INTRAPERITONEAL IL-6 SIGNALING IN INCIDENT PATIENTS TREATED WITH ICODEXTRIN AND GLUCOSE BICARBONATE/LACTATE-BASED PERITONEAL DIALYSIS SOLUTIONS

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◆ **Objective:** In this study, we compared the activity of interleukin-6 (IL-6), a marker of ongoing peritoneal inflammation and biocompatibility, and its other signaling components, the soluble IL-6 receptor (sIL-6R) and soluble Gp130 (sGp130), in peritoneal effluent from patients treated with icodextrin-based (E) peritoneal dialysis (PD) solution and glucose-based bicarbonate/lactate-buffered (P) solution.

◆ **Methods:** Using baseline peritoneal ultrafiltration capacity, 33 stable incident PD patients were allocated either to P only ($n = 20$) or to P plus E for the overnight dwell ($n = 13$). We used ELISA to determine IL-6, sIL-6R, and sGp130 in timed overnight effluent at 1, 6, and 12 months after PD initiation. Flow cytometry was used to measure expression of IL-6R and Gp130 on isolated peritoneal leukocytes at the same time points. Peritonitis was an exclusion criterion.

◆ **Results:** At all time points, levels of IL-6 and sIL-6R, and the appearance rates of IL-6 (90.5 pg/min vs. 481.1 pg/min, $p < 0.001$; 138.6 pg/min vs. 1187.5 pg/min, $p < 0.001$; and 56.1 pg/min vs. 1386.0 pg/min, $p < 0.001$), sIL-6R (2035.3 pg/min vs. 4907.0 pg/min, $p < 0.01$; 1375.0 pg/min vs. 6348.4 pg/min, $p < 0.01$; and 1881.3 pg/min vs. 5437.8 pg/min, $p < 0.01$), and sGp130 (37.6 ng/min vs. 65.4 ng/min, $p < 0.01$; 39.2 ng/min vs. 80.6 ng/min, $p < 0.01$; 27.8 ng/min vs. 71.0 ng/min, $p < 0.01$) were significantly higher in peritoneal effluent from E-treated patients than from P-treated patients. Expression of IL-6R and Gp130 on individual leukocyte types isolated from PD effluent did not differ between E- and P-treated patients. The numbers of white blood cells present in effluent were higher in E-treated than in P-treated patients at all time points, but no significant differences were seen in the differential counts or in the number of exfoliated mesothelial cells. The IL-6 parameters in effluent from E-treated patients correlated with their plasma C-reactive protein. Despite the increased

activation of the IL-6 system, no increase in peritoneal permeability as assessed by the dialysate-to-plasma ratio of creatinine in E effluent or by systemic inflammation was observed throughout the study.

◆ **Conclusions:** Higher levels of IL-6, its soluble receptors, and leukocyte expression were observed in E-treated than in P-treated patients, but this difference was not associated with alterations in peritoneal permeability or systemic inflammation during 1 year of follow-up. Leukocyte counts in effluent from E-treated patients were within the normal range previously reported for glucose solutions. This lack of clinical consequences may be a result of a parallel rise in sIL-6R and sGp130, which are known to control the biologic activity of IL-6. The utility of IL-6 level determinations, in isolation, for assessing the biocompatibility of PD solutions is questionable.

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Peritoneal dialysis (PD) fluid with glucose polymer (icodextrin) as a colloid osmotic agent was developed to provide for ultrafiltration (UF) even with long dwell times and increased peritoneal permeability (1-4). Use of icodextrin solution in clinical practice is associated with a variety of additional benefits related particularly to volume control and metabolism, but also to quality of life (5-8). Use of icodextrin is associated with prolonged maintenance of stable peritoneal membrane function (6) and, in observational studies, with lower rates of UF failure and mortality (9,10). The formulation of icodextrin-based PD solution eliminates 3 of the 4 main aspects of bioincompatibility, being that it is glucose-free, low in glucose degradation products, and iso-osmolar compared with uremic serum (1,11). Nevertheless, some studies

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have suggested that icodextrin is more likely than conventional glucose-based solution to induce intraperitoneal inflammation (12–15). However, those studies were conducted in prevalent patients with a history of peritonitis, which has the effect of enhancing the persistence of intraperitoneal inflammation over long periods of time (16–18).

