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Membrane Biology During Peritoneal Dialysis

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1. Introduction

Peritoneal dialysis (PD) is a life-supporting renal replacement therapy used by 10-15% of patients with end-stage renal failure worldwide. The success of long-term PD depends entirely on the longevity and integrity of the peritoneal membrane. The peritoneum is covered by a mesothelial monolayer beneath which is a basement membrane and submesothelial layer that contains collagen, fibroblasts, adipose tissue, blood vessels and lymphatics. During PD, peritoneal cells are repeatedly exposed to a non-physiological hypertonic environment with high glucose content and low pH. Mesothelial cells (MCs) play an important role in regulating the inflammatory response in the peritoneal cavity: they produce pro-inflammatory cytokines and chemoattractants. By secreting these chemokines or cytokines, MCs contribute to the recruitment of leukocytes following the expression of adhesion molecules. Chronic changes in the peritoneum with fibrosis develop after years of peritoneal dialysis. The most marked changes are in cases of severe and recurrent peritonitis. Others have made similar observations that long-term exposure to peritoneal dialysis solutions appears to increase fibrosis and the probability of ultrafiltration failure. Encapsulating peritoneal sclerosis represents the most severe and fatal complication of membrane failure.

Conventional peritoneal dialysis fluids (PDFs) make use of the osmotic gradient generated by glucose. Years of exposure to PDFs compounded with peritonitis result in the formation of an avascular layer of interstitial matrix and plasma proteins in the sub-mesothelial compact zone and an epithelial-to-mesenchymal transition (EMT) of mesothelial cells [1]. The fibrotic process in the peritoneal membrane is developed following acute and chronic release of inflammatory mediators related to PD. Independent extrinsic and intrinsic events (Table 1) contribute to chronic inflammation in patients on PD leading to complications including peritoneal membrane ultrafiltration failure, fluid overload, protein energy wasting and even atherosclerosis.

2. Extrinsic factors

2.1 Uremia

It has been shown that the peritoneum of uremic and current hemodialysis patients who have never exposed to PD is abnormal as well; this finding implies that uremia induces inflammation in the peritoneum [2]. There is a marked increase in vasculopathy below the compact zone.

Extrinsic Factors
• Uremia • PDFs • Infections – especially peritonitis
Intrinsic Factors
• Mesothelium • Sub-mesothelial compact zone • Sub-mesothelial blood vessels • Epithelial-to-mesenchymal transition (EMT) • Receptors for GDPs and AGE • Macrophages • Peritoneal adipocytes

Table 1. Events promoting chronic inflammation in PD

2.2 Peritoneal Dialysis Fluids (PDFs)

D-glucose is a reactive compound that exerts effect on the mesothelial cells directly by up-regulating the synthesis of transforming growth factor-β (TGF-β) and connective tissue growth factor by MCs or through its degradation pathway into glucose degradation products (GDPs) and formation of advanced glycation end-products (AGEs). Exposure to GDPs leads to enhanced cytotoxic damage and pro-inflammatory response in MCs stimulating the production of vascular endothelial growth factor (VEGF) that enhances vascular permeability and angiogenesis. GDPs also down-regulate the expression of intercellular tight junction proteins like ZO-1, occludine and claudin-1 in MCs, again via VEGF [3].

Factors such as the buffer, glucose or GDPs formed during heat sterilization, are critical in determining the biocompatibility of different PDFs. Mesothelial cell repair (remesothelialization) after exposure to GDPs is impaired, independent of D-glucose concentration. After exposure of mesenchymal cells to PDFs, the expression of cytokeratin 18 and E-cadherin is reduced while the expression of α-SMA and vimentin as a sign of EMT is increased [4]. Expression of intercellular tight junction proteins is down-regulated after incubation with PDFs.

2.3 Infection

Bacterial peritonitis is associated with a sharp increase in total cell and neutrophil counts (400-fold) in PDFs up to 2-3 weeks after peritonitis despite clinical remission [5]. There was a progressive increase in the percentage of mesothelial cells or dead cells in the total cell population in PDFs. Dialysate levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF–α) and TGF-β increased markedly on day 1 before their levels decreased gradually [5,6]. This active release of pro-inflammatory cytokines and sclerogenic growth factors may continue some time despite clinical remission of peritonitis. The peritoneal cytokine networks after peritonitis may potentially affect the physiological properties of the peritoneal membrane [5].

