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Matrix Metalloproteinases Cause Peritoneal Injury in Peritoneal Dialysis

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1. Introduction

Long-term peritoneal dialysis (PD) leads to peritoneal injury with functional decline, such as ultrafiltration loss. Peritoneal injury is often accompanied by histological changes, such as peritoneal fibrosis and sclerosis. These complications involve evident diffuse fibrous thickening and/or edema of the peritoneum, and chronic inflammation (epithelial to mesenchymal transition of mesothelial cells as well as migration and proliferation of polynuclear leucocytes, macrophages, and mesenchymal cells in the peritoneum). At worst, peritoneal injury leads to encapsulating peritoneal sclerosis (EPS), a serious complication of PD [1-6]. At early stage of EPS (preEPS stage), peritoneal effluent with signs of inflammation is often observed [2]. At advanced stages of EPS, the small intestine adheres and is encapsulated within a collagen rich thick peritoneum to form a cocoon-like mass. As a result, EPS is associated with clinical symptoms, such as loss of appetite, nausea, vomiting, and emaciation due to malnutrition, as well as symptoms of intestinal obstruction that include abdominal pain, diarrhea, constipation, or lowered peristaltic bowel sounds. The incidence of EPS is not high: it occurs in about 0.4%–3.3% of patients who undergo PD. However, EPS has a high mortality rate, about half of the patients with EPS die [2-5]. The causes of functional disorders of the peritoneum are believed to be fibrosis, sclerosis, inflammation, angiogenesis, and vasculopathy. Peritoneal injury is probably caused by multiple factors, such as infection with bacteria or fungi resulting in peritonitis [2, 5, 6]; antiseptics [7-11]; exogenous materials like particulates and plasticizers [7]; and continuous exposure to nonphysiological PD solutions having high concentrations of glucose and glucose degradation products (GDPs), low pH, and high osmolarity [2, 12, 13]. Administration of corticosteroids, tamoxifen, immunosuppressive agents, and total parenteral nutrition are effective in the early stage of EPS development [2-4, 6]. However, for advanced EPS, in which bowel adhesions have formed, the only effective therapeutic method is surgical dissection of the encapsulated peritoneum; this must be performed by skilled surgeons using specialized techniques [2-5, 7]. It is important to monitor peritoneal injury, and develop methods for an early diagnosis of EPS. At present, major diagnostic methods for EPS include abdominal palpation (for identification of a mass) and finding clinical symptoms of bowel obstruction, like those found in the ileus [2]. However, these are not objective criteria and it is not rare that no typical symptoms are found even in advanced cases of EPS. Some physicians utilize diagnostic imaging methods for detection of EPS, such

as X-ray, computed tomography, and ultrasonography; however, these methods are not suitable for early diagnosis because they can detect only EPS in an advanced stage [2, 3, 6]. C-reactive protein (CRP) and interleukin-6 (IL-6) are often used as biochemical markers for inflammation [2, 6, 14, 15]. However, since their levels also increase during infectious peritonitis, they are inadequate to be used as definitive diagnostic markers that can differentiate EPS from infectious peritonitis [14]. As mentioned previously, corticosteroids and immunosuppressive agents have been employed as effective initial therapies for EPS [2-4, 6]; however these drugs, compromise the immune system with the risk of aggravating symptoms when administered to patients with infectious peritonitis. Therefore, a method can differentiate EPS from infectious peritonitis is required for the early diagnosis of EPS. To perform PD safely, it is important to monitor peritoneal injury that may progress to EPS and diagnose EPS at an early stage; it is then necessary to prevent peritoneal injury from developing into severe EPS.

