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Inflammatory effects of peritoneal dialysis: Evidence of systemic monocyte activation

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Inflammatory effects of peritoneal dialysis: Evidence of systemic monocyte activation. We evaluated in peritonitis-free patients undergoing continuous ambulatory peritoneal dialysis (CAPD) the release of both interleukin-6 (IL-6) and β-2-microglobulin (β_2m) by cultured peripheral blood mononuclear cells (PBMC), as well as the levels of serum amyloid A (SAA), that is, the main hepatic acute phase protein during inflammation. The same measurements were obtained in hemodialysis (HD) patients, uremic non-dialyzed patients (ESRD) and healthy controls (CON). In CAPD, IL-6 production from PBMC was markedly increased in comparison to the control value (600.7 ± 104.3 vs. 14.2 ± 3.6 pg/3 × 10^6 PBMC/24 hr, $P < 0.005$). Similarly, a striking enhancement of the PBMC release of β_2m was detected in CAPD with respect to CON (10.1 ± 2.6 vs. 0.063 ± 0.013 μg/3 × 10^6 PBMC/24 hr, $P < 0.001$). Also, the SAA levels were significantly greater in CAPD patients (21.3 ± 8.7 μg/dl) than in controls (3.14 ± 0.17 μg/dl, $P < 0.05$). Analogous increases of both IL-6 and β_2m cell releases, as well as of SAA levels, were observed in HD patients. No difference concerning the three parameters was detected between CON and ESRD. In conclusion, CAPD induces *per se* PBMC activation with an enhanced release of both IL-6 and β_2m; this is associated to higher levels of SAA. These systemic inflammatory effects are comparable to those observed in HD patients indicating that CAPD is similar to HD in terms of biocompatibility of the treatment.

Poor biocompatibility is a relevant characteristic of hemodialysis treatment (HD); it has been implicated in the pathophysiology of some HD-induced acute symptoms such as fever, nausea, headache and hypotension [1]. A long-term consequence of this phenomenon is hemodialysis-related amyloidosis (HRA) [2, 3]. Indeed, the type of dialysis membrane used strongly influences both the production of β-2-microglobulin (β_2m), which is the main protein constituent of HRA deposits [4, 5], and the prevalence over time of the clinical signs of HRA [6]. These effects have been essentially attributed to systemic inflammatory events in which activation of circulating monocytes with increased production of cytokines appears to play a central role [7–11].

Until now the study of the biocompatibility of substitutive treatments in uremic patients has focused mainly on the extracorporeal hemodialysis, while little information concerning peritoneal dialysis has been provided. Nevertheless, this procedure is believed to induce a local inflammatory response independently from bacterial invasion [12–15]. Furthermore, the presence of β_2m-amyloidosis has also been shown in patients treated with continous ambulatory peritoneal dialysis (CAPD) [16, 17]. These findings are therefore consistent with the hypothesis that peritoneal dialysis is poorly biocompatible as the extracorporeal treatment.

Interestingly, we have recently demonstrated an enhanced production of interleukin 6 (IL-6) by peripheral blood mononuclear cells (PBMC) harvested from HD patients treated with cuprophan membrane [18]. This cytokine plays a relevant role in the regulation of the hepatic acute phase protein response to inflammation [19–21]; however, the potential relationship between IL-6 and acute phase proteins has not been evaluated in either HD or CAPD patients. Furthermore, we showed in the same study a strong relationship between IL-6 production, secondary to the blood interaction with cellulosic membrane, and β_2m synthesis [18]. High circulating levels of β_2m have been demonstrated in CAPD patients as well [16, 22]; however, whether this is merely dependent to reduced renal catabolism/excretion or, alternatively, to enhanced cell production as in HD remains unclear.

The aim of the present study was to investigate the systemic inflammatory effects of continuous peritoneal dialysis. According to our previous protocol in HD [18], we evaluated the release of both IL-6 and β_2m by cultured PBMC obtained from CAPD patients. The levels of serum amyloid A (SAA), the main hepatic acute phase protein during inflammation [23, 24], were also assessed. To gain insights into the specific effects of peritoneal dialysis on these three inflammation markers, the same measurements were compared with the data obtained from HD patients, uremic nondialyzed patients and healthy controls.