The important player in the control of the inflammatory process is the pleiotropic cytokine interleukin 6 (IL-6). Its bioactivity at the tissue level is regulated both by binding to its cognate soluble receptor (sIL-6R) and by interaction with its signal transducing subunit, soluble glycoprotein 130 (sGp130). Circulating Gp130 receptor acts as an antagonist of the biologic functions of IL-6, and binding of sIL-6R to IL-6 in plasma extends IL-6 bioactivity. Both of the soluble IL-6 receptors are generated by shedding (19).

Despite the complexities of that system, human studies designed to concomitantly monitor IL-6 and its soluble receptor have been fairly scanty in the field of PD (18). The exact role of the intraperitoneal IL-6 system has not been well characterized to date (18) even though IL-6 is considered a marker of ongoing intraperitoneal inflammation and is commonly used to assess the biocompatibility of PD solutions (20–23).

Thus, our study was designed to prospectively compare parameters of intraperitoneal IL-6 signaling in peritoneal effluents from icodextrin-based and glucose-based bicarbonate/lactate-buffered PD solution, including IL-6R and Gp130 expression on leukocytes isolated from PD effluent in incident PD patients without bacterial peritonitis.

METHODS

The patients eligible for inclusion in the study were those completing a 3-week break-in period after insertion of a PD catheter, with continuous ambulatory PD initiated at 4 daily 1500 – 2000 mL exchanges with a glucose-based bicarbonate/lactate-buffered PD solution [P (Physioneal: Baxter Healthcare, Castlebar, Ireland)]. A 4-hour dwell using P solution with 2.27% glucose was performed the next day. When UF from the 4-hour dwell was more than 400 mL, patients were scheduled for PD with P solution only; otherwise, an icodextrin-based PD fluid [E (Extraneal: Baxter Healthcare)] was prescribed for the nighttime dwell. The P group included 20 patients (11 men), with a median age of 50 years (range: 20 – 72 years). The underlying condition leading to end-stage renal disease was diabetes mellitus in 9 patients, tubulointerstitial nephritis in 3, glomerulonephritis in 4, and nephrosclerosis and polycystic kidney disease

in 2 patients each. The E group consisted of 13 patients (11 men), with a median age of 61 years (range: 38 – 84 years). The causes of end-stage renal disease in this group were diabetes mellitus in 7 patients, interstitial nephritis in 2 patients, nephrosclerosis in 2 patients, and chronic glomerulonephritis and bilateral nephrectomy in 1 patient each. All patients had long been in a clinically stable condition, free of autoimmune disease, cancer, and systemic infection. None of the patients was treated with *N*-acetylcysteine, which is known to lower plasma IL-6 levels in PD patients (24). The study protocol was approved by the local ethics committee, and patients signed an informed consent before entering the study.

At 1, 6, and 12 months after continuous ambulatory PD initiation, all patients were assessed for dialysis adequacy, and a peritoneal equilibration test was performed using the PD Adequest software package according to the manufacturer's instructions (Baxter Healthcare, McGaw Park, IL, USA). At the same time, overnight peritoneal effluent was collected for evaluation of IL-6 signaling parameters. A sampling time window of ± 2 weeks was accepted for the visits at months 6 and 12. Patients who developed peritonitis during the study were excluded from follow-up. Overnight peritoneal effluent collections were allowed at 1 month after completion of treatment in patients developing other systemic infections. The PD prescription included 3 – 5 exchanges of 1500 – 2500 mL each, with glucose concentrations depending on hydration status or with E for the overnight dwell in patients allocated to the E group.

The night before each study visit, patients instilled the respective PD fluid (P with 2.27% glucose or E) at 2200 h; the effluent was drained the next morning at 0800 h in the outpatient PD unit on ice. Aliquots of the PD effluent were then transferred into 500-mL conical tubes and centrifuged at 3000 rpm at 10°C for 35 minutes. Aliquots of the supernatant were then transferred into 1.8 Nunc CryoTubes (Thermo Fisher Scientific, Waltham, MA, USA) and kept frozen at –80°C until analysis. The cell pellets were resuspended in 50 mL phosphate-buffered saline (Sigma-Aldrich, Kent, UK) and centrifuged at 3000 rpm at 10°C for 20 minutes. The resulting supernatant was discarded, and the cell pellets were resuspended in 5 mL phosphate-buffered saline. A volume of 400 μ L was used for cell counting in a Coulter counter (Beckman-Coulter, Brea, CA, USA). The total number of cells per dialysate bag was calculated and then divided by the overnight effluent volume to determine the number of leukocytes per milliliter of overnight effluent. The rest of cells were used for differential cell counts (after cytopspin, stained with Jenee-Giemsa) and for flow cytometry. Before flow cytometry, cells were incubated with blocking buffer [25%

