

Pathogenesis and treatment of peritoneal membrane failure

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Abstract Peritoneal dialysis (PD) is a viable treatment option for end stage renal disease (ESRD) patients worldwide. PD may provide a survival advantages over hemodialysis (HD) in the early years of treatment. However, the benefits of PD are short-lived, as peritoneal membrane failure ensues in many patients, owing mainly to structural and functional changes in the peritoneal membrane from the use of conventional bio-incompatible PD solutions, which are hyperosmolar, acidic, have lactate buffer and contain high concentrations of glucose and glucose degradation products (GDPs). Current data suggest that chronic exposure of the peritoneum to contemporary PD fluids provokes activation of various inflammatory, fibrogenic and angiogenic cytokines, interplay of which leads to progressive peritoneal fibrosis, vasculopathy and neoangiogenesis. There is emerging evidence that peritoneal vascular changes are mainly responsible for increased solute transport and ultrafiltration failure in long-term PD. However, the precise pathophysiologic mechanisms initiating and propagating peritoneal fibrosis and angiogenesis remain elusive. The protection of the peritoneal membrane from long-term toxic and metabolic effects of high GDP-containing, conventional, glucose-based solutions is a prime objective to improve PD outcome. Recent development of new, more biocompatible, PD solutions should help to preserve peritoneal membrane function, promote ultrafiltration, improve nutritional status and, hopefully, preserve

peritoneal membrane and improve overall PD outcomes. Elucidation of molecular mechanisms involved in the cellular responses leading to peritoneal fibrosis and angiogenesis spurs new therapeutic strategies that might protect the peritoneal membrane against the consequences of long-standing PD.

Keywords Peritoneal dialysis · Peritoneal membrane · Peritoneal membrane failure · New peritoneal dialysis solutions

Introduction

Peritoneal dialysis (PD) has been a successful and effective form of therapy for end stage renal disease (ESRD) globally. It is the preferred form of dialysis modality worldwide for children with ESRD [1]. There is growing evidence to suggest that PD provides at least an equal, if not superior, mode of dialysis compared to hemodialysis (HD) [2]. Most of these outcome data come from adult patients on continuous ambulatory peritoneal dialysis (CAPD). The benefits of PD are, however, limited to the first few years of treatment, and almost 50% of adult, as well as pediatric patients have to be moved to HD within 4 to 5 years because of failure of the technique [3, 4]. Causes of treatment failure include recurrent episodes of peritonitis, loss of residual renal function (RRF), inadequate solute clearance and loss of peritoneal membrane function [3–6]. With innovations in PD techniques, there have been significant improvements in peritonitis rate and solute clearance. However, one major cause of long-term PD failure that remains unaddressed is related to the ongoing peritoneal structural and functional changes from the use of conventional bio-incompatible PD fluids, leading to mem-

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brane failure. This review will focus on the pathogenesis and treatment of peritoneal membrane failure.

Structural changes in the peritoneum during peritoneal dialysis

The efficacy of peritoneal dialysis depends on the structural and functional integrity of the peritoneum, which is a thin layer (40 μm) of membrane lining the peritoneal cavity.

It consists of a mesothelial monolayer and an underlying connective tissue interstitium comprising collagen, mucopolysaccharides, parenchymal cells, blood vessels and lymphatic elements (Fig. 1) [7]. It covers the inner surface of the abdominal wall (parietal peritoneum, 10–15%) and most visceral organs (visceral peritoneum 85–90%). In PD, it is the effective, not the anatomical, peritoneal surface area that is important for solute and water exchange. The effective surface area relates to the contact between the peritoneal fluid and the peritoneal microvasculature. Only a third of the peritoneum is in effective contact with the dialysis solution in the peritoneal cavity. Furthermore, although representing 85% of total anatomical peritoneal surface area, visceral peritoneum contributes only about 30% of the total PD exchange [8]. In normal circumstances, the closed peritoneal cavity contains a very small amount of surfactant-like phospholipid-rich fluid, secreted mainly by mesothelial cells that share structural similarities with surfactant-secreting type 2 alveolar cells [9]. During PD,

