Few studies have attempted to evaluate the relationship between peritoneal permeability and fluid status in peritoneal dialysis (PD). The aim of the present study was to clarify the relationship between change in the dialysate-to-plasma ratio of creatinine (D/P Cr) and change in fluid status as evaluated by natriuretic peptides.

We studied 49 PD patients (29 men, 62 ± 11 years, 36.7% with diabetes) who underwent a peritoneal equilibration test at least twice after PD initiation. We evaluated correlations between the rate of change in the D/P Cr (RC-D/P Cr), the rate of change in a human atrial natriuretic polypeptide (RC-αhANP), and the rate of change in brain natriuretic peptide (RC-BNP).

The RC-αhANP was strongly correlated with RC-BNP (r = 0.637, p < 0.001). In contrast, the RC-D/P Cr was not correlated with RC-αhANP (r = 0.041, p = 0.781) or with RC-BNP (r = 0.114, p = 0.435). However, positive correlations between RC-D/P Cr and RC-αhANP (r = 0.530, p = 0.006) and between RC-D/P Cr and RC-BNP (r = 0.625, p = 0.001) were observed in patients with increased D/P Cr.

The present study showed a positive correlation between change in peritoneal transport characteristics and change in fluid status in patients whose D/P Cr increased.

Key words
Natriuretic peptides, fluid status, peritoneal transport characteristics

Introduction
Appropriate management of fluid balance is an important factor for the continuation of peritoneal dialysis (PD) (1). Preservation of residual renal function and avoidance of ultrafiltration failure are important for the maintenance of fluid balance in PD patients. However, a previous study indicated that more than 30% of PD patients in Japan experience overhydration (2).

Ultrafiltration failure because of high peritoneal permeability is thought to cause fluid overload in PD patients (3). Ultrafiltration failure because of the onset of high peritoneal permeability during treatment with PD (4) and early exposure to higher intraperitoneal glucose concentrations has been associated with more rapid deterioration in membrane function (3). Moreover, Konings et al. (5) reported a positive correlation between overhydration and the dialysate-to-plasma ratio of creatinine (D/P Cr) as a measure of peritoneal permeability. However, in their study, the D/P Cr was evaluated cross-sectionally, and fluid status was assessed longitudinally. In addition, fluid status was assessed by the deuterium oxide dilution method.

The aim of the present study was to clarify the relationship between change in peritoneal transport characteristics and change in fluid status as evaluated by natriuretic peptides.

Methods
This retrospective multicenter cohort study was performed between January 2008 and December 2013. The study was approved by the institutional review board of the St. Marianna University School of Medicine. The study subjects were PD patients who had undergone a peritoneal equilibration test (PET) at least twice after initiation of PD at St. Marianna University School of Medicine Hospital or Kawasaki Municipal
Tama Hospital. Patients who developed peritonitis during the observation period and patients with symptoms of heart failure were excluded.

A standard or fast PET was performed in all study patients to evaluate peritoneal transport characteristics. The first PET was performed within 2 – 3 months after PD initiation, and the second PET was performed 6 months after the first PET. Alpha human atrial natriuretic polypeptide (αhANP) was measured by fluorescence enzyme immunoassay (LSI Medience Corporation, Tokyo, Japan), and brain natriuretic peptide (BNP) was measured by chemiluminescent enzyme immunoassay (LSI Medience Corporation). The natriuretic peptides evaluated in the present study were measured within 1 month before or after each PET. We evaluated correlations between the rate of change in the D/P Cr (RC-D/P Cr), the rate of change in αhANP (RC-αhANP), and the rate of change in BNP (RC-BNP).

**Statistical analysis**

Data are expressed as mean ± standard deviation. Paired data were compared using a nonparametric Wilcoxon signed-rank test. For correlations between continuous variables, a Spearman rank correlation test was used. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software application (version 18: SPSS Japan, Tokyo, Japan).

**Results**

We analyzed 49 PD patients (29 men, 20 women; mean age: 62 ± 11 years; 36.7% with diabetes). Table I shows the baseline characteristics of the patients. No significant differences in D/P Cr, αhANP, and BNP were observed from the first to the second PET. However, body weight increased significantly from the first to the second PET (59.2 ± 8.6 kg vs. 60.4 ± 10.9 kg, p = 0.006).

