An Update on RAAS Blockade and Peritoneal Membrane Preservation: The Ace of Art

Wassawon Wontanatawatot MD*, Somchai Eiam-ong MD*,
Asada Leelahavanichkul MD*, Talerngsak Kanjanabuch MD*

** Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*

Peritoneal membrane changes over time in long-term peritoneal dialysis (PD) patients lead to dialysis failure and increased morbidity as well as mortality. Bio-incompatable PD solution, peritonitis, and uremia are hypothesized in causing membrane damage. Fibrous organization and angiogenesis of peritoneum are crucial morphological alterations which can diminish the efficacy of exchange and cause ultrafiltration failure. Pathophysiologic mechanisms of membrane damage have been extensively studied to innovate therapeutic strategies. One of the potential mechanisms is a presence of local renin-angiotensin-aldosterone system (RAAS) by which injured peritoneal mesothelial cell-derived angiotensin-II (AII) causes activations in TGF-β, VEGF expression, and epithelial-to-mesenchymal transition (EMT) which contributes to extracellular matrix accumulation and neoangiogenesis in submesothelial tissues. Clinical evidence of RAAS blockade on human peritoneal membrane remains under investigation and is still inconclusive but relevant data seem to demonstrate its benefit on membrane preservation. Longitudinal effect of RAAS blockade on membrane structural, functional, and clinical relationships and strategies to use angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), aldosterone antagonist, and direct renin inhibitor are an interesting field to be explored.

***Keywords**: RAAS blockade, ACEI, ARB, Peritoneal membrane preservation*

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The number of chronic peritoneal dialysis (PD) patients rapidly soars after the "PD First" policy has been launched nationwide in Thailand. Many strategies to improve dialysis technique have been developed during the past decade. However, long-term PD patients still suffer from inadequacy of dialysis and ultrafiltration failure caused by peritoneal membrane fibrosis day after day. The peritoneal membrane serves as a dialyzer of PD but it cannot be reused or changed as the dialyzer of hemodialysis. Therefore, the strategies to preserve peritoneal membrane are an area of increasing interest. Recently, the pathophysiologic mechanisms of peritoneal membrane damage have been explored and these include the role of peritoneal renin-angiotensin-aldosterone system (RAAS). Herein, the authors reviewed the evidence of RAAS blockade for the protection of peritoneal membrane to improve better outcome of all PD patients.

Correspondence to:
Wontanatawatot W, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
Phone: 0-2256-4251 ext. 103
E-mail: wassa_jo@hotmail.com

The change of peritoneal membrane after PD: morphological and functional relationship

The peritoneal membrane consists of mesothelial monolayer and the underlying submesothelial compact zone which comprises extracellular matrix (ECM), fibroblasts, mast cells, macrophage, capillaries, and lymphatic vessles. During PD, diffusion and ultrafiltration are processed across these layers. A previous peritoneal biopsy study revealed morphologic changes of peritoneal membrane in PD patients[1]. Indeed, uremic patients exhibited reactive mesothelial cell changes and increased submesothelial compact zone thickness, when compared with healthy adult control. Moreover, these changes are more pronounced in PD patients when compared with uremic patients not on dialysis[2]. The important changes of peritoneal membrane associated with time on PD include mesothelial cell loss, increased compact zone fibrosis, vascular changing of

subendothelial hyalinization with luminal narrowing or obliteration, and neoangiogenesis (Fig. 1)[3]

After long-term PD, the mesothelial cell is injured by an exposure to conventional dialysate, which contains high glucose concentration, glucose degradation products (GDPs), lactate, low pH; recurrent peritonitis; and systemic inflammation including uremia[4,5]. The process of remesothelialization occurs to regenerate the new mesothelial cell. Repeated peritoneal membrane injury over time results in impaired membrane adaptation and causes repairing with fibrosis (Fig. 1).

These morphologic changes are correlated with the functional impairment. Ultrafiltration failure is a crucially functional abnormality, leading to loss of survival advantage[6]. Davies et al[7] reported reduced peritoneal ultrafiltration capacity but increased in small solute transport over time on PD. The peritoneal neoangiogenesis results in enhanced effective peritoneal surface area exchange and could augment rapid small solute transport whereas lymphangiogenesis results in increased lymphatic absorption rates[8]. This situation leads to impaired free water transport caused by a rapid disappearance of the osmotic gradient and reduced peritoneal osmotic conductance to glucose[9]. The thickened submesothelial fibrotic layer hampers osmotic pressure and diminishes the efficacy of the exchanges. In summary, loss of mesothelium, submesothelial fibrosis, and (lymph) angiogenesis are typical morphologic features observed in long-term PD and could contribute to technical failure.