During tissue injury, such as sclerosis or fibrosis, tissue destruction and excessive remodeling occur. In such events, matrix metalloproteinases (MMPs) degrade components of the extracellular matrix (ECM) and play significant roles in regulating angiogenesis, epithelial to mesenchymal transition, and migration of cells that promote fibroplasias or inflammation. MMP-1, an interstitial collagenase, degrades types I, II, III, VII, and X collagen. MMP-2, a gelatinase, degrades gelatin, type IV collagen, fibronectin, laminin, proteoglycan, and elastin. MMP-3, a stromelysin, degrades proteoglycan, gelatin, fibronectin, laminin, elastin, and type IV collagen. MMP-9, a gelatinase, degrades gelatin, type IV collagen, proteoglycans, elastin, and entactin. Membrane-type MMP-1 (MT1-MMP) contains a C-terminal transmembrane domain that anchors to the plasma membrane and cleaves proMMP-2 to produce its active form on the cell surface. Tissue inhibitors of MMP (TIMPs) inhibit ECM degradation by MMPs and play important roles in the proteolytic/antiproteolytic balance. TIMP-2 inhibits the activity of MT-MMPs, but TIMP-1 does not. MMP expression is enhanced in various tissues during inflammation, fibrosis and sclerosis. Increased serum levels of MMP-1 and MMP-3 in rheumatoid arthritis [16], MMP-1, MMP-8, and MMP-9 in cystic fibrosis [17], MMP-9 in chronic obstructive pulmonary disease [18], MMP-2, MMP-9, and TIMP-1 in acute coronary syndrome [19], MMP-9 and TIMP-1 in aortic sclerosis [20], MMP-2 in liver cirrhosis [21], MMP-2 and TIMP-1 in hepatic fibrosis [22], and MMP-2 in chronic kidney disease [23, 24] suggest a relationship between MMP levels and pathology of tissue injury.

2. Production of MMP-2 in animal models of peritoneal injury

MMP-2 production increases in animal models of peritoneal injury induced by stimuli such as antiseptics, exogenous materials, and GDPs.

In rodent models of peritoneal injury, the development of EPS was analyzed by injecting the antiseptic chlorhexidine gluconate into the peritoneal cavity to induce inflammation [7-11]. In this model, MMP-2 levels in the peritoneal effluent and MMP-2 gene expression in the peritoneum correlated with changes in thickness of the peritoneum, inflammation, D/D0 glucose levels, and net ultrafiltration. In another model, peritoneal injury was induced by injecting talc, an exogenous material, into the peritoneal cavity. MMP-2 levels in the peritoneal effluent and MMP-2 gene expression in the peritoneum increased with the development of peritoneal injury [7]. GDPs are generated in PD solutions during heat sterilization and storage, and contribute to the bioincompatibility of conventional PD

solutions. MMP-2 levels in the peritoneal effluent increased in models of peritoneal injury induced by methylglyoxal (MGO) or formaldehyde, both extremely toxic GDPs [12, 13]. In models of peritoneal injury induced by chlorhexidine gluconate and MGO, abdominal cocoons were often formed, while in models induced by talc and formaldehyde, adhesions of the peritoneum were observed [7-9, 11, 12]. In many animal models of peritoneal injury, MMP-2 levels in the peritoneal effluent correlated with changes in inflammation, thickness of the peritoneum, D/D0 glucose levels, and net ultrafiltration. Thus, peritoneal injury is caused by increased MMP-2 induced by various stimuli, such as antiseptics, exogenous materials, and GDPs in the PD solution. Therefore, MMP-2 may play an important role in the development of peritoneal injury leading to EPS.