normal rabbit serum (Dako Cytomation, Ely, UK)], 25% human AB serum (HD Supplies, Botolph Claydon, UK), and 50% phosphate-buffered saline to prevent nonspecific binding. Cells were labeled with fluorescein isothiocyanate and phycoerythrin monoclonal antibodies directed against CD3, CD14, CXCR1, IL-6R (BD Pharmingen, Oxford, UK) and Gp130 (R&D Systems, Abingdon, UK). Stained cells were measured using a Coulter Epics XL flow cytometer (Beckman-Coulter). The instrument was standardized daily for fluorescence and light scatter alignment using calibrating fluorospheres (Beckman-Coulter). The proportions of monocytes (CD14+), lymphocytes (CD3+), and granulocytes (CXCR1+) were assessed by means of their light scatter characteristics in combination with anti-CD14, anti-CD3, and anti-CXCR1 antibody labeling. The percentage expressions of IL-6R and Gp130 antigens were determined separately on all 3 subpopulations. Isotypic controls were applied so that the positivity thresholds of the assayed antigens could be better distinguished. Data for 50 000 cells were gathered in list mode files and analyzed using System II software.

Levels of IL-6, sIL-6R, and sGp130 were determined in dialysate effluent by ELISA (R&D Systems). The minimum detectable concentrations were 0.7 pg/mL, 6.5 pg/mL, and 0.08 ng/mL respectively. The intra- and inter-assay variations were 2.7% and 4.5% for IL-6, 4.5% and 5.1% for sIL-6R, and 4.8% and 4.1% for sGp130. The dialysate appearance rates of IL-6 (app-IL-6), sIL-6R (app-sIL-6R), and sGp130 (app-sGp130) were calculated as the

dialysate concentration times the drained volume, divided by the dwell time in minutes.

Basic biochemical parameters were measured using standard laboratory techniques unless stated otherwise. Immunoturbidimetry [K-Assay: Kamiya Biomedical, Seattle, WA, USA (detection limit: 1 mg/L; normal range: 1 – 10 mg/L, not the high-sensitivity assay)] was used to determine C-reactive protein (CRP).

Results are given as medians and ranges. The P and E groups were compared using the Mann-Whitney rank sum test, and data at various time points within the individual groups were compared using the Wilcoxon signed rank test. Correlations were tested using a Spearman test. A *p* value less than 0.05 was considered significant.

RESULTS

Patients allocated to the E group were older (61 years vs. 50 years, *p* < 0.05) and, as is evident from Table 1, had a higher small-solute transport rate as assessed by their dialysate-to-plasma ratio of creatinine (D/P Cr). Despite the higher small-solute transport rate, the E group reached significantly higher UF from the overnight dwell throughout the study. The two groups did not differ significantly in systemic inflammatory markers (Table 1).

In E effluent, we observed a significantly higher white blood cell count (Figure 1), higher levels of IL-6 and sIL-6R (Table 2), and a higher app-IL-6 and its soluble receptors (Figures 2 – 4), but expression of IL-6R and

TABLE 1
Basic Clinical Data

Variable	Value [median (range)]					
	Glucose solution (bicarbonate/lactate buffer)			Icodextrin solution		
	1 Month	6 Months	12 Months	1 Month	6 Months	12 Months
Plasma CRP (mg/L)	2.0 (1.0 to 15.0)	1.0 (1.0 to 9.0)	2.0 (1.0 to 7.0)	2.0 (1.0 to 18.0)	2.0 (1.0 to 26.0)	4.0 (1.0 to 26.0)
WBC ($\times 10^9/L$)	6.40 (4.20 to 9.50)	6.20 (4.10 to 9.00)	6.00 (4.20 to 9.10)	6.90 (4.90 to 9.30)	6.40 (4.80 to 13.00)	5.80 (3.60 to 10.00)
D/P creatinine	0.63 (0.40 to 0.79)	0.73 (0.60 to 0.79)	0.74 (0.54 to 0.76)	0.82 ^a (0.50 to 0.89)	0.82 ^b (0.65 to 0.98)	0.76 (0.59 to 0.91)
Ultrafiltration ^c (mL)	30 (-470 to 1400)	190 (-400 to 530)	115 (0 to 260)	609 ^d (200 to 1580)	630 ^b (100 to 1205)	490 ^a (0 to 1050)

CRP = C-reactive protein; WBC = white blood cell count in peripheral blood; D/P = dialysate-to-plasma ratio at the 4th hour of a peritoneal equilibration test.