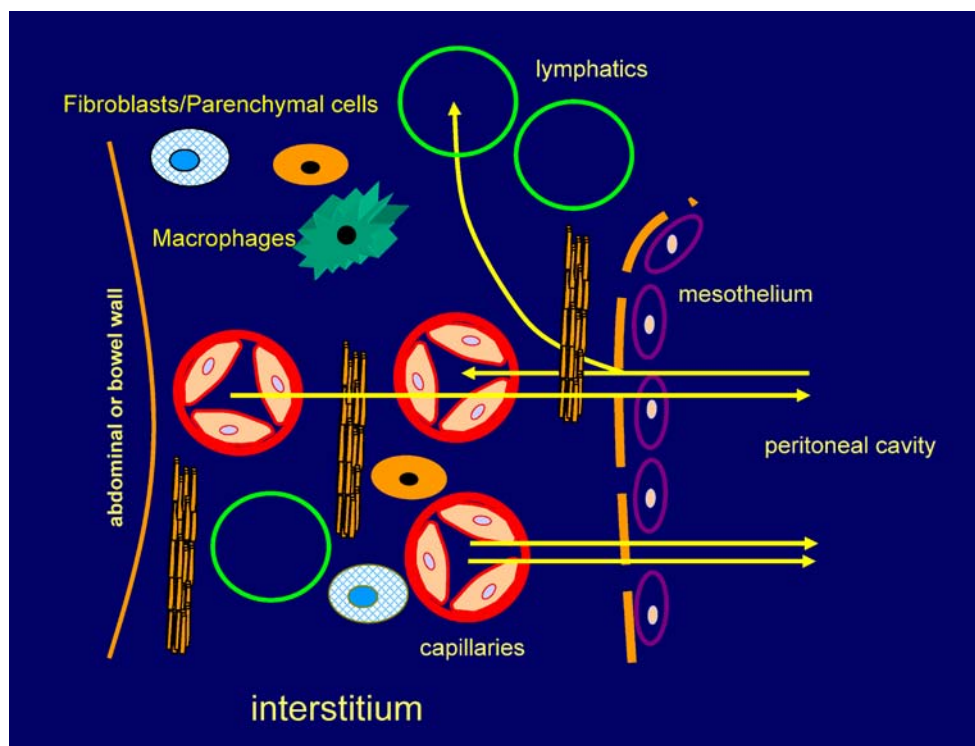
the peritoneum is forced to adapt a foreign mode in which surface phospholipids are replaced by large volumes of dialysis solutions, along with all their problems of bio-incompatibility (described below), leading to changes in the peritoneal tissue.

Current understanding of peritoneal morphology during long-term PD rests heavily on the compilation of data derived from peritoneal biopsy samples taken during various events. Because the peritoneal membrane is not easily accessible, biopsy samples are generally taken during insertion or removal of catheters, unrelated abdominal surgery or kidney transplantation. These studies suggest that long-term PD is associated with progressive morphologic changes in various components of the peritoneal membrane [10].

Before initiation of PD, the mesothelium has a normal morphologic appearance, with cells lying tightly close to each other and having numerous microvilli on their surfaces [11]. After several months on PD, there is a gradual reduction in the number, and, finally, by 8 to 10 months, a total disappearance of microvilli. The intercellular junctions start opening up, leading to separation of mesothelial cells from each other. Eventually, the mesothelial cells become non-viable and are exfoliated from the peritoneum. Areas of denuded mesothelium can be seen as early as 3 months in a patient on PD [12].

Besides the changes in the mesothelium, striking changes take place in the sub-mesothelial interstitium. There is a gradual increase in the thickness of the sub-

Fig. 1 Peritoneal membrane. It consists of a single layer of mesothelial cells and underlying connective tissue interstitium, comprising collagen, mucopolysaccharides, capillaries, lymphatic elements and cells. The major resistance to fluid and solute transport comes from the capillary endothelium and the interstitial matrix surrounding the capillary wall



mesothelial interstitium due to edema and increased deposition of type IV collagen [10]. The median thickness of the peritoneum in healthy individuals is 40 μm (range 30–70 μm). The thickness of the sub-mesothelial layer increases in uremic patients (median 150 μm) who have never been on PD. The thickness further increases, progressively, from 180 μm in patients who have been on PD for fewer than 24 months to up to 600 μm in patients who have been on PD for more than 8 years.

