Chapter 4

Inflammation in Peritoneal Dialysis

Joseph C.K. Leung, Loretta Y. Y. Chan,
Kar Neng Lai and Sydney C.W. Tang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55964

1. Introduction

The prevalence of kidney disease has grown continuously. The loss of kidney function during acute kidney disease may occur rapidly and reversibly, and most unfortunately, may progress to end-stage renal disease (ESRD) in which renal replacement therapy (RRT) is required. Due to the short supply of donor kidneys, RRT is now dominated by dialysis. Dialysis can be applied intermittently or continuously using extracorporeal (hemodialysis or HD) or para-corporeal (peritoneal dialysis or PD) methods. Among patients with ESRD, the choice of PD or HD varies considerably from country to country and is related to non-medical factors such as finance, physician preferences, and social culture [1]. It has been suggested that PD should be offered as the first-line dialysis modality [2]. Compared with HD, PD offers better preservation of residual renal function, lower risk of infection with hepatitis B and C, better outcome after transplantation, preservation of vascular access, easy to place on home therapy, simplicity of the technique, and lower costs [3, 4]. The predominant problems associated with PD are ultrafiltration failure and peritonitis. Dialysis patients after an episode of peritonitis may still be affected by prolonged systemic chronic inflammation [5]. Likewise, PD maintains a state of intraperitoneal micro-inflammation that affects the structure and function of the peritoneal membrane, and impairs ultrafiltration efficiency. An understanding of the mechanism in peritoneal inflammation will provide new insight to better preserve the function of the peritoneum membrane, with a goal to improve the quality of life in patients under PD.

2. Inflammatory response during peritoneal dialysis

Inflammation is the body's natural defense involving cascades of immediate immunological responses towards various stimuli, including pathogens, necrotic cells, injury, or irritants.

Acute inflammation is a protective machinery by which the injurious stimuli will be removed and the healing process initiated. On the other hand, chronic inflammation develops if the conditions causing acute inflammation is not resolved over a period of time. Intriguingly, chronic inflammation may be due to excessive physiological responses, such as the wound repairing process, which are intrinsically essential for maintaining normal life. Certain stimuli may directly provoke chronic rather than acute inflammation. Peritoneal inflammation of the microenvironment in the peritoneal cavity during PD generally presents in two major forms: (i) acute inflammation triggered by microbial infection, and (ii) low-grade inflammation or "para-inflammation" under various exogenous or endogenous stimulations during PD. These two forms of inflammation affects the membrane structure and function, and is associated with increased mortality.

2.1. Acute inflammation in PD

The most common form of acute inflammation of peritoneum in PD is peritonitis, which is a serious and the most frequent complication leading to hospitalization and catheter loss [6, 7]. Peritonitis causes a high infection-related mortality in PD patients [8, 9]. The leading cause of PD-associated peritonitis is contamination, predominately with the microorganisms from skin and environment, which is most commonly occur during the dialysis procedure such as PD exchange [10]. Exit site infection (ESI) in which transmigration of microorganisms from the exit site along the PD catheter into the peritoneal cavity, may cause tunnel infections and peritonitis [11, 12]. Enteric peritonitis is a less common cause but important, due to the severity of the inflammation process [13]. Fungal peritonitis accounts for about 4–6% of episodes of the total incidence of the peritonitis, and is with high mortality [14]. Rapidly resolving the infection is the primary approach to treat peritonitis, even if this involve the need for prompt removal of the peritoneal catheter. Before the causative microorganism is identified, initial therapy with broad spectrum antibiotic which is active against the most commonly occurring organisms, will be given according to the guideline from the International Society for Peritoneal Dialysis (ISPD) [9]. It is recommended that in addition to the standard initial protocol, specific regime tailored to the geographic and cultural characteristics, the relevant organisms and their antibiotic resistance pattern should be considered [15]. Detailed examination of the causality of infection-related peritonitis is important for the management. The molecular pathways of inflammation induced by different microbial pathogens are somehow redundant, yet also complex and diverse [16, 17].

2.2. Chronic inflammation in PD

An inherent immune dysfunction in PD patients and the continuous non-specific immune cell stimulation by dialysis procedure contribute to the chronic inflammatory state of patients under the long-term dialysis [18]. Patients on maintenance PD have increased intra-peritoneal levels of hyaluronan and cytokines including interleukin (IL)-1β, IL-6 and transforming growth factor-β (TGF-β) [19, 20]. Chronic inflammation remains an important cause of morbidity in patients with ESRD. During continuous ambulatory peritoneal dialysis (CAPD), peritoneal cells are repeatedly exposed to non-physiologic dialysis fluid (PDF) with low pH and high glucose [21]. PDF also contains toxic substance like glucose degradation products (GDP) generated during the sterilization process and the advanced glycation end products (AGE), which can be formed by amadori reaction between sugar and protein during long-term PD [22]. Dialysis patients are likely to gain fat mass following absorption of glucose from the peritoneal dialysate [23]. Adipocyte in adipose tissue is the major source of adipokines such as leptin, adiponectin and other inflammatory mediators. Adipose tissue is also an important contributor to the peritoneal and systemic inflammation [24, 25]. Exposure of peritoneal cells to the non-physiological dialysate during CAPD leads to "para-inflammation" [26], which is a protective mechanism helping the peritoneum to adapt to the noxious conditions during PD and to restore peritoneum functionality. Regrettably, after repeated exposure to various insults in PDF, dysregulated para-inflammation may eventually develop chronically to inflammatory states associated with ultrafiltration failure. A key feature of chronic inflammation is peritoneal fibrosis [27, 28], in which fibroblasts proliferate or are recruited to the inflamed peritoneum with the activation of cascades of inflammatory or fibrotic cytokines [29, 30].

3. The Mechanisms and pathways of inflammation in PD

The inflammatory pathway of PD consists of modulators, mediators and effectors. A simplified schema for PD-related inflammation is illustrated in Figure 1. The complex interaction among the components involved and the related machinery will determine the outcome of the immune response induced by PD.

3.1. Modulators:

Modulators of PD-related inflammation can be exogenous or endogenous. It should be noted that exogenous modulators may promote or amplify the effects of the endogenous modulators during the process of PD-related inflammation. Intriguingly, the interaction between modulators and the ongoing inflammatory events may form a vicious cycle to amplify the inflammatory process.

3.1.1. Exogenous modulators

The innate immune system recognized catheters used for PD as the foreign bodies. Severe biofilm formation on the catheters have been observed in PD patients without detectable infection [31]. Histologic and functional evidences obtained from rodent model have shown that the catheter insertion may have induced a classic inflammatory reaction characterized by formation of fibrin clots in the peritoneum [32]. Mechanical stress during PD is related to the infiltration of large volume of PDF, especially for achieving specific target of small solute clearance. Volume stress during PD are associated with significant increments in endothelin (ET)-1, a vasoactive peptide that may induce peritoneal fibrosis and indirectly contribute to technique failure in CAPD [33]. ET-1 induces the release of proinflammatory cytokines and increases the deposition of extracellular matrix (ECM) by regulating production and turnover of matrix components. In addition, high fill volumes increase circulating norepinephrine levels

