Impact of systemic and local peritoneal inflammation on peritoneal solute transport rate in new peritoneal dialysis patients: a 1-year prospective study

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Abstract

Background. The association between peritoneal solute transport rates (PSTRs) and inflammatory markers in patients on peritoneal dialysis (PD) is still under investigation. We aimed to elucidate their relationship during the first year on PD.

Methods. We performed a prospective observational study with 187 incident PD patients who were treated with either biocompatible solution (BCS) or conventional solution (CS). Peritoneal dialysate effluent (PDE) and blood samples for the markers and the calculation of mass transfer area coefficient of creatinine (MTAC) were performed at 1, 6 and 12 months after commencing PD.

Results. Of the 187 enrolled patients, 110 completed a 1-year study protocol. All PDE markers [interleukin-6 (IL-6), transforming growth factor-β (TGF-β), TGF-β-induced gene-h3 (βig-h3), vascular endothelial growth factor (VEGF)] except CA125 increased over time, whereas PSTRs, high-sensitivity C-reactive protein (hs-CRP) and serum IL-6 levels did not change. Serum albumin and log PDE appearance rates (ARs) of IL-6, TGF-β and CA125 predicted MTAC. The Δ value (12-month minus 1-month) of PDE AR of IL-6 was correlated with those of all other PDE markers. Both 12-month IL-6 and ΔIL-6 ARs in PDE were highest in the upper MTAC tertile. PSTRs in the CS group, unlike BCS, had a tendency to increase over time, demonstrating a time-by-group interaction. Solution type and MTAC were not associated with patient and technique survival.

Conclusions. The change in PSTR during the first year of PD is related to PDE IL-6 AR, which may represent intra-peritoneal inflammation; however, there does not seem to be a close association between PSTR and the degree of systemic inflammation.

Introduction

Continuous ambulatory peritoneal dialysis (PD) carries the chronic difficulty of preserving peritoneal membrane integrity over the long term. Bioincompatible dialysate itself can cause peritoneal membrane inflammation, leading to functional decline and ultrafiltration failure. In parallel with these outcomes, the peritoneum develops many structural abnormalities, including loss of the mesothelial cell (MC) monolayer, an increased number of fibroblasts, submesothelial fibrosis and augmented vessel number [1,2].

Many cytokines are involved in these processes. Interleukin-6 (IL-6) is a mediator of the inflammatory response in the peritoneal cavity [3], and transforming growth factor-β (TGF-β) plays a role in peritoneal fibrosis by stimulating resident fibroblast proliferation [4,5] and by inducing MC epithelial-to-mesenchymal transition (EMT) [6]. Vascular endothelial growth factor (VEGF) is a cytokine involved in peritoneal angiogenesis and probably vessel permeability [7].

A high permeability of the peritoneal membrane, defined as a fast peritoneal solute transport rate (PSTR), was reported to be related with adverse outcome in PD patients; however, previous studies have reported conflicting results [8–10]. Recently, several studies have revealed the relationship between PSTR and intraperitoneal cytokines based on the pathophysiologic mechanisms of the structural changes [11,12]. However, PD duration or the specific patient population can affect the relationship. The time
course of intraperitoneal cytokine response and their interaction in the beginning of PD remains unclear.

In addition, recent findings have indicated that uraemia itself may be responsible for histological and functional changes in the peritoneum even before the initiation of PD [1], which may represent changes related to chronic systemic inflammation [13]. However, in PD patients, the influence of comorbidity [14–16] or systemic inflammation [11,16–19] on the PSTR remains controversial. Moreover, clinical evidence of a link between systemic and local peritoneal inflammation has yet to be demonstrated.

We prospectively sought to assess how intraperitoneal cytokines and systemic inflammatory markers change as time passes during the first year of dialysis in incident PD patients and the relationship with changes in PSTR. Additionally, we evaluated whether initial PSTR could affect PD outcome in this patient group.

