may chroni-
cally activate the peripheral blood mononuclear cells (PBMC), thereby causing the release of proinflammatory cytokines, such as interleukin (IL)-1 and, even more, IL-6. A spontaneous increase of IL-6 release by cultured PBMCs was first shown by our group in uremic patients dialyzed with cuprophan membranes. When the same patients were switched to a more biocompatible synthetic membrane, the IL-6 production became comparable with that observed in healthy control subjects. Similar results were obtained with the release of IL-6 soluble receptor.

IL-6 is the major regulator of the hepatic acute phase response in the course of inflammation. It stimulates (up to 1,000-fold or more) hepatic synthesis of both C-reactive protein (CRP) and serum amyloid A (SAA), and reduces the circulating levels of serum albumin, prealbumin, and transferrin (ie, the visceral proteins usually adopted as nutritional markers). Protein malnutrition, a condition associated with an albumin concentration less than 3.5 g/dL, has been shown to be a major risk factor for increased mortality in hemodialysis patients. But serum albumin concentrations have been shown to be negatively correlated, in hemodialysis patients, both with the circulating levels of acute-phase proteins and with the IL-6 plasma levels, thereby suggesting that hypoalbuminemia represents, at least in part, a negative acute-phase protein response to inflammatory stimuli and may also be considered a marker of the inflammatory status. According to this hypothesis, plasma levels of both CRP and IL-6 have been indicated as strong predictors of mortality in these patients.

A few studies have been focused on the relationship between the type of membrane adopted and the serum albumin concentration. But no studies are present in the literature in which IL-6 release by PBMC, serum albumin, and plasma concentrations of CRP have been simultaneously and longitudinally measured in the same patients dialyzed with different membranes. And we know that the release of IL-6 by cultured PBMCs, together with cytokine gene expression, represents the most appropriate and reliable method to study the biocompatibility of dialysis membranes. The purpose of the present study was to cover this gap.

In this study, to compare membranes with similar diffusive performance but different biocompatibility characteristics, we have only used cellullosic membranes. In particular, we have made comparisons between unsubstituted (cuprophan) and substituted (synthetically modified cellulose [SMC] and cellulose diacetate) cellullosic membranes. SMC is a new cellulose-based membrane obtained by the replacement of hydrophilic hydroxyl groups by highly hydrophobic benzyl groups with significant improvement in terms of complement activation and leukocyte adherence.

PATIENTS AND METHODS

Patient Selection and Dialysis Procedures

We have studied 18 patients (10 men, 8 women, mean age: 48 ± 16.4 SD years) undergoing standard bicarbonate dialysis for at least 1 year before the study. All patients were dialyzed, 3 times a week, for at least 6 months before the study with new cuprophan membranes (filters manufactured by Bellco, Mirandola, Italy; mean membrane surface, 1.3 m²; thickness, 8 µm; sterilization, ethylene oxide).

No patient was clinically malnourished or had diabetes mellitus. No patient had clinical or laboratory evidence for infective, neoplastic, or inflammatory disease, or was assuming any anti-inflammatory or immunodepressive drug. Eight healthy laboratory staff volunteers (5 men, 3 women, mean age, 42.8 ± 11.2 SD years) have been also enrolled as a control group. All patients gave their informed consent before the study.

In all phases of the study, dialysate was prepared with bicarbonate dry powder cartridges after water had been filtered through hydrophobic membranes. Kt/V urea and protein catabolic rate were estimated every 15 days. Kt/V was calculated by the Daugirdas equation and kept between 1.2 to 1.3 in all phases of the study. The normalized protein catabolic rate (nPCR, g/kg/day) was evaluated according to Depner and Daugirdas equations. Namely, nPCR was calculated at midweek by the following equation:

\[ nPCR = \frac{Co}{[25.8 + 1.15 Kt/V + 56.4/(Kt/V)]} + 0.168 \]

where Co is midweek predialysis BUN concentration. Specific attention was devoted to dietary protein and caloric intake of patients with the help of a dietitian. Specifically, all patients were addressed, with frequent dietary advice, to follow the same protein (1.0–1.2 g/kg/day) and caloric intake (30–35 Kcal/kg/day) throughout the study.

Concerning the solute transport characteristics, to compare the 3 membranes, we used the following equation to calculate the clearances (Cl, mL/min) of urea, creatinine, and phosphate:

\[ Cl = \frac{Qbi(Cbi-Cbo) + QfCbo}{Cbi} \]
where Qb is the blood flow rate (mL/min), Qf is the ultrafiltration flow rate (mL/min), and Cb is the solute plasma concentration (mg/dL); i = at the inlet of the filter and o = at the outlet, respectively.