Methods

Patient selection

We studied 24 patients with end-stage renal disease: 7 patients were undialyzed and constituted the ESRD group, 8 patients were on CAPD, and 9 were on HD (Table 1). Seven healthy laboratory staff volunteers (3 males and 4 females, mean age 35.7 ± 8.3 years) were included in the study as controls (CON). All subjects gave an informed consent prior to the study.

Tables 2 and 3 list the main biochemical and renal characteristics of ESRD, HD and CAPD patients. All CAPD patients were daily treated with four exchanges of 2 liters of dialysate (1.36% to 3.86% glucose, Baxter, Italy). The HD procedure was regularly performed three times a week (4 hr/session) with bicarbonate

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Table 1. Clinical characteristics of patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD)

	ESRD	CAPD	HD
N	7	8	9
Male/female	4/3	4/4	5/4
Age *years*	57.2 ± 7.3	58.5 ± 7.3	53.2 ± 12.7
Dialytic age *months*	—	21.3 ± 8.7	23.5 ± 10.6
Primary renal disease			
Chronic glomerulonephritis	4	3	4
Chronic pyelonephritis	1	1	—
Polycystic kidney disease	1	—	2
Obstructive uropathy	—	2	1
Hypertension	1	2	2

Data are expressed as mean ± SEM.

Table 2. Biochemical data of patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD)

	ESRD	CAPD	HD
Albumin *g/dl*	3.6 ± 0.5	3.6 ± 0.3	3.8 ± 0.2
Total protein *g/dl*	6.8 ± 0.4	6.9 ± 0.5	7.1 ± 0.5
Cholesterol *mg/dl*	192 ± 71	155 ± 68	187 ± 94
Creatinine *mg/dl*	6.4 ± 2.1	6.0 ± 2.3	10.3 ± 4.0
BUN *mg/dl*	62.4 ± 8.3	59.1 ± 10.7	87.4 ± 13.2

Data are expressed as mean ± SEM.

Table 3. GFR, urinary output and weekly Kt/V of patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD)

	ESRD	CAPD	HD
GFR *ml/min*	12.4 ± 2.5	2.6 ± 0.9	1.1 ± 0.3
Urinary output *ml/day*	1130 ± 260	280 ± 195	90 ± 85
Kt/V	—	1.9 ± 0.3	2.9 ± 0.5

Data are expressed as mean ± SEM.

dialysate and using cuprophan membranes (membrane surface 1.2 m^2; sterilization with ethylene oxide; Bellco Italy).

None of the patients had clinical evidence of acute infection or autoimmune disease, nor were they taking any drug interfering with the immune response. No patient had diabetes mellitus. CAPD patients were peritonitis-free during the last six months prior to the study.

Kt/V_{urea} was estimated in HD patients as follows [25]:

$$Kt/V_{urea} = -\ln(R[-0.03) + (4 \text{ to } 3.5 \times R) \times UF/W$$

Where R is the ratio of the post-dialysis to the pre-dialysis plasma urea, UF is the ultrafiltration volume (L) during dialysis, and W is the post-dialysis weight (kg). In CAPD patients, Kt/V was calculated from the product of the dialysate outflow during a 24 hours period and average dialysate to plasma ratio of urea (D/P_{urea}). The volume of distribution (V) was considered equal to total body water and was estimated from the Watson equation [26].

Cell cultures

In HD patients, blood samples were collected in the morning before the second dialysis session of the week. The samples from CAPD patients were drawn after the overnight exchange. Peripheral blood mononuclear cells (PBMC) were isolated and set up as primary *in vitro* cultures as previously described [18, 27]. Briefly, in order to obtain PBMC from heparinized whole blood samples, we used Ficoll-Hypaque (Flow Laboratories, Irvine, Scotland, UK) gradient density centrifugation at 400 g for 30 minutes at room temperature. The interphase layer was washed twice (at 300 g for 10 min) with RPMI 1640 (Flow Laboratories); the cells were then resuspended in 15 ml polypropylene round bottom tubes (Falcon) at a concentration of 3×10^6/ml in the following culture media: Iscove's medium (Flow Laboratories) supplemented with 1% heat-inactivated fetal bovine serum (Sigma Chimica, Milan; Italy) and antibiotics (100 U/ml penicillin and 100 μg/ml streptomycin, Sigma). PBMC were cultured in either the absence or the presence of 10 μg/ml of lipopolysaccharide (LPS) of Neisseria meningitidis (Sigma). The dosage of LPS was chosen on the basis of preliminar work in our lab and previous studies by other groups that demonstrated a maximal release of IL-6 under these conditions [10, 28]. After 24 hours of incubation at 37°C, in a humidified atmosphere containing 5% CO_2, cell-free supernatants were collected by centrifugation for 10 minutes at 400 g, passaged through a millipore filter (0.2 μ, Sigma), and stored at −20°C.