In addition to change in the thickness of the interstitial matrix, there is an increase in the number interstitial cells during PD. Peritoneal mesenchymal cells entrapped in the interstitial stroma have, historically, been considered to be the primary cells involved in peritoneal fibrosis. Alternatively, mesothelial cells may trans-differentiate from an epithelial phenotype and play an active role in peritoneal fibrosis [12, 13].

Changes in peritoneal vasculature mirror mesothelial and interstitial alterations. The basal lamina of peritoneal capillaries is normal before treatment in non-diabetic patients. However, re-duplication of the capillary basement lamina is observed in the patients after a few months on PD. Later, multiple re-duplications, even exceeding five layers, can be seen. In diabetic patients, the re-duplication of the capillary basement membrane is already present on the initial biopsy and becomes exaggerated upon exposure to conventional dialysate solutions. Consequently, after the patient has been on PD for many months (usually more than 36 months), the layers fuse to give the appearance of a thickened membrane. The thickness of the capillary membrane increases with PD vintage until the capillary is completely occluded [10, 12]. In addition to structural changes, the number of blood vessels per unit length of the peritoneal surface also increases with PD vintage [12].

Functional changes in peritoneal membrane with long-term PD

There is mounting evidence that, with time, ultrafiltration (UF) capacity of the peritoneal membrane is progressively lost, with concomitant increase in the peritoneal small solute transport rate [14]. Most of the data come from studies of adults. In pediatric patients, studies are sparse and short-term and demonstrate an increased transport rate in patients who had suffered prior peritonitis [15]. The upsurge in small solute transport, as measured by calculation of the mass transfer area coefficient (MTAC) or dialysate-to-plasma ratio (D/P), of small solutes such as urea and creatinine, reflects an increase in effective peritoneal surface area due to proliferation of peritoneal capillaries [16].

Altered peritoneal membrane function over time has a significant impact on both technique and patient survival

[10, 12–15, 17]. As the prevalence of UF failure increases, it becomes the predominant reason for drop out in long-term PD patients [3, 18]. Reduced UF capacity leads to chronic volume overload, with resultant congestive heart failure and cardiovascular death [18–20]. Poor UF can also lead to low drain volumes and, consequently, to poor solute clearance and, thus, lower dialysis adequacy. In addition, patients with UF failure experience rapid absorption of glucose from the dialysate (with inhibition of appetite) and a greater loss of proteins in the dialysate, leading to poor nutritional status and adverse outcomes [18–20].

Molecular mechanisms of peritoneal membrane changes

There is growing evidence that expansion of peritoneal vasculature is the major determinant of increased solute transport across the peritoneum in long-term PD. However, the biopsy studies show peritoneal fibrosis alongside vascular changes with PD vintage. The relationship between peritoneal fibrosis, angiogenesis, small solute transport and UF is not clearly defined. Fibrosis and angiogenesis may be two separate responses to peritoneal injury or, more likely, be intimately related.

In response to peritoneal injury, mesothelial cells produce fibrogenic cytokine, transforming growth factor (TGF) β_1 [21]. TGF β_1 is a multifactorial cytokine and is involved in many wound-healing processes such as fibroblast activation, collagen deposition, inhibition of fibrinolysis through plasminogen activator inhibitor (PAI-1) and maintenance of fibrosis through inhibition of matrix metalloproteinase (MMP). In addition, TGF β_1 has angiogenic properties. TGF β_1 induces submesothelial fibrosis and likely plays a role in peritoneal neovascularization [22]. TGF β_1 is also implicated in epithelial mesenchymal transition, whereby mesothelial cells trans-differentiate into myofibroblasts, which are key cellular regulators of extracellular matrix and are closely associated with peritoneal fibrosis [13, 21, 22]. Along with TGF β_1 , other cytokines, such as PAI-1, are likely involved at an early stage of peritoneal fibrosis with the inhibition of fibrinolytic activity on the surface of the peritoneal tissue and subsequent accumulation of fibrin, which forms the initial scaffold for subsequent peritoneal fibrosis [22].