**Study Design**

We have performed an observational prospective cross-over study. During the study, all patients have changed 3 different membranes and have served, in all phases, as their own controls.

In the first phase (phase 1) of the study, all patients were evaluated during bicarbonate standard dialysis with cuprophan (CU) membrane for at least 6 months. The same patients were then switched to standard dialysis with SMC membrane (NC 1485, 1.4 mg, ethylene oxide (ETO), Beloco) for 6 months (phase 2). After this period the patients were newly shifted to a dialysis with a cellulose diacetate (CD) membrane (DN 1813–15, 1.3–1.5 mg, ETO, Nipro, Japan) for the following 6 months (phase 3). All filters were adopted for the first time; no reprocessing procedure was allowed throughout the study. No significant difference (<25%) in ultrafiltration rate, dialysis dose, dialysis time, blood flow rate, heparin, dialysate composition, and support therapy (erythropoietin, 1–25 Vitamin D, and so forth) was observed in all phases of the study.

Blood samples were drawn at the end of the CU period, after both 3 and 6 months of dialysis with SMC membrane (SMC1 and SMC2, respectively), and after 3 and 6 months of dialysis with CD membranes (CD1 and CD2, respectively). Blood samples were always drawn in a steady state condition, namely, in the absence of any intercurrent illness, and just before the onset of the second dialysis of the week. Similarly, blood samples were also drawn in healthy control subjects in the absence of any clinical problem.

**Blood Samples and Cell Cultures**

PBMCs were obtained from heparinized blood samples of 10 mL. PBMCs were harvested and set up in cultures by a Ficoll-Hypaque (Flow Laboratories, Irvine, UK) gradient density centrifugation (400g over 30 min). Mononuclear cells were washed twice with RPMI 1640 culture medium (Flow Laboratories), ultrafiltered to avoid microbial contamination (Gambro, Sweden), and resuspended in 15 mL polypropylene round bottom tubes (Falcon, Becton Dickinson, Lincoln Park, NJ) in an Iscove’s culture medium (Flow Laboratories) supplemented with 1% heat-inactivated fetal bovine serum (Sigma Chimica, Milan, Italy) and antibiotics (penicillin and streptomycin) at a concentration of 2 × 10^5/mL. PBMCs were cultured for 24 hours at 37°C in a 5% CO2 saturated humidity incubator.

PBMC cultures were prepared either in the absence or presence of a mitogenic stimulation with 200 ng/mL of bacterial (Escherichia coli) lipopolysaccharide (LPS) (Sigma). At the end of the incubation period, cell-free supernatants were collected by centrifugation and stored at −20°C.

The cell cultures contained about 95% PBMCs with a mean value of 75% lymphocytes and 12% monocytes; no difference was observed in this cell distribution (between lymphocytes and monocytes) in the different phases of the study. More than 95% of PBMCs were viable, as determined by trypan blue dye exclusion at the beginning of the culture, and more than 90% before supernatant collection.

**Analytical Determinations**

Urea concentration was determined in the plasma of both control subjects and uremic patients with a Beckman autoanalyzer (Beckman Instruments, Fullerton, CA).

Albumin and CRP were quantified by nephelometry by using a BNA II Nephelometer (Dade Behring Inc, Newark, DE) with specific antibodies produced by rabbit immunization with highly purified albumin and CRP, respectively. For accuracy and precision, N/T protein control sera were used after each first opening of an antiserum vial as well as for each series of patient serum samples. The following reference values were applied for serum samples from healthy adults (2.5–97.5 percentile): albumin 3.50 to 5.20 g/dL and CRP 0 to 5 mg/L (minimum detection limit: 1.2 mg/L). The variation coefficient of both inter- and intra-assay is less than 5% for either albumin or CRP.

**IL-6 Assay**

IL-6 concentrations in PBMC cultures supernatant were measured by enzyme-linked immunosorbent assays (ELISAs) by using a commercially available kit (Quantikine, R&D Systems, Minneapolis, MN). All samples (including standards) were analyzed in duplicate at the same time. This assay runs by using a quantitative sandwich enzyme immunoassay technique described previously.6 The IL-6 assay lower detection limit is less than 0.70 pg/mL and the variation coefficient of both inter- and intra-assays is less than 5%.