3. Intrinsic factors

3.1 Mesothelium

Peritoneal mesothelial cells are biologically active and play distinctive biological roles other than local host defense [3]. The MCs are sensitive to the effect of pH despite the

conventional PDFs are usually buffered from pH of 5.2–7.4 in 15–30 min in clinical studies while TGF-β production by MCs is less with bicarbonate-buffered PDF. Glucose in the PDF can bring about major changes in the environment of the mesothelial cells as well as that of the cells underlying the mesothelium and the production of various cytokines are increased as a result of this exposure (Table 2). The peritoneal membrane also synthesizes prosteoglycans, expresses AGE receptors and produces aquaporins [3,7]. It is noteworthy that glucose may exert little effect on the synthesis of specific mediators, such as VEGF yet its synthesis is greatly enhanced by GDPs or AGE. Serial peritoneal biopsy study shows denudation of the mesothelial monolayer as early as six months after maintenance PD.

- Synthesis of chemokines: MCP-1, RANTES, Interferon-γ-inducible protein-10
- Synthesis of fibrogenic cytokines – TGF-β, bFGF
- Synthesis of prosteoglycans
- Induction of angiogenesis – VEGF
- Expression of AGE receptors

Table 2. Biological role of peritoneal mesothelium

3.2 Sub-mesothelial compact zone

After years of continuous peritoneal dialysis, a good percentage of patients would have marked increase in the thickness of the submesothelial compact zone. The layer resembles scar tissue with a relatively amorphous, avascular appearance. Animal studies reveal that a spotty inflammation is detected at different places of the peritoneum in the first few weeks of exposure to PDF. With time, these areas of inflammation and sclerosis gradually coalesce and become more uniform to cover much of the peritoneum that is in contact with the PDF. As the fibrosis becomes more uniform, the patient will gradually lose ultrafiltration.

3.3 Sub-mesothelial blood vessels

In parallel with fibrosis, the peritoneum shows a progressive increase in capillary number (angiogenesis) and vasculopathy, which are involved in both the elevation of small solute transport across the peritoneal membrane and ultrafiltration failure. GDPs stimulate VEGF production by MCs [8]. Local production of VEGF during PD appears to play a central role in the processes leading to peritoneal neo-angiogenesis and functional decline. The changes in the structure of the peritoneal function over time on PD as found in functional tests has been confirmed in biopsy studies performed on patients [2]. These show both neo-angiogenesis and fibrosis as the underlying morphological changes contributing to these phenomena. As mentioned previously, uptake of the glucose by sub-mesothelial blood vessels will be quite rapid following increased permeability due to abnormal angiogenic vessels and the increased surface area of the microvasculature. This results in dissipation of the osmotic driving force through increased area and solute transport. In addition, disruption of intercellular tight junction in MCs may occur following down-regulation of ZO-1 expression in which VEGF plays an important role [3,8].

3.4 Epithelial-to-mesenchymal transition (EMT)

Chronic exposure of the mesothelium to sterile PDFs may result in an EMT. Local inflammation and oxidative stress, which results from the continuous peritoneal injury,

accelerate the EMT of peritoneal mesothelial cells resulting in peritoneal fibrosis and ultrafiltration failure. EMT is a process by which the MCs undergo a progressive loss of epithelial phenotype and acquire fibroblast-like characteristics, which allows these cells to invade the mesothelial stroma contributing to angiogenesis, fibrosis and ultrafiltration failure. Yanez-Mo *et al*. [9] recovered and cultured human MCs from the spent dialysate of 54 stable patients. Eighty-five percent of these patients had no previous peritonitis. Omental fibroblasts were separated from three of omental MCs samples from 39 CAPD patients. There was a transition from an epithelial type of mesothelial cell to a fibroblast-like cell with loss of normal markers of the mesothelium and phenotypic changes following progressive and continuous exposure to PDFs. For patients who were exposed to dialysate for more than 12 months, their mesothelial cells changed from 75% cobblestone phenotype to less than 30% with the remainder being fibroblast-like. In some patients they observed that in less than 9 months there was loss of cytokeratin in the mesothelial cell layer. These findings suggest chronic exposure to the peritoneum to the current glucose-based PDFs could lead to morphologic and phenotypic changes in the mesothelium with 24 months.