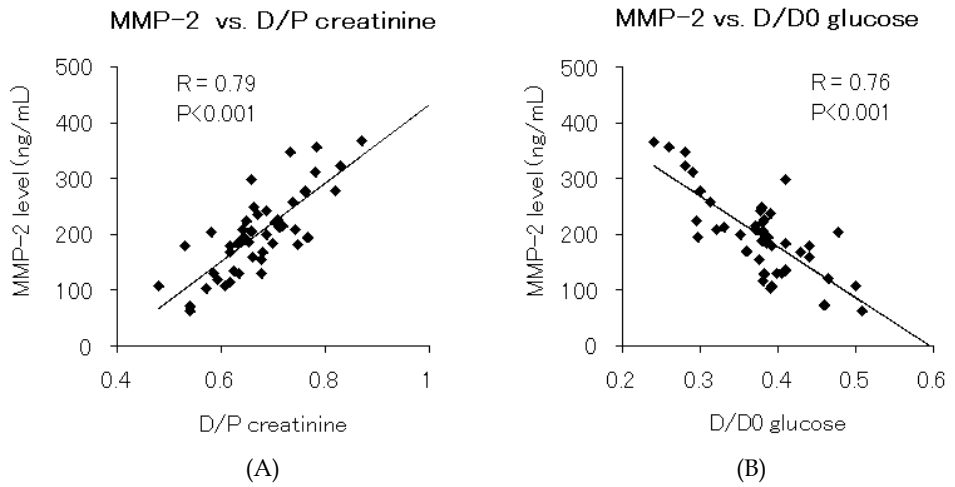
3. MMPs as peritoneal injury markers in clinical diagnosis

Results of the peritoneal equilibration test (PET) performed clinically have shown that MMP-2, -3, and TIMP-1 levels in the peritoneal effluent correlate with peritoneal injury (Figure 1) [25, 26]. PET is the method most frequently used to estimate PD efficiency and peritoneal injury [2, 27]. MMP-3 levels are influenced by gender and etiology of end-stage renal disease [26] and TIMP-1 expression is known to be induced by various factors, such as IL-1, tumor necrosis factor-α, and transforming growth factor-β [23]; however, MMP-2 is usually expressed constitutively. MMP-3 and TIMP-1 may therefore be more easily affected by various factors than MMP-2. The measured D/S ratios of MMP-3 were nearly equal to the predicted D/S ratios when MMP-3 was transported only from the circulation [26]. This result suggests that most MMP-3 in the peritoneal effluent may be transported from the circulation. In contrast, the measured D/S ratios of MMP-2 and TIMP-1 were significantly higher than those predicted [26]. In addition, the correlation coefficient between the drainage levels of MMP-2 and TIMP-1 was higher than that between the drainage levels of MMP-2 and MMP-3 [26]. The difference between the measured D/S ratio and the predicted ratio may be attributable to the local production of MMP-2 and TIMP-1 in the peritoneal tissue along with their transport from the circulation [28]. In addition, MMP-1 and TIMP-2 were not detected in the peritoneal effluent of most patients. Therefore, MMP-1 and TIMP-2 are unsuitable as markers for determining the extent of peritoneal injury. These results suggest that MMP-2 may be a more useful marker of peritoneal injury with increased solute transport than other MMPs or TIMPs.

IL-6, hyaluronic acid, and cancer antigen (CA) 125 are often used as markers of peritoneal injury [2, 29]. In the study by Kaku et al., although the sample size was not sufficient for a statistically significant relationship, the correlation coefficient between the peritoneal solute transport rate and MMP-2 levels was higher than that for IL-6, hyaluronic acid, or CA125 [15].

MMP-2 and/or MMP-9 degrade the endothelial basal lamina and increase vascular permeability [30]. Swann et al. have also reported that an increase in the permeability of the blood-brain barrier is associated with an increase in MMP levels, which digests the endothelial basal lamina that forms the barrier [31]. In PD, the microvascular wall and probably the interstitial tissue are the main barriers for peritoneal fluid and solute transport. MMP-2 digests type IV collagen and laminin, which are the main basement membrane components of the microvascular wall and the mesothelial layer. Thus, injury to the basement membrane by MMP-2 may result in fast solute transport rates. Giebel et al. have reported that elevated MMP-2 or MMP-9 expression in the retina may facilitate an increase

in vascular permeability by degrading occludin, the tight junction protein of endothelial or epithelial cells [32]. Osada et al. have reported that MMP-2 was mainly observed around



(A) (B)

Fig. 1. **Relationship between the peritoneal solute transport rate and MMP-2 levels in the peritoneal effluent.**
The peritoneal solute transport rate was assessed using PET. MMP-2 levels in the peritoneal effluent obtained from PET were analyzed by enzyme-linked immunosorbent assay. (A) D/P creatinine ratios versus MMP-2 levels. (B) D/D0 glucose ratios versus MMP-2 levels.

the blood vessels in the peritoneal tissues from long-term PD patients [33]. In PD, destruction of the tight junction of endothelial cells by MMP-2 may result in hyperpermeability of the peritoneum. From these studies, it is apparent that MMP-2 may directly increase the permeability of the peritoneum by destruction of the basement membrane and tight junction of endothelial cells.