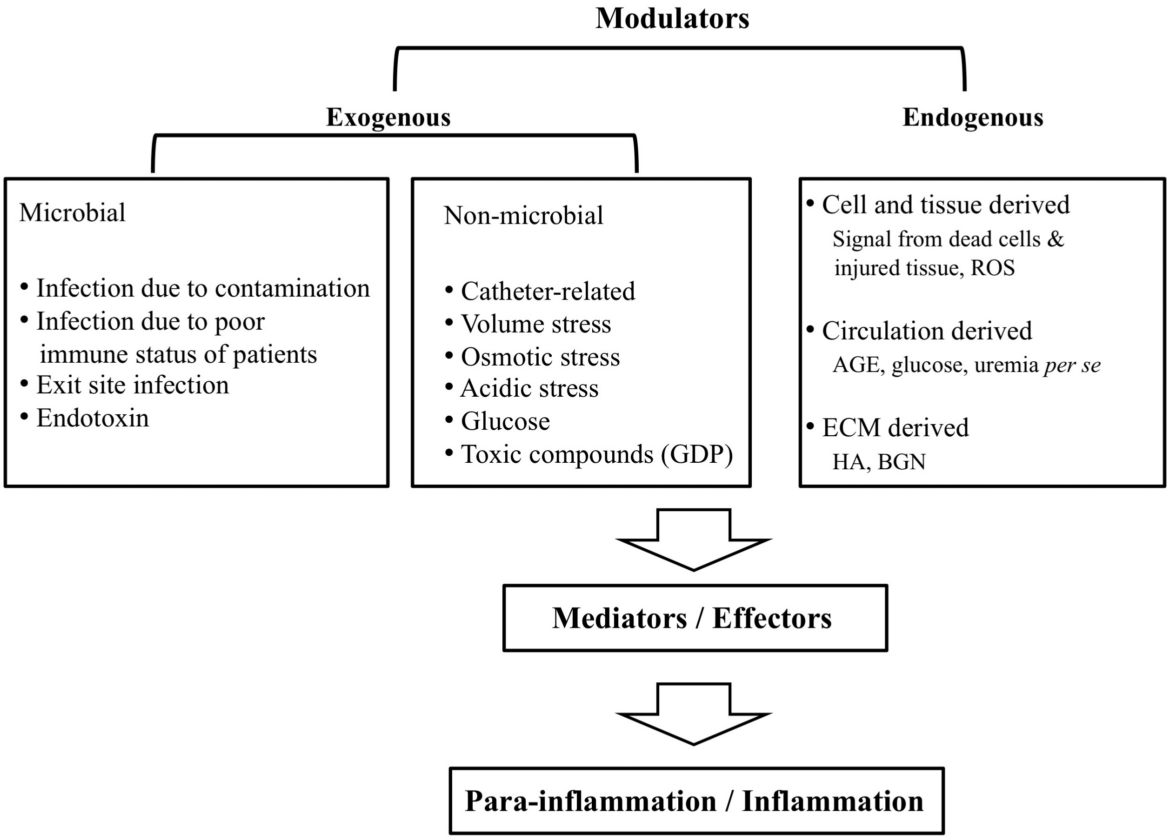


Figure 1. Pathway of the development of PD-related inflammation

[34], blood pressure, intraperitoneal pressure [35], and elicit proinflammatory effects by increasing peritoneal IL-6 and tumor necrosis factor-α (TNF-α) concentration [36]. During PD, cells lining the peritoneal cavity are exposed from time to time to the hyperosmotic environment, and this osmotic stress induces apoptosis of the peritoneal cells [37, 38]. Local acidosis occurs artificially during PD due to the non-physiological properties of PDF which has an acidic pH value. Exposure of macrophages to an acidic environment leads to the increased production of TNF-α through the up-regulation of inducible nitric oxide synthase (iNOS) activity and the activation of nuclear factor-κB (NF-κB) [39]. On the contrary, low pH PDF lead to rapid intracellular acidification and suppression of host defense activity [40, 41]. The acidic PDF induces stress on the endoplasmic reticulum (ER) and suppresses the induction of monocyte chemotactic protein-1 (MCP-1) in the peritoneum through de-activation of NF-κB pathway [42, 43], and this may impair the peritoneal defense mechanisms by interfering with migration of phagocytic cells. Obviously, further study is needed to clarify the role of acidic-stress on PD-related inflammation. High glucose content in PDF induces immunological, structural and functional abnormalities in peritoneal cells during CAPD [44, 45]. High glucose induces vascular inflammatory processes through up-regulation of endothelial cell adhesion molecules, reduction of nitric oxide (NO) release, activation of reactive oxygen species (ROS) and NF-κB [46, 47]. Storage or heat sterilization of PDF generates the toxic substances GDP. Dialysis with GDP-containing PDF is associated with increased vascular endothelial growth

factor (VEGF) production and peritoneal vascularization [48]. GDP decrease the expression of tight junction associated protein, zonula occludens protein 1 (ZO-1), in human peritoneal mesothelial cells (HPMC) *via* the VEGF [49]. Glucose or GDP in PDF may cause AGE formation, which further provoke additional inflammatory stimuli on the peritoneal environment under PD [22, 50, 51]. Contamination and the inherent poor immune status of the PD patients contribute to the microbial stress during PD. Microbial contamination or ESI during PD may evolve to peritonitis, which elicits a virulent acute inflammatory response and is an important cause of hospitalization, catheter loss, and technique failure. The most common contaminated micro-organisms are coagulase-negative *Staphylococcus, S. aureus, Streptococcus*, and Gram-negative bacteria. Much less common are mycobacterium and fungal peritonitis. Skin organisms contamination including *Staphylococcus, Corynebacterium, and Bacillus* species cause mild inflammatory responses. Exit site infection with *Staphylococcus epidermidis* or *Pseudomonas aeruginosa* is difficult to treat, with frequent progression to tunnel infections and peritonitis. Fungal peritonitis generally requires catheter removal. It is worth mentioned that sustained inflammation is observed in patients on PD with peritonitis even after resolution of the clinical symptoms of peritonitis [52]. The C-reactive protein (CRP) remains significantly higher than baseline by day 42 after an episode of peritonitis [5]. Release of neutrophil gelatinase-associated lipocalin (NGAL) into the peritoneal dialysate effluent (PDE) by HPMC is induced following an acute episode of CAPD-related peritonitis, and is related to the up-regulation of the IL-1β concentration [53]. Lipopolysaccharide (LPS), a major component of Gram-negative bacterial cell walls, is a potent immuno-stimulatory product [54]. Endotoxemia is common in PD patients and circulating LPS may derived from the gastrointestinal tract during enteric peritonitis [55]. The level of circulating LPS correlates with the severity of systemic inflammation, suggesting that endotoxemia may contribute to accelerated atherosclerosis in PD patients.

3.1.2. Endogenous modulators

Uremia is associated with the immune dysfunction and is a significant risk factor for cardiovascular abnormalities and death in chronic kidney disease (CKD) patients [56], and this risk is further increased when CKD has progressed to ESRD requiring dialysis. Dialysis decreases the impact of uremia, yet does not remove it completely. In PD patients, uremia fuels the inflammatory state and introduces stress on the peritoneum due to the formation of carbonyl products. It accelerates the formation of advanced oxidation protein products (AOPP) and AGE, that induces an upregulation of the receptors of advanced glycation end products (RAGE) [57]. Binding of AGE to RAGE alone [58], or in combination with the Toll-like receptor (TLR)s, elicits the inflammatory activity [59]. It has been suggested that the high-mobility group box 1 protein (HMGB1) may play a central role in mediating inflammation, and interactions involving the HMGB1-TLR-RAGE axis trigger NF-κB activation and proinflammatory cytokines induction [60]. Cytotoxic injury to mesothelial cells induces ROS, depletes ATP, and triggers the extracellular release of HMGB1, which initiates a chronic inflammatory response [61]. Serum adipokine levels are significantly elevated in uremic patients with CKD [62], and elevated plasma concentrations of adiponectin and leptin have been reported [63, 64]. Leptin activates immune system and serves as a mediator of inflammation [65]. Glucose-based PDF induces a higher leptin secretion by a murine adipocyte cell line 3T3-L1 compared to dialysate with physiological glucose concentration *via* the hexosamine pathway [66]. We have demonstrated that the full-length isoform of leptin receptor, Ob-Rb, is expressed in HPMC and its expression is up-regulated following exposure to glucose [67]. Glucose increases leptin synthesis by peritoneal adipocytes and the adipocyte-derived leptin can induce TGF-β production by HPMC through the Ob-Rb [67]. Adiponectin exerts protective functions on innate and adaptive immunity, including the reduction of phagocytic activity, IL-6 and TNF-α production by macrophage, T-cell response, and the induction of anti-inflammatory cytokines by monocytes, macrophages and dendritic cells [68]. In a recent study using rat PD model, glucose-based PDF down-regulates adiponectin synthesis by adipocytes through an increased ROS generation [69].

In uremic patients under PD, chronic inflammatory processes induce the oxidative stress, generating excess ROS, reactive nitrogen species (RNS), and DNA-reactive aldehydes. These pro-oxidants overwhelm *in vivo* antioxidant defenses, and lead to increased oxidative damage of peritoneal structure and function [70]. The link between oxidative stress and inflammation has been demonstrated in liver injury, where oxidative stress induces the proinflammatory signaling and macrophage activation [71]. In HPMC, ROS amplifies the high glucose-induced expression of fibronectin [72], angiotensin II (AngII) and TGF-β [44].

Heat-shock proteins (HSP), a marker of the cellular stress response, is the main effector of the cellular reparative machinery. Induction of HSP expression will counteract cellular injury caused by PDF exposure. PDF induces HSP release by cultured HPMC [73, 74]. In an experimental model of PD, PDF infusion causes cellular injury but also up-regulates HSP-72 [75]. In HPMC under sublethal injury, secretion of HSP-72 correlates with the release of proinflammatory IL-8 [76].

Breakdown products of the ECM during tissue injury, may serve as the endogenous modulator of inflammation. There is growing evidence that ECM molecules may deliver proinflammatory signals [77, 78]. In the context of PD, expression and release of hyaluronan (HA) and biglycan (BGN) is well recognized. HPMC synthesize and secrete ECM proteins including BGN and HA, which are detectable in PDE [19, 79, 80]. Under physiological conditions, HA is present as an inert high-molecular-weight polymer. Upon tissue injury, HA is broken down into inflammatory low-molecular-weight fragments, which activate the TLR4 and promote either an inflammatory or a tissue-repair response [81, 82]. Other than HA, BGN also implicate in modulating the proinflammatory functions. BGN can act as a “danger” motif, a potential innate antigen analogous to pathogen-associated molecular pattern (PAMP), which signal through TLR4 and TLR2 to initiate the inflammatory cascade [83]. BGN binds with TGF-β and TNF-α to regulate the proinflammatory cytokine activity [84, 85]. Markedly elevated TNF-α and IL-1β is found in PDE from CAPD patients with peritonitis [86]. The activity of proinflammatory master cytokine IL-1β is regulated by sequentially synthesis and cleavage of pro-IL-1 by caspase-1 (also named as IL-1 converting enzyme) [87, 88]. The production of pro-IL-1 is signaled by TLR and the activation of caspase-1 requires the assembly and activity of a cytosolic multi-protein complex known as the inflammasome, consisting of nucleotide-binding oligomerization-like receptor family members (NLRs) [89]. NLRP3 is the best characterized NLRs which recruits caspase-1 to the inflammasome. In macrophage, soluble BGN induces the NLRP3 inflammasome, activating caspase-1 and releasing mature IL-1β [90]. Most notably, the pro-inflammatory events initiated by HA or BGN are also ROS dependent [91]. Figure 2 illustrates the complex interaction amount various endogenous modulators in relation to peritoneal inflammation.