^a Unpaired Wilcoxon *p* < 0.05 vs. glucose solution as assessed at the same time point.

^b Unpaired Wilcoxon *p* < 0.01 vs. glucose solution as assessed at the same time point.

^c From a 10-hour night dwell.

^d Unpaired Wilcoxon *p* < 0.001 vs. glucose solution as assessed at the same time point.

Gp130 on peritoneal leukocytes (Table 2) and the white blood cell differential (Table 3) did not differ between the groups using the tested solutions.

Longitudinal follow-up of individual parameters throughout the study revealed an increase in D/P Cr in

Figure 1 — White blood cell count in peritoneal effluent from glucose-based (GLU) or icodextrin-based (ICO) dialysis solution 1, 6, and 12 months after peritoneal dialysis initiation.

the P group between months 1 and 6 ($p < 0.05$, Wilcoxon signed rank test). No other significant changes in D/P Cr or other variables at months 6 and 12 compared with baseline were seen.

Figure 2 — Appearance rate of interleukin 6 (IL-6) in peritoneal effluent from glucose-based (GLU) or icodextrin-based (ICO) dialysis solution 1, 6, and 12 months after peritoneal dialysis initiation.

TABLE 2
Parameters of IL-6 Signaling in Peritoneal Dialysis Effluent

Variable	Value [median (range)]					
	Glucose solution (bicarbonate/lactate buffer)			Icodextrin solution		
	1 Month	6 Months	12 Months	1 Month	6 Months	12 Months
IL-6 (pg/mL)	36.0 (9.0–180.0)	34.0 (10.0–87.0)	21.0 (8.0–382.0)	105.0 ^a (42.0–747.0)	285.0 ^b (75.0–599.0)	329.0 ^c (47.0–450.0)
sIL-6R (pg/mL)	844.0 (224.0–2225.0)	720.5 (382.0–2035.0)	511.0 (451.0–1670.0)	1050.0 ^a (563.0–2185.0)	1375.0 ^c (734.0–2960.0)	1284.0 ^c (705.0–2672.0)
sGp130 (ng/mL)	13.9 (3.4–36.2)	11.6 (7.1–30.9)	9.2 (5.2–28.8)	15.1 (9.4–32.2)	15.9 (10.2–31.4)	14.3 (9.0–28.8)
CD3+ IL-6R+ cells (%)	5.77 (1.18–15.90)	5.14 (2.07–9.24)	2.42 (0.56–7.08)	3.03 (0.95–10.00)	4.40 (0.98–11.90)	2.59 (0.52–10.30)
CD3+ Gp130+ cells (%)	4.15 (1.04–7.20)	3.42 (1.14–84.90)	3.18 (2.01–3.45)	2.17 (0.38–14.60)	2.41 (1.44–7.27)	1.64 (0.47–4.06)
CD14+ IL6R+ cells (%)	30.60 (6.50–74.50)	23.25 (11.10–64.40)	28.80 (2.17–55.20)	21.90 (7.08–78.10)	25.10 (3.19–67.10)	22.00 (7.30–57.50)
CD14+ Gp130+ cells (%)	19.20 (3.35–46.00)	16.90 (3.44–30.80)	10.40 (6.20–21.40)	10.80 (0.67–29.40)	12.20 (3.86–20.70)	12.60 (3.86–34.80)
CXCR1+ IL-6R+ cells (%)	3.580 (1.630–9.620)	10.515 (5.700–38.600)	10.965 (6.530–15.400)	3.220 (0.350–14.200)	6.105 (0.440–21.000)	7.515 (3.770–13.000)
CXCR1+ Gp130+ cells (%)	3.000 (1.650–9.050)	4.580 (1.140–12.500)	12.230 (9.420–20.100)	3.730 (0.410–18.200)	5.440 (1.530–12.400)	7.560 (1.770–18.300)

IL-6 = interleukin 6; sIL-6R = soluble interleukin-6 receptor; sGp130 = soluble glycoprotein 130; IL-6R = interleukin-6 receptor; Gp130 = glycoprotein 130.

^a Unpaired Wilcoxon $p < 0.01$ vs. glucose solution as assessed at the same time point.

