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Matrix metalloproteinase levels in the drained dialysate reflect the peritoneal solute transport rate: a multicentre study in Japan

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Abstract

Background. Long-term peritoneal dialysis (PD) leads to peritoneal injury with high solute transport of the peritoneal membrane. At worst, peritoneal injury leads to encapsulating peritoneal sclerosis with an extremely high mortality rate. To perform PD safely and adequately, it is necessary to monitor peritoneal injury. The aim of this study was to investigate the potential of matrix metalloproteinases (MMPs) as new indicators of peritoneal injury.

Methods. The subjects included 215 PD patients with end-stage renal disease at 20 centres in Japan. MMPs or tissue inhibitors of MMP (TIMPs) in the drained dialysate were quantified with enzyme-linked immunosorbent assay. The peritoneal solute transport rate was assessed to estimate peritoneal injury and PD efficiency by the peritoneal equilibration test (PET).

Results. MMP-2, MMP-3 and TIMP-1 levels in the drained dialysate obtained by the PET were correlated with the D/P Cr ratios ($\rho = 0.69$, $\rho = 0.52$, $\rho = 0.55$, respectively) and the D/D0 glucose ratios ($\rho = -0.60$, $\rho = -0.47$, $\rho = -0.48$, respectively). The measured D/S ratios of MMP-2 and TIMP-1 were significantly higher than the expected D/S ratios when MMP-2 and TIMP-1 would have been transported from only the circulation. The measured D/S ratios of MMP-3 nearly corresponded to the expected ratios. MMP-1 and TIMP-2 in the drainage were undetected in most patients.

Conclusions. From these results, most MMP-2 in the drained dialysate may be produced from the peritoneum, and MMP-2 is expected to be a useful marker of peritoneal injury or change in peritoneal solute transport.

Keywords: matrix metalloproteinase; peritoneal dialysis; peritoneal injury; peritoneal solute transport

Introduction

Peritoneal dialysis (PD) is a common treatment for patients with end-stage renal disease with reduced or absent renal function. Long-term PD leads to peritoneal injury with functional decline, such as ultrafiltration loss and an increased solute transport rate. These complications resulting in the end of PD treatment are serious problems. At worst, peritoneal injury leads to encapsulating peritoneal sclerosis (EPS), which is the most serious complication in patients undergoing PD [1–3]. The mortality rate of EPS is extremely high. To perform PD safely and adequately, it is important to monitor peritoneal injury and PD efficiency.

The cause of functional disorder of the peritoneum is thought to be fibrosis, sclerosis, inflammation, angiogenesis and vasculopathy. Peritoneal injury probably develops through multiple factors, such as infectious peritonitis and continuous exposure to unphysiologic PD fluid with high concentrations of glucose, glucose degradation products, low pH and high osmolarity [1–4].

Because solute transport of the peritoneal membrane increases with peritoneal injury, the transport rate is often measured to estimate peritoneal injury by the peritoneal equilibration test (PET) [3,5]; however, the PET is invasive because it requires blood sampling. In addition, patients need to spend half a day in the hospital because the test takes a long time, so many hospitals do not perform the PET. It is therefore necessary to evaluate peritoneal injury using an easy and non-invasive method.

In cases of fibrosis, sclerosis or inflammation of various organs, such as the artery, lung, liver and kidney, tissue destruction and excessive remodelling occur [6]. In such events, matrix metalloproteinases (MMPs) degrade components of the extracellular matrix (ECM) and play important roles in angiogenesis and the migration of cells that promote fibroplasias or inflammation. MMP-1, an interstitial collagenase, degrades collagen types I, II, III, VII and X. MMP-2, which is a gelatinase, degrades gelatin, collagen type IV, fibronectin, laminin, proteoglycan and elastin. MMP-3, which is a stromelysin, degrades proteoglycan, gelatin, fibronectin, laminin, elastin and collagen type IV. MMP-9, which is a gelatinase, degrades gelatin, collagen type IV, proteoglycan, elastin and entactin. Tissue inhibitors of MMP (TIMPs) inhibit the degradation of ECM by MMPs and play important roles in the proteolytic/antiproteolytic balance. TIMP-2 inhibits the

activity of membrane-type MMPs, but TIMP-1 does not. Because peritoneal injury is often accompanied with marked fibrous thickening, sclerosis or inflammation of the peritoneum, levels of MMPs or TIMPs are likely increased in this complication [2]. We have previously reported the potential of MMP-2 as a marker of peritoneal injury, increased solute transport or progression to EPS during PD [7,8].