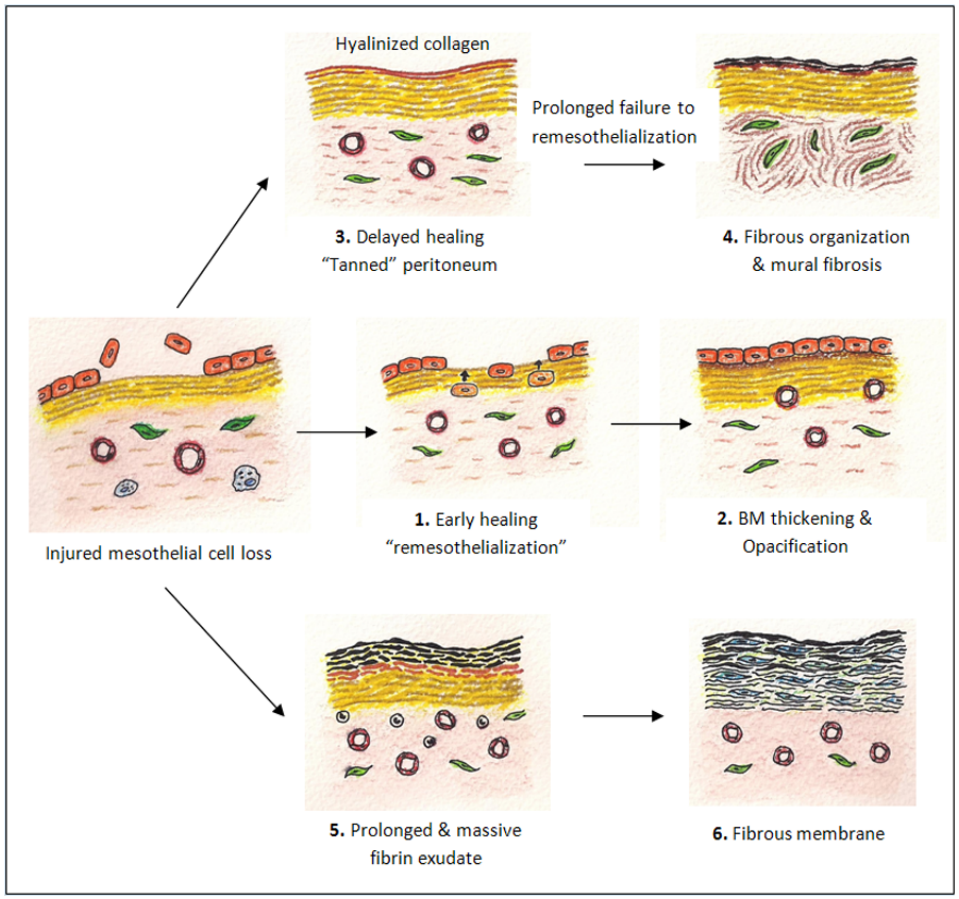

Fig. 1 The changing of peritoneal membrane over time. In normal situation (1,2); after the mesothelial cell is injured and losses from the membrane, remesothelialization occurs to repair the denuded area to a healed peritoneum. A tanned peritoneum (3,4) is generated in a situation of repeated injury and delayed healing. This will turn to a fibrous peritoneum. In a prolonged and severe peritoneal injury (5,6), fibrous organization rapidly develops and results in membrane failure

Mechanism of peritoneal membrane damage and role of peritoneal RAAS

Peritoneal tissue remodeling resembles a chronic inflammation. Several factors influence peritoneal tissue integrity, including systemic effect of uremia and local effect of the components of conventional PD fluid stated earlier, plasticizer, presence of the catheter, and peritonitis. Moreover, instillation of the dialysate as well as pressure itself is an inflammatory trigger[10,11]. Several studies have demonstrated that fibrosis and angiogenesis appear to be intimately linked through common initiating growth factors, inflammatory cytokines, and the epithelial-to-mesenchymal transition (EMT) process[12] (Fig. 2).

The definite pathophysiology of peritoneal changes during long-term PD remains inconclusive. Potential mechanisms of membrane changes started after exposure of peritoneal cells to stimuli. Activated mesothelial cells produce angiogenic and fibrotic factors such as transforming growth factor beta 1 (TGF-β), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF-2), hyaluronic acid (HA), interleukin-6 (IL-6), tumor necrotic factor alpha (TNF-α), and also generates chemokines to recruit leukocytes[13,14]. Peritoneal macrophage and mast cells are also activated and release cytokines including prostaglandin-E2 (PGE-2), IL-1, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), TNF-α , TGF-β, and VEGF[15]. Many inflammatory mediators affect resident fibroblast proliferation and in turn, stimulate fibroblasts to produce PGE-2, ECM components such as HA, fibronectin, and collagen[16]. Inducible endothelial cells by the growth factors express vascular cell adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM). These processes result in alteration of peritoneal tissue repair, ECM deposit, and neoangiogenesis[17].

