The most serious problem in peritoneal dialysis (PD) is the risk of final complication by encapsulating peritoneal sclerosis (EPS) because of peritoneal deterioration. Markers useful for the noninvasive evaluation of peritoneal deterioration are therefore required. In this multicenter prospective study of stable PD patients, we compared the dialysate-to-plasma (D/P) concentration ratios of albumin, immunoglobulin G, and $\alpha_2$-macroglobulin, and effluent levels of interleukin 6 (IL-6) and fibrinogen/fibrin degradation products (FDPs) to clarify the relationship between inflammation, fibrinolysis markers, and permeability to large molecules.

At the beginning of the present study, significantly positive correlations were noted between the IL-6 and FDP concentrations and the D/P ratios of albumin and $\alpha_2$-macroglobulin. In addition, a significantly positive correlation was noted between the FDP and IL-6 concentrations. However, the D/P ratio of creatinine obtained by peritoneal equilibration test did not positively correlate with those markers. Moreover, a significantly positive correlation was noted between changes in the effluent concentrations of FDPs and IL-6 and in permeability markers for large molecules.

The effluent IL-6 and FDP concentrations reflect a chronic inflammatory state in the peritoneum, which is associated with increased permeability to large molecules. In individual PD patients, careful observation of the clinical course and evaluation of changes in such markers are expected to predict peritoneal deterioration and the development of EPS.

Key words
Peritoneal deterioration, interleukin 6, fibrinogen/fibrin degradation products, large molecules

Introduction
The most serious problem in peritoneal dialysis (PD) is deterioration of the peritoneum with duration of PD, resulting in fibrosis of the peritoneum (1) and increased permeability because of neoangiogenesis (2). To date, many effluent markers have been evaluated to detect peritoneal deterioration. The effluent concentration of cancer antigen 125 (CA125) is used as a marker of mesothelial cell activity (3). Effluent hyaluronan concentration is used as a marker of fibrosis (4). The peritoneal equilibration test (PET) is the most basic method of evaluating peritoneal permeability. Increases in the dialysate-to-plasma concentration ratio of creatinine (D/P Cr) reflect increased peritoneal permeability and increased neoangiogenesis. However, D/P Cr evaluates permeability only for small molecules. Neoangiogenesis in the deteriorated peritoneum may also reflect increased permeability to large molecules. Therefore, it is necessary to evaluate peritoneal permeability to large molecules.

Encapsulating peritoneal sclerosis (EPS) is feared as a final complication of PD. Although the incidence of EPS is only 2.5% among all PD patients, the incidence and mortality rates both rapidly increase in chronic PD patients who have undergone PD for more than 8 years (5). With regard to the causes of EPS, the combination of peritoneal deterioration and inflammation may cause fibrinogenesis and capsule formation before ileus symptoms manifest themselves (6).

The effluent concentration of interleukin 6 (IL-6) has been measured to evaluate such an inflammatory state in the peritoneum, and both the effluent IL-6 concentration and the duration of PD were reportedly increased in PD patients with peritoneal inflammation (7–10). In addition, the effluent concentration of fibrinogen/fibrin degradation products (FDPs) has also...
been evaluated as a marker of increased fibrinolysis in the peritoneum (11,12).

In the present prospective study of stable PD patients, we compared effluent levels of IL-6 and FDPs, and D/P ratios of albumin, immunoglobulin G (IgG), and $\alpha_2$-macroglobulin as markers of permeability to large molecules to clarify the relationship between inflammatory and fibrinolysis markers and permeability to large molecules.

**Patients and methods**

The subjects were 43 patients undergoing PD at seven medical institutions in Japan. After informed consent was obtained from the patients, all were registered and followed for 2 years. At the start, and at 6-month intervals, blood samples and overnight effluents (8-hour dwell) were collected. If peritonitis occurred in a patient during the course of the study, examination was resumed after more than a 4-week interval had passed between complete healing of the peritonitis and the study examination. On the day of the examination, a PET was performed. The dialysis solution used was a conventional acidic solution containing glucose.

Examination items included effluent concentrations of IL-6 (chemiluminescent enzyme immunoassay) and FDPs (latex photometric immunoassay), and plasma and effluent concentrations of albumin (latex agglutination immunoassay), IgG (latex agglutination immunoassay), and $\alpha_2$-macroglobulin (nephelometry). The D/P Cr obtained by PET was used to evaluate peritoneal permeability to small molecules, and the D/P ratios of albumin, IgG, and $\alpha_2$-macroglobulin were used to evaluate peritoneal permeability to large molecules. Using the method reported by Yamamoto et al. (13), the total peritoneal mesothelial cell area was also measured.