The aim of the present study was to investigate the potential of MMPs and TIMPs, especially MMP-2, as new indicators of peritoneal injury with high solute transport of the peritoneal membrane. We compared the peritoneal

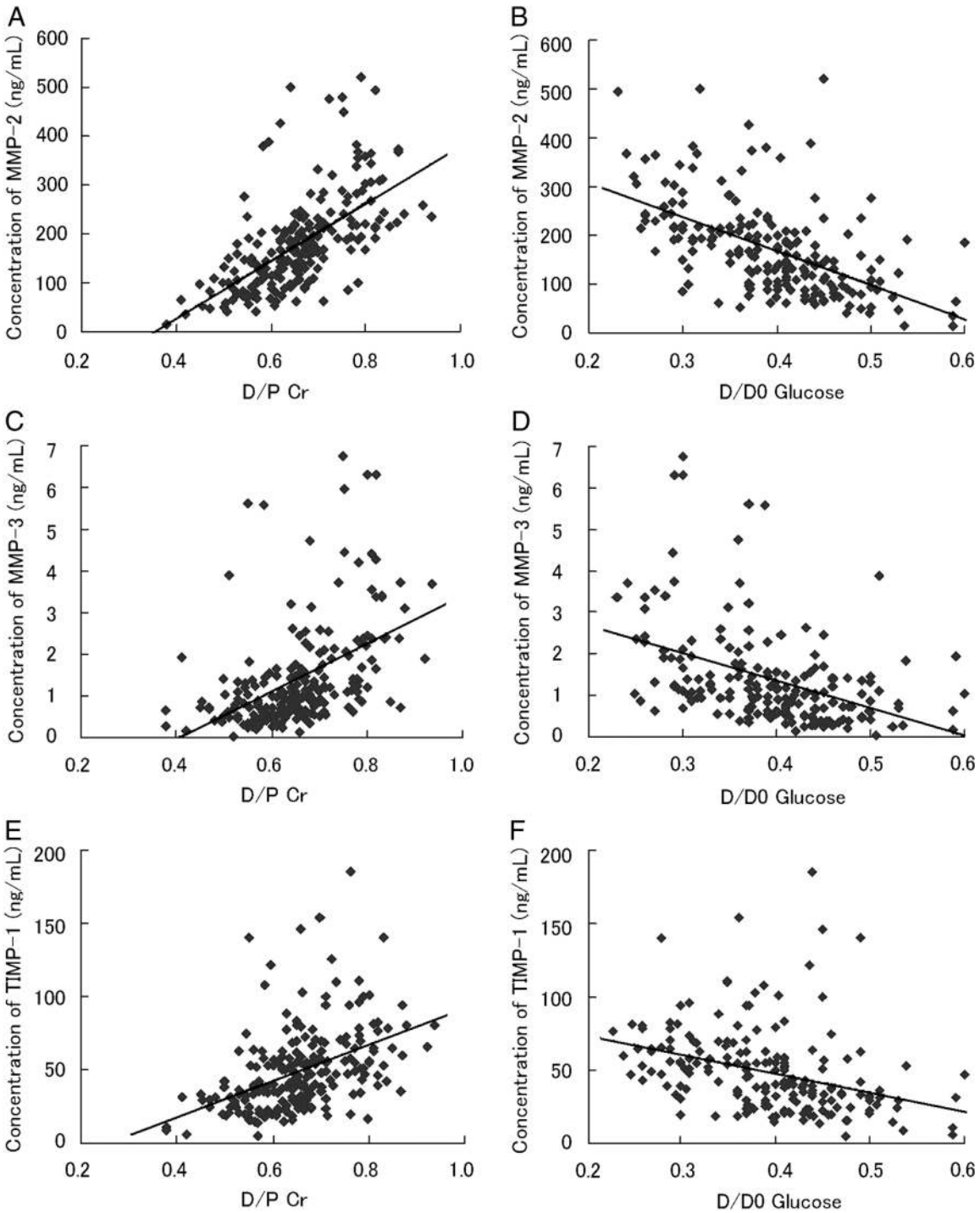

Fig. 1. The peritoneal solute transport rate and MMP levels in the drained dialysate. (**A**) D/P Cr ratio versus MMP-2 level. (**B**) D/D0 glucose ratio versus MMP-2 level. (**C**) D/P Cr ratio versus MMP-3 level. (**D**) D/D0 glucose ratio versus MMP-3 level. (**E**) D/P Cr ratio versus TIMP-1 level. (**F**) D/D0 glucose ratio versus TIMP-1 level.

solute transport rate with the concentrations of MMPs or TIMPs in the drained dialysate.