A multi-center clinical study and a case report revealed markedly increased MMP-2 levels in peritoneal effluents of patients with moderate peritoneal injury with ascites [2, 25, 34]. In addition, EPS was shown to develop in more than half the patients having MMP-2 levels of more than 600 ng/ml, although half of the patients had been treated with steroids [26]. On the other hand, MMP-2 levels in the effluents of patients with EPS tended to be lower than those of patients with moderate peritoneal injury [26]. In advance-stage of EPS, the inflammation is weak and then MMP-2 levels in the effluents may be decreased. These findings suggest that a change in MMP-2 levels may be used as indicator of peritoneal injury or progression to EPS.

MMP-9 is hardly detected in the peritoneal effluent of patients without infectious peritonitis. However, in patients with infectious peritonitis, MMP-9 levels in the peritoneal effluent increased markedly with a slight increase in MMP-2 levels [25, 35, 36]. These findings suggest that peritoneal injury that may lead to EPS can be clearly distinguished from infectious peritonitis by analyzing MMP-2 and MMP-9 levels in the peritoneal effluent (Figure 2). Many biomarkers, such as IL-6 and CRP, increase during peritoneal injury and infectious peritonitis. Therefore, MMP-2 may be a useful indicator for peritoneal injury that can differentiate from infectious peritonitis.

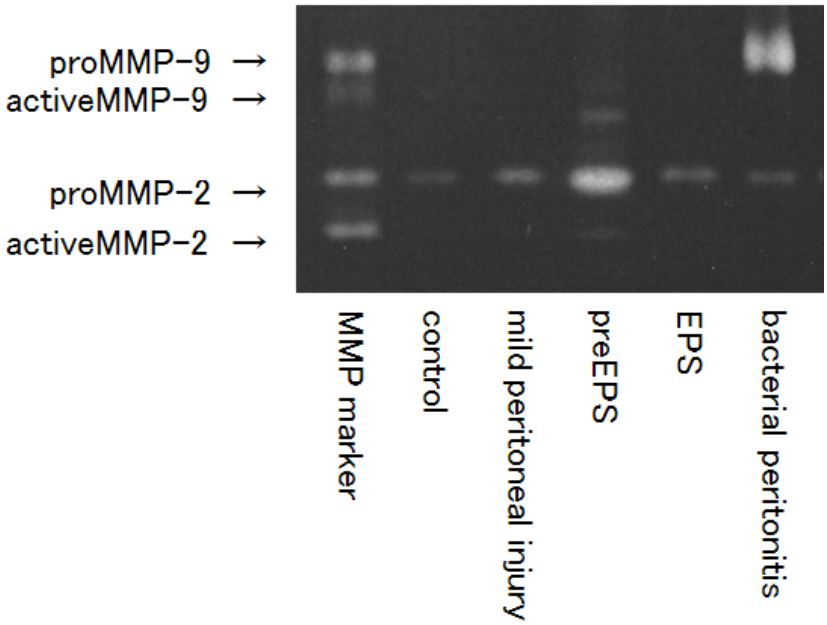


Fig. 2. **Analysis of the peritoneal effluent with gelatin zymography.**
Gelatinases in the peritoneal effluent were analyzed by gelatin zymography. Gelatinases were detected as unstained proteolytic bands in gel stained with Coomassie Brilliant Blue. Lane 1: MMP marker (Chemicon International, Inc., Temecula, CA, USA). Lane 2: Control patient. Lane 3: Patient with mild peritoneal injury. Lane 4: Patient with moderate peritoneal injury (preEPS). Lane 5: Patient with severe peritoneal injury (EPS). Lane 6: Patient with bacterial peritonitis.