Data are expressed mean ± standard deviation. Statistical analyses were carried out using the Pearson correlation test. Values of $p < 0.05$ were considered statistically significant.

**Results**

From among 43 registered patients, we analyzed the results of 31 patients (18 men, 13 women; mean age: 58 ± 14 years; mean PD duration: 49.4 ± 31.4 months) who were examined for more than 1 year. The original diseases in these patients were chronic glomerulonephritis ($n = 28$), diabetic nephropathy ($n = 2$), and lupus nephritis ($n = 1$). Twelve months after initiation of this study, 1 patient withdrew from PD because of the occurrence of peritonitis.

Table I shows the values obtained at the beginning of the study for effluent markers, D/P Cr, and total peritoneal mesothelial cell area. Based on the results of the PET, 3 patients were categorized as high transporters, 12 as high-average transporters, 10 as low-average transporters, and 6 as low transporters.

Table II and Figure 1 show correlations among the various effluent markers obtained at the beginning of the study. Significant positive correlations were noted between the effluent IL-6 concentration and the D/P ratios of albumin, IgG, and $\alpha_2$-macroglobulin. Similarly, effluent FDP concentration correlated positively with the D/P ratios of albumin, IgG, and $\alpha_2$-macroglobulin. Furthermore, a significantly positive correlation was noted between the effluent concentrations of FDPs and IL-6 (Figure 1). However, the D/P Cr did not correlate with any of these markers.

Table III and Figure 2 show the correlations between changes in the effluent concentrations of IL-6 and FDPs, and changes in markers of permeability to large molecules over 6 months in the patients in whom examinations were performed at 6-month intervals.

**Table I** Effluent markers obtained at the beginning of the study

<table>
<thead>
<tr>
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<th>Effluent markers obtained at the beginning of the study</th>
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<tbody>
<tr>
<td>PET D/P Cr</td>
<td>0.62±0.16</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>55.5±111.1</td>
</tr>
<tr>
<td>FDPs (ng/mL)</td>
<td>6,530±5,051</td>
</tr>
<tr>
<td>D/P albumin</td>
<td>0.016±0.009</td>
</tr>
<tr>
<td>D/P IgG</td>
<td>0.009±0.005</td>
</tr>
<tr>
<td>D/P $\alpha_2$-macroglobulin</td>
<td>0.004±0.003</td>
</tr>
<tr>
<td>Total PMC area (µm²)</td>
<td>293±42.1</td>
</tr>
</tbody>
</table>

PET = peritoneal equilibration test; D/P Cr = dialysate-to-plasma ratio of creatinine; IL-6 = interleukin 6; FDPs = fibrin/fibrinogen degradation products; IgG = immunoglobulin G; PMC = peritoneal mesothelial cell.

**Table II** Correlation (correlation coefficient) between effluent markers obtained at the beginning of the study ($n = 31$)

<table>
<thead>
<tr>
<th>Effluent IL-6</th>
<th>Effluent FDPs</th>
</tr>
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<tbody>
<tr>
<td>Effluent FDPs</td>
<td>0.491a</td>
</tr>
<tr>
<td>D/P albumin</td>
<td>0.738a</td>
</tr>
<tr>
<td>D/P IgG</td>
<td>0.724a</td>
</tr>
<tr>
<td>D/P $\alpha_2$-macroglobulin</td>
<td>0.725a</td>
</tr>
</tbody>
</table>

$^a$ $p < 0.0001$.

$^b$ $p < 0.003$.

IL-6 = interleukin 6; FDPs = fibrin/fibrinogen degradation products; D/P = dialysate-to-plasma ratio; IgG = immunoglobulin G.
Significantly positive correlations were noted between changes in effluent FDPs and changes in the D/P of albumin, IgG, and \( \alpha_2 \)-macroglobulin. Moreover, changes in effluent IL-6 were significantly correlated with D/P albumin. In addition, changes in the effluent concentration of IL-6 were positively correlated with changes in the effluent concentration of FDPs (Figure 2).

During the observation period (2 years), no patient showed abnormal changes in total peritoneal mesothelial cell area; that measurement always remained at a level below 400 \( \mu \text{m}^2 \).

Discussion

Many suggested markers of peritoneal deterioration have been evaluated to date. The PET is a representative method of evaluating peritoneal deterioration. In addition, CA125 is used as an index of mesothelial cell activity (3), and hyaluronan is used as a marker of fibrosis (4). The D/P Cr obtained by PET increases with the progression of peritoneal neoangiogenesis, reflecting the severity of peritoneal deterioration (2). However, changes in CA125 and hyaluronan vary in individual PD patients. Clear results therefore cannot be obtained by cross-sectional studies.