Subjects and methods

Patients and study design

Between October 2002 and July 2006, 187 incident PD patients who were at least 18 years old were enrolled in Kyungpook National University Hospital and Yeungnam University Hospital (Daegu, Korea), and followed up for 1 year with a protocol including the peritoneal equilibration tests (PETs), biochemical assays and adequacy/nutrition assessments at 1, 6 and 12 months after initiating PD. Both patient and technique survival times were calculated from the 1-month time point to the date of death, transfer to haemodialysis (HD), transplantation, loss to follow-up or 30 November 2008. Technique failure was defined as transfer to HD because of peritonitis, ultrafiltration failure, inadequate dialysis, exit and tunnel infection or mechanical problems. The choice of PD solution was at the discretion of each patient's treating physicians or centre. According to type of the prescribed PD solution, the participants were separated into two groups: the conventional solution (CS) group and the biocompatible solution (BCS) group. CS included Dianeal® (Baxter Healthcare, Woodlands, Singapore) and Stay-Safe® (Fresenius Medical Care, Bazen, Fukuoka, Japan). Likewise, Physiopain® (Baxter) or Stay-Safe® Balance (Fresenius) was prescribed as BCS. None of these patients received simultaneous treatment with other PD solutions such as icodextrin or amino acid-containing solution. Each patient's comorbidity status was analysed on the basis of the Davies comorbidity score [14], which encompasses seven comorbidity conditions, leading to three risk groups designated as low (none), intermediate (one or two) and high (three or more comorbid diseases) risk. All patients gave informed consent.

Peritoneal transport kinetics

The PET using 3.86% glucose PD fluid was performed as described elsewhere [20]. In brief, after an overnight dwell with 1.36% glucose PD fluid, patients received a 4-hour dwell with 3.86% glucose PD fluid. Dialysate samples were taken at 0, 1, 2 and 4 hours during the test. Blood samples were taken at 2 hours. The dialysate-to-plasma ratio for creatinine (D/P) was calculated as dialysate concentration at each time point divided by plasma concentration. All measurements were performed when the patients were at least 1 month after an episode of peritonitis. The mass transfer area coefficient of creatinine (MTAC), normalized for 1.73 m² of the body surface area, was calculated according to the modification [21] of the Garred model [22], in which creatinine concentration was expressed per volume of plasma water (aqueous concentration) [23]. Body surface area was estimated by the Du Bois equation [24]. For further analysis, patients who completed 1-year prospective study protocol were stratified into tertiles of change in MTAC (ΔMTAC) which was calculated by subtracting MTAC at 1 month from MTAC after 1 year.

Biochemical assays

Serum and peritoneal dialysate effluent (PDE) creatinine were measured by the Jaffé method with a sensitivity of 0.2 mg/dL. To measure serum [IL-6, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)] and PDE marker levels (IL-6, TGF-β and VEGF), we used a commercially available enzyme-linked immunosorbent assay (ELISA) test kit (Quantikine®; R&D Systems, Minneapolis, MN) according to the manufacturer's directions. The minimum detectable doses were 0.7 pg/mL for IL-6, 4.61 pg/mL for TGF-β, 9 pg/mL for VEGF, 0.35 ng/mL for ICAM-1 and 0.6 ng/mL for VEGF. PDE concentration of TGF-β-induced gene-h3 (βig-h3) was determined by indirect competitive ELISA (REGEN Biotech, Seoul, Korea). An ELISA (BioCheck, Foster City, CA) was used to assess PDE cancer antigen 125 (CA125) level, with a sensitivity of 0.1 mg/L. All PDE samples for the biomarker assessment were obtained from the overnight PDE (from exchanges with 2 L 1.36% glucose dialysate) from the night preceding the PET and were stored at −70°C until analysis. The appearance rates (ARs) were calculated by multiplying the concentrations in effluent by drained volume and dividing by the dwell time.

Adequacy and nutritional status analysis

Weekly urea clearance (Kt/Vurea) and total creatinine clearance (Ccr) were calculated using standard formulas. Residual renal function (RRF) was estimated by calculating the average residual urea clearance from 24-hour urine collection. Body mass index (BMI) was calculated as the weight divided by the square of height. Lean body mass was estimated from creatinine kinetics using the previously proposed formula [25], and % lean body mass was calculated as a percentage of body weight. As previously described [26], protein equivalent of nitrogen appearance was calculated and subsequently normalized to each patient's standardized body weight.