Materials and methods

Patients

From January 2005 to March 2010, 215 PD patients with end-stage renal disease at 20 centres in Japan were analysed. The populations consisted of 122 male and 93 female patients with a median (interquartile range) age of 57 years (48–65 years), who had been treated with PD for a median (interquartile range) of 47 months (22–69 months). Patients who had been treated with PD for <3 months were excluded. The aetiology of end-stage renal disease was diabetes mellitus in 34 patients (16%). The peritonitis episode was median (interquartile range) time of 0 times (0–1 times). Patients with bacterial peritonitis and appendicitis at the time of the analysis or in the 4 preceding weeks were excluded.

The Ethics Committee of Jichi Medical School approved this study protocol, and informed consent was obtained from each patient. MMPs and TIMP-1 in the serum were analysed in only 20 patients from whom informed consent for analysis of the serum was obtained. This study was registered in the University Hospital Medical Information Network-Clinical Trials Registry, which is the Japanese public clinical trials registry.

PET

The peritoneal solute transport rate was assessed with the PET [5]. Intra-abdominal fluid was drained, and PD fluid containing 2.27–2.5% glucose was injected intraperitoneally. The creatinine (Cr) level of the drained dialysate obtained 4 h after injection (D) was divided by that of blood (P) to obtain the D/P Cr ratio. The glucose level of the drained dialysate obtained 4 h after injection (D) was divided by that obtained immediately after injection (D0) to obtain the D/D0 glucose ratio.

Analysis of MMPs and TIMPs

The concentrations of MMP-1, -2, -3 and TIMP-1, -2 in the drained dialysate obtained at the PET were measured by enzyme-linked immunosorbent assay (MMP-2, TIMP-1, -2, GE Healthcare, NJ, USA; MMP-1, -3, R&D, Minneapolis, MI, USA).

MMP-2, -3 and TIMP-1 levels in the serum were analysed in 20 patients (median age: 58 years; median PD duration: 15 months, 75% males, 20% diabetes) from whom informed consent was obtained. Regression lines were calculated based on the power relationship between the molecular weights of β2-microglobulin (MW: 11 800 Da), albumin (MW: 69 000 Da), transferrin (MW: 85 000 Da) and IgG (MW: 150 000 Da) and their measured dialysate/serum (D/S) ratios when plotted on a double logarithmic scale [9]. These proteins were transported from the circulation to the peritoneal cavity by osmotic pressure of the PD fluid. By interpolation of the molecular weights of MMP-2, -3 and TIMP-1 in the regression equation, the expected D/S ratios were calculated, assuming that their concentration in the dialysate would be determined by transport only from the circulation.

Statistical analysis

Data are expressed as medians with the spread from the 25th to 75th percentiles. A P-value of <0.05 was accepted as significant. Comparisons between groups were performed with the Wilcoxon test. Relationships between clinical variable and MMP or TIMP levels were analysed with Spearman's correlation coefficient test. Statistical analyses were performed with the SAS System for Windows, version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Relationships between the peritoneal solute transport rate and MMP-2, -3 or TIMP-1 concentrations

The peritoneal solute transport rate determined by the PET was correlated with MMP-2, -3 or TIMP-1 concentrations in the drained dialysate (Figure 1 and Table 1). The correlation coefficient between MMP-2 and TIMP-1 levels in the drainage was more significant than between MMP-2 and MMP-3 levels (MMP-2 vs MMP-3, $P < 0.001$, $\rho = 0.59$; MMP-2 vs TIMP-1, $P < 0.001$, $\rho = 0.77$) (Figure 2).

The relationships between MMP-2, -3 or TIMP-1 levels and age or PD duration are shown in Table 1 and Figure 3. The level of MMP-2 is not significantly different by sex

Table 1. Correlation coefficients between MMP or TIMP-1 levels in the drained dialysate and patient characteristics

	MMP-2	MMP-3	TIMP-1
Age (years)	0.11	0.015	0.11
PD duration (months)	0.21	0.20	0.22
Peritonitis episode (times)	0.19	0.20	0.085
D/P Cr	0.69	0.55	0.52
D/D0 glucose	–0.60	–0.48	–0.47

ρ-Values indicate relationships between MMP or TIMP-1 levels and the clinical variable by Spearman's correlation coefficient.