One of the key components of peritoneal change with long term-PD is peritoneal vascular proliferation and associated increased capillary permeability. Given the involvement of nitric oxide (NO) in the regulation of vascular tone and permeability, its role in peritoneal vasculature has been suggested. Indeed, there is a fivefold increase in the activity of peritoneal endothelial NO synthetase (eNOS) in long-term (>18 months) PD patients [23]. This upregulation of eNOS correlates positively with

PD duration and suggests a significant increase in endothelial area in long-term PD patients. In addition to that of eNOS, the expression of vascular endothelial growth factor (VEGF) is upregulated in the peritoneal membrane of long-standing PD patients [23]. Furthermore, VEGF has been found in PD effluent, and its level positively correlates with small solute permeability [24]. Thus, upregulation of VEGF might trigger vascular proliferation in the peritoneal membrane. However, the nature of stimuli involved in upregulation of VEGF remains to be elucidated. Arguably, induction of other growth factors, such as TGF β 1, local ischemia or inflammatory cytokines, such as interleukin 6, may ensue.

Based upon recent studies, evidence is emerging that activation of the renin–angiotensin system (RAS) may play a pivotal role in peritoneal fibrosis and angiogenesis. In vitro studies have shown that losartan inhibited the expression of TGF β 1 in human peritoneal mesothelial cells exposed to high glucose dialysate [25]. Additionally, recent studies have shown the involvement of angiotensin II (ANG II) in the regulation of angiogenic cytokines such as VEGF and angiopoietin [26]. Furthermore, blockade of angiotensin (AT)1 and AT2 receptors antagonizes the action of ANG II on expression of VEGF and angiopoietin [26]. Besides this, captopril, enalapril and losartan inhibit the overproduction of VEGF by proinflammatory cytokines in human mesothelial cells [27]. These data suggest that pharmacological manipulation of the renin–angiotensin system may help in the preservation of the peritoneal membrane.

Recently, the role of parathyroid hormone-related protein (PTHrP) as a major regulator of the RAS has emerged [28]. Furthermore, PTHrP has also been described to play a part in growth and differentiation as well as production of surfactant from alveolar type II cells, which are structurally similar to peritoneal mesothelial cells, thereby suggesting a possible role of PTHrP in the growth and function of mesothelial cells [29].

Recent data suggest that oxidant stress may also play a contributory role in triggering peritoneal and systemic inflammatory changes that ultimately lead to membrane failure. Oxidant stress is an imbalance between the production of reactive oxygen species (ROS) and the protective capacity of the antioxidant system in favor of the former. ROS increase the transcription of the interleukin 6 (IL-6) gene via activation of nuclear factor-kappa B (NFkB) [30]. Furthermore, there is impaired antioxidant status in PD patients, as plasma levels of ascorbic acid (AA) and glutathione (GSH) are low, and activities of glutathione peroxidase and gamma glutamylcysteine synthetase are impaired [31]. Thus, PD patients exhibit increased oxidant stress and impaired antioxidant screen. Intervention of the redox system may lead to better long-term survival of the peritoneum.

Potential causative factors for peritoneal membrane changes in long-term PD

During PD, the peritoneum is continuously exposed to unphysiologic conventional dialysis solutions, which are hyperosmolar, acidic and have high glucose and lactate content. Additionally, during heat sterilization and storage of the dialysate, glucose is degraded to reactive substances called glucose degradation products (GDPs). Clinical and experimental data suggest that any of the aforesaid elements, particularly GDPs, can be potentially toxic to the peritoneal membrane [32]. Furthermore, bio-incompatibility of fluids may depend upon the contact of the peritoneal membrane with the fluids. Nocturnal intermittent peritoneal dialysis (NIPD), with daytime “dry abdomen”, reduces the contact time and has been shown to decrease serum and peritoneal inflammatory markers, as well as improve UF, when compared with CAPD and continuous cyclic peritoneal dialysis (CCPD) [33]. Unlike in adults, NIPD and CCPD are much more often used than CAPD in children. This may impact on the biocompatibility of PD fluids in children compared to adults.

In addition to various components of PD fluids, antiseptics such as povidone–iodine, solutions of chlorhexidine used to sterilize the connections for PD, release of plastic particles and plasticizers from bags and tubes for dialysis, and foreign body response from PD catheter implantation are other potential risk factors for peritoneal membrane damage from inflammation and fibrosis [34].