EMT is a cellular program consisting of losses of cell to cell and cell to matrix interactions, cell polarity and cytoskeletal rearrangement, and basement membrane degradation with subsequent migration or invasion[18] (Fig. 3). TGF-β appears to be the major inducer of EMT while the representative cell is myofibroblast[19]. Selgas et al[20] demonstrated that soon after initiating PD, mesothelial cells showed a progressive loss of epithelial phenotype but acquired the fibroblast-like characteristics. Immunohistochemical studies of peritoneal biopsies from PD patients demonstrated the expression of mesothelial markers in stromal spindle-like cells, suggesting that they stemmed

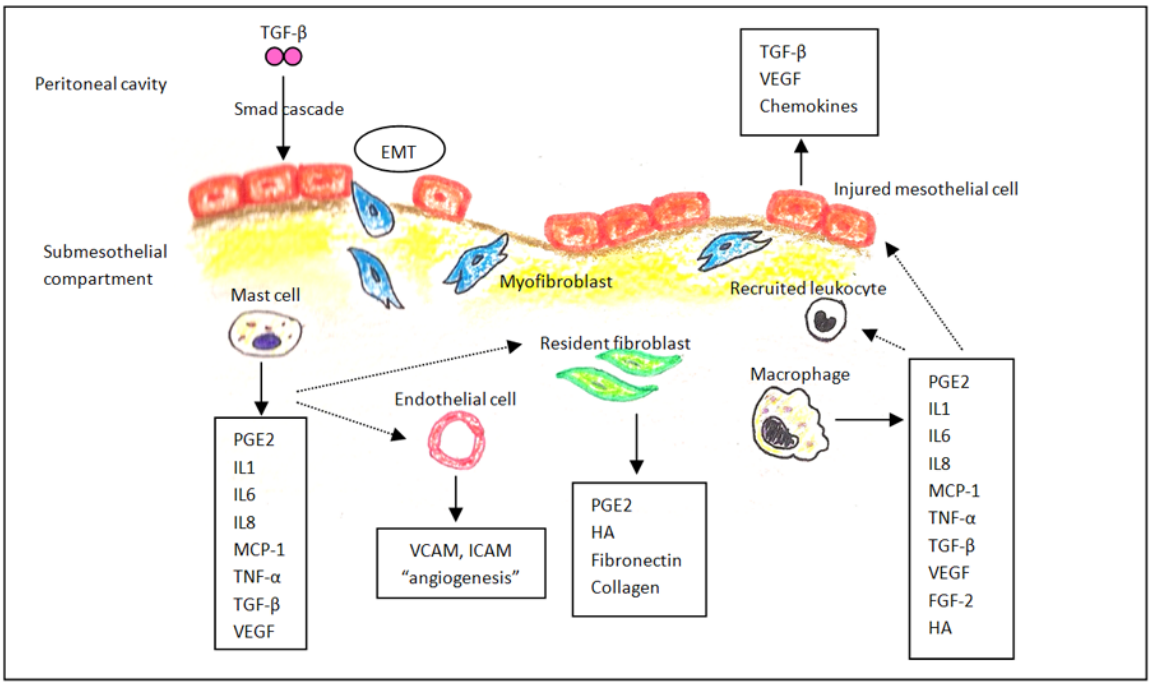

Fig. 2 Potential mechanisms of membrane changes. After EMT process, PD patient's peritoneum reveals myofibroblastic conversion of mesothelial cell, which expresses markers of mesothelial cell, mesenchymal cell, and angiogenic factor. Cellular system of inflammatory response is processed to induce fibrosis and neoangiogenesis of membrane

from the local conversion of mesothelial cells. Mesothelial cell undergoing EMT also expressed angiogenic molecules, indicating an interconnected process of EMT and neoangiogenesis[21,22]. TGF-β could trigger four different intracellular signal pathways with the Smads cascade being the most important factor affecting cell proliferation, differentiation, adhesion, and apoptosis[19].

Accumulating evidence over decades clearly reveals the concept of "local" or "tissue" RAAS. Recent data have shown that injured mesothelial cells produce their own local RAAS and this appears to be a close link between local angiotensin II (Ang II) and TGF-β[23-28] (Table 1). Noh et al[29] demonstrated the capability of human peritoneal mesothelial cells (HPMC) in producing Ang II protein which could mediate high glucose-induced upregulation of TGF-β and fibronectin expressions. Kyuden et al[30] have confirmed this finding and could illustrate the effect of RAAS blockade in inhibiting the high glucose-induced TGF-β production. A recent study in renal tubular cells indicated that the mechanism by which elevated glucose could activate RAAS might be initiated by increased production of reactive oxygen species (ROS) (Fig. 3). Data from Lee et al[31] also revealed that high glucose activated protein kinase C signalling in HPMC,