Statistics

In a first step, measurement values below the limit of detection of the laboratory parameters (PDE IL-6, TGF-β, βig-h3, CA125, serum IL-6, ICAM-1 and VCAM-1) were removed from analysis, which made up 3.0% of the total number of those data points. Values with normal distribution are expressed as mean ± SD, while those without normal distribution are shown as median (interquartile range) unless otherwise stated. Differences between two groups were determined with unpaired t-tests or χ² tests. Comparison among three groups was performed using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests. Bonferroni (which assume equal variance) or Dunnnett T3 tests (which do not assume equal variance) were used as subsequent post hoc testing. Using log data where appropriate, a repeated measures ANOVA was performed to assess interactions between changes in clinical parameters with time course and PD solution type (time-by-group effect), as well as serial changes of the parameters. The results have been expressed as the geometric mean [95% confidence interval (CI)] with back transformation of logarithmic data as necessary. Partial correlations were performed while adjusting for the confounding factors (age, sex, BMI, presence or absence of diabetes, Davies comorbidity score, RRF, PD solution type, peritonitis episode and time point for PET). When more than one partial correlation was found, dominant relationships were examined using multiple regression. Spearman's rank correlation was used to determine the relationship between Δ values. Survival outcomes were analysed using the univariate Kaplan–Meier method with the Breslow test and multivariate Cox proportional hazards model. P < 0.05 was considered significant. Statistical analysis was performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL).

Results

Study population

During the 1-year study period, 77 out of 187 patients were excluded; 34 had died, 18 switched to HD, 14 dropped out because of poor adherence or condition, 6 transferred to another hospital and 5 received kidney transplantation. Table 1 gives the demographic characteristics of the final study group (n = 110) and dropouts (n = 77).
Within the demographics of the final study group, there were similar values between the CS (n = 55) and BCS users (n = 55) except for a proportion of diabetics (36.4% versus 58.2%, P = 0.022). The peritonitis incidence during first year on PD was 0.29 per patient-year, which was not significantly different between the CS and BCS (data not shown).

**Longitudinal evolution of clinical and biochemical parameters**

During the 1-year follow-up period, Kt/V urea, C Cr, and RRF decreased continuously over time, whereas BMI increased. In all patients, values of PDE ARs increased continuously over time for IL-6, TGF-β, βig-h3 and VEGF but not for CA125. On the other hand, we identified no significant changes throughout the study period in serum concentrations of IL-6 and hs-CRP, and PSTRs, including MTAC and 4-hour D/P. Both serum ICAM-1 and VCAM-1 levels changed significantly over time and showed a V-shaped profile (Figure 1).

**Influence of clinical and biochemical parameters on MTAC**

MTAC significantly correlated with natural log-transformed (log) serum hs-CRP (r = 0.115, P = 0.039), ICAM-1 (r = 0.114, P = 0.043), VCAM-1 (r = 0.127, P = 0.024), log PDE ARs of IL-6 (r = 0.374, P < 0.001), TGF-β (r = 0.314, P < 0.001), CA125 (r = 0.331, P < 0.001) and serum albumin levels (r = −0.434, P < 0.001, Table 2). On multivariate analysis, serum albumin level (P < 0.001), log PDE ARs of IL-6 (P < 0.001), CA125 (P = 0.001) and TGF-β (P = 0.009) were independently associated with MTAC (Table 3).

**Comparison among the tertiles based on the change in MTAC**

The cutoff values for the tertiles were as follows: lower (i.e. highest decline in MTAC; n = 37) <-1.7 mL/min/1.73 m²; middle (i.e. lowest change; n = 36) between −1.7 and 0.9 mL/min/1.73 m²; and upper tertile (i.e. highest increase; n = 36) >0.9 mL/min/1.73 m². In the upper tertile, significantly higher values of ΔPDE ARs for IL-6 (P < 0.01 versus lower; P < 0.05 versus middle) and CA125 (P < 0.05 versus middle), and lower values of Δserum albumin (P < 0.01 versus lower) were observed (Figure 2). Age, sex, proportion of diabetic patients, Davies comorbidity score, time point for the PET, proportion of patients treated with BCS, peritonitis incidence and adequacy and nutrition parameters at the 1-year assessment were not significantly different among the tertiles (data not shown).