Low pH and lactate

Conventional PD solutions have a pH of 5.2 and a lactate concentration of 40 mmol/l. Infusion pain is the most direct and immediate clinical consequence of low pH [35]. Furthermore, in vitro studies have demonstrated the toxic effects of low pH and lactate on mesothelial cells and peritoneal host defense [36]. The raising of the pH of dialysate to 6.5 or higher prevents impairment of various cell functions and diminution of infusion pain [35, 36].

Hyperosmolality

The effects of hyperosmolality on the peritoneal membrane have mainly been investigated by in vitro studies. The available data suggest that hyperosmolality somewhat contributes to suppressed mesangial cell growth and production of various compounds by mesangial cells, including TGF β 1, prostaglandins, tissue type plasminogen activator and fibronectin [37]. However, the results of in vitro studies need to be confirmed for in vivo situations.

Glucose

To be effective as an osmotic agent, glucose must typically be at concentrations 15–40 times physiological levels (1,370–3,860 mg/dl). Consequently, glucose is absorbed into the blood and may be associated with metabolic problems such as hyperglycemia, hyperinsulinemia, hyperlipidemia and obesity. Furthermore, glucose may also influence cell function through hyperosmolarity, GDPs and reactions mediated by advanced glycation end products (AGEs). Experimental evidence suggests that glucose may be toxic to the peritoneal mesothelial cells and leukocytes [38]. Moreover, increase in the rate of fibroblast proliferation and collagen synthesis, and up regulation of TGF β 1 and VEGF expression, suggest that glucose may play a direct role in peritoneal fibrosis and neoangiogenesis [38, 39].

Glucose degradation products

During heat sterilization and storage, some glucose in PD fluids is degraded to highly reactive substances composed of aldehydes and dicarbonyl compounds and referred to as glucose degradation products. These are the major factors associated with bio-incompatibility of the conventional glucose-based PD solutions. The presence and toxicity of GDPs in PD fluids has been well demonstrated in experimental studies [40]. Although all GDPs are highly reactive carbonyl compounds of small molecular weight and known to be extremely toxic, the recently identified 3,4 dideoxyglucosone-3-ene (3,4-DGE) is reported to be the most biologically active of all the GDPs identified so far [41]. The presence of GDPs in PD fluid seems to be a major factor responsible for mesothelial cell loss observed during the course of peritoneal dialysis. GDPs also enhance the production of VEGF by peritoneal cells. Additionally, it is now well recognized that GDPs are much stronger promoters of AGEs than glucose per se [40–42]. AGEs are known to accumulate over time and are considered to participate in remodeling and fibrosis of the peritoneal membrane.

Advanced glycation end products

Glucose can also contribute indirectly to peritoneal membrane alterations through formation of AGEs [43–45]. AGEs have been implicated in various activities that can adversely affect peritoneal membrane, including protein cross-linking, inflammation, angiogenesis, vascular smooth muscle proliferation and increased nitric oxide production [43–45]. A recent histochemical analysis of peritoneal membrane biopsy demonstrated co-localization of AGEs with TGF- β , VEGF and macrophage colony-stimulating

factor (M-CSF), suggesting that AGE-receptor binding activates signaling pathways leading to the development of peritoneal fibrosis and neovascularization [43]. Furthermore, AGEs have been shown to reduce mesothelial cell viability and increase the expression of vascular cell adhesion molecule-1 (VCAM-1) and plasminogen activator inhibitor-1 (PAI-1) in mesothelial cells [44, 45]. Thus AGEs play a significant role in peritoneal membrane alteration in long-term PD.

Therapeutic strategies to protect peritoneal membrane against consequences of long-term PD

Strategies to protect the peritoneum should be aimed at reducing exposure to the contemporary bio-incompatible dialysis solutions (Table 1). Furthermore, with the increased understanding of the molecular mechanisms involved in peritoneal membrane alteration, therapeutic maneuvers to target the precise molecular pathways offer exciting new approaches to the preservation of the peritoneum (Table 1).

Low GDP PD solutions

Presence of GDPs in conventional glucose–lactate solutions is the major factor responsible for peritoneal membrane changes in long-term PD. Experimental data suggests that the minimization of GDPs in PD fluids leads to preservation of the peritoneal membrane [32]. Three new PD solutions have recently been introduced for clinical use. They offer significant advancement in the acute and chronic effects of bio-incompatible PD solutions such as infusion pain, loss of ultrafiltration, impaired host defense, malnutrition and technique failure.