The relative number of PBMC was not different in the four groups, being, on average, 35% of the white cells (33 to 38%). PBMC contained 80% of lymphocytes and 20% of monocytes; the percentage of monocytes was similar in the different groups. Cell viability was determined by Trypan blue exclusion test and yielded 98% viable cells.

Assays

All the samples from the different groups of patients were analyzed at the same time.

IL-6 immunoassay. IL-6 was measured in supernatants from PBMC by a sandwich ELISA (Biokine, Cambridge, MA, USA) in which a monoclonal antibody to human IL-6 was used, a lyophilized horseradish peroxidase conjugated goat anti-mouse which binds to the monoclonal portion of the sandwich. The lower detection limit was 7 pg/ml. The coefficient of variation of intra-assay was 5% and inter-assay was 9%.

β_2m assay. A commercially available FIA kit (Eurogenetic, Tessenderlo, Belgium) was used to quantify the β_2m concentration in the culture supernatant. The sensitivity of this assay was 0.05 μg/ml; the coefficient of variation of intra-assay was 3.8% and inter-assay was 5.6%.

SAA assay. SAA concentration was measured by using an enzyme-immunoassay method (Hemagen diagnostic, Waltham, MA, USA), based on the disruption of noncovalent interactions occurring between SAA and other plasma constituents and the subsequent self-coating of microwells by SAA. A peroxidase-conjugated rabbit-anti-human SAA which binds to SAA adsorbed on wells, was used. The lower detection limit was 3 μg/ml; the coefficient of variation of intra-assay was 4.1% and inter-assay was 6.8%.

Statistical analysis

Statistical analysis was performed using the analysis of variance (ANOVA) and linear regression analysis. Data are expressed as mean ± SEM; statistical significance was defined as $P < 0.05$.

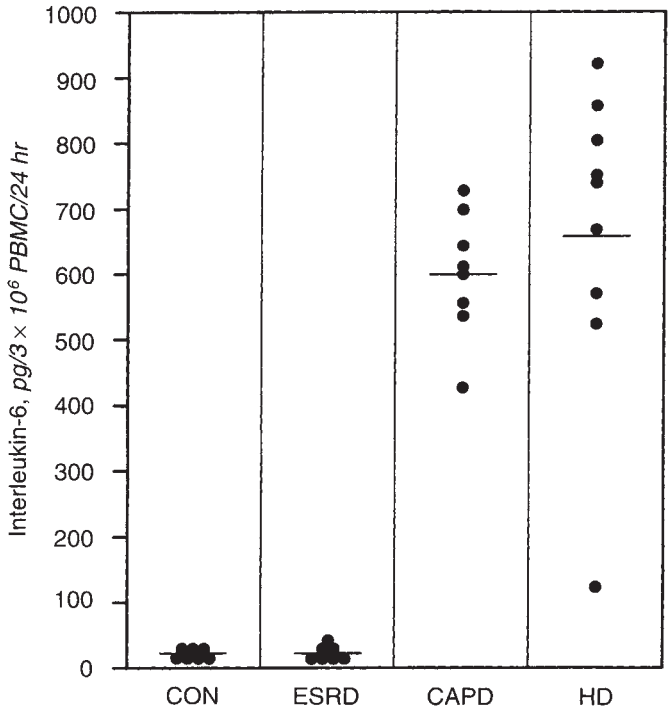

Fig. 1 *Interleukin-6 (IL-6) production in 24-hr cultured peripheral blood mononuclear cells (PBMC) harvested from control subjects (CON), and from patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD), and in extracorporeal hemodialysis (HD).* IL-6 production in CAPD and HD is significantly greater than in CON and ESRD ($P < 0.01$).