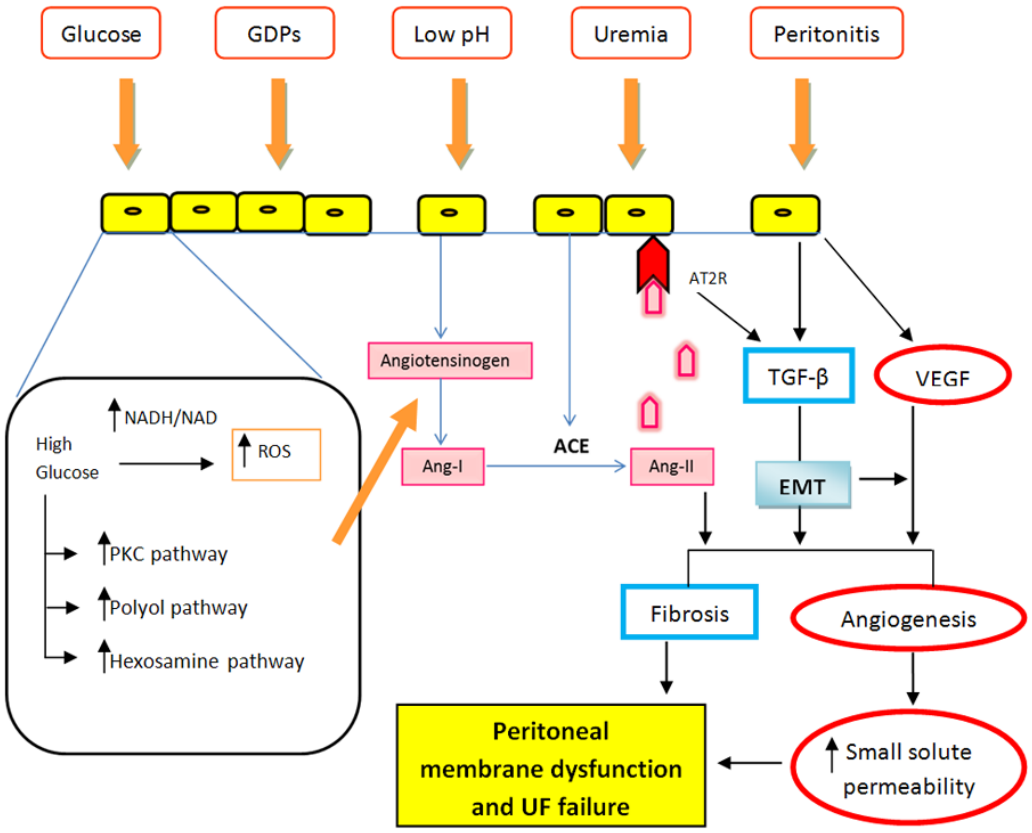

Fig. 3 Proposed mechanisms of peritoneal damage. Mesothelial cell is injured by a variety of local and systemic stimuli. Local RAAS is activated and induces mesothelial cell production of profibrotic and pro-angiogenic cytokines, leading to peritoneal membrane failure. Furthermore, intracellular signal cascades induced by TGF-β implicate in epithelial-to-mesenchymal transition (EMT) forming the myofibroblast and VEGF production. Noteworthy, peritoneal RAAS can directly induce peritoneal fibrosis and neoangiogenesis apart from the pathways of TGF-β and VEGF. By the mechanism of high glucose concentration, this increases the NADH/NAD ratio, which fuels reactive oxygen species (ROS) generation by mitochondria and cytoplasmic NADH oxidases. Increased ROS affects to shift of glucose flux through the alternative pathways of protein kinase C (PKC), polyol, and hexosamine pathway. This leads to activation of angiotensinogen gene, resulting in increased Ang II production that acts as an autocrine manner. (AT2R; angiotensin II receptor, Ang-I; angiotensin I, Ang-II; angiotensin II, ACE; angiotensin converting enzyme)

Table 1. Peritoneal-altered factors mediated by angiotensin II

Growth factors	*TGF-β, platelet-derived growth factor (PDGF), epidermal growth factor (EGF)*
Cytokines	*interleukin-6 (IL-6), Tumor necrotic factor alpha (TNF-α)*
Chemokines	*monocyte chemoattractant protein type 1 (MCP-1), regulated upon activation: normal T cell expressed/secreted (RANTES)*
Adhesion molecules	*vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), P-selectin*
Peptides	*endothelin 1 (ET-1)*
Lipids	*prostaglandins, platelet activating factor (PAF)*
Cyclooxygenase 2 (COX-2)	
Nitric oxide (NO)	
Collagen metabolism	*matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinase (TIMP), collagen tissue growth factor*

leading to increased expression of TGF-β. In addition to the high glucose concentration, animal studies demonstrated that other components of the bio-incompatible PD solution were associated with mesothelial cell damage and peritoneal thickening, and this effect can be elucidated when systemic RAAS blockade were used. Ersoy et al[32] showed that rats with PD peritonitis had higher TGF-β levels which could induce peritoneal fibrosis. This fibrosis was abrogated after receiving irbesartan, a member of angiotensin II receptor blocker (ARB), and spironolactone, a member of aldosterone antagonist. Besides TGF-β mediated by local RAAS activation, Ang II and aldosterone have direct stimulatory effects on TGF-β indepentdent pathway in controlling proinflammatory cytokines and chemokines to aggravate the fibrosis, and on angiogenic factors especially VEGF and angiopoietin. Rizkalla et al[33] showed that Ang II induced angiogenesis and the use of ARB can mitigate the expression of VEGF and angiopoietin. The proposed mechanisms of peritoneal damage and the role of RAAS were summarized in Fig. 3.