**Effluent IL-6: relationship with MTAC and other biomarkers**

We noted a significant correlation between the values of ΔMTAC and ΔPDE AR of IL-6 (r = 0.306, P = 0.002, Figure 3A). Furthermore, the value of ΔPDE AR of IL-6 was positively correlated with ΔPDE ARs of TGF-β (r = 0.263, P = 0.009, Figure 3B), βig-h3 (r = 0.245, P = 0.014, Figure 3C), VEGF (r = 0.226, P = 0.025, Figure 3D) and CA125 (r = 0.33, P = 0.001, Figure 3E). In addition, significant interrelations emerged between ΔPDE ARs of VEGF and CA125 (r = 0.271, P = 0.006), as well as between ΔPDE ARs of TGF-β and βig-h3 (r = 0.257, P = 0.009). In serum, we identified a significant correlation between ΔIL-6 and Δhs-CRP (r = 0.401, P < 0.001), and ΔVCAM-1 correlated significantly with ΔICAM-1 (r = 0.404, P < 0.001).

The ΔPDE AR of IL-6 did not correlate with any changes in any of the investigated systemic inflammatory markers. The partial correlation analysis, however, revealed that the log PDE AR of IL-6 correlated significantly with serum concentrations of albumin (r = −0.203, P < 0.001), log hs-CRP (r = 0.168, P = 0.003), log serum IL-6 (r = 0.141, P = 0.014), log ICAM-1 (r = 0.194, P = 0.001) and log VCAM-1 (r = 0.128, P = 0.027).

**Serial changes of MTAC according to the type of PD solution**

The effects of different types of PD fluid on MTAC depended on the PD duration (P = 0.013 for time-by-group factor).

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### Table 1. Baseline characteristics of patients alive on PD (n = 110) versus dropouts (n = 77) during 1-year study period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 187)</th>
<th>Patients alive on PD (n = 110)</th>
<th>Patients dropped out (n = 77)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.0 ± 15.0</td>
<td>51.9 ± 13.5</td>
<td>57.1 ± 16.6</td>
<td>0.025</td>
</tr>
<tr>
<td>Male/female</td>
<td>105/82</td>
<td>63/47</td>
<td>42/35</td>
<td>0.711</td>
</tr>
<tr>
<td>PD fluid type (CS/BCS)</td>
<td>106/81</td>
<td>55/55</td>
<td>51/26</td>
<td>0.027</td>
</tr>
<tr>
<td>Diabetics</td>
<td>106</td>
<td>52 (47.3)*</td>
<td>54 (70.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>98</td>
<td>47 (42.7)</td>
<td>51 (66.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>38 (34.5)</td>
<td>14 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>28</td>
<td>18 (16.4)</td>
<td>10 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>7 (6.4)</td>
<td>2 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Davies comorbidity score</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>0: low</td>
<td>61</td>
<td>46 (41.8)</td>
<td>15 (19.5)</td>
<td></td>
</tr>
<tr>
<td>1–2: intermediate</td>
<td>119</td>
<td>63 (57.3)</td>
<td>57 (74.0)</td>
<td></td>
</tr>
<tr>
<td>3–7: high</td>
<td>7</td>
<td>1 (0.9)</td>
<td>5 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number (percent) unless noted otherwise. BCS, biocompatible solution; CS, conventional solution; PD, peritoneal dialysis. *P = 0.022 for comparisons of the CS and BCS users [20 of 55 (36.4%) versus 32 of 55 (58.2%)].
interaction, Figure 4). The same interaction for 4-hour D/P was also statistically significant ($P = 0.011$). However, the results for other parameters did not reach statistical significance (data not shown).

Survival of all patients ($n = 187$)

During a median follow-up of 31 months (range, 1–72 months) after the 1-month time point, there were 59 PD-
related deaths and 34 technique failures. The major causes of mortality were cardiovascular disease (49.2%), followed by peritonitis (18.6%) and fatal cachexia (15.3%). The technique failure resulted from peritonitis (79.4%), mechanical malfunction (14.7%) and exit-site and tunnel infection (5.9%). On univariate analysis, patient and technique survival curves did not differ either between PD fluid subgroups or among the baseline MTAC tertiles (Figure 5). In a multivariable Cox model which included age, sex, presence or absence of diabetes, Davies comorbidity score, residual renal function, solution type, peritonitis episode and time point, AR, appearance rate; β-h3, transforming growth factor-β-induced gene-h3; CA125, cancer antigen 125; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; VEGF, vascular endothelial growth factor.