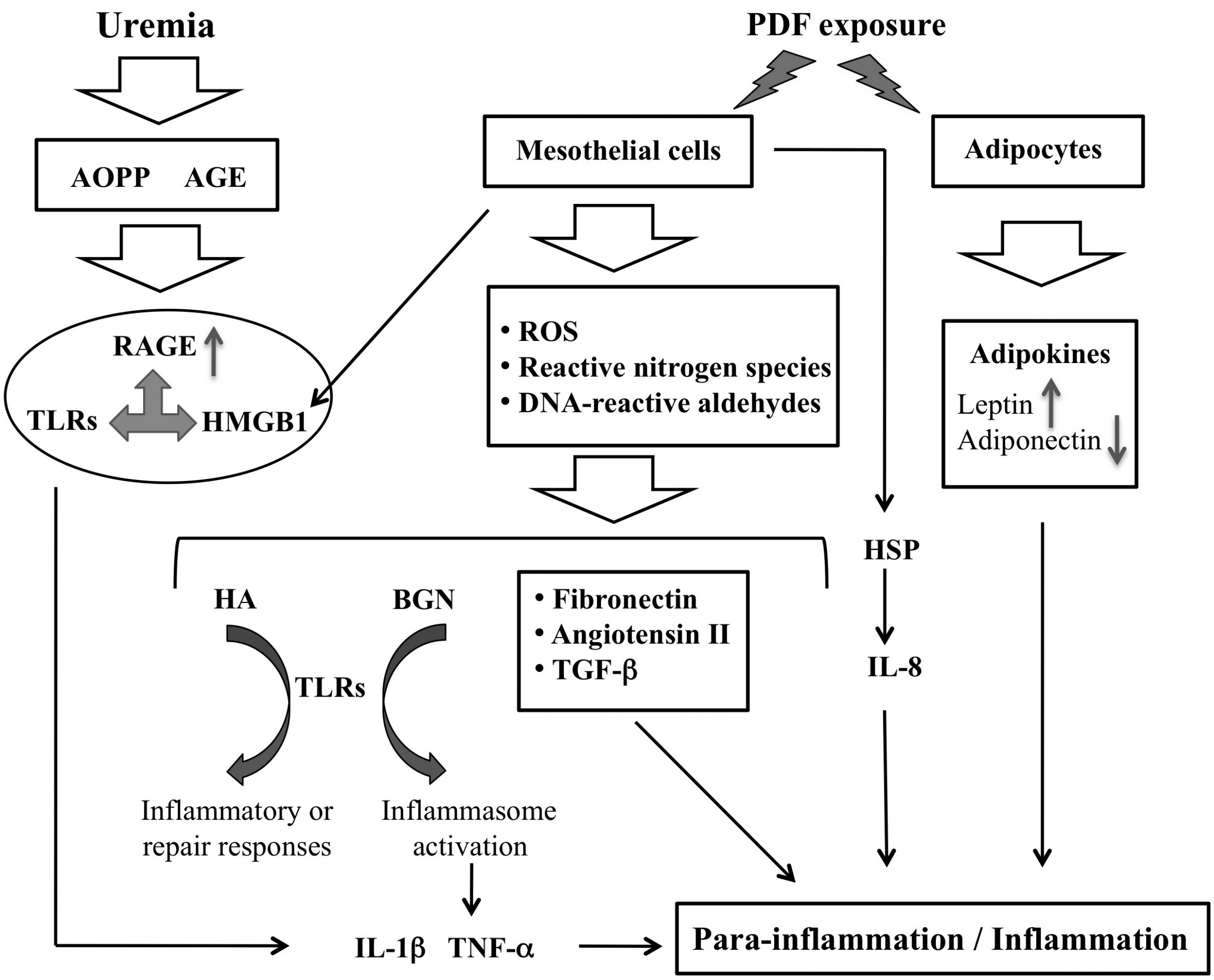
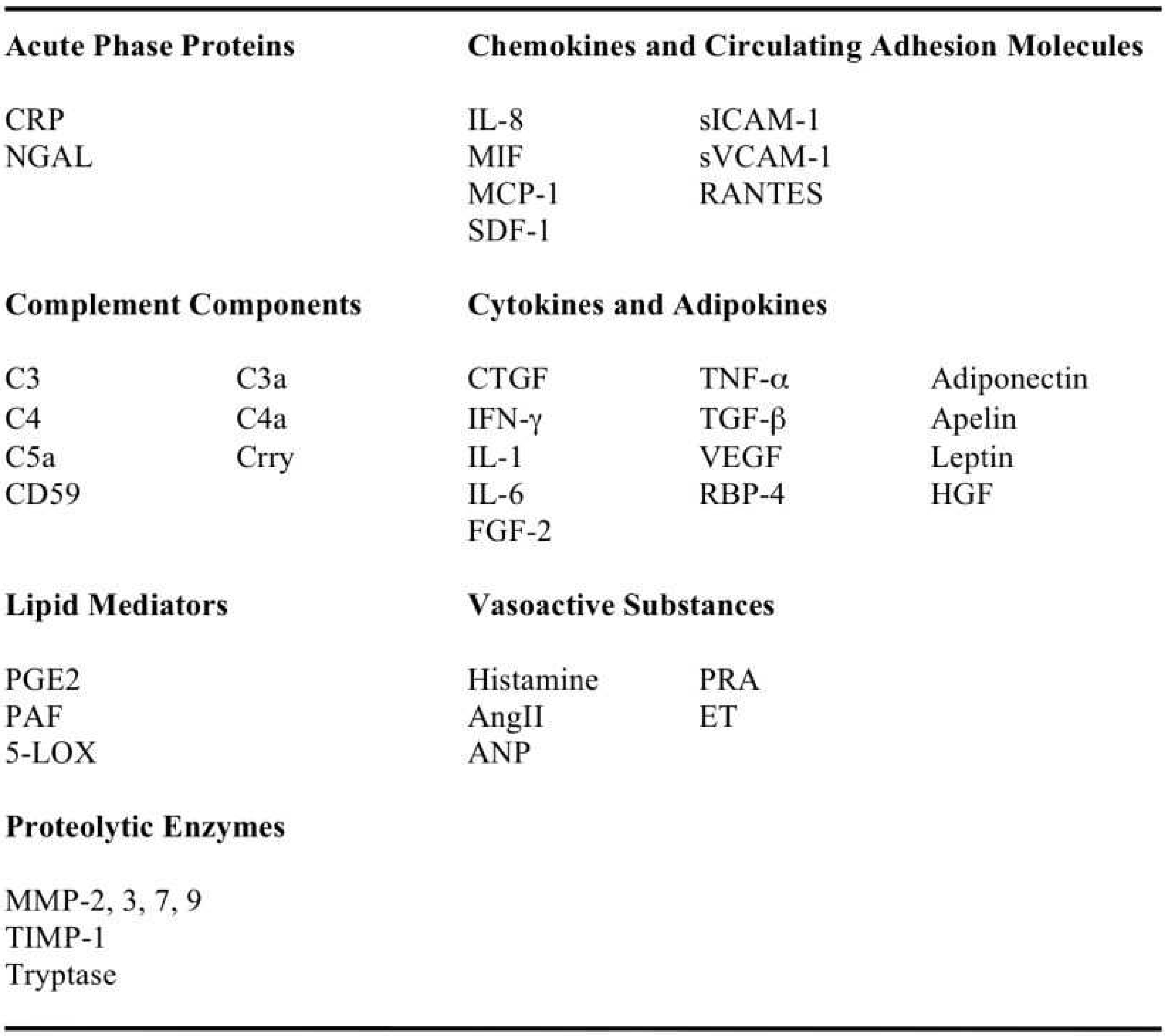


Figure 2. Endogenous modulators in the regulation of peritoneal inflammation

4. Mediators

An array of inflammatory mediators is significantly induced or up-regulated following PD, and is known to modulate the structure and function of the peritoneal membrane, as well as the function of the downstream effectors of the inflammatory pathway. Of equally important, these mediators also play a central role in the maintenance of homeostasis in peritoneum. These mediators are either derived from plasma proteins or secreted by infiltrating or resident peritoneal cells. While many of these inflammatory mediators have overlapped effects on the vasculature and on the recruitment of leukocytes, other mediators may perform additional specific functions and are produced directly in response to particular stimulation by PD-related modulators. It should be noted that some mediators can induce the production of other inflammatory mediators and it is important to understand the logic underlying this hierarchy of mediators induction. The soluble mediators of PD-related inflammation classified according to their biochemical properties is shown in Table 1.



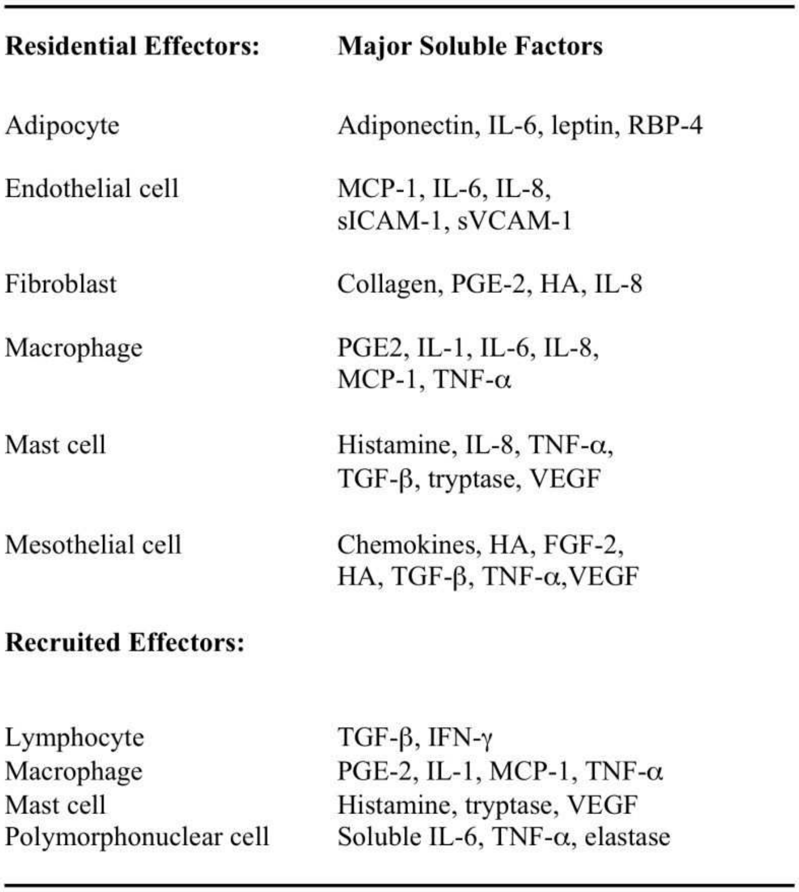
Acute Phase Proteins		**Chemokines and Circulating Adhesion Molecules**		
CRP		IL-8	sICAM-1	
NGAL		MIF	sVCAM-1	
		MCP-1	RANTES	
		SDF-1		
Complement Components		**Cytokines and Adipokines**		
C3	C3a	CTGF	TNF-α	Adiponectin
C4	C4a	IFN-γ	TGF-β	Apelin
C5a	Crry	IL-1	VEGF	Leptin
CD59		IL-6	RBP-4	HGF
		FGF-2		
Lipid Mediators		**Vasoactive Substances**		
PGE2		Histamine	PRA	
PAF		AngII	ET	
5-LOX		ANP		
Proteolytic Enzymes				
MMP-2, 3, 7, 9				
TIMP-1				
Tryptase				

There are many other members in each category, only those commonly reported are listed.