Table 1 Step strategies to protect the peritoneal membrane

Measures
Reduction of exposure to glucose and reactive carbonyl compounds
Icodextrin
Amino-acid PD fluids
Dual chambered/low GDP solutions
Use of inhibitors of AGE
Aminoguanidine
Inhibition of L-arginine-NO pathway
Compete binding of L-arginine to NOS (L-NAME)
Modulation of angiogenesis
Interference with VEGF
Interference with receptor binding
Interfere with endothelial cell adhesion and migration
Inhibition of angiotensin
Antioxidant screening
Gene therapy

Icodextrin-based solution Icodextrin is a large polymer of glucose (16 kDa), which is produced by the hydrolysis of cornstarch and consists of glucose units linked predominantly by α 1–4 glucosidic bonds. Icodextrin 7.5% PD solution is iso-osmolar with plasma (284 mosmol/kg) and employs colloidal, rather than crystalloid, osmotic pressure to yield a sustained ultrafiltration profile that is equivalent to, or better than, that of 4.25% dextrose solution. There is limited experience of the use of icodextrin in children. It is able to produce sustained UF and enhance small solute clearance in children [46, 47]. Icodextrin also enhances sodium removal and improves small solute as well as β microglobulin clearance [47]. However, it may be associated with greater protein loss [5]. Moreover, UF with icodextrin may correlate with age in very young patients (median age 2.8 years, range 1–8 years) [48]. They may reabsorb icodextrin even with a dwell time of 6 h and thus require much shorter dwell times of 3–6 h, unlike adults and older children [48]. In contrast, long-term clinical experience with icodextrin in adults now extends over many years in Europe, and icodextrin has been demonstrated to extend PD technique survival in patients with UF failure [49]. Although icodextrin has some features of conventional dextrose-based PD solutions (low pH, lactate buffer), it is more biocompatible with the peritoneum because it is iso-osmolar, has low GDP concentration and demonstrates a significant reduction in cell cytotoxicity and AGE formation [50]. The use of icodextrin was shown to slow deterioration of membrane function in the recently conducted European APD Outcomes Study (EAPOS) [51]. Icodextrin usage is accompanied by a sustained, reversible, rise in plasma levels of oligosaccharides, particularly maltose, though no clinical adverse effects have been reported, even after several years of continuous use. A decline in serum amylase level due to interference of icodextrin metabolites with amylase assay has been observed. It is, therefore, recommended that one should not rely on serum amylase alone in diagnosing pancreatitis in patients on icodextrin. Icodextrin usage can falsely elevate serum glucose readings when glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ)-based assays are used. It is recommended that clinicians should avoid the use of GDH-PQQ-based glucose-monitoring systems for diabetic PD patients on icodextrin. Icodextrin can reversibly increase serum alkaline phosphatase (ALP) levels due to the competitive inhibition of hepatic clearance. Elevated ALP level is not associated with any adverse events or abnormality in other liver function tests. ALP values rapidly normalize upon discontinuation of icodextrin. Other adverse effects, especially reversible skin reactions (2.5%), have also been reported [49]. Icodextrin was recently approved by the Food and Drug Administration (FDA) for use in long dwells of patients with high and high-average transport characteristics.

Amino acid-based solutions Malnutrition is a common problem in PD and is associated with a daily peritoneal loss of 6–9 g protein in adults [52] and approximately 0.81 g/kg in children [53]. Various amino-acid (AA) solutions have been proposed as alternative osmotic agents to glucose to potentially improve nitrogen balance and concurrently reduce the glucose load. Amino-acid PD solutions are not available in the USA, but a 1.1% amino-acid solution is now commercially available in Europe and Asia for CAPD patients. One daily exchange with a 1.1% solution results in the absorption of about 13–20 g amino acids and may improve biochemical and anthropometric nutritional parameters in adults and children [54, 55]. Although there are several studies showing some nutritional benefit of AA-based solutions, the long-term efficacy of AA solutions in PD is yet unclear. A recent long-term study showed improvement in several nutritional parameters but no change in serum albumin in 46 malnourished patients on CAPD who received one daily exchange with a 1.1% AA solution for 1 year [55].