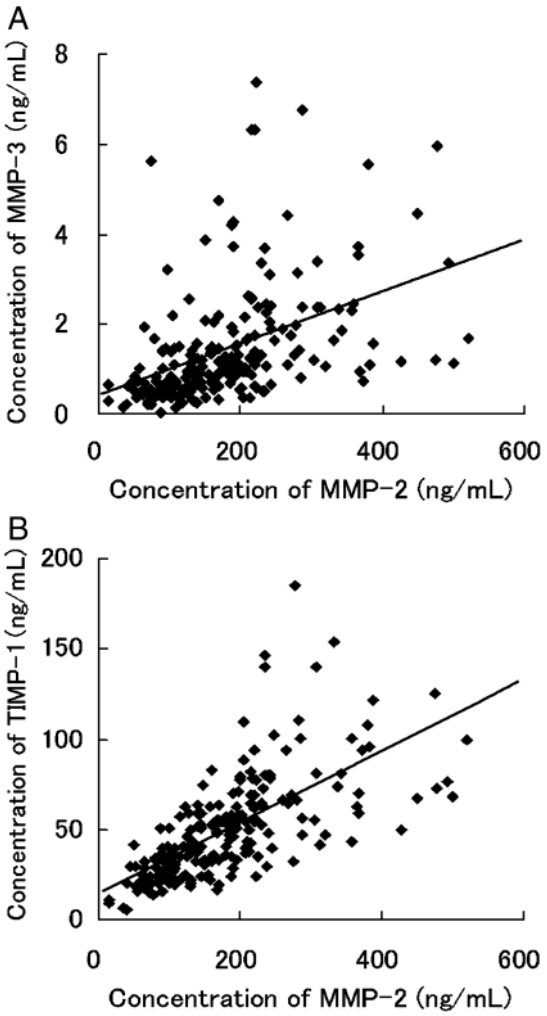

Fig. 2. Relationships of MMP levels in the drained dialysate. (**A**) Relationship between MMP-2 and MMP-3 levels. (**B**) Relationship between MMP-2 and TIMP-1 levels.