Table 1. Mediators of PD-related inflammation

4.1. Acute phase proteins

Emerging evidences have suggested that acute phase proteins generated during PD may have additional function instead of just serving as the markers of inflammation. CRP plays a proinflammatory role in activating monocyte chemotactic protein [92]. Data from studies on endothelial cells, monocytes-macrophages and smooth muscle cells support a direct role for CRP in atherogenesis [93-95]. NGAL has been evaluated as an urinary biomarker for detecting the early onset of renal tubular cell injury [96]. In CAPD, NGAL in PDE is a marker for neutrophil-dependent bacterial peritonitis, and is also synthesized by HPMC induced specifically by IL1-β [53]. NGAL directly involves in the pathogenesis of CKD and cardiovascular abnormality [97].



Residential Effectors:	**Major Soluble Factors**
Adipocyte	Adiponectin, IL-6, leptin, RBP-4
Endothelial cell	MCP-1, IL-6, IL-8, sICAM-1, sVCAM-1
Fibroblast	Collagen, PGE-2, HA, IL-8
Macrophage	PGE2, IL-1, IL-6, IL-8, MCP-1, TNF-α
Mast cell	Histamine, IL-8, TNF-α, TGF-β, tryptase, VEGF
Mesothelial cell	Chemokines, HA, FGF-2, HA, TGF-β, TNF-α,VEGF
Recruited Effectors:	
Lymphocyte	TGF-β, IFN-γ
Macrophage	PGE-2, IL-1, MCP-1, TNF-α
Mast cell	Histamine, tryptase, VEGF
Polymorphonuclear cell	Soluble IL-6, TNF-α, elastase

Table 2. Effectors in PD-related Inflammation

4.2. Chemokines and circulating adhesion molecules

In response to modulators of peritoneal inflammation, chemokines are produced by peritoneal cells including HPMC [98], macrophages [43], adipocytes [99], to control leukocyte extravasation and chemotaxis towards the affected tissues. These chemokines includes IL-8 [98, 100], MCP-1 [98, 101], macrophage inhibitory factor (MIF) [102], and regulated upon activation normal T cell expressed and secreted (RANTES) [98, 101]. Strikingly, HPMC express the α-chemokine stromal derived factor-1 (SDF-1) [103]. The expression levels of SDF-1 is up-regulated by TGF-β1 treatment, resulting in an increased migratory potential of HPMC, which is suggested to be involved in the re-epithelialization of denuded basement membrane at the site of peritoneal injury [104]. Soluble adhesion molecules including soluble intercellular adhesion molecule-1 (sICAM-1) [105] and soluble vascular cell adhesion molecule-1 (sVCAM-1) [106] are produced by endothelial cells during PD, and their concentration correlates with atherogenesis or cardiovascular functions.

4.3. Complement components

Complement activation during PD plays key roles in the maintenance of host homeostasis by eliminating infectious microorganisms and injured cells. Complement activation releases a number of biologically active products that drive peritoneal inflammation [107]. The complement fragments, C3a, C4a and C5a (also known as anaphylatoxins), are produced by several pathways of complement activation. These complement components promote the recruitment of granulocytes and monocytes, and induce mast-cell degranulation, thereby affecting the vasculature of the peritoneum in PD. The synthesis of C3 and C4 by HPMC are regulated by PDF [108]. In rodent model, blocking C5a reduces influx of neutrophils and improve ultrafiltration [109]. Inhibiting the complement activation by complement regulators (CRegs), Crry and CD59, may protect the peritoneal membrane from long-term PD injury [110].

4.4. Cytokines and adipokines

Numerous cytokines are produced by peritoneal cells, infiltrating macrophages or mast cells (Table 1). These cytokines play pluripotent pleiotropic roles in the peritoneal inflammation, participate in the host defense mechanisms and the induction of the acute-phase response. During peritonitis, there is increased release of IL-1β, IL-6, TGF-β and TNF-α by HPMC [52]. These cytokines may autocrinally induce epithelial to mesenchymal transition (EMT) in HPMC, and this further promotes peritoneal inflammation and fibrosis [29, 111, 112]. In the uremic pre-dialysis and PD patients, there is increased peritoneal expression of the fibroblast growth factor-2 (FGF-2) and VEGF [113]. Compared to patients dialysed with low-GDP containing PDF, patients dialysed with less-biocompatible PDF have increased concentration of TNF-α, hepatocyte growth factor (HGF), and IL-6 in the dialysate [102]. AGE and GDP in PDF differentially regulate the synthesis of connective tissue growth factor (CTGF) by peritoneal resident cells. The CTGF synthesis by HPMC can be further amplified by TGF-β released from peritoneal fibroblast or endothelial cells [114]. Crosstalk among peritoneal cells and their cytokines may amply the inflammatory cascade. The differential activation of different transcriptional factors and the diverse response of HPMC towards CTGF, TGF-β and VEGF, suggest that peritoneal cytokines have an overlapping and yet distinct role on peritoneal target cells. Other than the cytokines, peritoneal adipocytes can mediate various physiological processes through the secretion of an array of adipokines including leptin, adiponectin, apelin, retinol-binding protein-4 (RBP-4) [103, 115]. These adipokines have distinct functions on peritoneum during PD. For example, leptin augments myofibroblastic conversion of HPMC [116]. The relative levels of leptin and adiponectin in dialysate from PD patients may indicate the risk of cardiovascular disease [117].

4.5. Lipid mediators

Two major classes of lipid mediators, eicosanoids and platelet-activating factors (PAF), are derived from phosphatidylcholine, a member of the phospholipid family that is present in the inner leaflet of cellular membranes. Prostaglandins E2 (PGE2) is generated from eicosanoids, whereas PAF is produced by the acetylation of lysophosphatidic acid. PGE2 causes vasodilation and modulates the change of peritoneal permeability in PD after peritonitis [118]. PAF activates several processes that occur during the inflammatory response, including the recruitment of leukocytes, vascular permeability and platelet activation. Oxidative stress during PD causes unrestrained synthesis of PAF through interfering the proper function of alpha 1-proteinase inhibitor, a PAF inhibitor, [119]. Esterified eicosanoids are produced from 5-Lipoxygenase (5-LOX) by neutrophils after peritonitis, and enhance the generation of IL-8 and superoxide [120].

4.6. Proteolytic enzymes

Proteolytic enzymes have diverse roles in inflammation, in part through degrading ECM and basement-membrane proteins. These proteases have important roles in many processes, including host defense, tissue remodeling and leukocyte migration. Matrix metalloproteinase (MMP) is the most important family of proteolytic enzymes in mesothelial homeostasis and wound repair. Of equal important is the endogenous tissue inhibitors of metalloproteinase (TIMP), which moderate MMP activity. The balance between MMPs and TIMPs, helps to regulate ECM turnover during tissue remodeling in PD. MMP-2 has been associated with the oxidative stress marker in PD [121]. Activation of MMP-2 causes peritoneal injury during peritoneal dialysis in rats [122]. Neutral-pH PDF improves peritoneal function and decreases MMP-2 in patients undergoing CAPD [123]. MMP-2 and TIMP-1 levels in peritoneal effluents reflect solute transport rate and are associated with peritoneal injury [124]. Regression analysis revealed that both the MMP-7 and TIMP-1, are excellent predictors of cellular stress in dialyzed patients using HSP-27 as the marker [125]. The number of mast cells is increased in PD patients [126], and mast cell tryptase is a serine protease implicated in promoting angiogenesis and fibrosis [126, 127].

4.7. Vasoactive substances

Vasoactive amines modulate the vascular permeability, vasodilation, or vasoconstriction of the peritoneal vasculature during PD, and are produced in an all-or-none manner during degranulation from mast cells and platelets. PDF induces peritoneal histamine release from mast cells [128], and this further causes calcium flux, which activates HPMC and influences cytoskeleton organization [129]. The neuropeptide substance P exaggerates the affected microvascular tone, albumin loss and reduced ultrafiltration in a rat PD model [128]. Plasma levels of atrial natriuretic peptide (ANP), pro-renin activity (PRA), and ET are increased in uremic patients on long-term CAPD, and suggesting the risk of development of myocardial function [130]. AngII activates macrophages and fibroblast to secrete proinflammatory cytokines, chemokines, and VEGF [131]. AngII plays important roles in regulating peritoneal extracellular volume and in the development of peritoneal fibrosis [132, 133].

5. Effectors

The effectors of PD inflammatory response are the residential peritoneal cells and the recruited leukocytes. Residential peritoneal effector cells are adipocytes, endothelial cells, fibroblasts, macrophages, mast cells and mesothelial cells. Recruited leukocytes include polymorphonuclear cells (PMN), T or B lymphocytes, macrophages and mast cells. Table 2 shows the cell types and their released mediators, which are of relevance to the PD-induced inflammation.

Upon PD, both the exogenous or endogenous modulators activate peritoneal adipocytes, macrophages and mesothelial cells, which produce inflammatory cytokines, adipokines and growth factors. These mediators will further promote the secretion of angiogenic factors, fibrotic cytokines and growth factors, by fibroblasts, endothelial cells and mast cells through paracrine interaction. In the meantime, residential HPMC, adipocyte and macrophage also release chemotatic mediators to recruit the exogenous inflammatory immune effectors. All these events orchestrate to amplify the inflammatory cascades and eventually lead to the loss of ultrafiltration and development of peritoneal fibrosis.