**Statistical Analysis**

Statistical analysis was performed by using t tests for paired and unpaired data, and the analysis of variance for repeated measures followed by Newman-Keuls, as a post hoc test. Linear regression analysis (with Pearson’s correlation coefficient) was also used. Unless otherwise reported, results are expressed as mean ± SEM; statistical significance was defined as P less than 0.05.

**RESULTS**

As shown in Fig 1, when the patients were switched from CU to the SMC membrane, after 3 months they showed a significant reduction in the release of IL-6 by PBMCs cultured in the absence of any mitogenic stimulation (569.3 ± 24.5 pg/mL in CU and 436.2 ± 47.4 pg/mL in SMC1, P < 0.05). This effect was more evident after 6 months of dialysis with this modified cellulosic membrane (220 ± 35.3 pg/mL in SMC2, P < 0.01 versus CU and SMC1). These values were, however, still higher than those obtained in healthy control subjects (49.25 ± 12.34 pg/mL, P < 0.005 versus SMC2, not shown in Fig 1). The passage to a CD membrane
was followed by a progressive new increase in IL-6 spontaneous production (332.3 ± 30.7 and 351.2 ± 35.8 pg/mL in CD1 and CD2, respectively), as compared with SMC2 (P < 0.05 versus unstimulated CU; §P < 0.05 versus other unstimulated groups; *P < 0.05 versus corresponding unstimulated). When PBMCs were challenged with LPS (Fig 1), no difference was observed in IL-6 release by PBMCs, as compared with basal condition, when patients were dialyzed with CU (585.7 ± 14.83 pg/mL); on the contrary, when SMC membranes were used, an increase in IL-6 release, as compared with basal condition, was progressively evidenced under mitogenic stimulation (564.7 ± 20.42 pg/mL in SMC1, P < 0.05 versus basal and 419.9 ± 11.58 pg/mL in SMC2, P < 0.01 versus basal, respectively); the passage to the CD membrane reduced progressively the difference between the responses by unstimulated and stimulated PBMCs (418.2 ± 12.97 in CD1, P < 0.05 versus basal condition in CD2 (407.2 ± 20.09 pg/mL). A statistically significant positive relationship was found between the spontaneous production of IL-6 and its release under LPS stimulation (r = 0.446, P < 0.0001), suggesting that the grade of activation in basal conditions probably influences the highest value attainable after stimulation.

In Fig 2, plasma levels of CRP in the different phases of the study are reported. A progressive significant (P < 0.01) reduction of plasma values of CRP when the patients were switched from CU to the SMC membrane is evident (23.3 ± 4.7, 11.0 ± 2.1, and 7.9 ± 1.5 mg/L in CU, SMC1, and SMC2, respectively). When the patients were shifted to a CD membrane, a not significant increase in CRP values was evidenced. The values obtained (12.2 ± 3.1 and 12.9 ± 2.8 mg/L in CD1 and CD2, respectively), however, were still significantly lower than CU (P < 0.01).

In Fig 2, the behavior of serum albumin in the various phases of the study is also reported. It is evident that a progressive increase of this protein occurred when the patients were shifted from CU to SMC, though a significant difference was not evidenced after 3 months (3.25 ± 0.09 g/dL in CU and 3.43 ± 0.09 g/dL in SMC1). After 6 months the difference became statistically significant (3.64 ± 0.07 g/dL in SMC2, P < 0.01 versus CU). When the patients were switched to CD, serum albumin levels showed a slight decrease from those observed in SMC2. The values obtained (3.56 ± 0.07 and 3.52 ± 0.06 g/dL in

![Fig 1. IL-6 release after incubation of both unstimulated (□) and stimulated (■) PBMC for 24 hours. The results (expressed as mean ± SEM) are obtained from the same 18 uremic patients regularly dialyzed with a CU membrane and then shifted first to a new SMC membrane (SMC1 after 3 months, SMC2 after 6 months, respectively), and then to a CD membrane (CD1 after 3 months, CD2 after 6 months, respectively). *P < 0.05 versus unstimulated CU; §P < 0.05 versus other unstimulated groups; °P < 0.05 versus corresponding unstimulated.](image1)

![Fig 2. Plasma levels of CRP (——) and serum albumin (ALB) (——) concentration in the same patients dialyzed with the same membranes as in Figure 1. The results are expressed as mean ± SEM. *P < 0.05 versus CU; **P < 0.01 versus CU.](image2)
CD1 and CD2, respectively), however, were still significantly higher ($P < 0.05$) than CU.