Transforming growth factor-β, more specifically TGF-β1, is one of the main mediators of the PD solutions' profibrotic effects through the Smads 2 and 3 pathways. These effects include fibroblast activation, collagen deposition, inhibition of fibrinolysis, maintenance of fibrosis and neoangiogenesis [3]. Acting through the Smad pathway, TGF-β induces β-catenin formation which in conjunction with Activator Protein-1 activates matrix metalloproteinase-9 expression facilitating the invasion of the extracellular matrix [10]. Interestingly, angiotensin II inhibitors (which are TGF-β activity suppressors) have recently been shown to reduce peritoneal fibrosis and neoangiogenesis, as well as to prevent the increase of small solute transport in long-term PD patients [11]. Non-viral microbubble-delivery of Smad7 transgene markedly abolishes the peritoneal fibrosis induced by glucose-containing PDF [12]. Neutrophil gelatinase-associated lipocalin (NGAL) is specifically induced in human peritoneal MCs by interleukin-1β. Leung *et al.* [13] demonstrated that incubation of human peritoneal MCs with recombinant NGAL reversed the TGF- β-induced up-regulation of Snail and vimentin but rescued the down-regulation of E-cadherin. Their *in vitro* data suggest that NGAL may exert a protective effect in modulating the EMT activated following peritonitis.

Lately, Bajo *et al*. [14] demonstrated a clear association between GDPs present in conventional heat-sterilized PDFs and the induction of EMT in the peritoneal membrane. To date, no study has investigated the direct correlation between the inflammatory environment created as a consequence of recurrent peritonitis episodes and EMT, but many of the inflammatory cytokines known to be involved in driving EMT such as IL-1β, tumor necrosis factor-α (TNF-α) and TGF-β are present at high concentrations within the peritoneal membrane during peritonitis, and more importantly perhaps, the levels of these cytokines may remain elevated after the acute inflammatory response has subsided [5]. Clearly, the constant exposure of the mesothelial cells to increased levels of inflammatory cytokines and growth factors that have a known role to play in driving EMT could significantly increase the process of EMT-driven membrane fibrosis. In their study, Bajo et al. [14] reported no correlation between number of previous peritonitis episodes and mesothelial cell EMT observed in these patients; however, their results do suggest that the severity and duration of the peritonitis episode may supersede the protective effects of the low-GDP PDFs.

3.5 Receptors for GDPs and AGE

AGEs have been detected immunohistochemically in the peritoneum of PD patients. Receptor for advanced glycation end-products (RAGE) is the best characterized signal transduction receptor for AGEs. Primarily binding of AGEs to their receptor was regarded as a scavenger receptor involved in AGE removal and AGE clearance. However, ligand binding to RAGE results in an activation of key signal transduction pathways, such as NF-κB and multiple cellular signaling cascades like activation of MAP kinase. Local interaction between RAGE and AGEs/GDPs leads to the development of peritoneal inflammation, neo-angiogenesis and, finally, fibrosis. Anti-RAGE antibody partially prevents the development of submesothelial and interstitial fibrosis and EMT in an animal model of peritoneal fibrosis [15]. Aminoguanidine (AG) prevents formation of AGE. Supplementation of AG to PDF showed inhibitory effects on peritoneal AGE accumulation, mesothelial denudation, submesothelial monocyte infiltration, peritoneal permeability and ultrafiltration, and preserved the functional capacity of peritoneal macrophages in the rat. PDF-induced fibrosis was significantly reduced by AG [16]. The use of AG in human is limited by its pH and toxicity.