6. New PDF and immune responses

Emerging evidences suggest the beneficial effects on peritoneal function by using new PDF with decreasing acidity, reducing GDP concentration, and with non-glucose osmotic agents such as amino acids or glucose polymers. *In vitro* cell culture studies have demonstrated enhanced biocompatibility with improved survival of peritoneal cells exposed to new PDF [134-136]. Data from animal models of PD using new PDF also have shown reduced fibrosis and neoangiogenesis, improved macrophage function, and better maintained ultrafiltration [137, 138]. In humans, the use of glucose-polymer-based solution reduced the cholesterol levels with enhanced lipid oxidation and improved serum profiles of adipokines [139-141]. Despite these beneficial effects, use of glucose-polymer-based solution may increase levels of AGE and other immune mediators including IL-6, TNF-α and HA [142-144]. The use of amino-acid-based PDE improves protein malnutrition but exerts negative metabolic effects of increasing serum urea and homocysteine levels [145]. Moreover, PDE level of IL-6 is increased, reflecting the activation of inflammatory response of the peritoneal membrane [146]. The use of glucose-based neutral pH PDF achieves less activation of peritoneal membrane the best preservation of its integrity. The levels of AGE, HA, VEGF and IL-6 are not altered and the effluent-derived macrophage phagocytic function is enhanced [147-150].

7. Conclusion

The PD-related inflammation is an exceedingly complex process. Although some of the destructive events of PD-induced inflammation can be prevented, nevertheless, other long-term damage is understandably unavoidable. The incidences of peritonitis, exit site infection and catheter malfunction may be decreased with better patient education, optimal exit site care, the use of oral prophylactic antibiotics after wet contamination, and the use of the disconnect systems. The inflammatory modulators in the conventional PDF may be reduced or removed by using novel PDF-based replacement of glucose with icodextrin and amino acids, lactate with bicarbonate at a neutral to physiological pH.

There are potential therapeutic options to minimize peritoneal inflammation in PD patients, but yet need extensive research for further confirmation [151]. Acute peritonitis may be prevented by the use of chemokine receptor blockers, mast cell stabilizers or corticosteroid to block excessive macrophage activity. Chronic PD-related inflammation may be targeted by inhibiting various signaling pathways involved in the inflammatory cascade, or by the introduction of anti-inflammatory agents including anti-RAGE antibodies, bone morphogenetic protein-7 (BMP-7) or Smad7 transgene delivery.

Desperately, if patients have not been given kidney transplant, peritoneum fibrosis will be developed eventually with long term PD. Even after kidney transplant, the restoration and repair of the already injured and thickened peritoneum are still required. Thus, the uppermost challenge is to preserve and at the best, to restore the peritoneum function. Stem cells transplantation either from bone marrow or using mesenchymal stem cells, although still in its infancy, may be an attractive intervention for the repair or replenishment of the cellular reservoir of multi-potential cells of the damaged peritoneal tissue. Further investigation along this direction is warranted.

List of abbreviations

AGE Advanced glycation end products

Ang II Angiotensin II

ANP Atrial natriuretic peptide

AOPP Advanced oxidation protein products

BGN Biglycan

BMP-7 Bone Morphogenetic Protein-7

CAPD Continuous ambulatory peritoneal dialysis

CKD Chronic kidney disease

CRegs Complement regulators

CRP C-reactive protein

GDP Glucose degradation products

ECM Extracellular matrix

EMT Epithelial to mesenchymal transition

ER	Endoplasmic reticulum
ESI	Exit site infection
ESRD	End-stage renal disease
ET	Endothelin
FGF-2	Fibroblast growth factor-2
HA	Hyaluronan
HD	Hemodialysis
HGF	Hepatocyte growth factor
HMGB1	High-mobility group box 1 protein
HPMC	Human peritoneal mesothelial cells
HSP	Heat-shock proteins
iNOS	Inducible nitric oxide synthase
IFN-γ	Interferon- γ
IL	Interleukin
ISPD	International Society for Peritoneal Dialysis
5-LOX	5-Lipoxygenase
LPS	Lipopolysaccharide
MCP-1	Monocyte chemotactic protein-1
MMP	Metalloproteinase
NF-κB	Nuclear factor-κB
NGAL	Neutrophil gelatinase-associated lipocalin
NLRs	Nucleotide-binding oligomerization-like receptor family members
PAF	Platelet-activating factors
PAMP	Pathogen-associated molecular patterns
PD	Peritoneal dialysis
PDE	Peritoneal dialysate effluent
PGE2	Prostaglandins E2
PDF	Peritoneal dialysis fluid
PMN	Polymorphonuclear cells
PRA	Pro-renin activity

RAGE Receptors of advanced glycation end products

RANTES Regulated upon activation normal T cell expressed and secreted

RBP-4 Retinol-binding protein-4

RNS Reactive nitrogen species

ROS Reactive oxygen species

RRF Renal replacement therapy

SDF-1 Stromal derived factor-1

sICAM-1 Soluble intercellular adhesion molecule-1

sVCAM-1 Soluble vascular cell adhesion molecule-1

TGF-β Transforming growth factor-β

TIMP Tissue inhibitors of metalloproteinases

TLR Toll-like receptor

TNF-α Tumor necrosis factor-α

VEGF Vascular endothelial growth factor

ZO-1 Zonula occludens protein-1

Acknowledgements

We apologize to the investigators whose work was not cited due to space limitations. The study was supported by the Baxter Extramural Grant and was partly supported by L & T Charitable Foundation and the House of INDOCAFE.

Author details

Joseph C.K. Leung[1], Loretta Y. Y. Chan[1], Kar Neng Lai[2] and Sydney C.W. Tang[1]

*Address all correspondence to: jckleung@hku.hk

1 Department of Medicine, Queen Mary Hospital, University of Hong Kong, Pokfulam, Hong Kong, China

2 Nephrology Center, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong, China

References

[1] Nissenson AR, Prichard SS, Cheng IK, Gokal R, Kubota M, Maiorca R, Riella MC, Rottembourg J, Stewart JH. ESRD modality selection into the 21st century: the importance of non medical factors. ASAIO J 1997;43(3):143-50.

[2] Chaudhary K, Sangha H, Khanna R. Peritoneal dialysis first: rationale. Clin J Am Soc Nephrol 2011;6(2):447-56.

[3] Berger A, Edelsberg J, Inglese GW, Bhattacharyya SK, Oster G. Cost comparison of peritoneal dialysis versus hemodialysis in end-stage renal disease. Am J Manag Care 2009;15(8):509-18.

[4] Gokal R, Blake PG, Passlick-Deetjen J, Schaub TP, Prichard S, Burkart JM. What is the evidence that peritoneal dialysis is underutilized as an ESRD therapy? Semin Dial 2002;15(3):149-61.

[5] Lam MF, Leung JC, Lo WK, Tam S, Chong MC, Lui SL, Tse KC, Chan TM, Lai KN. Hyperleptinaemia and chronic inflammation after peritonitis predicts poor nutritional status and mortality in patients on peritoneal dialysis. Nephrol Dial Transplant 2007;22(5):1445-50.

[6] Piraino B. Insights on peritoneal dialysis-related infections. Contrib Nephrol 2009;163:161-8.

[7] Fried LF, Bernardini J, Johnston JR, Piraino B. Peritonitis influences mortality in peritoneal dialysis patients. J Am Soc Nephrol 1996;7(10):2176-82.

[8] Perez Fontan M, Rodriguez-Carmona A, Garcia-Naveiro R, Rosales M, Villaverde P, Valdes F. Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. Perit Dial Int 2005;25(3):274-84.

[9] Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye WC, Salzer W, Schaefer F, Struijk DG. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010;30(4):393-423.

[10] Yap DY, Chu WL, Ng F, Yip TP, Lui SL, Lo WK. Risk Factors and Outcome of Contamination in Patients on Peritoneal Dialysis--a Single-Center Experience of 15 Years. Perit Dial Int 2012.

[11] van Diepen AT, Tomlinson GA, Jassal SV. The Association between Exit Site Infection and Subsequent Peritonitis among Peritoneal Dialysis Patients. Clin J Am Soc Nephrol 2012.

[12] Pecoits-Filho R, Stenvinkel P, Wang AY, Heimburger O, Lindholm B. Chronic inflammation in peritoneal dialysis: the search for the holy grail? Perit Dial Int 2004;24(4):327-39.

[13] Kern EO, Newman LN, Cacho CP, Schulak JA, Weiss MF. Abdominal catastrophe revisited: the risk and outcome of enteric peritoneal contamination. Perit Dial Int 2002;22(3):323-34.

[14] Levallois J, Nadeau-Fredette AC, Labbe AC, Laverdiere M, Ouimet D, Vallee M. Ten-year experience with fungal peritonitis in peritoneal dialysis patients: antifungal susceptibility patterns in a North-American center. Int J Infect Dis 2012;16(1):e41-3.

[15] Li PK, Chow KM. Infectious complications in dialysis--epidemiology and outcomes. Nat Rev Nephrol 2012;8(2):77-88.

[16] Cinel I, Opal SM. Molecular biology of inflammation and sepsis: a primer. Crit Care Med 2009;37(1):291-304.

[17] Feezor RJ, Oberholzer C, Baker HV, Novick D, Rubinstein M, Moldawer LL, Pribble J, Souza S, Dinarello CA, Ertel W, Oberholzer A. Molecular characterization of the acute inflammatory response to infections with gram-negative versus gram-positive bacteria. Infect Immun 2003;71(10):5803-13.

[18] Amore A, Coppo R. Immunological basis of inflammation in dialysis. Nephrol Dial Transplant 2002;17 Suppl 8:16-24.

[19] Lai KN, Szeto CC, Lai KB, Lam CW, Chan DT, Leung JC. Increased production of hyaluronan by peritoneal cells and its significance in patients on CAPD. Am J Kidney Dis 1999;33(2):318-24.