A positive linear relationship ($r = 0.3264$, $P < 0.002$) was observed between IL-6 spontaneous release values and the circulating levels of CRP; conversely, a negative linear relationship was observed both when plotting serum albumin concentrations and IL-6 release values ($r = -0.247$, $P < 0.05$) and when plotting serum albumin concentrations and CRP plasma values ($r = -0.433$, $P < 0.001$).

No statistically significant difference was observed in the clearances of small solutes with the 3 membranes used in the study (Table 1). Similarly, no difference was observed in nPCR (range, 1.22–1.36 g/kg/day), in $K_t/V$ (range, 1.24–1.44), and in body mass index (BMI) in the different phases of the study (Table 2).

**DISCUSSION**

The role played by the type of membrane on the clinical outcome of dialysis patients, in terms of mortality and morbidity, is so far still a matter of debate, even though it is well recognized that a different kind of membrane may elicit a different proinflammatory cytokine release by PBMCs. Hakim et al have shown that the relative risk for mortality of patients dialyzed with a modified cellulose or synthetic membrane was at least 20% less than that of patients treated with an unsubstituted cellulose membrane. Furthermore, the use of a more biocompatible membrane may positively affect serum albumin concentration.

This study was mainly addressed to evaluate the behavior of a serum albumin and CRP in relation to IL-6 release by PBMCs in patients dialyzed consecutively with 3 different membranes.

**Table 1. Clearances of Some Small Solutes Obtained With the Membranes Used in the Study**

<table>
<thead>
<tr>
<th>Solute</th>
<th>NT 1508</th>
<th>NC 1485</th>
<th>DN 1813</th>
<th>DN 1815</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>184 ± 7</td>
<td>183 ± 6</td>
<td>178 ± 7</td>
<td>180 ± 6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>165 ± 5</td>
<td>168 ± 1</td>
<td>160 ± 8</td>
<td>163 ± 4</td>
</tr>
<tr>
<td>Phosphate</td>
<td>147 ± 8</td>
<td>149 ± 1</td>
<td>140 ± 9</td>
<td>145 ± 5</td>
</tr>
</tbody>
</table>

 NOTE. Values determined in vivo: Qbi 300 mL/min; ultrafiltration flow rate 10 mL/min; dialysate flow rate 500 mL/min (n = 10 for each membrane used). Results expressed as mL/min (mean ± SD).

First of all, we have checked the different biocompatibility of the 3 membranes by measuring the release of IL-6 by cultured PBMCs. Our results clearly show that PBMC harvested from uremic patients regularly undergoing hemodialysis treatment with a CU membrane, significantly reduced the spontaneous release of IL-6 when the same patients were dialyzed, for at least 6 months, with a more biocompatible SMC membrane. The IL-6 release values, however, remained significantly higher than those exhibited by healthy control subjects. When the same patients were switched from SMC to a CD membrane, a progressive worsening of the biocompatibility status was observed, as compared with SMC, though the biocompatibility of CD membrane was still significantly better than that observed with CU.

The PBMC release of IL-6 under mitogenic stimulation confirmed the previous results of our group as well as of other investigators. In particular, in patients dialyzed with a CU membrane, the production of IL-6 by stimulated PBMCs was not different from that obtained in an unstimulated condition. On the other hand, the chronic use of more biocompatible, less complement-activating, membranes (such as SMC) could reverse this alteration, probably second to a down-regulation of recurrently activated PBMCs to release cytokines.

Thus, taken together, these results show a better biocompatibility of the SMC membrane than that of CU, and, to some extent, of CD. These effects, probably secondary to a lesser complement activation, are caused by the introduction in the SMC membrane of highly hydrophobic groups into the cellulosic structure.

**Table 2. BMI = Dry Body Weight (Kg)/Height (m²), nPCR (g/kg/day), and Kt/V (U) Values in the Various Phases of the Study**

<table>
<thead>
<tr>
<th></th>
<th>CU</th>
<th>SMC1</th>
<th>SMC2</th>
<th>CD1</th>
<th>CD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>SD</td>
<td>4.2</td>
<td>3.8</td>
<td>3.9</td>
<td>4.5</td>
<td>4.7</td>
</tr>
<tr>
<td>nPCR</td>
<td>1.29</td>
<td>1.29</td>
<td>1.30</td>
<td>1.30</td>
<td>1.31</td>
</tr>
<tr>
<td>SD</td>
<td>0.05</td>
<td>0.04</td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>$K_t/V$</td>
<td>1.36</td>
<td>1.35</td>
<td>1.38</td>
<td>1.38</td>
<td>1.39</td>
</tr>
<tr>
<td>SD</td>
<td>0.06</td>
<td>0.06</td>
<td>0.05</td>
<td>0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