A positive correlation between RC-αhANP and RC-BNP was observed (r = 0.637, p < 0.001). No correlations were observed between RC-D/P Cr and RC-αhANP (r = 0.041, p = 0.781) and between RC-D/P Cr and RC-BNP (r = 0.114, p = 0.435). On the other hand, in patients who experienced increased D/P Cr, significant positive correlations were observed between RC-D/P Cr and RC-αhANP (r = 0.530, p = 0.006) and between RC-D/P Cr and RC-BNP (r = 0.625, p = 0.001; Figure 1).

**Table 1** Clinical profiles of enrolled patients at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62±11</td>
</tr>
<tr>
<td>Men/women (n)</td>
<td>29/20</td>
</tr>
<tr>
<td>With/without DM (n)</td>
<td>18/31</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59.2±8.6</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>5.9±1.8</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>6.2±2.7</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9±0.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.8±1.5</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.5±1.2</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>0.63±0.13</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>266.9±590.7</td>
</tr>
<tr>
<td>αhANP (pg/mL)</td>
<td>119.5±208.1</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; D/P Cr = dialysate-to-plasma ratio of creatinine; BNP = brain natriuretic peptide; αhANP = alpha human atrial natriuretic polypeptide.

**Discussion**

Assessment of fluid status is extremely difficult in PD patients. Konings et al. (5) assessed fluid status using sodium bromide dilution or deuterium oxide dilution. Those methods have some limitations, including assumptions about hydration of the free fat mass, which can vary with age and sex, and the time requirement for the measurements. Other methods of evaluating fluid status are physical examination, cardiothoracic index, blood pressure, and inferior vena cava diameter (6). However, those methods are poorly reproducible, difficult to measure, and inaccurate. Although bioimpedance analysis is a safe and easy method and appears to be more useful and sensitive than other techniques for assessing volume status in PD patients (7), it necessitates the purchase of expensive analysis equipment. We therefore evaluated fluid status in our study subjects using αhANP and BNP measurements.

Change in αhANP depends on atrial pressure. In contrast, BNP is secreted from the cardiac ventricles; it reflects cardiac muscle damage and is less changeable in the short term (8,9,10), making it unsuitable as an...
indicator of appropriate dry weight in hemodialysis patients. On the other hand, some reports have indicated that BNP is correlated with fluid status in hemodialysis patients (11,12). However, a significant correlation between αhANP and BNP has been reported in PD patients (13), and the present study shows a significant correlation between those two peptides.

Assessment of fluid status by natriuretic peptides has some advantages in PD patients. First, measurement of the natriuretic peptides is simple and inexpensive and yields quantitative values. Second, the usefulness of natriuretic peptides in the diagnosis of fluid status has already been demonstrated in PD patients. In recent years, Crepaldi et al. (14) reported that BNP correlates positively with fluid overload as measured by bioimpedance and that the correlation is stronger during the first 6 months on PD. Interestingly, we observed an association between fluid status and peritoneal permeability in patients whose D/P Cr increased during their first 6 months on PD.

Regarding the relationship between high peritoneal permeability and overhydration, three mechanisms are envisioned. First, peritoneal permeability is enhanced by the use of high-glucose PD solution in patients with overhydration. Second, ultrafiltration failure leads to fluid overload in patients with deteriorating residual renal function. Third, cytokines induced by fluid overload cause angiogenesis, which leads to high peritoneal permeability. Takara et al. (15) also reported that change in D/P Cr is correlated with change in extracellular water. They reported a correlation between BNP and D/P Cr in patients whose D/P Cr increased by more than 0.125. However, Takara et al. studied the amount of change rather than the rate of change of each variable.

From the present study, it can be concluded that high peritoneal permeability correlates with overhydration in PD patients. Conversely, peritoneal function cannot be precisely assessed without correcting overhydration. In the present study, proving a causal relationship was not possible.

The main limitations of our study include the relatively small number of patients, the short observation period, and the retrospective cohort design. Further
investigations involving more patients and using prospective long-term observation are needed to support our hypothesis.

Conclusions
We observed a positive correlation between change in peritoneal transport characteristics and change in natriuretic peptides in patients whose D/P Cr increased during the 6 months after PD initiation.

Disclosures
The authors have no conflicts of interest to declare.

References
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