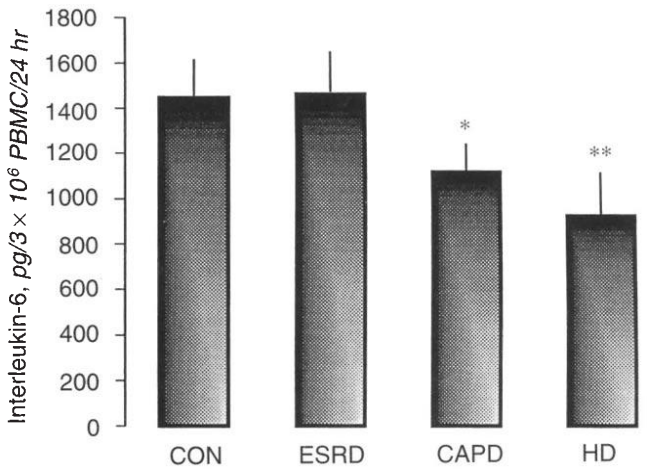

Fig. 2. *Interleukin-6 (IL-6) production in 24-hr cultured peripheral blood mononuclear cells (PBMC) stimulated by 10 μl/ml of LPS and harvested from control subjects (CON), and in patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD).* *$P < 0.05$ versus CON and ESRD; **$P < 0.05$ versus CON, ESRD and CAPD.

Results

PBMC production of IL-6

As depicted in Figure 1, IL-6 production from unstimulated PBMC was significantly higher in CAPD patients (600.7 ± 104.3 pg/3 × 10^6 PBMC/24 hr) and HD patients (664.3 ± 138.9 pg/3 × 10^6 PBMC/24 hr) than the value measured in both ESRD patients (18.6 ± 4.0 pg/3 × 10^6 PBMC/24 hr, $P < 0.005$) and healthy controls (14.2 ± 3.6 pg/3 × 10^6 PBMC/24 hr, $P < 0.005$). IL-6 production was analogous in HD and CAPD. Similarly, no difference was detected between healthy subjects and ESRD patients.

When PBMC collected from ESRD and CON were stimulated by a 24-hour LPS incubation the production of IL-6 markedly increased up to 1462.0 ± 179.5 and 1446.3 ± 142.8 pg/3 × 10^6 PBMC/24 hr, respectively (Fig. 2). In CAPD and HD, IL-6 release after LPS stimulation was 1117.8 ± 138.6 and 925.4 ± 161.8 pg/3 × 10^6 PBMC/24 hr, respectively. These values were significantly lower than those observed in ESRD and CON (Fig. 2).

PBMC release of β_2m

The release of β_2m from unstimulated PBMC was markedly increased in CAPD (10.1 ± 1.6 μg/3 × 10^6 PBMC/24 hr) and HD (12.7 ± 2.3 μg/3 × 10^6 PBMC/24 hr) in comparison with data obtained in healthy controls (0.063 ± 0.010 μg/3 × 10^6 PBMC/24 hr, $P < 0.001$) and ESRD patients (0.16 ± 0.03 μg/3 × 10^6 PBMC/24 hr, $P < 0.01$; Fig. 3).

No difference was detected in the β_2m release between CAPD and HD, as well as between healthy subjects and ESRD patients.

Serum levels of SAA

The values of SAA were significantly greater in CAPD (21.3 ± 9.7 μg/ml) and HD (34.1 ± 14.8 μg/ml) than in ESRD (5.3 ± 2.2 μg/ml, $P < 0.05$) and controls (3.14 ± 0.17 μg/ml, $P < 0.05$) (Fig. 4).

No significant difference was observed in the SAA values between CAPD and HD, and between ESRD and CON.

Regression analysis

Highly significant linear correlations were obtained between IL-6 and β_2m synthesis ($r = 0.805$, $P < 0.001$), IL-6 and SAA values ($r = 0.691$, $P < 0.005$), and between β_2m release and SAA levels ($r = 0.815$, $P < 0.001$).

Discussion

Peritoneal dialysis has long been considered more biocompatible than HD; this assumption has been essentially based on the absence of the main factors underlying the poor biocompatibility of the extracorporeal circulation, such as the blood interaction with artificial membranes and the back-filtration/diffusion of endotoxin fragments from dialysate [29, 30]. Nevertheless, in the last few years, different studies in CAPD patients have demonstrated the presence of chronic sterile inflammation at the level of the peritoneum [14]. Recent studies have evidenced significant intraperitoneal levels of IL-6 generated by peritoneal macrophages and/or mesothelial cells in absence of peritonitis [31, 32]. Overall these data suggest *local* inflammatory effects strictly dependent on the CAPD treatment *per se*.

The present study adds new important information on this issue: we provide first-time evidence that regular peritoneal dialysis induces *systemic* activation of monocytes in absence of peritonitis or other apparent cause of inflammation.