RAAS blockade and its role in peritoneal membrane preservation

During early years of dialysis, PD patients have a greater survival benefit compared with hemodialysis patients. However, after long-term PD, a certain number of PD patients have to encounter dialysis failure. This is caused by peritoneal membrane damage together with the loss of residual renal function and increased rate of cardiovascular events. Angiotensin-converting enzyme inhibitors (ACEI) and ARB have provided a great benefit to decrease mortality and morbidity in high risk cardiovascular patients including end stage renal disease. As mentioned above, local RAAS activation in PD patients plays the major role in peritoneal membrane alterations. Blocking of this process has been hypothesized to preserve membrane integrity upon the benefit on cardiovascular events. Attenuation of local RAAS activation by using biocompatible dialysate and the preventive strategies to reduce peritonitis rate are also important. Most studies explore the effect of ACEI and ARB, but other RAAS blockade agents such as aldosterone antagonist and direct renin inhibitor are still limitedly investigated.

In vitro study by Yao et al[33] showed that high concentration glucose stimulates the expression of Smad-2 protein and TGF-β1 on HPMC and this effect was inhibited by addition of losartan. Noh et al[34]. found that imidapril mitigated fibronectin production from stimulated HPMC by high glucose solution. Sauter et al[35] exhibited the effect of captopril, enalapril, and losartan to abrogate VEGF production from HPMC. In animal model, Duman et al[36] studied the effect of ACEI and ARB in rat peritoneum after administering intraperitoneal saline, 4.25% dextrose or in combination with oral enalapril, lisinopril, quinapril, and losartan. The present tudy showed that the ACEI and ARB groups had lesser degree of peritoneal membrane thickening, peritoneal protein loss, lowered levels of TGF-β and VEGF, compared with the control group. This effect did not differ between ACEI and ARB groups. Furthermore, the addition of ARB to ACEI did not show the greater benefit compared with the group using single agent. On the following trial in PD rats, the same investigators found that intra-peritoneal route of enalapril had the same benefit on membrane preservation[37]. In contrast, Kumano et al[38] and Imai et al[39] demonstrated increased loss of peritoneal protein and decreased expression of peritoneal aquaporin accompanied by ultrafiltration failure in ACEI or ARB treated group.

Clinical evidence in human is scarce and

inconclusive but the relevant data seem to illustrate the benefit of RAAS blockade on membrane preservation. Favazza et al[40] presented 9 PD patients receiving enalapril 40 mg per day for 2 weeks. All patients had well-controlled blood pressure and increased peritoneal small solute excretion. Coronel et al[41] displayed the effect of captopril 50 mg per day on peritoneal protein loss in 12 PD patients but no significant change in solute transport. Six PD patients from the study by Ripley et al[42] received oral enalapril and intra-peritoneal enalaprilat. There were no effects on peritoneal solute transport despite the plasma ACE levels were suppressed. In 2004, Coronel et al[43] investigated the effect of 1-month treatment with irbesartan in 15 long-term PD patients. The benefit was shown in decreasing peritoneal protein loss but still no appreciable change in transport status. Two year later, Jearnsujiwimol et al[44] demonstrated the effect of candesartan on 7 PD patients. The present study confirmed the beneficial effect of RAAS blockade on decreased peritoneal protein loss but showed no benefit on small solute transport. In contrast, Agraharkar et al[45] could not show the benefit of ARB on peritoneal protein loss.

Krediet et al[46] retrospectively revealed the effect of ACEI/ARB on a decreased mass transfer area coefficient (MTAC) of urea and creatinine in 30 long-term PD patients. The control group showed increased MTAC of urea and creatinine and this reflects the pattern of high transporter. The present study demonstrated no different effect on ultrafiltration in both groups. Kolesnyk et al[47] retrospectively analyzed data from 66 patients treated with PD for at least 2 years, during which at least 2 standard peritoneal permeability analyses were performed. Thirty-six patients were treated with ACEI and/or ARB, while 30 patients did not receive any of these agents. In the ACEI/ARB group, small solute transport was decreased, while it was increased in the control group during the time on PD. The same investigators analyzed a cohort data from 217 PD patients by the Netherlands Cooperative Study on Adeuacy of Dialysis (NECOSAD), of whom 120 received ACEI/ARB, 87 did not and 10 did receive for less than 25% of their time on PD[48]. The value of D/P creatinine ratio was correlated with PD duration but the rise of the slope of D/P creatinine over time was less steep in the treated groups. This effect was more pronounced in the long-term use of ACEI/ARB-treated patients. However, no differences in PD technique survival were observed. Recently, Fang et al[49] showed that treatment with ACEI/ARB in PD patients was associated with dramatically reduced mortality indepentdent of blood pressure and other clinical and demographic variables. These previous studies did not show significantly adverse events such as hyperkalemia and hypotension in ACEI/ARB-treated group.