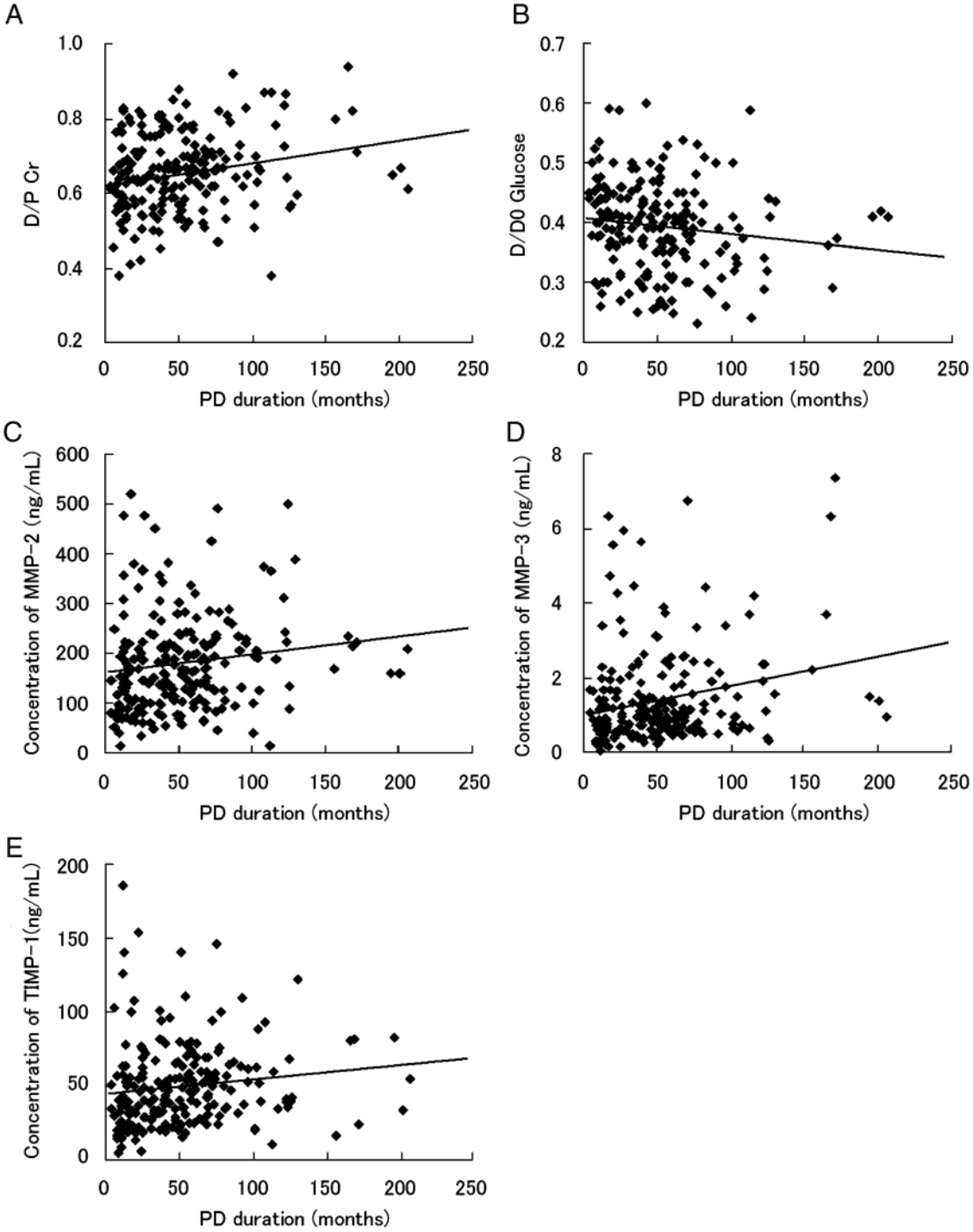

Fig. 3. Relationships between duration of PD and MMP levels in the drained dialysate. (**A**) PD duration versus D/P Cr ratio. (**B**) PD duration versus D/D0 glucose ratio. (**C**) PD duration versus MMP-2 level. (**D**) PD duration versus MMP-3 level. (**E**) PD duration versus TIMP-1 level.

and the aetiology of renal failure (non-diabetic/diabetic), but the levels of MMP-3 or TIMP-1 are significantly different by sex (Table 2).

In all patients whose serum was analysed, the levels of MMP-2, -3 and TIMP-1 in the serum were higher than in the drained dialysate. The peritoneal transport line was calculated based on least squares regression analysis between the measured D/S ratios of the serum proteins, such as β 2-microglobulin, albumin, transferrin and IgG, and their molecular weights (Figure 4). The measured D/S ratios of MMP-2, MMP-3 and TIMP-1 were also plotted on the line. The slope of the regression line represented the size selectivity of the peritoneal membrane, but the measured D/S ratios of MMP-2 and TIMP-1 were outside the line. The regression line for each individual patient was also calculated. Based on each regression line, the expected D/S ratios

Table 2. The relationships between sex or aetiology and MMP levels in the drained dialysate

	D/P Cr	D/D0 glucose	MMP-2 (ng/mL)	MMP-3 (ng/mL)	TIMP-1 (ng/mL)
Sex					
Male	0.66 (0.59–0.75)	0.40 (0.36–0.44)	169 (104–223)	0.34 (0.74–2.29)	39 (26–58)
Female	0.65 (0.58–0.70)	0.40 (0.32–0.45)	165 (116–219)	0.84 (0.52–1.19)	51 (35–63)
P	0.24	0.92	0.87	<0.001	0.033
Aetiology of renal failure					
Non-DM	0.65 (0.58–0.71)	0.40 (0.35–0.44)	167 (107–221)	1.06 (0.64–1.73)	43 (30–63)
DM	0.67 (0.60–0.76)	0.39 (0.35–0.45)	170 (111–238)	0.79 (0.44–1.38)	48 (25–70)
P	0.38	0.98	0.92	0.044	0.96

Data are shown as medians with interquartile ranges (25th and 75th).
DM, diabetes; non-DM, non-diabetes.

of MMP-2, MMP-3 and TIMP-1 were predicted assuming that their concentration in the drainage would be determined by transport only from the circulation. The measured D/S ratios of MMP-2 and TIMP-1 were significantly higher than the expected D/S ratios calculated from the regression line ($P < 0.001$), but there was no significant difference between the measured D/S ratios and the expected D/S ratios in MMP-3 ($P = 0.74$) (Figure 5).