Table 2. Partial correlation analysis between the mass transfer area coefficient of creatinine and the biochemical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td>-0.434</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log hs-CRP</td>
<td>0.115</td>
<td>0.030</td>
</tr>
<tr>
<td>Log serum IL-6</td>
<td>0.083</td>
<td>0.142</td>
</tr>
<tr>
<td>Log serum ICAM-1</td>
<td>0.114</td>
<td>0.043</td>
</tr>
<tr>
<td>Log serum VCAM-1</td>
<td>0.127</td>
<td>0.024</td>
</tr>
<tr>
<td>Log PDE IL-6 AR</td>
<td>0.374</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log PDE TGF-β AR</td>
<td>0.314</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log PDE β-h3 AR</td>
<td>0.021</td>
<td>0.717</td>
</tr>
<tr>
<td>Log PDE VEGF AR</td>
<td>0.058</td>
<td>0.314</td>
</tr>
<tr>
<td>Log PDE CA125 AR</td>
<td>0.331</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are adjusted for age, sex, body mass index, presence or absence of diabetes, Davies comorbidity score, residual renal function, solution type, peritonitis episode and time point. AR, appearance rate; CA125, cancer antigen 125; IL-6, interleukin-6; PDE, peritoneal dialysate effluent; TGF-β, transforming growth factor-β.

Discussion

This study revealed the significant contributions of PDE IL-6, TGF-β, CA125 and serum albumin to the prediction of MTAC, at least during the early phase of PD. From among the predictors, the PDE ARs of IL-6, TGF-β and the levels of serum albumin significantly increased, while MTAC and PDE CA125 AR showed no change over time. In addition, both 12-month IL-6 and ΔIL-6 ARs in PDE were significantly highest in the upper tertile of ΔMTAC.

Several studies have been conducted to elucidate possible links between systemic/intraperitoneal IL-6 and PSTR in PD. One study reported increased plasma and PDE levels of IL-6 in the high transporter group and an association between PSTR and the IL-6 system [11]. Another study also indicated both that IL-6 levels were increased and that they were associated with PSTR during the first PD year [27]. In contrast, the results of the present study show that PDE levels but not serum levels of IL-6 were significantly increased and associated with MTAC. This finding suggests a possible link between PSTR and local inflammation, rather than systemic inflammation, during the first year on PD. The results are in partial agreement with those of a recent study showing that serum and PDE IL-6 levels did not differ between fast and slow transporters, and identifying no relationship between D/P and serum IL-6, but finding a positive association of the time course of the D/P with PDE IL-6 [28]. The discrepancy between our results and those of previous studies may be due to different PD duration, study population or design.

Our data show that PDE TGF-β was a significant predictor of MTAC. In previous findings consistent with those of the current study, a cross-sectional study of 76 PD patients revealed that dialysate TGF-β1 positively correlated with 4-hour D/P and MTAC [29]. On the other hand, a study in an animal model demonstrated that β-h3, induced by TGF-β1, might be associated not only with adhesion and migration of MCs during the wound-healing process in vitro but also with the functional deterioration of the peritoneum, suggesting that β-h3 in human peritoneal MCs might play a potential role in PD [30]. In our data, PDE β-h3, in contrast to TGF-β, was not associated with MTAC.

Effluent CA125 is likely to depend on MC mass or turnover [31]. The correlation between PDE CA125 and