Peripheral blood mononuclear cells harvested from CAPD

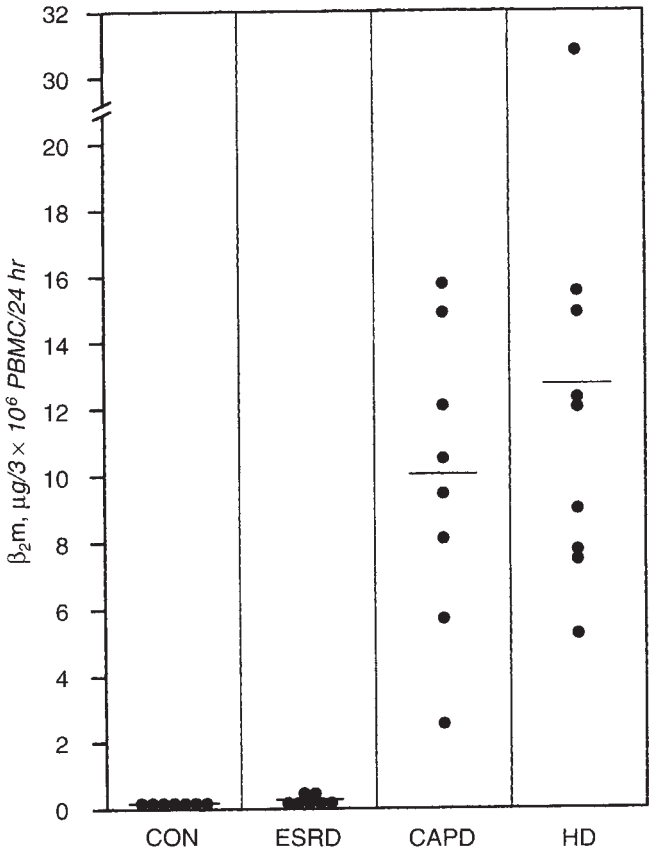

Fig. 3. *β-2-microglobulin (β_2m) release in 24-hr cultured peripheral blood mononuclear cells (PBMC) harvested from control subjects (CON), and in patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD).* β_2m release in CAPD and HD is significantly greater than in CON and ESRD ($P < 0.01$).

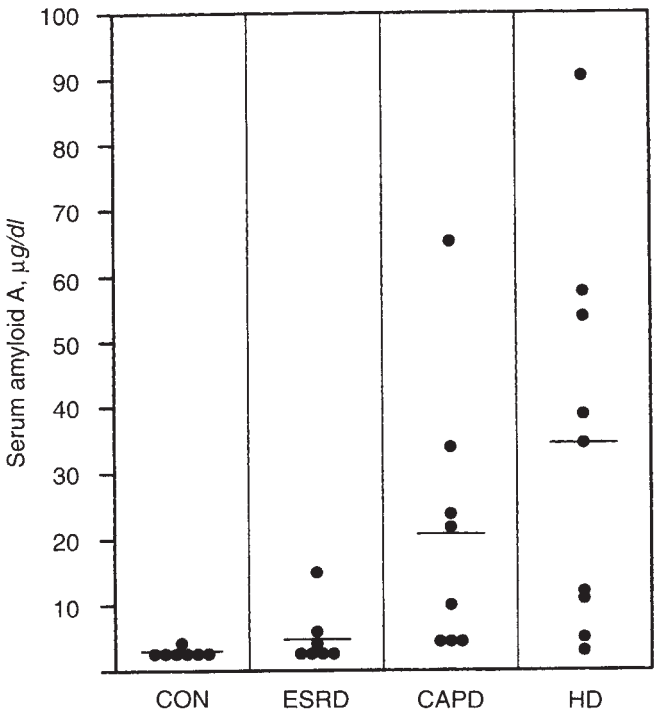

Fig. 4. *Serum levels of amyloid A (SAA) in control subjects (CON), and in patients with end-stage renal disease not dialyzed (ESRD), undergoing continous ambulatory peritoneal dialysis (CAPD) and in extracorporeal hemodialysis (HD).* Serum levels of SAA in CAPD and HD are significantly greater than in CON and ESRD ($P < 0.05$).

patients released higher amounts of IL-6 than those obtained from healthy controls. This inflammatory cytokine plays a relevant role in the pathophysiology of the low biocompatibility of the HD treatment [11, 18]. Interestingly, in the current study, the amount of IL-6 released by cultured PBMC from CAPD patients was comparable to that detected in PBMC drawn from HD patients of analogous dialytic age and treated with cuprophan membrane. This observation suggests an analogous degree of activation of the circulating monocytes in the two treatments.