The levels of MMP-1 and TIMP-2 in the drained dialysate were undetected in most patients (<0.1 ng/mL and <8 ng/mL, respectively).

Discussion

Peritoneal injury with decreased PD efficiency is a serious problem in PD. It is important to monitor peritoneal injury and the change in the peritoneal solute transport rate. The PET was the most popular method to estimate PD efficiency and peritoneal injury [3,5,10]. We previously reported the potential of MMP-2 as a marker of peritoneal injury, increased solute transport or progression to EPS during PD [7]. In the present study, the results of the PET correlated with the MMP-2, -3 and TIMP-1 levels in the drained dialysate. The total quantity of MMP-2 in the drainage was also correlated with the membrane transport ratio (data not shown). The correlation coefficients between the peritoneal solute transport rate and the level of MMP-2 were higher than the levels of MMP-3 or TIMP-1. The MMP-3 level was biased by gender difference or the aetiology of end-stage renal disease. The TIMP-1 level was also biased by gender difference. It is known that the expression of TIMP-1 is induced by various factors, such as interleukin-1, tumour necrosis factor-α and transforming growth factor-β [6], but usually MMP-2 is expressed constitutively. MMP-3 and TIMP-1 might therefore be more easily affected by various factors than MMP-2. Meanwhile, MMP-1 and TIMP-2 were not detected in the drained dialysate from most patients. We have previously reported that MMP-9 was undetected in most patients without infectious peritonitis [7]. So MMP-1, -9 and TIMP-2 are unsuitable as markers. These results suggest that MMP-2 may be a more useful indicator of peritoneal injury with increased solute transport than other MMPs or TIMPs. Interleukin-6, hyaluronate and cancer antigen (CA) 125 are often used as markers of peritoneal injury [10]. Kaku *et al.* demonstrated that the sample size was not necessarily sufficient but the correlation coefficient between the peritoneal solute transport rate and the level of MMP-2 was higher than that of interleukin-6, hya-

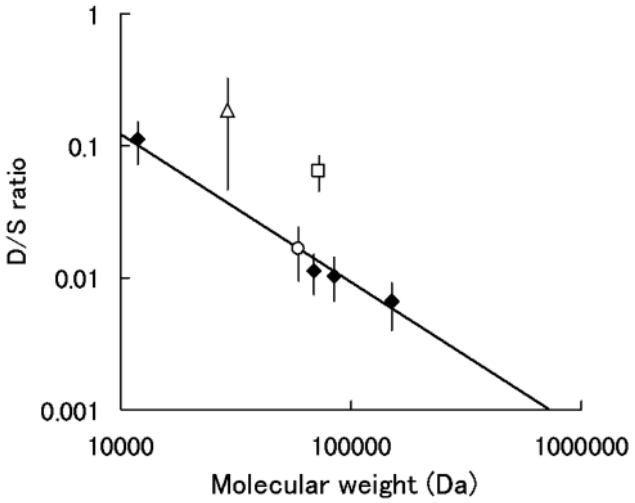

Fig. 4. Regression line between the molecular weights of serum proteins, such as β2-microglobulin (MW: 11 800 Da), albumin (MW: 69 000 Da), transferrin (MW: 85 000 Da) and IgG (MW: 150 000 Da), and their measured D/S ratios. The measured D/S ratios of MMP-2 (open square), MMP-3 (open circle) and TIMP-1 (open triangle) are plotted in relation to their molecular weight. Data are shown as the mean ± SD.

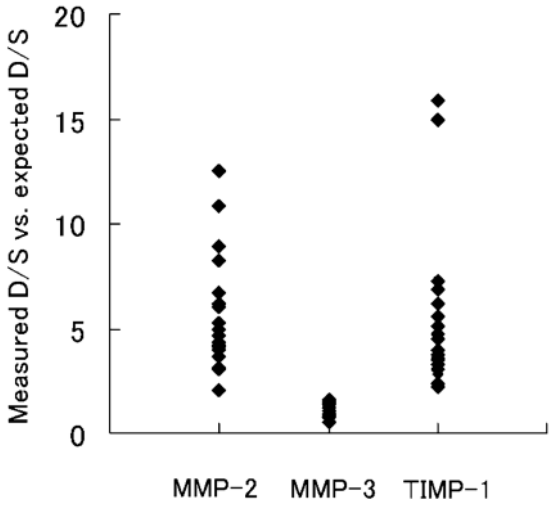

Fig. 5. The rate of the measured D/S ratio to the expected D/S ratio of MMPs and TIMP-1. The data are shown as the values obtained by dividing the measured D/S ratios by the expected D/S ratios. The measured D/S ratios were calculated from the actual measurement values. The expected D/S ratios were calculated from the regression line of individual patients.

luronate and CA125 [11]. MMP-2 may be expected to be a superior indicator of peritoneal injury.