[20] Lai KN, Lai KB, Szeto CC, Lam CW, Leung JC. Growth factors in continuous ambulatory peritoneal dialysis effluent. Their relation with peritoneal transport of small solutes. Am J Nephrol 1999;19(3):416-22.

[21] Di Paolo N, Sacchi G, De Mia M, Gaggiotti E, Capotondo L, Rossi P, Bernini M, Pucci AM, Ibba L, Sabatelli P, et al. Morphology of the peritoneal membrane during continuous ambulatory peritoneal dialysis. Nephron 1986;44(3):204-11.

[22] Lamb EJ, Cattell WR, Dawnay AB. In vitro formation of advanced glycation end products in peritoneal dialysis fluid. Kidney Int 1995;47(6):1768-74.

[23] Axelsson J, Rashid Qureshi A, Suliman ME, Honda H, Pecoits-Filho R, Heimburger O, Lindholm B, Cederholm T, Stenvinkel P. Truncal fat mass as a contributor to inflammation in end-stage renal disease. Am J Clin Nutr 2004;80(5):1222-9.

[24] Axelsson J, Heimburger O, Stenvinkel P. Adipose tissue and inflammation in chronic kidney disease. Contrib Nephrol 2006;151:165-74.

[25] Axelsson J, Heimburger O, Lindholm B, Stenvinkel P. Adipose tissue and its relation to inflammation: the role of adipokines. J Ren Nutr 2005;15(1):131-6.

[26] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454(7203):428-35.

[27] Kaneko K, Hamada C, Tomino Y. Peritoneal fibrosis intervention. Perit Dial Int 2007;27 Suppl 2:S82-6.

[28] Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, Mackenzie RK, Williams GT. Morphologic changes in the peritoneal membrane of patients with renal disease. J Am Soc Nephrol 2002;13(2):470-9.

[29] Margetts PJ, Bonniaud P. Basic mechanisms and clinical implications of peritoneal fibrosis. Perit Dial Int 2003;23(6):530-41.

[30] Lai KN, Tang SC, Leung JC. Mediators of inflammation and fibrosis. Perit Dial Int 2007;27 Suppl 2:S65-71.

[31] Swartz R, Messana J, Holmes C, Williams J. Biofilm formation on peritoneal catheters does not require the presence of infection. ASAIO Trans 1991;37(4):626-34.

[32] Flessner MF. Inflammation from sterile dialysis solutions and the longevity of the peritoneal barrier. Clin Nephrol 2007;68(6):341-8.

[33] Morgera S, Kuchinke S, Budde K, Lun A, Hocher B, Neumayer HH. Volume stress-induced peritoneal endothelin-1 release in continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 1999;10(12):2585-90.

[34] Vlachojannis JG, Tsakas S, Alexandri S, Petropoulou C, Goumenos DS. Continuous ambulatory peritoneal dialysis is responsible for an increase in plasma norepinephrine. Perit Dial Int 2000;20(3):322-7.

[35] de Jesus Ventura M, Amato D, Correa-Rotter R, Paniagua R. Relationship between fill volume, intraperitoneal pressure, body size, and subjective discomfort perception in CAPD patients. Mexican Nephrology Collaborative Study Group. Perit Dial Int 2000;20(2):188-93.

[36] Paniagua R, Ventura Mde J, Rodriguez E, Sil J, Galindo T, Hurtado ME, Alcantara G, Chimalpopoca A, Gonzalez I, Sanjurjo A, Barron L, Amato D, Mujais S. Impact of fill volume on peritoneal clearances and cytokine appearance in peritoneal dialysis. Perit Dial Int 2004;24(2):156-62.

[37] Gastaldello K, Husson C, Dondeyne JP, Vanherweghem JL, Tielemans C. Cytotoxicity of mononuclear cells as induced by peritoneal dialysis fluids: insight into mechanisms that regulate osmotic stress-related apoptosis. Perit Dial Int 2008;28(6):655-66.

[38] Gotloib L. Mechanisms of cell death during peritoneal dialysis. A role for osmotic and oxidative stress. Contrib Nephrol 2009;163:35-44.

[39] Bellocq A, Suberville S, Philippe C, Bertrand F, Perez J, Fouqueray B, Cherqui G, Baud L. Low environmental pH is responsible for the induction of nitric-oxide synthase in macrophages. Evidence for involvement of nuclear factor-kappaB activation. J Biol Chem 1998;273(9):5086-92.

[40] Witowski J, Topley N, Jorres A, Liberek T, Coles GA, Williams JD. Effect of lactate-buffered peritoneal dialysis fluids on human peritoneal mesothelial cell interleukin-6 and prostaglandin synthesis. Kidney Int 1995;47(1):282-93.

[41] Mortier S, Lameire NH, De Vriese AS. The effects of peritoneal dialysis solutions on peritoneal host defense. Perit Dial Int 2004;24(2):123-38.

[42] Johno H, Ogata R, Nakajima S, Hiramatsu N, Kobayashi T, Hara H, Kitamura M. Acidic stress-ER stress axis for blunted activation of NF-kappaB in mesothelial cells exposed to peritoneal dialysis fluid. Nephrol Dial Transplant 2012.

[43] Ogata R, Hiramatsu N, Hayakawa K, Nakajima S, Yao J, Kobayashi T, Kitamura M. Impairment of MCP-1 expression in mesothelial cells exposed to peritoneal dialysis fluid by osmotic stress and acidic stress. Perit Dial Int 2011;31(1):80-9.

[44] 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(1):38-47.

[45] Ha H, Yu MR, Lee HB. High glucose-induced PKC activation mediates TGF-beta 1 and fibronectin synthesis by peritoneal mesothelial cells. Kidney Int 2001;59(2): 463-70.

[46] Lee YJ, Kang DG, Kim JS, Lee HS. Effect of Buddleja officinalis on high-glucose-induced vascular inflammation in human umbilical vein endothelial cells. Exp Biol Med (Maywood) 2008;233(6):694-700.

[47] Booth G, Stalker TJ, Lefer AM, Scalia R. Elevated ambient glucose induces acute inflammatory events in the microvasculature: effects of insulin. Am J Physiol Endocrinol Metab 2001;280(6):E848-56.

[48] Park SH, Lee EG, Kim IS, Kim YJ, Cho DK, Kim YL. Effect of glucose degradation products on the peritoneal membrane in a chronic inflammatory infusion model of peritoneal dialysis in the rat. Perit Dial Int 2004;24(2):115-22.

[49] Leung JC, Chan LY, Li FF, Tang SC, Chan KW, Chan TM, Lam MF, Wieslander A, Lai KN. Glucose degradation products downregulate ZO-1 expression in human peritoneal mesothelial cells: the role of VEGF. Nephrol Dial Transplant 2005;20(7): 1336-49.

[50] Tauer A, Zhang X, Schaub TP, Zimmeck T, Niwa T, Passlick-Deetjen J, Pischetsrieder M. Formation of advanced glycation end products during CAPD. Am J Kidney Dis 2003;41(3 Suppl 1):S57-60.

[51] Schwedler S, Schinzel R, Vaith P, Wanner C. Inflammation and advanced glycation end products in uremia: simple coexistence, potentiation or causal relationship? Kidney Int Suppl 2001;78:S32-6.

[52] Lai KN, Lai KB, Lam CW, Chan TM, Li FK, Leung JC. Changes of cytokine profiles during peritonitis in patients on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2000;35(4):644-52.

[53] Leung JC, Lam MF, Tang SC, Chan LY, Tam KY, Yip TP, Lai KN. Roles of neutrophil gelatinase-associated lipocalin in continuous ambulatory peritoneal dialysis-related peritonitis. J Clin Immunol 2009;29(3):365-78.

[54] Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wagner H, Takeda K, Akira S. A Toll-like receptor recognizes bacterial DNA. Nature 2000;408(6813):740-5.

[55] Szeto CC, Kwan BC, Chow KM, Lai KB, Chung KY, Leung CB, Li PK. Endotoxemia is related to systemic inflammation and atherosclerosis in peritoneal dialysis patients. Clin J Am Soc Nephrol 2008;3(2):431-6.

[56] Wanner C, Zimmermann J, Schwedler S, Metzger T. Inflammation and cardiovascular risk in dialysis patients. Kidney Int Suppl 2002(80):99-102.

[57] De Vriese AS. The John F. Maher Recipient Lecture 2004: Rage in the peritoneum. Perit Dial Int 2005;25(1):8-11.

[58] Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, Avila C, Kambham N, Bierhaus A, Nawroth P, Neurath MF, Slattery T, Beach D, McClary J, Nagashima M, Morser J, Stern D, Schmidt AM. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 1999;97(7):889-901.

[59] Veloso CA, Fernandes JS, Volpe CM, Fagundes-Netto FS, Reis JS, Chaves MM, Nogueira-Machado JA. TLR4 and RAGE: similar routes leading to inflammation in type 2 diabetic patients. Diabetes Metab 2011;37(4):336-42.

[60] Nogueira-Machado JA, Volpe CM, Veloso CA, Chaves MM. HMGB1, TLR and RAGE: a functional tripod that leads to diabetic inflammation. Expert Opin Ther Targets 2011;15(8):1023-35.

[61] Yang H, Rivera Z, Jube S, Nasu M, Bertino P, Goparaju C, Franzoso G, Lotze MT, Krausz T, Pass HI, Bianchi ME, Carbone M. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. Proc Natl Acad Sci U S A 2010;107(28):12611-6.

[62] Teta D. Adipokines as uremic toxins. J Ren Nutr 2012;22(1):81-5.

[63] Duranton F, Cohen G, De Smet R, Rodriguez M, Jankowski J, Vanholder R, Argiles A. Normal and pathologic concentrations of uremic toxins. J Am Soc Nephrol 2012;23(7):1258-70.

[64] Huang JW, Yen CJ, Chiang HW, Hung KY, Tsai TJ, Wu KD. Adiponectin in peritoneal dialysis patients: a comparison with hemodialysis patients and subjects with normal renal function. Am J Kidney Dis 2004;43(6):1047-55.