In the present study, we focused on IL-6, a marker of inflammation, and FDPs, a marker of fibrinolysis. The level of IL-6 is reportedly increased in a state of acute intraperitoneal inflammation (7–10). An in vitro study suggests that exposure to bioincompatible dialysis solutions increases IL-6 production (14). In addition, Fujimori et al. (7) reported that IL-6 production increases with the duration of PD in chronic PD patients. That is, exposure to acidic dialysis solutions containing glucose prolongs the course of chronic inflammation, thus probably increasing the effluent IL-6 concentration. However, effluent IL-6 concentration is reportedly associated with increased peritoneal permeability and vice versa (8,9). Therefore, no consensus has been reached regarding the correlation between effluent IL-6 concentration and peritoneal permeability.

Zemel et al. (10) reported that, in stable PD patients, effluent IL-6 concentration correlated with an increased transport rate for large solutes but not for smaller molecules. Pecoits–Filho et al. (8) reported that the effluent IL-6 concentration correlated with increased permeability to small and large molecules, probably because intraperitoneal inflammation in-

<table>
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<tr>
<th>( \Delta D/F )</th>
<th>( \Delta D/P ) albumin</th>
<th>( \Delta D/P ) IgG</th>
<th>( \Delta D/P ) ( \alpha_2 )-macroglobulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>FDPs</td>
<td>0.530&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Δ/D/P albumin</td>
<td>0.392&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.482&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Δ/D/P IgG</td>
<td>0.280&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.628&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Δ/D/P ( \alpha_2 )-macroglobulin</td>
<td>0.229&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.644&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> \( p < 0.001 \)

<sup>b</sup> \( p < 0.01 \)

<sup>c</sup> Nonsignificant.

IL-6 = interleukin 6; FDPs = fibrin/fibrinogen degradation products; D/P = dialysate-to-plasma ratio; IgG = immunoglobulin G.
duces peritoneal neoangiogenesis via cytokines such as vascular endothelial growth factor. With regard to this correlation with permeability, detailed observation of individual cases is required.

Dobbie (15) reported that unphysiologic PD solutions induce persistent low-grade serositis. That serositis could increase the transfer of coagulation factors from blood to the peritoneal cavity, resulting in a hypercoagulatory state. Increased fibrin generation is accompanied by increased fibrinolysis, as indicated by remarkably high peritoneal FDPs (11,12). However, it remains unclear whether this increase in coagulation factors is associated with peritoneal permeability, or whether increased levels of coagulation factors may be associated with changes in the balance between fibrin degradation and production.

Therefore, chronic inflammation induced by repeated exposure to PD solutions surely increases the effluent concentrations of IL-6 and FDPs. In the present study, a positive correlation was noted between the effluent concentrations of IL-6 and FDPs. In addition, the effluent concentrations of IL-6 and FDPs both positively correlated with the D/P ratios of albumin, IgG, and α2-macroglobulin, markers of peritoneal permeability to large molecules. However, neither the effluent concentration of IL-6 nor that of FDPs positively correlated with the D/P Cr, a marker of peritoneal permeability to small molecules.

Cross-sectional studies could not clarify the relationships of the various markers with the duration of PD. Moreover, during our 2-year observation period, changes in each marker varied in the individual PD patients. However, changes in the IL-6 concentration obtained every 6 months correlated positively with changes in the FDP concentration, suggesting that both markers reflect changes in inflammatory state. In addition, those markers also correlated with changes in the markers of permeability to large molecules, suggesting that the inflammatory state increased permeability.

Encapsulating peritoneal sclerosis is feared as a final complication of PD. Although the causes of EPS remain unclear, the combination of a deteriorated peritoneum and inflammation may promote fibrinogenesis and capsule formation before ileus symptoms manifest themselves (6,15).

The effluent and ascites levels of inflammatory and fibrinolysis markers have been reported to increase before the development of EPS (6). We encountered a surgically treated case of EPS that occurred in a chronic hemodialysis patient without any hepatic disease, in whom persistent retention of ascites was the cause of EPS (16). In that patient, levels of inflammatory and of fibrinolysis and coagulation system markers such as IL-6, thrombin–antithrombin III complex (TAT), and FDPs were increased in the ascites, suggesting the involvement not only of simple ascites retention, but also of inflammation. Periodic measurement of effluent IL-6 and FDP concentrations may therefore facilitate prediction of EPS development.

During the 2-year observation period, no patient developed EPS. However, some PD patients had been treated with PD for more than 10 years. Careful observation is therefore required.

Conclusions
Effluent concentrations of IL-6 and FDPs reflect a chronic inflammatory state in the peritoneum, which is associated with increased permeability to large molecules. Therefore, carefully observing the clinical course of individual PD patients and evaluating changes in those markers may help to predict the development of EPS.

Acknowledgment
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