To the authors' knowledge, up to now, no randomized controlled trials (RCTs) were published to conclude the effect of RAAS blockade on peritoneal membrane. The present study in the year 2010 (unpublished data) was conducted in a randomized controlled trial to demonstrate the protective effect of dual RAAS inhibition on peritoneal membrane in both morphological and functional aspects. Ninety-three naive PD patients with hypertension were randomized into 3 groups to receive enalapril, enalapril plus losartan, and control group. The control group received other classes of anti-hypertensive drugs besides RAAS blockade. The present examined the patients at baseline and after 6th-month with modified peritoneal equilibration test as an index of peritoneal membrane function. The over-night effluence was collected for measuring dialysate cancer antigen 125 (CA-125) as a marker of anatomical change. Since the dialysate CA-125 is known as a non-invasive parameter representing mesothelial cell mass. After the study was completed, the treated groups showed a decrease in D/P creatinine ratio, but increases in D/D0 glucose, peritoneal ultrafiltration, and dialysate CA-125 appearance rate. The increase in net ultrafiltration was more pronounced in the dual blockade group, but the other effects did not differ from the single RAAS blockade agent. Further longitudinal study in RCT to assess the effect of RAAS blockade on peritoneal membrane and clinical correlation are required.

In conclusion, RAAS plays a major role on peritoneal membrane alteration. After RAAS activation, the important mediators such as TGF-β, VEGF, and EMT induce membrane fibrosis and neoangiogenesis. Blocking of RAAS and directly attenuating the local RAAS activation are the potential strategies to preserve peritoneal membrane. Additional studies are needed to confirm this protective effect of RAAS blockade and produce a long-term benefit of care to all PD patients.

Potential conflicts of interest

None.

References

1. Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, et al. Morphologic changes

in the peritoneal membrane of patients with renal disease. J Am Soc Nephrol 2002; 13: 470-9.
2. Bertoli SV, Buzzi L, Ciurlino D, Maccario M, Martino S. Morpho-functional study of peritoneum in peritoneal dialysis patients. J Nephrol 2003; 16: 373-8.
3. Schilte MN, Celie JW, Wee PM, Beelen RH, van den Born J. Factors contributing to peritoneal tissue remodeling in peritoneal dialysis. Perit Dial Int 2009; 29: 605-17.
4. Fusshoeller A. Histomorphological and functional changes of the peritoneal membrane during long-term peritoneal dialysis. Pediatr Nephrol 2008; 23: 19-25.
5. Zareie M, Keuning ED, ter Wee PM, Schalkwijk CG, Beelen RH, van den Born J. Improved biocompatibility of bicarbonate/lactate-buffered PDF is not related to pH. Nephrol Dial Transplant 2006; 21: 208-16.
6. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol 2000; 11: 556-64.
7. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. Kidney Int 2004; 66: 2437-45.
8. Mortier S, De Vriese AS, Lameire N. Recent concepts in the molecular biology of the peritoneal membrane - implications for more biocompatible dialysis solutions. Blood Purif 2003; 21: 14-23.
9. Kim YL. Update on mechanisms of ultrafiltration failure. Perit Dial Int 2009; 29 (Suppl 2): S123-7.
10. Flessner MF, Credit K, Henderson K, Vanpelt HM, Potter R, He Z, et al. Peritoneal changes after exposure to sterile solutions by catheter. J Am Soc Nephrol 2007; 18: 2294-302.
11. Aroeira LS, Aguilera A, Sanchez-Tomero JA, Bajo MA, del Peso G, Jimenez-Heffernan JA, et al. Epithelial to mesenchymal transition and peritoneal membrane failure in peritoneal dialysis patients: pathologic significance and potential therapeutic interventions. J Am Soc Nephrol 2007; 18: 2004-13.
12. Yanez-Mo M, Lara-Pezzi E, Selgas R, Ramirez-Huesca M, Dominguez-Jimenez C, Jimenez-Heffernan JA, et al. Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells. N Engl J Med 2003; 348: 403-13.
13. Kyuden Y, Ito T, Masaki T, Yorioka N, Kohno N. Tgf-beta1 induced by high glucose is controlled by angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker on cultured human peritoneal mesothelial cells. Perit Dial Int 2005; 25: 483-91.
14. Fracasso A, Baggio B, Ossi E, Del Prete D, Bonfante L, Bazzato G, et al. Glycosaminoglycans prevent the functional and morphological peritoneal derangement in an experimental model of peritoneal fibrosis. Am J Kidney Dis 1999; 33: 105-10.
15. Nakamoto H, Imai H, Fukushima R, Ishida Y, Yamanouchi Y, Suzuki H. Role of the renin-angiotensin system in the pathogenesis of peritoneal fibrosis. Perit Dial Int 2008; 28 (Suppl 3): S83-7.
16. Witowski J, Jorres A. Preventing peritoneal fibrosis—an ace up our sleeve? Perit Dial Int 2005; 25: 25-9.
17. Honda K, Nitta K, Horita S, Yumura W, Nihei H, Nagai R, et al. Accumulation of advanced glycation end products in the peritoneal vasculature of continuous ambulatory peritoneal dialysis patients with low ultra-filtration. Nephrol Dial Transplant 1999; 14: 1541-9.
18. Krediet RT, Coester AM, Kolesnyk I, de Graaff M, Zweers MM, Smit W, et al. Karl d. Nolph state of the art lecture: feasible and future options for salvation of the peritoneal membrane. Perit Dial Int 2009; 29 (Suppl 2): S195-7.
19. Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. N Engl J Med 2000; 342: 1350-8.
20. Selgas R, Bajo A, Jimenez-Heffernan JA, Sanchez-Tomero JA, Del Peso G, Aguilera A, et al. Epithelial-to-mesenchymal transition of the mesothelial cell—its role in the response of the peritoneum to dialysis. Nephrol Dial Transplant 2006; 21 (Suppl 2): ii2-7.
21. Devuyst O, Margetts PJ, Topley N. The pathophysiology of the peritoneal membrane. J Am Soc Nephrol 2010; 21: 1077-85.
22. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev 2000; 52: 639-72.
23. Nishimura H, Ito Y, Mizuno M, Tanaka A, Morita Y, Maruyama S, et al. Mineralocorticoid receptor blockade ameliorates peritoneal fibrosis in new rat peritonitis model. Am J Physiol Renal Physiol 2008; 294: F1084-93.
24. Nessim SJ, Perl J, Bargman JM. The renin-angiotensin-aldosterone system in peritoneal