^b Unpaired Wilcoxon $p < 0.001$ vs. glucose solution as assessed at the same time point.

^c Unpaired Wilcoxon $p < 0.05$ vs. glucose solution as assessed at the same time point.

In the P group at month 1, app-IL-6, app-sIL-6R, and app-sGp130 were significantly correlated (mutual and by definition) with effluent concentrations of IL-6, sIL-6R, and sGp130 (data not shown). However, app-IL-6, app-sIL-6R, and app-sGp130 were also significantly correlated with the white blood cell count per milliliter of effluent ($r = 0.62, p < 0.01$; $r = 0.59, p < 0.01$; and $r = 0.56, p < 0.05$ respectively). No correlation was observed between app-IL-6 and expression of IL-6R and Gp130 on peritoneal leukocytes, between app-sIL-6R and D/P Cr, or between app-sGp130 and systemic inflammatory markers.

In the E group at month 1, appearance rates of IL-6 and its soluble receptors correlated with the respective effluent concentrations of IL-6, sIL-6R, and sGp130. The correlation between app-IL-6 and plasma CRP almost reached statistical significance ($r = 0.54, p = 0.0517$). Soluble IL-6R correlated with effluent levels of IL-6 and sGp130 ($r = 0.96, p < 0.001$ and $r = 0.75, p < 0.01$ respectively) and with app-sGp130 ($r = 0.75, p < 0.01$) and plasma CRP ($r = 0.59, p < 0.05$). The appearance rate of sGp130 correlated with the effluent level of IL-6 ($r = 0.60,$

$p < 0.05$) and with plasma CRP ($r = 0.57, p < 0.05$). Not surprisingly, we also observed a significant correlation between plasma CRP and effluent levels of IL-6, sIL-6R, and sGp130 ($r = 0.59, p < 0.05$; $r = 0.62, p < 0.05$; and $r = 0.73, p < 0.01$ respectively).

Neither patient group showed a correlation between the levels or appearance rates of IL-6 system components in peritoneal effluent and drained volume or UF.

DISCUSSION

In our view, the most important finding of the present study is the evidence of higher levels of IL-6 and sIL-6R and higher app-IL-6, app-sIL-6R, and app-sGp130 in E effluent compared with P effluent. Taking into account the use of IL-6 as a marker of biocompatibility and the freedom of E solution from 3 of the 4 generally recognized factors of bioincompatibility (excepting low pH and high lactate), that finding comes as a surprise. Instillation of dialysis solution into the peritoneal cavity is followed by rapid equilibration of low pH and high lactate. As a

Figure 3 — Appearance rate of soluble interleukin 6 (IL-6) receptor in peritoneal effluent from glucose-based (GLU) or icodextrin-based (ICO) dialysis solution 1, 6, and 12 months after peritoneal dialysis initiation.

Figure 4 — Appearance rate of soluble glycoprotein 130 (sGp130) in peritoneal effluent from glucose-based (GLU) or icodextrin-based (ICO) dialysis solution 1, 6, and 12 months after peritoneal dialysis initiation.

TABLE 3
White Blood Cell Differential in Peritoneal Dialysis Effluent

Variable	Value [median (range)] ^a					
	Glucose solution (bicarbonate/lactate buffer)			Icodextrin solution		
	1 Month	6 Months	12 Months	1 Month	6 Months	12 Months
Lymphocytes	0.471 (0.018–7.429)	1.517 (0.028–18.668)	0.531 (0.018–4.738)	3.009 (0.134–19.381)	6.840 (0.03–26.195)	2.100 (0.122–11.262)
Monocytes	1.786 (0.132–17.335)	3.243 (0.110–27.711)	1.294 (0.022–11.399)	16.697 (1.628–74.852)	29.083 (0.326–85.013)	14.822 (2.554–56.001)
Granulocytes	0.204 (0.008–5.02)	0.263 (0.002–3.102)	0.160 (0.006–2.333)	1.102 (0.1–9.106)	1.280 (0.015–10.225)	1.17 (0.164–6.25)

^a No significant differences demonstrated by unpaired Wilcoxon test.

result, those factors are unlikely to play a significant role late into a 10-hour dwell—that is, the time after which peritoneal effluent levels were determined in our study. A nonsignificant trend toward higher IL-6 levels in icodextrin effluent has also been reported in two other studies that used conventional glucose-based solution (low pH and high lactate) as a control solution. Therefore, it seems that the factor causing increased activation of the IL-6 signaling system in icodextrin-treated patients is likely to be different from the current generally recognized factors of bioincompatibility.