It is now evident that RAGE is much more than a single receptor for AGEs or a scavenger receptor; it has a broad repertoire of ligands. The key pathophysiological step seems to be GDP-dependent AGE formation in the uremic milieu, through which an enhanced expression of RAGE in the peritoneum could be observed. Recently, other AGE receptors, including AGE-R-1 (p 60), AGE-R-2 (p 90) and AGE-R-3 (gallectin-3) are also found to be expressed on MCs [17]. Different GDPs exert differential regulation on the regulation and expression of these receptors on human peritoneal MCs [17]. However, the functional significance of these various forms has not yet been completely delineated.

3.6 Macrophages

Resident macrophages increase markedly with bacterial peritonitis and are able to enhance the release of peroxide and pro-inflammatory cytokines including interleukin-1β and TNF-α. TGF-β complementary DNA (cDNA) molecules per macrophage are significantly greater than those of macrophages in non-infective PDFs throughout the peritonitis period [5]. There was no significant correlation between PDFs levels of TGF-β and TGF-β cDNA molecules per macrophage, suggesting that peritoneal macrophages are not the predominant source of TGF-β in PDFs.

4. The “less recognized” inflammatory role of peritoneal adipocytes in PD

Adipose tissue is abundant in omental or mesenteric peritoneum but less so in parietal, intestinal and diaphragmatic peritoneum. Contrary to the prevailing view that adipose tissue functions only as an energy storage depot, compelling evidence reveals that adipocytes can mediate various physiological processes through secretion of an array of mediators and adipokines that include leptin, adiponectin, resistin, TNF-α, IL-6, TGF-β, VEGF and other growth factors [18]. Moreover, adipocytes express receptors for leptin, insulin growth factor-1 (IGF-1), TNF-α, IL-6, TGF-β and may form a network of local autocrine, paracrine and endocrine signals [19]. All of these adipokines exert important endocrine functions in chronic kidney diseases and may also contribute to systemic inflammation in these patients. This is of special significance in patients undergoing PD as

the initiation of treatment is often associated with an increase in fat mass that could be associated with the genetic effect on energy metabolism in addition to glucose absorption from the PDFs [20]. A recent study indicates that an increased fat mass in PD, like in other patient groups, may indeed have adverse metabolic consequences with increased systemic inflammation and worst survival [21]. Interestingly, there is a difference in the release of growth factors between visceral and subcutaneous adipose tissue [22]. The omental adipose tissue, most affected by PD, releases IL-6 two to three folds higher than the subcutaneous fat tissue [23]. The visceral (truncal) fat mass correlates significantly with circulating IL-6 levels but not for non-truncal fat mass [24].

Ultrastructural study reveals that a portion of omental adipocytes protrude from the mesothelial surface, thus may come into direct contact with dialysate [25]. In addition, dialysate may also reach the parietal adipose tissue when the mesothelial monolayer is damaged. It is therefore logical to postulate that with repeated exposure to PDFs and the continuous change in peritoneal physiology during PD, peritoneal adipocytes will inevitably be "activated". Although much work has focused on peritoneal mesothelial cells, scant attention has been paid to the role of peritoneal adipocytes during PD.

5. Crosstalk between peritoneal cells and adipocytes

Leptin is a peptide hormone mainly derived from adipocytes and is cleared principally by the kidney. The serum leptin concentration is increased in patients with chronic renal failure or undergoing dialysis [26,27] and the serum leptin increases by 189% within a month after the initiation of PD treatment [28]. Leptin is also elevated during acute infection, in response to proinflammatory cytokines including IL-1β and TNF-α [26]. In the kidney, leptin stimulates cell proliferation and synthesis of collagen IV and TGF-β in glomerular endothelial cells. In glomerular mesangial cells, leptin increases the glucose transport, up-regulates the expression of TGF-β type II receptor and the synthesis of collagen I through phosphatidylinositol-3-kinase related pathway [26]. Available data suggests that leptin triggers a paracrine interaction between glomerular endothelial and mesangial cells through the increased synthesis of TGF-β in glomerular endothelial cells and upregulated TGF-β receptor expression in mesangial cells. Whether such paracrine interaction is operating between peritoneal adipocytes and MCs remains to be explored. To the best of our knowledge, there is only one previous study on the effect of PDF on adipocytes that demonstrates increased leptin synthesis in a murine adipocyte cell line (3T3-L1) by glucose-containing PDFs [29]. It is likely that proinflammatory mediators released by MCs upon exposure to PDF could induce functional alteration of adjacent adipocytes. The likely candidates are IL-1β and TNF-α, TGF-β, VEGF and IL-6. Indeed, a recent *in vitro* study has shown that IL-6 modulates leptin production and lipid metabolism in human adipose tissue [30]. Using MC and adipocyte cell cultures established in our laboratory, we have shown that high glucose content in dialysate fluid is one of the major culprits that causes structural and functional abnormalities in peritoneal cells during PD [8,31,32]. Glucose significantly increases the protein synthesis of leptin by adipocytes in a dose-dependent manner and up-regulates the expression of leptin receptor, Ob-Rb, in MCs [31]. The increased leptin production by adipocytes and enhanced Ob-Rb expression in MC following exposure to glucose suggest the existence of a cross-talk mechanism between adipocytes and MCs that may be relevant in peritoneal membrane dysfunction developed during peritoneal dialysis.