Minami et al. investigated the correlations between β_2-microglobulin (β_2MG) and peritoneal injury biomarkers (e.g. hyaluronic acid, IL-6, MMP-2) in the peritoneal effluent obtained from a 7.5% icodextrin-based PD solution (ICO effluent) [37]. β_2MG, hyaluronic acid, and MMP-2 levels in the ICO effluent were significantly higher than those in the 2.27% glucose-based PD solution effluent. There was a trend toward higher IL-6 levels in the ICO effluent, although no significant differences were seen. There were positive correlations between the levels of various biomarkers and β_2MG. Those authors proposed that subclinical injury of the peritoneum by ICO treatment may accelerate peritoneal permeability to increase β_2MG in the effluent.
Nishina et al. have reported that MMP-2 levels decreased in the peritoneal effluent and peritoneal function improved when conventional solutions (acidic pH and containing high levels of GDPs) were replaced with new PD solutions (neutral pH and containing low levels of GDPs) in high-transporter patients undergoing PD [38].
Thus MMPs are possible markers of peritoneal injury that can differentiate from infectious peritonitis. A diagnostic method using peritoneal effluents enables easy sampling, is non-invasive, and is not painful for patients. An MMP-9 test kit has been developed to diagnose

infectious peritonitis. This kit consists of an anti-MMP-9 antibody conjugated to a colloidal dye designed to detect MMP-9 in a nitrocellulose membrane dipstick assay based on immunochromatography [36, 39]. The diagnosis can be successfully completed within 10 min. If such a test kit were developed for MMP-2, peritoneal injury could be monitored easily and rapidly at home.

4. Production of MMP-2 in the peritoneum

MMP-2 in the peritoneal tissue and effluent is considered to be primarily derived from activated cells in the peritoneum.

Gene expression analysis and/or immunohistochemistry analysis revealed that MMP-2, MT1-MMP, and TIMP-2 are produced in the peritoneal tissue [7-13, 25]. MMP-2 is produced by peritoneal cells, such as macrophages, mesenchymal cells, endothelial cells, and mesothelial cells (Figures 3 and 4, Table). These peritoneal cells are activated by various stimuli, such as infectious peritonitis; exogenous materials like particulates; antiseptics; advanced glycation products; and GDPs and also the pH of the PD solution. These activated cells produce various cytokines, growth factors, and other mediators that induce peritoneal injury. Macrophages may infiltrate or migrate into the peritoneum while ECM is being degraded by MMP-2 produced by these cells [8, 12]. In cultured human mesothelial cells, the production of MMP-2 is upregulated by transforming growth factor-β and is decreased by thrombin [40-42]. Activated mesothelial cells transform to mesenchymal cells and then the epithelial-to-mesenchymal transition of mesothelial cells subsequently induces MMP-2 production [13, 43]. Transformed mesothelial cells may invade the peritoneum while ECM is being digested by MMP-2 and upregulates the production of vascular endothelial growth factor that enhances angiogenesis, nitric oxide synthesis, and vascular permeability [25, 26].