The measured D/S ratios of MMP-3 almost corresponded to the expected D/S ratios that were predicted if MMP-3 in the drainage were transported only from the circulation. This result suggested that most MMP-3 in the peritoneal effluent might be transported from the circulation. In contrast, the measured D/S ratios of MMP-2 and TIMP-1 were significantly higher than the expected ratios. In addition, the correlation coefficient between MMP-2 and TIMP-1 levels in the drainage was higher than that between MMP-2 and MMP-3 levels. The difference between the measured D/S ratio and the expected ratio may be attributed to the local production of MMP-2 and TIMP-1 in the peritoneal tissue besides transport from the circulation [4,7,9,12]. We have previously reported that myofibroblasts, macrophages and endothelial cells in the peritoneum produced MMP-2 [4,7,12,13]. Most MMP-2 in the drained dialysate may be produced from these cells in the peritoneum.

Ro *et al.* reported that MMP inhibitor controlled angiogenesis, infiltration of macrophage and peritoneal fibrosis in peritoneal sclerosis model rats [14]. These results suggest that MMPs may play an important role in peritoneal injury. As a result of peritoneal tissue destruction and remodelling with ECM degradation by MMPs, peritoneal injury with high solute transport may be induced. Because MMP-2 is produced mainly in the peritoneum and directly destroys peritoneal tissue, the MMP-2 level in the drainage may reflect injury to the peritoneum.

It is known that MMP-2 and/or MMP-9 are able to degrade the endothelial basal lamina and increase vascular permeability [15]. Swann *et al.* also reported that an increase in blood-brain barrier permeability is associated with an increased level of MMP, which digests the endothelial basal lamina that composes the barrier [16]. In PD, the microvascular wall and mesothelial layer are the main barriers for the transport of peritoneal effluent and solute. MMP-2 digests collagen type IV and laminin, which are the main components of the basement membrane of the microvascular wall and mesothelial layer. The basement membrane, injured by MMP-2, may result in hyperpermeability of the peritoneum. Giebel *et al.* reported that elevated expression of MMP-2 or MMP-9 in the retina may facilitate an increase in vascular permeability by the degradation of occludin, the tight junction protein of endothelial or epithelial cells [17]. In PD, destruction of the tight junction by MMP-2 may result in hyperpermeability of the peritoneum. MMP-2 may therefore directly increase peritoneal permeability via destruction of the basement membrane and tight junction of endothelial or mesothelial cells.

The epithelial-to-mesenchymal transition of mesothelial cells induced the production of MMP-2 [18,19]. Activated mesothelial cells that have transformed to mesenchymal cells invade the peritoneum while ECM is digested by MMP-2. These transformed mesothelial cells up-regulate the production of vascular endothelial growth factor which enhances angiogenesis, nitric oxide synthesis and vascular permeability and, as a result, peritoneal permeability may be increased [4,19]. Del Peso *et al.* reported that the transition of mesothelial cells to mesenchymal cells was an early event during PD and was associated with high peritoneal transport [20]. The transition of mesothelial cells may be one reason why the MMP-2 level in the drainage reflects the peritoneal transport ratio.

We usually analyse the MMP-2 level in the drainage routinely every 12 months for the patients without problems and measure it once a month for patients with peritoneal injury. In the present study, the peritoneal solute transport rate correlated with the MMP-2 level but did not completely coincide with it. Future studies should examine changes to the MMP-2 levels in relation to the progression of peritoneal injury.

Conclusion

In conclusion, the MMP-2 level in the drained dialysate was correlated with the D/P Cr ratio and it is thought that most MMP-2 was produced in the peritoneum. Degradation of the peritoneum by MMP-2 may result in high solute transport of the peritoneal membrane. MMP-2 may be useful as an indicator of peritoneal injury with increased solute transport.

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Conflict of interest statement. This study was funded by Terumo Co. (Tokyo, Japan). There was no involvement that might raise a question of bias in this work or in the conclusions, implications or opinions stated. The results presented in this paper have not been published previously in whole or part.

Appendix

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