Of note, as opposed to unstimulated conditions, the cell production after the 24 hour incubation with LPS was lower in CAPD and HD patients with respect to both ESRD and CON groups (Fig. 2). This observation is consistent with the hypothesis of a chronic monocyte activation in dialyzed patients. Indeed, the reduced response to LPS in CAPD and HD was possibly dependent on a down-regulation of IL-6 production due to the chronic stimulation of these cells. Similar findings supporting this hypothesis have been reported by our group [18] and recently by Zaoui and Hakim as well [33].

As for IL-6 release, also the PBMC production of β_2m was markedly enhanced in CAPD to levels comparable to those measured in patients undergoing extracorporeal dialysis. β_2m can be considered a marker of systemic inflammation. Indeed, an augmented synthesis of this protein occurs in rheumatic disorders and infectious diseases [34–36]; moreover, its release is stimulated by both T and B cell antigens [37]. This process is regulated by various inflammatory cytokines, such as tumor necrosis factor, γ-interferon and interleukin-2 [38–40]. On this regard, our and other groups have previously demonstrated that PBMC cultured from HD patients treated with cuprophan membranes produce, proportionally to IL-6, more β_2m than patients dialyzed with biocompatible membranes [5, 18]. The highly significant linear correlation between IL-6 and β_2m production observed in the current study further support these findings.

Previous studies have evidenced an increase of the serum levels of β_2m and various cytokines in HD and CAPD patients [11, 16, 22, 41]. In the current work the cell production of both IL-6 and β_2m was similarly low in uremic non-dialyzed patients and healthy controls. This finding does not suggest that the chronic activation of peripheral monocytes is determined by the retention of uremic solutes. Alternatively, it can be at least partially attributed to the enhanced cell generation induced by the dialytic treatment *per se*.

The pathophysiological mechanisms underlying the activation of systemic monocytes in our CAPD patients are not readily apparent. While some authors believe that dialysis fluids used in CAPD inhibit cytokine generation [42, 43], recent *in vitro* studies have demonstrated that diethylexylphtalate, a "plasticizer" released by storage bags, induces cytokine release from PBMC cells [44]. Moreover, Dinarello and Krueger have reported the presence in the peritoneal dialysis effluent of natural muramyl dipeptides derived from bacterial cell wall that are capable to activate mononuclear cells with a potency tenfold greater than endotoxins

[45]. It is therefore conceivable to hypothesize that these cells may have been stimulated upon the contact with some specific substances in the peritoneum. Another factor potentially contributing to the induction of systemic monocytes is possibly represented by the complement activation which has been reported in peritonitis-free CAPD patients [46].

Interestingly, in both HD and CAPD groups, the increased PBMC production of either IL-6 or β_2m was paralleled by a striking increment of serum amyloid A levels, that is, the main acute phase protein secreted by hepatocytes during inflammation [23, 24]. The systemic concentration of SAA was significantly higher than the value detected in the two control groups of uremic non-dialyzed patients and healthy subjects, thus suggesting enhanced SAA production rather than reduced renal catabolism/excretion. This finding therefore constitutes further evidence of a systemic inflammatory response to the dialytic therapy which is not influenced by the type of substitutive treatment adopted. SAA production during inflammation is essentially induced by the direct interaction of IL-6 with the hepatocytes [23]. Accordingly, the strong linear correlation detected between IL-6 production by PBMC and SAA levels indicates that IL-6 may be involved in the increase of SAA levels in both HD and CAPD as well.

In conclusion, the present controlled study demonstrates that: (a) CAPD patients free of peritonitis show a marked enhancement of the PBMC release of IL-6 and β_2m that is associated with an increment in SAA levels; (b) comparable changes of these inflammation markers are detected in HD patients; (c) conversely, both the IL-6 and β_2m cell production and the SAA levels result similarly low in healthy and uremic non-dialyzed subjects. Therefore, CAPD induces *per se* systemic inflammatory events similarly as the extracorporeal treatment. These findings are consistent with the concept that regular peritoneal dialysis may not be different from hemodialysis in terms of biocompatibility.

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