Table 3. Multiple linear regression analysis (stepwise method) of the variables influencing the mass transfer area coefficient of creatinine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Standard error</td>
<td>β</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>-2.540</td>
<td>0.368</td>
<td>-0.366</td>
</tr>
<tr>
<td>Log PDE IL-6 AR</td>
<td>0.646</td>
<td>0.156</td>
<td>0.214</td>
</tr>
<tr>
<td>Log PDE CA125 AR</td>
<td>0.412</td>
<td>0.120</td>
<td>0.169</td>
</tr>
<tr>
<td>Log PDE TGF-β AR</td>
<td>0.632</td>
<td>0.241</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Values are adjusted for age, sex, body mass index, presence or absence of diabetes, Davies comorbidity score, residual renal function, solution type, peritonitis episode and time point. Adjusted R² is 0.334 (P < 0.001). Dependent variable: mass transfer area coefficient of creatinine; independent variables: serum albumin, log PDE IL-6 AR, log serum intercellular adhesion molecule-1, log PDE TGF-β AR and log PDE CA125 AR. AR, appearance rate; CA125, cancer antigen 125; IL-6, interleukin-6; PDE, peritoneal dialysate effluent; TGF-β, transforming growth factor-β.
PSTRs seems to vanish over time on PD, probably because of the decline in MC mass and the increase in effective peritoneal surface area [32]. The relationships between these factors at the early stage of PD in previous studies [15,28,33,34] are in accordance with our data. Some of those studies suggested that VEGF produced by reactive MCs might be the link between PSTR and MCs [15,34]. Moreover, recent ex vivo and in vivo findings indicated that MCs that have undergone EMT were the main source of VEGF, which might be responsible for a high PSTR [7]. In our study, however, we found a lack of correlation between VEGF and MTAC, probably because of a satisfactory preservation of peritoneal transport properties in our patients, at least in the first PD year. Instead, we found that PDE VEGF AR at 12 months was significantly higher in the upper ΔMTAC tertile than in the lower tertile, suggesting that a correlation between them might exist after 1 year on PD.

With the exception of our finding for serum albumin, this study also showed no association between MTAC and systemic inflammation, results that are in line with several recent investigations [9,15,28]. It has been reported that hypoalbuminaemia was associated with high PSTR in new PD patients [16,35]. However, hypoalbuminaemia in PD is considered multifactorial, with dialysis-related and non-dialysis-related factors, alone or in combination. Thus, the possibility remains that these common factors or confounders affect the interpretation of the relationship between serum albumin and MTAC. On the other hand, both VCAM-1 and ICAM-1, which represent endothelial cell dysfunction, may be important mediators of inflammation in dialysis patients [36,37], although our data indicated that these markers had no correlation with MTAC. Why marker levels were relatively high at 1 month (initial) is unclear, and further study would be necessary to investigate the roles of VCAM-1 and ICAM-1 on PSTR. No significant serial changes of serum IL-6 and hs-CRP may be ascribed to generally low comorbidity.

Interestingly, our research showed that ΔPDE IL-6 AR was positively correlated with the Δ values not only of MTAC but also all of other investigated PDE markers. A cross-sectional study previously revealed a significant correlation between PDE IL-6 and VEGF [11]. Furthermore, we observed a positive correlation between ΔPDE VEGF and CA125. These findings, therefore, may provide the opportunity to infer a connection between PDE IL-6 and CA125 during the initial stage of PD. We also found weak but significant correlations between PDE IL-6 and all examined serum markers. These observational data are compatible with the hypothesis that PDE IL-6 may be a mediator between local and systemic inflammations, particularly during the early phase of PD.
Fig. 3. Relationship between changes in peritoneal dialysis effluent appearance rate of interleukin-6 (ΔPDE IL-6 AR) and those in mass transfer area coefficient of creatinine (ΔMTAC) and those of intraperitoneal biomarkers during first year. The value of ΔPDE IL-6 AR was positively correlated with ΔMTAC (A) and changes of all other biomarkers, including transforming growth factor-β (TGF-β) (B), TGF-β-induced gene-h3 (βig-h3) (C), vascular endothelial growth factor (VEGF) (D), and cancer antigen 125 (CA125) (E).
This report demonstrated differences between the CS and BCS groups for PSTRs, indicated by the significant time-by-group interaction effects. A previous randomized study revealed that BCS had no negative effects on PSTRs in the incident PD patients with 2-year follow-up [38]. Recent data showed that PDE level of CA125 was significantly higher in patients treated with BCS, while there was no change in the level of either VEGF or tumour necrosis factor $\alpha$, suggesting an improvement in the intraperitoneal milieu or homeostasis [39]. Moreover, one experimental study also indicated that BCS might positively affect the preservation of MC integrity [40]. Unlike such indications, however, our data revealed no significant effect of PD with BCS on changes in PDE CA125 levels or the inflammatory markers. As our results suggest, both patient and technique survivals were similar between solution groups and among the MTAC tertiles.