It is tempting to consider glucose polymer or its metabolites as this unknown factor. The effect of glucose polymer on peritoneal mesothelial cells and monocytes has been investigated in two studies (25,26). Both concluded that glucose polymer lowered IL-6 secretion from those cells. Other cells in the dialyzed peritoneal cavity that are able to secrete IL-6 (adipocytes, endothelial cells, and fibroblasts) have not yet been tested in this respect.

The finding that the leukocyte count in E effluent is higher than that in biocompatible glucose-based (P) solution, without variation in the differential, is consistent with data reported by Parikova and colleagues (27). It should be emphasized that the leukocyte counts in E effluent remained within the normal range reported in previous studies for glucose solutions (28). Any potential association between leukocyte count and circulating dextran antibodies was not demonstrated in the present study.

Could the higher activation of the IL-6 signaling system with E solution compared with P solution be the result of a role played by some patient-related factor rather than by a solution-related factor?

There is no doubt that one potential factor could be an increase in intraperitoneal pressure. Use of higher fill volumes of glucose solutions, resulting in a rise in intraperitoneal pressure, has been shown to increase the appearance rates of IL-6 in peritoneal effluent by as much as 43%. Our E group patients had a larger drained volume and higher UF after the overnight dwell throughout the study. However, based on our study, we were unable to confirm this possibility, because measurement of intraperitoneal pressure was not included in the study protocol. We observed no correlation between app-IL-6, app-sIL-6R, or app-sGp130 and drained volume or UF that could possibly indirectly document an association between intraperitoneal pressure and IL-6 system activation (29).

Another factor to be considered is the effect of peritoneal permeability and increased rates of peritoneal transport of higher molecular weight substances in the presence of increased convective transport attributable to polymer-induced colloid osmosis (7,18,30). The D/P Cr has been shown to correlate with levels of IL-6 and its

soluble receptor in dialysate, just as D/P albumin correlates with IL-6 in effluent. Because the E group in our study had a significantly higher small-solute transport rate and most likely had higher peritoneal permeability for larger solutes, it can reasonably be argued that this factor may also have had an effect on the increased levels of IL-6 and its soluble receptors in E effluent. Another factor partly contributing to the increased app-IL-6, app-sIL-6R, and app-sGp130 in E effluent was the increased clearance rate of higher molecular weight molecules because of the increased rate of convective peritoneal transport in the presence of glucose polymer-induced colloidal osmosis (7,30) and, possibly, because of genetics (31).

In addition to peritoneal permeability, the degree of systemic inflammation affects dialysate IL-6 levels. In the present study, plasma levels of IL-6, which seem to be the most sensitive marker of micro-inflammation in dialysis patients (32), were not determined, but a correlation between plasma CRP and parameters of dialysate IL-6 signaling was demonstrated in the E group and not in the P group. That finding suggests that the increased activity of IL-6 signaling factors in E effluent may be at least partly connected to systemic inflammation.

Compared with a comprehensive study investigating various issues related to IL-6 and sIL-6R in PD (18), our 1-year study did not demonstrate increased levels or appearance rates of IL-6, sIL-6R, and sGp130 in peritoneal effluent or increased peritoneal transport rates and levels of circulating inflammatory markers (CRP, white blood cell count) compared with baseline, whether patients were treated with P or E solution. A possible explanation may be the fact that the protocol excluded from follow-up patients who developed peritonitis and those in whom increased systemic and peritoneal inflammation persisted after peritonitis (16,18). The E group patients in our study showed higher activation of IL-6 signaling in peritoneal effluent, but that activation was not associated with increased peritoneal permeability. Those findings might be a result of the relatively short follow-up, but might also reflect the fact that patients were treated using solutions with higher levels of bio-compatibility. In addition, the increase in IL-6 and sIL-6R was accompanied by a parallel rise in sGp130, which may attenuate the biologic activity of IL-6. That finding may require a critical reappraisal of the relevance of isolated determinations of IL-6 as a marker of biocompatibility of PD solutions.

CONCLUSIONS

Increased activation of the IL-6 signaling system in icodextrin peritoneal effluent might be a result not only

of the solution *per se*, but also of patient-related factors. The clinical relevance of isolated determinations of IL-6 as a marker of biocompatibility of PD solution may need to be reappraised. Given the relatively small number of patients in the present study, this work has to be considered solely hypothesis-generating.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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