dialysis: is what is good for the kidney also good for the peritoneum? Kidney Int 2010; 78: 23-8.
25. Duman S. The renin-angiotensin system and peritoneal dialysis. Perit Dial Int 2004; 24: 5-9.
26. Ardaillou R, Chansel D. Synthesis and effects of active fragments of angiotensin II. Kidney Int 1997; 52: 1458-68.
27. Duman S, Sen S, Asci G, Basci A, Akcicek F. Effect of valsartan versus lisinopril on peritoneal alterations in rats [abstract]. Perit Dial Int 2002; 22: 112.
28. Duman S, Sen S, Duman C, Asci G, Basci A, Akcicek F. Improvement of peritoneal alterations induced by hypertonic PD solutions by ACE inhibitors and by AR blockers [abstract]. Nephrol Dial Transplant 2003; 18 (Suppl 4): 474.
29. Noh H, Ha H, Yu MR, Kim YO, Kim JH, Lee HB. Angiotensin II mediates high glucose-induced TGF-beta1 and fibronectin upregulation in HPMC through reactive oxygen species. Perit Dial Int 2005; 25: 38-47.
30. Lee HB, Yu MR, Song JS, Ha H. Reactive oxygen species amplify protein kinase C signaling in high glucose-induced fibronectin expression by human peritoneal mesothelial cells. Kidney Int 2004; 65: 1170-9.
31. Ersoy R, Celik A, Yilmaz O, Sarioglu S, Sis B, Akan P, et al. The effects of irbesartan and spironolactone in prevention of peritoneal fibrosis in rats. Perit Dial Int 2007; 27: 424-31.
32. Rizkalla B, Forbes JM, Cooper ME, Cao Z. Increased renal vascular endothelial growth factor and angiopoietins by angiotensin II infusion is mediated by both AT1 and AT2 receptors. J Am Soc Nephrol 2003; 14: 3061-71.
33. Yao Q, Lindholm B, Qian J. Inhibition of the effect of high glucose (HG) on the expression of Smad in human peritoneal mesothelial cells [abstract]. J Am Soc Nephrol 2003; 14: 215A.
34. Noh H, Kim HJ, Yu MR, Ha H, Lee HB. Renin angiotensin system in human peritoneal mesothelial cells [abstract]. J Am Soc Nephrol 2003; 14: 218A.
35. Sauter M, Cohen CD, Wornle M, Mussack T, Ladurner R, Sitter T. ACE inhibitor and AT1-receptor blocker attenuate the production of VEGF in mesothelial cells. Perit Dial Int 2007; 27: 167-72.
36. Duman S, Gunal AI, Sen S, Asci G, Ozkahya M, Terzioglu E, et al. Does enalapril prevent peritoneal fibrosis induced by hypertonic (3.86%) peritoneal dialysis solution? Perit Dial Int 2001; 21: 219-24.
37. Duman S, Wieczorowska-Tobis K, Styszynski A, Kwiatkowska B, Breborowicz A, Oreopoulos DG. Intraperitoneal enalapril ameliorates morphologic changes induced by hypertonic peritoneal dialysis solutions in rat peritoneum. Adv Perit Dial 2004; 20: 31-6.
38. Kumano K, Go M, Ning H, Sakai T. Effects of vasodilators on peritoneal solute and fluid transport in rat peritoneal dialysis. Adv Perit Dial 1996; 12: 27-32.
39. Imai H, Nakamoto H, Ishida Y, Yamanouchi Y, Inoue T, Okada H, et al. Renin-angiotensin system plays an important role in the regulation of water transport in the peritoneum. Adv Perit Dial 2001; 17: 20-4.
40. Favazza A, Motanaro D, Messa P, Antonucci F, Gropuzzo M, Mioni G. Peritoneal clearances in hypertensive CAPD patients after oral administration of clonidine, enalapril, and nifedipine. Perit Dial Int 1992; 12: 287-91.
41. Coronel F, Hortal L, Naranjo P, Cruceyra A, Barrientos A. Captopril, proteinuria and peritoneal protein leakage in diabetic patients. Nephron 1989; 51: 443.
42. Ripley EB, Gehr TW, Kish CW, Sica DA. Hormonal, blood pressure, and peritoneal transport response to short-term ACE inhibition. Perit Dial Int 1994; 14: 378-83.
43. Coronel F, Berni A, Cigarran S, Calvo N, Herrero JA. Effects of angiotensin II receptor blocker (irbesartan) on peritoneal membrane functions. Adv Perit Dial 2004; 20: 27-30.
44. Jearnsujitwimol V, Eiam-Ong S, Kanjanabuch T, Wathanavaha A, Pansin P. The effect of angiotensin II receptor blocker on peritoneal membrane transports in continuous ambulatory peritoneal dialysis patients. J Med Assoc Thai 2006; 89 (Suppl 2): S188-95.
45. Agraharkar M, Du Y, Man WC, Henry S, Kuo TF, Ahuja T. Angiotensin II receptor blockade (ARB) and peritoneal protein loss in peritoneal dialysis patients [abstract]. J Am Soc Nephrol 2003; 14: 858A.
46. Krediet RT. Dialysate cancer antigen 125 concentration as marker of peritoneal membrane status in patients treated with chronic peritoneal dialysis. Perit Dial Int 2001; 21: 560-7.
47. Kolesnyk I, Noordzij M, Dekker FW, Boeschoten EW, Krediet RT. A positive effect of AII inhibitors on peritoneal membrane function in long-term PD patients. Nephrol Dial Transplant 2009; 24: 272-7.
48. Kolesnyk I, Dekker FW, Noordzij M, le Cessie S,