Amino-acid solutions also improve biocompatibility, as they lack glucose and GDPs and have a more physiologic pH (6.2). Ex vivo studies show better phagocytic function of peritoneal macrophages, as well as reduced neoangiogenesis, fibrosis and mesothelial damage in animals exposed to AA-based solution [56]. However, despite significant reduction of glucose and GDP load and higher dialysate CA125 levels [57], there are no reports of long-term patient or technique survival with AA solutions.

The use of amino-acid solutions can result in azotemia and metabolic acidosis because of increased nitrogen load, and, therefore, only one or a maximum two daily exchanges of AA solutions are recommended [55].

Bicarbonate-buffered PD solutions Recently, multi-compartment bags have been developed to minimize GDP formation and have a bicarbonate buffer with a physiologic pH. One chamber contains glucose at a very high concentration (50% dextrose), calcium chloride and magnesium chloride at a pH of 3.5, while the other chamber contains sodium chloride and sodium bicarbonate with or without lactate. Mixing of the two fluids just prior to infusion results in a final solution with a pH close to the physiologic value (7.4) and a minimal GDP concentration [58–60]. Clinical and experimental studies indicate that the control of acidosis is at least as good as that with conventional PD solutions and that the new solutions may have a favorable impact on peritoneal membrane integrity [58–60]. One recent, randomized, controlled, crossover trial showed improvement in urine output and residual renal GFR but, paradoxically, an increase in small solute transport status, with dual-chambered bags [61]. Two recent non-randomized reports from Korea showed improved

survival in patients who used neutral pH solutions [62, 63]. A recent study showed a reduction in the frequency of peritonitis in CAPD patients using neutral pH solutions compared with those using conventional lactate-based dextrose solutions [64]. However, these results have not been reproduced by other recent studies [61, 63]. There is only limited experience of children with neutral pH solutions. When these solutions were used, a significant reduction in the systemic load of AGEs was reported in children [65]. Furthermore, it was shown that children experienced less intraperitoneal pressure and no infusion pain with these solutions [66]. Moreover, a more effective correction of metabolic acidosis and better preservation of mesothelium were observed [67]. Large controlled trials to show translation of biocompatibility to improved patient outcomes in adults and children are still lacking. Multi-chambered solutions are not available in the USA but have recently been introduced in Europe and Asia.

Future strategy for use of PD solutions

No currently available PD solution meets all requirements of an ideal solution: effective ultrafiltration, long-term preservation of peritoneal membrane, and correction of nutritional and metabolic abnormalities. However, the use of the new PD solutions in combination may help us to achieve these goals. Preliminary evidence from short-term studies of adults suggests that a combination of the three new solutions provides similar efficacy to that of standard glucose regimens and provides better preservation of mesothelial cell mass [68, 69]. A prospective long-term multi-centered European study is underway to compare the efficacy of the combination of newer PD solutions (icodextrin for the long dwell, one dwell of amino acid solution and remaining dwells with bicarbonate and lactate solution) with conventional glucose/lactate based-solution.

Future prospects

While the novel PD solutions offer an improvement in biocompatibility, they do not completely abolish the formation of GDPs, and their long-term effect on the peritoneum is not yet known. Identification of putative molecular mechanisms by which contemporary PD solutions provoke a number of cellular responses to stimulate angiogenesis, fibrosis and, eventually, membrane failure, kindle new therapeutic strategies that might protect the peritoneal membrane from the consequences of long-term PD. The modulation of angiogenesis, inhibition of AGE formation by the addition of aminoguanidines to PD solutions, the competitive inhibition of binding of L-arginine to NOS with NG-nitro-L-arginine methyl ester

(L-NAME), the use of angiotensin receptor blockers or the converting enzymes inhibitors, the addition of antioxidant screen to the PD fluids and, finally, the use of gene therapy to modify peritoneal membrane by targeting inflammatory, fibrogenic and angiogenic cytokines, offer exciting new approaches to the preservation of the peritoneal membrane [25, 27, 70–73] (Table 1). It remains to be seen if these maneuvers will prove clinically beneficial.

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