[65] Fernandez-Riejos P, Najib S, Santos-Alvarez J, Martin-Romero C, Perez-Perez A, Gonzalez-Yanes C, Sanchez-Margalet V. Role of leptin in the activation of immune cells. Mediators Inflamm 2010;2010:568343.

[66] Teta D, Tedjani A, Burnier M, Bevington A, Brown J, Harris K. Glucose-containing peritoneal dialysis fluids regulate leptin secretion from 3T3-L1 adipocytes. Nephrol Dial Transplant 2005;20(7):1329-35.

[67] Leung JC, Chan LY, Tang SC, Chu KM, Lai KN. Leptin induces TGF-beta synthesis through functional leptin receptor expressed by human peritoneal mesothelial cell. Kidney Int 2006;69(11):2078-86.

[68] Ouchi N, Walsh K. A novel role for adiponectin in the regulation of inflammation. Arterioscler Thromb Vasc Biol 2008;28(7):1219-21.

[69] Huh JY, Seo EY, Lee HB, Ha H. Glucose-based peritoneal dialysis solution suppresses adiponectin synthesis through oxidative stress in an experimental model of peritoneal dialysis. Perit Dial Int 2012;32(1):20-8.

[70] Noh H, Kim JS, Han KH, Lee GT, Song JS, Chung SH, Jeon JS, Ha H, Lee HB. Oxidative stress during peritoneal dialysis: implications in functional and structural changes in the membrane. Kidney Int 2006;69(11):2022-8.

[71] Ambade A, Mandrekar P. Oxidative stress and inflammation: essential partners in alcoholic liver disease. Int J Hepatol 2012;2012:853175.

[72] 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(4):1170-9.

[73] Aufricht C, Endemann M, Bidmon B, Arbeiter K, Mueller T, Regele H, Herkner K, Eickelberg O. Peritoneal dialysis fluids induce the stress response in human mesothelial cells. Perit Dial Int 2001;21(1):85-8.

[74] Arbeiter K, Bidmon B, Endemann M, Bender TO, Eickelberg O, Ruffingshofer D, Mueller T, Regele H, Herkner K, Aufricht C. Peritoneal dialysate fluid composition determines heat shock protein expression patterns in human mesothelial cells. Kidney Int 2001;60(5):1930-7.

[75] Boehm M, Bergmeister H, Kratochwill K, Vargha R, Lederhuber H, Aufricht C. Cellular stress-response modulators in the acute rat model of peritoneal dialysis. Pediatr Nephrol 2010;25(1):169-72.

[76] Bender TO, Riesenhuber A, Endemann M, Herkner K, Witowski J, Jorres A, Aufricht C. Correlation between HSP-72 expression and IL-8 secretion in human mesothelial cells. Int J Artif Organs 2007;30(3):199-203.

[77] Jameson JM, Cauvi G, Sharp LL, Witherden DA, Havran WL. Gammadelta T cell-induced hyaluronan production by epithelial cells regulates inflammation. J Exp Med 2005;201(8):1269-79.

[78] Nathan C. Points of control in inflammation. Nature 2002;420(6917):846-52.

[79] Yung S, Coles GA, Williams JD, Davies M. The source and possible significance of hyaluronan in the peritoneal cavity. Kidney Int 1994;46(2):527-33.

[80] Yung S, Thomas GJ, Stylianou E, Williams JD, Coles GA, Davies M. Source of peritoneal proteoglycans. Human peritoneal mesothelial cells synthesize and secrete mainly small dermatan sulfate proteoglycans. Am J Pathol 1995;146(2):520-9.

[81] Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiol Rev 2011;91(1):221-64.

[82] Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, Prestwich GD, Mascarenhas MM, Garg HG, Quinn DA, Homer RJ, Goldstein DR, Bucala R, Lee PJ, Medzhitov R, Noble PW. Regulation of lung injury and repair by Toll-like receptors and hyaluronan. Nat Med 2005;11(11):1173-9.

[83] Schaefer L, Babelova A, Kiss E, Hausser HJ, Baliova M, Krzyzankova M, Marsche G, Young MF, Mihalik D, Gotte M, Malle E, Schaefer RM, Grone HJ. The matrix component biglycan is proinflammatory and signals through Toll-like receptors 4 and 2 in macrophages. J Clin Invest 2005;115(8):2223-33.

[84] Hildebrand A, Romaris M, Rasmussen LM, Heinegard D, Twardzik DR, Border WA, Ruoslahti E. Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor beta. Biochem J 1994;302 (Pt 2): 527-34.

[85] Tufvesson E, Westergren-Thorsson G. Tumour necrosis factor-alpha interacts with biglycan and decorin. FEBS Lett 2002;530(1-3):124-8.

[86] Brauner A, Hylander B, Wretlind B. Tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-1 receptor antagonist in dialysate and serum from patients on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1996;27(3):402-8.

[87] van de Veerdonk FL, Netea MG, Dinarello CA, Joosten LA. Inflammasome activation and IL-1beta and IL-18 processing during infection. Trends Immunol 2011;32(3): 110-6.

[88] Netea MG, Simon A, van de Veerdonk F, Kullberg BJ, Van der Meer JW, Joosten LA. IL-1beta processing in host defense: beyond the inflammasomes. PLoS Pathog 2010;6(2):e1000661.

[89] Petrilli V, Dostert C, Muruve DA, Tschopp J. The inflammasome: a danger sensing complex triggering innate immunity. Curr Opin Immunol 2007;19(6):615-22.

[90] Babelova A, Moreth K, Tsalastra-Greul W, Zeng-Brouwers J, Eickelberg O, Young MF, Bruckner P, Pfeilschifter J, Schaefer RM, Grone HJ, Schaefer L. Biglycan, a dan-

ger signal that activates the NLRP3 inflammasome via toll-like and P2X receptors. J Biol Chem 2009;284(36):24035-48.

[91] Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. Annu Rev Cell Dev Biol 2007;23:435-61.

[92] Yeh ET. CRP as a mediator of disease. Circulation 2004;109(21 Suppl 1):II11-4.

[93] Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331(7):417-24.

[94] Lacson E, Jr., Levin NW. C-reactive protein and end-stage renal disease. Semin Dial 2004;17(6):438-48.

[95] Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103(21):2531-4.

[96] Soni SS, Cruz D, Bobek I, Chionh CY, Nalesso F, Lentini P, de Cal M, Corradi V, Virzi G, Ronco C. NGAL: a biomarker of acute kidney injury and other systemic conditions. Int Urol Nephrol 2010;42(1):141-50.

[97] Bolignano D, Coppolino G, Lacquaniti A, Buemi M. From kidney to cardiovascular diseases: NGAL as a biomarker beyond the confines of nephrology. Eur J Clin Invest 2010;40(3):273-6.

[98] Li FK, Davenport A, Robson RL, Loetscher P, Rothlein R, Williams JD, Topley N. Leukocyte migration across human peritoneal mesothelial cells is dependent on directed chemokine secretion and ICAM-1 expression. Kidney Int 1998;54(6):2170-83.

[99] Fain JN, Madan AK. Regulation of monocyte chemoattractant protein 1 (MCP-1) release by explants of human visceral adipose tissue. Int J Obes (Lond) 2005;29(11): 1299-307.

[100] Takayama F, Miyazaki T, Aoyama I, Tsukushi S, Sato M, Yamazaki C, Shimokata K, Niwa T. Involvement of interleukin-8 in dialysis-related arthritis. Kidney Int 1998;53(4):1007-13.

[101] Tekstra J, Visser CE, Tuk CW, Brouwer-Steenbergen JJ, Burger CW, Krediet RT, Beelen RH. Identification of the major chemokines that regulate cell influxes in peritoneal dialysis patients. J Am Soc Nephrol 1996;7(11):2379-84.

[102] Lai KN, Lam MF, Leung JC, Chan LY, Lam CW, Chan IH, Chan HW, Li CS, Wong SS, Ho YW, Cheuk A, Tong MK, Tang SC. A study of the clinical and biochemical profile of peritoneal dialysis fluid low in glucose degradation products. Perit Dial Int 2012;32(3):280-91.

[103] Lai KN, Leung JC. Peritoneal adipocytes and their role in inflammation during peritoneal dialysis. Mediators Inflamm 2010;2010:495416.

[104] Kajiyama H, Shibata K, Ino K, Nawa A, Mizutani S, Kikkawa F. Possible involvement of SDF-1alpha/CXCR4-DPPIV axis in TGF-beta1-induced enhancement of migratory potential in human peritoneal mesothelial cells. Cell Tissue Res 2007;330(2):221-9.

[105] Papagianni A, Kokolina E, Kalovoulos M, Vainas A, Dimitriadis C, Memmos D. Carotid atherosclerosis is associated with inflammation, malnutrition and intercellular adhesion molecule-1 in patients on continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2004;19(5):1258-63.

[106] Wang AY, Lam CW, Wang M, Woo J, Chan IH, Lui SF, Sanderson JE, Li PK. Circulating soluble vascular cell adhesion molecule 1: relationships with residual renal function, cardiac hypertrophy, and outcome of peritoneal dialysis patients. Am J Kidney Dis 2005;45(4):715-29.

[107] Barrington R, Zhang M, Fischer M, Carroll MC. The role of complement in inflammation and adaptive immunity. Immunol Rev 2001;180:5-15.

[108] Tang S, Leung JC, Chan LY, Tsang AW, Chen CX, Zhou W, Lai KN, Sacks SH. Regulation of complement C3 and C4 synthesis in human peritoneal mesothelial cells by peritoneal dialysis fluid. Clin Exp Immunol 2004;136(1):85-94.

[109] Mizuno T, Mizuno M, Morgan BP, Noda Y, Yamada K, Okada N, Yuzawa Y, Matsuo S, Ito Y. Specific collaboration between rat membrane complement regulators Crry and CD59 protects peritoneum from damage by autologous complement activation. Nephrol Dial Transplant 2011;26(6):1821-30.