6. Persistent release of proinflammatory mediators in patients under maintenance PD or after an episode of peritonitis

Patients on maintenance PD have increased intra-peritoneal levels of hyaluronan and cytokines including IL-1β, IL-6 and TGF-β [33,34]. Chronic inflammation remains an important cause of morbidity in patients with end-stage renal failure. The main causes for inflammation in PD patients are PD-related peritonitis, continuous exposure to dialysis solutions and exit site infection [35]. Patients on PD with peritonitis may experience prolonged inflammation even when clinical evaluation suggests resolution of PD-related peritonitis [5]. The highly sensitive C-reactive protein remains significantly higher than baseline even by day 42 after an episode of peritonitis [36].

A longitudinal study conducted in patients treated for PD-related peritonitis also revealed elevation of serum leptin levels during acute peritonitis. The rise was contributed to anorexia in the earlier stage. In contrast, the serum adiponectin levels fell showing an inverse correlation between these two adipokines during acute peritonitis. Furthermore, the protracted course of inflammation even after bacterial cure of peritonitis was likely to cause the loss of lean body mass and to increase mortality [36].

7. Clinical syndrome of chronic inflammation in PD

The above-mentioned dialysis risk factors and certain PD-specific characteristics are associated with the inflammatory burden possibly linking inflammation, increased peritoneal solute transport rate and declined residual renal function to poor outcome. Both local (intra-peritoneal) and systemic inflammation may additively be the cause and consequence of peritoneal membrane failure, and are important prognosticators of mortality in PD patients. Several factors deserve special emphasis. It has been shown that even with apparent clinical remission of PD-related peritonitis, dialysis patients, after an episode of peritonitis, may still be affected by prolonged systemic chronic inflammation. The significantly prolonged inflammation contributed to a poorer nutritional status and higher mortality [36]. The finding is consistent with our previous study that the level of cytokines in the peritoneal effluent remained higher than that in non-infective effluent throughout the 6-week post-peritonitis period in parallel with elevated serum C reactive protein (CRP), despite clinical remission [5]. One-sixth of these patients with prolonged elevation of serum CRP died of a cardiovascular event over a median period of 17 months [37]. Therefore, the prolonged inflammation is likely to potentiate atherogenesis and increase the risk of cardiovascular events.

Other than persistent low-grade inflammation, subclinical malnutrition may be another factor for the high mortality in these patients. Chronic inflammation with atherosclerosis is closely related to malnutrition, forming the malnutrition–inflammation–atherosclerosis (MIA) syndrome [37]. The underlying mechanism for malnourishment is likely to be multifactorial. Possible contributory factors include protein loss in the dialysate, the feeling of fullness due to PDF in abdomen, uremia-associated cachexia caused by leptin signaling through the hypothalamic melanocortin receptor [38], and protein energy wasting. The complications of membrane failure and fluid overload further enhance a higher incidence of cardiovascular events. Our proposal of a hypothetical mechanism of chronic inflammation in PD is shown in Figure 1.