 NOTE. Data are expressed as mean ± SD (n = 18 for each phase).
with the formation of a membrane surface that presents both hydrophilic and hydrophobic properties.\textsuperscript{26,27} This improvement, however, fails to match the level of biocompatibility offered by some synthetic materials.\textsuperscript{5}

Concerning the behavior of CRP, we have observed a significant reduction of this reactant protein when the same patients were shifted from CU to SMC membrane; 6 months of dialysis with SMC, however, was not sufficient to have the return of CRP within the normal range (0–5 mg/L).

CRP has been suggested to have a prognostic value in predicting cardiovascular events\textsuperscript{13,28,29} that still represent the leading cause of death in hemodialysis patients.\textsuperscript{30,31} But CRP values are dependent on IL-6 because IL-6 is the most powerful CRP stimulator; and high values of IL-6 have been indicated by Bologa et al\textsuperscript{15} to be the strongest predictor of mortality in hemodialysis patients. Furthermore, IL-6 has been shown to stimulate the proliferation of vascular smooth muscle cells with neointimal layer formation, an important factor of the atherosclerosis process.\textsuperscript{32}

The role played by IL-6 in stimulating the hepatic synthesis of CRP, by the induction of transcription of this reactant protein during the acute phase response,\textsuperscript{33,34} is confirmed in our study by the positive relationship between the spontaneous release of IL-6 by PBMCs and CRP circulating values. We had already shown, in uremic patients dialyzed with a CU membrane, elevated plasma levels of SAA, the other positive acute-phase protein, that were significantly and positively correlated with IL-6 release by PBMCs.\textsuperscript{23}

But another interesting and original result of this study is the observation that IL-6 release by PBMCs was significantly and negatively correlated with serum albumin. These data appear to strongly support the results obtained by other investigators.\textsuperscript{11,12,14,35} Kaysen et al\textsuperscript{12} in fact, have recently observed that, in addition to being regulated by dietary protein intake,\textsuperscript{36,37} albumin synthesis may be actively suppressed as part of the response to inflammation. Moreover, Ikizler et al\textsuperscript{38} have suggested that serum albumin and other nutritional markers (such as serum prealbumin and transferrin) have to be considered also as markers of inflammatory response and not just an index of the nutritional status of dialysis patients. On the other hand, IL-6 is considered to act synergistically with TNF-\(\alpha\) and IL-1 in down-regulating albumin messenger RNA, thereby inhibiting albumin synthesis by the liver.\textsuperscript{39,40} Consistent with this hypothesis, serum levels of CRP (ie, the reactant protein up-regulated by IL-6) were indicated as the most powerful predictors for decreasing levels of albumin concentration in hemodialysis patients.\textsuperscript{12}

Our study clearly shows that serum albumin concentration increases over the cut-off value of 3.5 g/dL after 6 months of dialysis with an SMC membrane, in the absence of any modification of protein catabolic rate and caloric intake. It also shows that serum albumin increase needs more time (6 months) to reach a statistical significance. These results are in agreement with the long half-life of this protein, predominantly catalyzed by endothelium, and give a strong support to the results of other studies showing that more biocompatible membranes lead to an increase in serum albumin concentration.\textsuperscript{16,18}

Our data were obtained for the first time in a well-controlled, longitudinal, cross-over study in which IL-6 release by PBMCs, CRP levels, and serum albumin concentration were regularly and repetitively evaluated in the same patients treated with 3 membranes with different biocompatibility. IL-6 release by PBMCs and CRP levels were observed to have an inverse relationship with serum albumin changes; serum albumin, in fact, appeared to decrease when the inflammatory status increased and vice versa, thereby showing unequivocally the reciprocal interdependence of these parameters. The linear regression analyses confirm the crucial interrelationships among IL-6 release, CRP, and serum albumin.

In conclusion, our results are the first to show unequivocally that a significant relationship exists between biocompatibility of the membranes and serum albumin changes; serum albumin levels are negatively correlated with the PBMC spontaneous IL-6 release values and CRP circulating levels. These albumin changes require some months to occur and are not secondary to variations of dietary protein intake.

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