[110] Mizuno M, Ito Y, Mizuno T, Harris CL, Suzuki Y, Okada N, Matsuo S, Morgan BP. Membrane complement regulators protect against fibrin exudation increases in a severe peritoneal inflammation model in rats. Am J Physiol Renal Physiol 2012;302(10):F1245-51.

[111] Yanez-Mo M, Lara-Pezzi E, Selgas R, Ramirez-Huesca M, Dominguez-Jimenez C, Jimenez-Heffernan JA, Aguilera A, Sanchez-Tomero JA, Bajo MA, Alvarez V, Castro MA, del Peso G, Cirujeda A, Gamallo C, Sanchez-Madrid F, Lopez-Cabrera M. Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells. N Engl J Med 2003;348(5):403-13.

[112] Yang AH, Chen JY, Lin JK. Myofibroblastic conversion of mesothelial cells. Kidney Int 2003;63(4):1530-9.

[113] Gao D, Zhao ZZ, Liang XH, Li Y, Cao Y, Liu ZS. Effect of peritoneal dialysis on expression of vascular endothelial growth factor, basic fibroblast growth factor and endostatin of the peritoneum in peritoneal dialysis patients. Nephrology (Carlton) 2011;16(8):736-42.

[114] Leung JC, Chan LY, Tam KY, Tang SC, Lam MF, Cheng AS, Chu KM, Lai KN. Regulation of CCN2/CTGF and related cytokines in cultured peritoneal cells under conditions simulating peritoneal dialysis. Nephrol Dial Transplant 2009;24(2):458-69.

[115] Friedman JM. Obesity in the new millennium. Nature 2000;404(6778):632-4.

[116] Yang AH, Huang SW, Chen JY, Lin JK, Chen CY. Leptin augments myofibroblastic conversion and fibrogenic activity of human peritoneal mesothelial cells: a functional implication for peritoneal fibrosis. Nephrol Dial Transplant 2007;22(3):756-62.

[117] Teta D, Maillard M, Halabi G, Burnier M. The leptin/adiponectin ratio: potential implications for peritoneal dialysis. Kidney Int Suppl 2008(108):S112-8.

[118] Zemel D, Betjes MG, Dinkla C, Struijk DG, Krediet RT. Analysis of inflammatory mediators and peritoneal permeability to macromolecules shortly before the onset of overt peritonitis in patients treated with CAPD. Perit Dial Int 1995;15(2):134-41.

[119] Mariano F, Tetta C, Montrucchio G, Cavalli PL, Camussi G. Role of alpha 1-proteinase inhibitor in restraining peritoneal inflammation in CAPD patients. Kidney Int 1992;42(3):735-42.

[120] Clark SR, Guy CJ, Scurr MJ, Taylor PR, Kift-Morgan AP, Hammond VJ, Thomas CP, Coles B, Roberts GW, Eberl M, Jones SA, Topley N, Kotecha S, O'Donnell VB. Esterified eicosanoids are acutely generated by 5-lipoxygenase in primary human neutrophils and in human and murine infection. Blood 2011;117(6):2033-43.

[121] Morishita Y, Watanabe M, Hirahara I, Akimoto T, Muto S, Kusano E. Level of 8-OHdG in drained dialysate appears to be a marker of peritoneal damage in peritoneal dialysis. Int J Nephrol Renovasc Dis 2012;5:9-14.

[122] Hirahara I, Ogawa Y, Kusano E, Asano Y. Activation of matrix metalloproteinase-2 causes peritoneal injury during peritoneal dialysis in rats. Nephrol Dial Transplant 2004;19(7):1732-41.

[123] Nishina M, Endoh M, Suzuki D, Tanabe R, Endoh H, Hirahara I, Sakai H. Neutral-pH peritoneal dialysis solution improves peritoneal function and decreases matrix metalloproteinase-2 (MMP-2) in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Clin Exp Nephrol 2004;8(4):339-43.

[124] Hirahara I, Inoue M, Okuda K, Ando Y, Muto S, Kusano E. The potential of matrix metalloproteinase-2 as a marker of peritoneal injury, increased solute transport, or progression to encapsulating peritoneal sclerosis during peritoneal dialysis--a multicentre study in Japan. Nephrol Dial Transplant 2007;22(2):560-7.

[125] Musial K, Zwolinska D. Hsp27 as a marker of cell damage in children on chronic dialysis. Cell Stress Chaperones 2012.

[126] Alscher DM, Braun N, Biegger D, Fritz P. Peritoneal mast cells in peritoneal dialysis patients, particularly in encapsulating peritoneal sclerosis patients. Am J Kidney Dis 2007;49(3):452-61.

[127] Kondo S, Kagami S, Kido H, Strutz F, Muller GA, Kuroda Y. Role of mast cell tryptase in renal interstitial fibrosis. J Am Soc Nephrol 2001;12(8):1668-76.

[128] Cavallini N, Delbro D, Tobin G, Braide M. Neuropeptide release augments serum albumin loss and reduces ultrafiltration in peritoneal dialysis. Perit Dial Int 2012;32(2): 168-76.

[129] Bird SD, Walker RJ. Mast cell histamine-induced calcium transients in cultured human peritoneal mesothelial cells. Perit Dial Int 1998;18(6):626-36.

[130] Lai KN, Li PK, Woo KS, Lui SF, Leung JC, Law E, Nicholls MG. Vasoactive hormones in uremic patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 1991;35(5):218-23.

[131] Duman S. The renin-angiotensin system and peritoneal dialysis. Perit Dial Int 2004;24(1):5-9.

[132] 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.

[133] Leung JC, Chan LY, Tang SC, Lam MF, Chow CW, Lim AI, Lai KN. Oxidative damages in tubular epithelial cells in IgA nephropathy: role of crosstalk between angiotensin II and aldosterone. J Transl Med 2011;9:169.

[134] Catalan MP, Reyero A, Egido J, Ortiz A. Acceleration of neutrophil apoptosis by glucose-containing peritoneal dialysis solutions: role of caspases. J Am Soc Nephrol 2001;12(11):2442-9.

[135] Ha H, Yu MR, Choi HN, Cha MK, Kang HS, Kim MH, Lee HB. Effects of conventional and new peritoneal dialysis solutions on human peritoneal mesothelial cell viability and proliferation. Perit Dial Int 2000;20 Suppl 5:S10-8.

[136] Jorres A, Williams JD, Topley N. Peritoneal dialysis solution biocompatibility: inhibitory mechanisms and recent studies with bicarbonate-buffered solutions. Perit Dial Int 1997;17 Suppl 2:S42-6.

[137] Hekking LH, Zareie M, Driesprong BA, Faict D, Welten AG, de Greeuw I, Schadee-Eestermans IL, Havenith CE, van den Born J, ter Wee PM, Beelen RH. Better preservation of peritoneal morphologic features and defense in rats after long-term exposure to a bicarbonate/lactate-buffered solution. J Am Soc Nephrol 2001;12(12): 2775-86.

[138] 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(1):208-16.

[139] Furuya R, Odamaki M, Kumagai H, Hishida A. Beneficial effects of icodextrin on plasma level of adipocytokines in peritoneal dialysis patients. Nephrol Dial Transplant 2006;21(2):494-8.

[140] Martikainen T, Teppo AM, Gronhagen-Riska C, Ekstrand A. Benefit of glucose-free dialysis solutions on glucose and lipid metabolism in peritoneal dialysis patients. Blood Purif 2005;23(4):303-10.

[141] Sisca S, Maggiore U. Beneficial effect of icodextrin on the hypertriglyceridemia of CAPD patients. Perit Dial Int 2002;22(6):727-9.

[142] Martikainen T, Ekstrand A, Honkanen E, Teppo AM, Gronhagen-Riska C. Do interleukin-6, hyaluronan, soluble intercellular adhesion molecule-1 and cancer antigen 125 in dialysate predict changes in peritoneal function? A 1-year follow-up study. Scand J Urol Nephrol 2005;39(5):410-6.

[143] Moriishi M, Kawanishi H, Watanabe H, Tsuchiya S. Effect of icodextrin-based peritoneal dialysis solution on peritoneal membrane. Adv Perit Dial 2005;21:21-4.

[144] Parikova A, Zweers MM, Struijk DG, Krediet RT. Peritoneal effluent markers of inflammation in patients treated with icodextrin-based and glucose-based dialysis solutions. Adv Perit Dial 2003;19:186-90.

[145] Yang SY, Huang JW, Shih KY, Hsu SP, Chu PL, Chu TS, Wu KD. Factors associated with increased plasma homocysteine in patients using an amino acid peritoneal dialysis fluid. Nephrol Dial Transplant 2005;20(1):161-6.

[146] Martikainen TA, Teppo AM, Gronhagen-Riska C, Ekstrand AV. Glucose-free dialysis solutions: inductors of inflammation or preservers of peritoneal membrane? Perit Dial Int 2005;25(5):453-60.

[147] Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, Passlick-Deetjen J. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int 2004;66(1):408-18.

[148] Jones S, Holmes CJ, Krediet RT, Mackenzie R, Faict D, Tranaeus A, Williams JD, Coles GA, Topley N. Bicarbonate/lactate-based peritoneal dialysis solution increases cancer antigen 125 and decreases hyaluronic acid levels. Kidney Int 2001;59(4): 1529-38.

[149] Cooker LA, Luneburg P, Holmes CJ, Jones S, Topley N. Interleukin-6 levels decrease in effluent from patients dialyzed with bicarbonate/lactate-based peritoneal dialysis solutions. Perit Dial Int 2001;21 Suppl 3:S102-7.

[150] Fusshoeller A, Plail M, Grabensee B, Plum J. Biocompatibility pattern of a bicarbonate/lactate-buffered peritoneal dialysis fluid in APD: a prospective, randomized study. Nephrol Dial Transplant 2004;19(8):2101-6.

[151] Lai KN, Leung JC. Inflammation in peritoneal dialysis. Nephron Clin Pract 2010;116(1):c11-8.