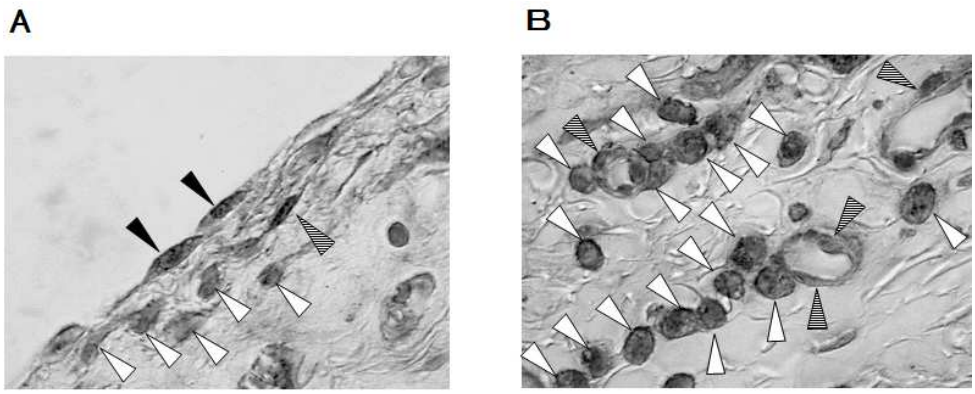


Fig. 3. **MMP-2 production in the peritoneum of rat models of peritoneal injury.**
MMP-2 production in the parietal peritoneum was immunohistologically analyzed using an anti-MMP-2 antibody. (A) The histological image of the parietal peritoneum of the talc-treated rats. Mesenchymal cells, macrophages, and peritoneal mesothelial cells that produce MMP-2 are shown by shaded arrow heads, open arrow heads, and closed arrow heads, respectively. (B) The histological image of the parietal peritoneum of the chlorhexidine gluconate-treated rats. Macrophages and vascular endothelial cells are shown by open arrow heads and shaded arrow heads, respectively.

MMP-2-producing cells	target of MMP-2	histological change
macrophages	ECM	inflammation
mesenchymal cells (fibroblasts)	ECM	fibrosis, inflammation
mesothelial cells	ECM, BM	EMT
endothelial cell	ECM, BM	angiogenesis

ECM: extracellular matrix, BM: basement membrane, EMT: epithelial-to-mesenchymal transition

Table 1. Tissue destruction by MMP-2 in the peritoneum

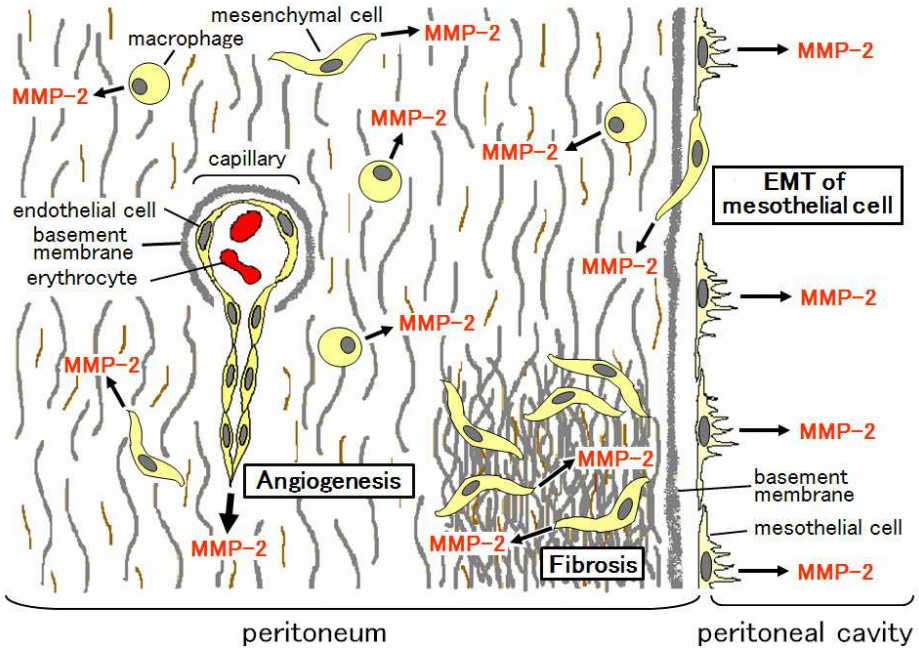


Fig. 4. **Tissue destruction by MMP-2 in the peritoneum.**
MMP-2 is assumed to destroy peritoneal tissue. Macrophages may infiltrate or migrate into the peritoneum while ECM is being degraded by the MMP-2 produced by these cells. Mesothelial cells may transform to mesenchymal cells (epithelial to mesenchymal transition: EMT) and infiltrate or migrate into the peritoneum, which is being digested by MMP-2. Activated mesenchymal cells synthesize ECM proteins that lead to peritoneal fibrosis or migrate during the disassemble of ECM of the peritoneum by MMP-2. Angiogenesis of capillaries may occur while ECM is being degraded by MMP-2 produced by activated endothelial cells.