Struijk DG, Krediet RT. Impact of ACE inhibitors and AII receptor blockers on peritoneal membrane transport characteristics in long-term peritoneal dialysis patients. Perit Dial Int 2007; 27: 446-53.

49. Fang W, Oreopoulos DG, Bargman JM. Use of ACE inhibitors or angiotensin receptor blockers and survival in patients on peritoneal dialysis. Nephrol Dial Transplant 2008; 23: 3704-10.

ผลของยาที่มีฤทธิ์ยับยั้งระบบ renin-angiotensin-aldosterone ต่อการชะลอความเสื่อมของผนังเยื่อบุช่องท้องในผู้ป่วยที่ล้างไตทางช่องท้อง

วรรษวรรน์ วรรธนทวาทศ, สมชาย เอี่ยมอ่อง, อัษฎาศ์ ลีศหวนิชกุล, เถลิงศักดิ์ กาญจนบุษย์

ผู้ป่วยที่ได้รับการล้างไตทางช่องท้องต่อเนื่องเป็นเวลานานต้องเผชิญกับปัญหาผนังเยื่อบุช่องท้องเสื่อมสภาพลง นำไปสู่การล้มเหลวของการล้างไตอัตราการทุพพลภาพ และการเสียชีวิตเพิ่มขึ้นสาเหตุหลักเนื่องมาจากการสัมผัสน้ำยาล้างไตทางช่องท้องที่มีความเข้มข้นของกลูโคสสูง การเกิดผนังเยื่อบุช่องท้องอักเสบ และการกระตุ้นกระบวนการอักเสบในร่างกายจาก uremic toxin ปัจจัยเหล่านี้ก่อให้เกิดการบาดเจ็บของเซลล์มีโซทีเลียมของผนังเยื่อบุช่องท้อง เกิดการกระตุ้นระบบ renin-angiotensin-aldosterone เฉพาะที่นำไปสู่การเพิ่มขึ้น ของสาร TGF-beta และ VEGF ซึ่งก่อให้เกิดพังผืดและการเพิ่มขึ้นของหลอดเลือดฝอยที่บริเวณผนังเยื่อบุช่องท้องนำไปสู่การแลกเปลี่ยนสารที่ผิดปกติและการขจัดน้ำที่ลดลง ในปัจจุบันแม้ยังไม่ได้ข้อสรุปถึงผลของการใช้ยากลุ่มที่สามารถยับยั้ง ระบบ renin-angiotensin-aldosterone ต่อการชะลอความเสื่อมของผนังเยื่อบุช่องท้องแต่มีแนวโน้มว่าการใช้ยาดังกล่าวน่าจะได้ผลดี อย่างไรก็ตามการศึกษาถึงผลระยะยาวของยากลุ่มนี้ต่อการเปลี่ยนแปลงของโครงสร้าง และหน้าที่ของผนังเยื่อบุช่องท้องควบคู่ไปกับการเปลี่ยนแปลงทางคลินิกรวมถึงการเลือกใช้ยาที่สามารถยับยั้งระบบ renin-angiotensin-aldosterone ในขั้นตอนที่ต่างกันส่งผลต่อผนังเยื่อบุช่องท้องอย่างไรนั้นยังต้องการข้อมูลอีกมาก