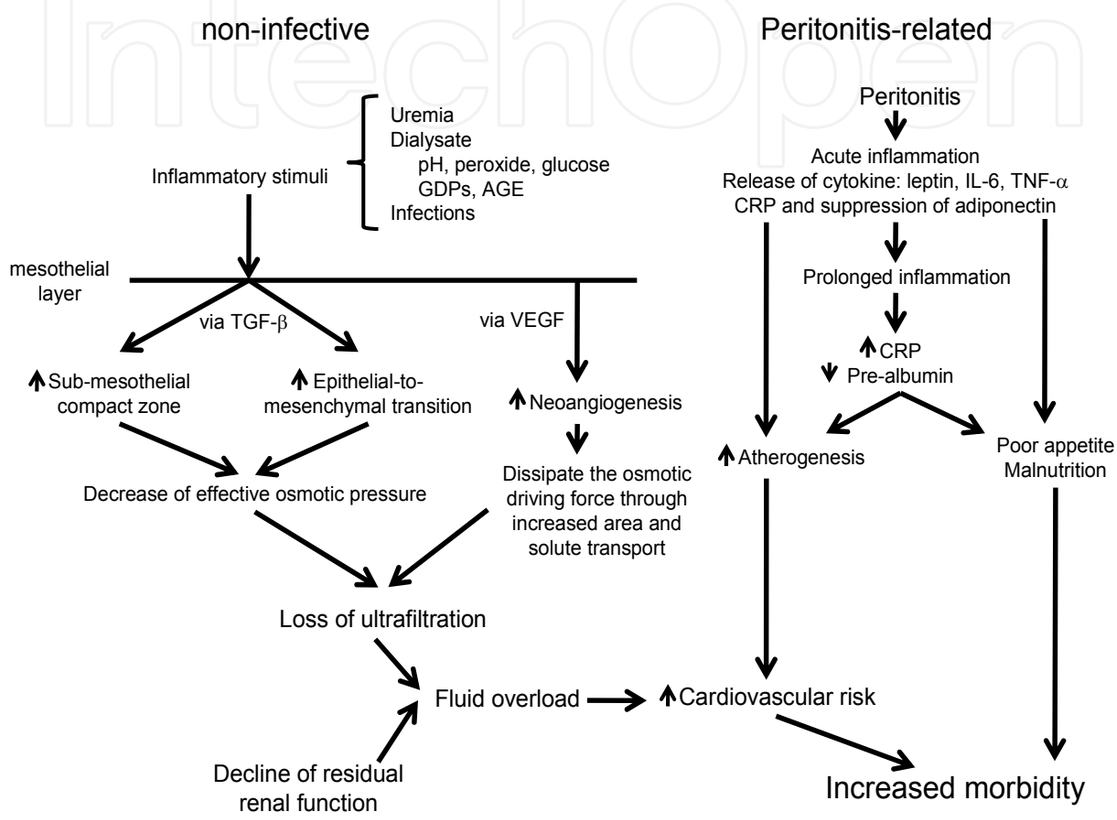

Fig. 1. Interactions between peritonitis-related and non-infective factors leading to chronic inflammation and increased morbidity in peritoneal dialysis patients

8. Newer osmotic agents in PDFs

Low-GDP PDFs clearly have an advantage over high GDP solutions [14,39]. But the continued presence of glucose remains a significant problem for the cells. Alternative hypertonic agents with additive that may prevent chronic inflammation will continue to be a subject of research.

9. Conclusion

During long-term maintenance PD, the peritoneal biology changes with chronic exposure to dialysate. Meticulous attention for chronic inflammation should be practiced in peritoneal dialysis patients, especially following peritonitis. Adequate nutritional support and screening for persistent inflammation are warranted such that the vicious circle like malnutrition–inflammation–atherosclerosis syndrome can be abolished.

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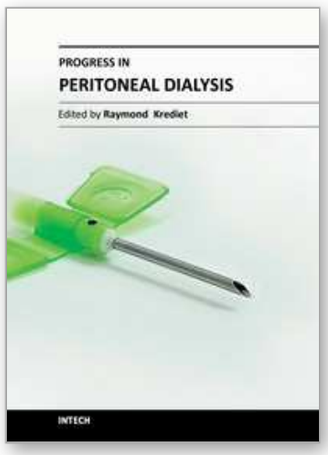

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