Del Peso et al. have reported that the transition of mesothelial cells to mesenchymal cells is an early event during PD and is associated with fast peritoneal transport [44], which may explain why drainage levels of MMP-2 reflects the peritoneal transport ratio. Activated mesenchymal cells, such as myofibroblasts or fibroblasts, synthesize ECM proteins or migrate during the disassemble of ECM of the peritoneum by MMP-2 or other proteinases [8-12, 33]. Presence of excessive ECM proteins, such as collagen, leads to peritoneal fibrosis

with peritoneal thickening and promotes the production of MMP-2 by myofibroblasts [9]. In addition, neomicrovascularization may occur while ECM is being degraded by MMP-2 produced by activated endothelial cells in the microvasculature [10, 12, 33].
According to the results of D/S ratio analysis, most MMP-2 in the peritoneal effluent is not transported from the circulation [26]. The measured D/S ratios of MMP-2 were higher than those predicted when MMP-2 was transported from the circulation only by diffusion.
In summary, MMP-2 is produced by various peritoneal cells activated by a variety of stimuli. Because MMP-2 is produced primarily in the peritoneum, its drainage levels may indicate the condition of peritoneal injury.

5. Protection from peritoneal injury by inhibition of MMP-2

Peritoneal injury may be avoided by drugs that inhibit MMP-2 activity. Ro et al. have reported that the MMP inhibitor ONO-4817 controlled angiogenesis, infiltration of macrophage, and peritoneal fibrosis in rat models of peritoneal sclerosis [10], which suggests the possibility of protection from peritoneal injury by inhibition of MMP-2 activities.
Angiotensin-converting enzyme (ACE) inhibitors have been shown to have inhibitory effects on MMP-2 activity [45, 46]. Yamamoto et al. have proposed a mechanism for the inhibitory specificity of ACE inhibitors against MMP-2 using three-dimensional models of the MMP-2-ACE inhibitor complex. Furthermore, these authors showed that ACE inhibitors directly inhibited MMP-2 activity in the peritoneal effluent from patients on PD [47]. In experimental animal models, use of ACE inhibitors protected the animals from peritoneal injury with fibrosis thickening and functional decline, such as increased solute transport [48-50]. Sampimon et al. have reported the clinical possibility of a protective effect of ACE inhibitors on the development of EPS although it did not achieve statistical significance [51].
Thus, randomized controlled trials are needed to determine the level of protection gained against peritoneal injury using drugs, such as ACE inhibitors, that have an inhibitory effect on MMP-2 activity.

6. Conclusions

MMPs play critical roles in peritoneal injury. To perform PD safely, it is important to clarify the mechanisms by which MMPs cause peritoneal injury. MMP levels in the peritoneal effluent may be used as markers of peritoneal injury that can differentiate early EPS from infectious peritonitis. In addition, patients undergoing PD may be protected against peritoneal injury by controlling MMP activities. Future studies should examine the changes in MMP-2 levels with regard to progression of peritoneal injury to EPS and confirm the effects of MMPs inhibitors in controlling peritoneal injury

7. References

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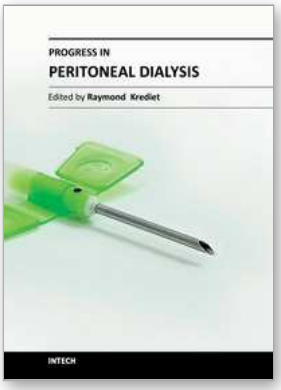

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Progress in Peritoneal Dialysis is based on judgement of a number of abstracts, submitted by interested people involved in various aspects of peritoneal dialysis. The book has a wide scope, ranging from in-vitro experiments, mathematical modelling, and clinical studies. The interested reader will find state of the art essays on various aspects of peritoneal dialysis relevant to expand their knowledge on this underused modality of renal replacement therapy.

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