Some study limitations may in part affect the findings. First is the potential for selection bias because this was not a randomized controlled study. Secondly, a possibility of informative censoring could not be excluded. Thirdly, each patient was prescribed one of four different kinds of PD solutions made by the two manufacturers, and no specific criteria were applied for selecting patients to be treated with the BCS, which might influence the longitudinal changes in the biomarkers to some degree. Finally, the frequency of diabetes in the CS group within 110 patients alive on PD during 1-year study protocol, reflecting

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**Fig. 4.** Serial changes of mass transfer area coefficient of creatinine (MTAC) according to the type of peritoneal dialysate [conventional solution (CS, $n = 55$) and biocompatible solution (BCS, $n = 55$)]. Data are expressed as mean ± SD. There was a significant time-by-group interaction for MTAC. *Significantly different results between CS and BCS groups ($P < 0.05$).

**Fig. 5.** Patient and technique survival curves of all patients ($n = 187$) after 1-month time point (by Kaplan–Meier analysis with Breslow test). Neither patient (A and B) nor technique survival curves (C and D) differed between biocompatible (BCS, $n = 81$) and conventional solutions (CS, $n = 106$) or among the upper (U, $n = 63$), middle (M, $n = 62$) and lower (L, $n = 62$) tertiles of mass transfer area coefficient of creatinine at 1 month after initiating peritoneal dialysis.
a state of chronic inflammation, was significantly lower than in the BCS, possibly mitigating the differences in inflammatory response between CS and BCS.

In conclusion, the change in PSTR during the first PD year is related to the appearance of PDE IL-6, which may, at least in part, represent the local peritoneal inflammation; however, there does not seem to be a strong association between PSTR and the degree of systemic inflammation. Because of the limitations of our study design, a well-designed and extensive study for confirming these findings will be required.

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Conflict of interest statement. None declared.

References

36. Małyszko J, Małyszko JS, Mysliwiec M. Endothelial cell injury markers in chronic renal failure on conservative treatment and continuous
Superior survival of high transporters treated with automated versus continuous ambulatory peritoneal dialysis

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Abstract

Background. Automated peritoneal dialysis (APD) is widely recommended for the management of high transporters by the International Society of Peritoneal Dialysis (ISPD), although there have been no adequate studies to date comparing the outcomes of APD and continuous ambulatory peritoneal dialysis (CAPD) in this high risk group.

Methods. The relative impact of APD versus CAPD on patient and technique survival rates was examined by both intention-to-treat (PD modality at Day 90) and ‘as-treated’ time-varying Cox proportional hazards model analyses in all patients who started PD in Australia or New Zealand between 1 April 1999 and 31 March 2004 and who had baseline peritoneal equilibration tests confirming the presence of high peritoneal transport status.

Results. During the study period, 4128 patients commenced PD. Of these, 628 patients were high transporters on PD at Day 90 (486 on CAPD and 142 on APD). Compared to high transporters treated with CAPD, APD-treated high transporters were more likely to be younger and Caucasian, and less likely to be diabetic. On multivariate intention-to-treat analysis, APD treatment was associated with superior survival [adjusted hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.35–0.87] and comparable death-censored technique survival (HR 0.88, 95% CI 0.64–1.21). Superior survival of high transporters treated with APD versus CAPD was also confirmed in supplemental as-treated analysis (HR 0.72, 95% CI 0.54–0.96), matched case-control analysis (HR 0.60, 95% CI 0.36–0.96) and subgroup analysis of high transporters treated entirely with APD versus those treated entirely with CAPD (HR 0.29, 95% CI 0.14–0.60). There were no statistically significant differences in patient survival or death-censored technique survival between APD and CAPD for any other transport group, except for low transporters, who experienced a higher mortality rate on APD compared with CAPD (HR 2.19, 95% CI 1.02–4.70).

Conclusions. APD treatment is associated with a significant survival advantage in high transporters compared with CAPD. However, APD treatment is associated with inferior survival in low transporters.

Keywords: automated peritoneal dialysis; continuous ambulatory peritoneal dialysis; outcomes; patient survival; peritoneal equilibration test