Protecting the peritoneal membrane in dialyzed patients

*Grzegorzewska AE**

Chair and Department of Nephrology, Transplantology and Internal Diseases, Poznań, Poland

Abstract

This review paper describes methods of protecting the peritoneal membrane in uremic patients chronically treated with peritoneal dialysis. Possible interventions involved in protection of the peritoneum aim at reducing peritoneal exposure to glucose, glucose degradation products and lactate; preventing or diminishing harmful effects of dialysis solutions; decreasing infection rate, especially peritonitis, and its consequences. Techniques reducing peritoneal exposure to bioincompatible solutions include peritoneal resting, replacing some glucose exchanges with amino acid-based, icodextrin-based or glycerol-based dialysis solution, using bicarbonate or pyruvate as a buffer, and administering solutions with low content of glucose degradation products. Preventing or diminishing harmful effects of dialysis solutions includes interventions with drugs, especially those given intraperitoneally. Decreasing local and systemic infection rate is also very or even the most important in maintaining relatively unchanged peritoneal membrane histology and function.

Key words: peritoneal membrane, dialysis solutions, peritoneal resting, drugs, infections.

Long-term peritoneal dialysis (PD) usually leads to peritoneal membrane failure. Main factors, important in pathogenesis of deterioration of the peritoneum, include continuous exposure to bioincompatible dialysis solutions and high peritonitis rate. Having in mind factors responsible for the peritoneal membrane failure, possible interventions in its protection aim in PD patients at: 1) reducing peritoneal exposure to glucose, glucose degradation products (GDPs), and lactate; 2) preventing or diminishing harmful effects of dialysis solutions; 3) decreasing infection rate, especially peritonitis occurrence and its harmful consequences.

* CORRESPONDING AUTHOR:
Chair and Department of Nephrology,
Transplantology and Internal Disease
University of Medical Sciences
al. Przybyszewskiego 49, 60-355 Poznań, Poland
Tel: +48 61 8691688; Mobile: +48 696084487; Fax: +48 618691700
e-mail: alicja_grzegorzewska@yahoo.com (Alicja E. Grzegorzewska)

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Reducing peritoneal exposure to bioincompatible solutions

Techniques include peritoneal resting, replacing some glucose exchanges with amino acid-based (AA-DS), icodextrin-based (PG-DS) or glycerol-based dialysis solution, using bicarbonate or pyruvate as a buffer, and administering solutions that have low content of GDPs [1].

Temporary discontinuation of continuous ambulatory peritoneal dialysis (CAPD) for 4 weeks in patients who developed a reduction in ultrafiltration capacity has been reported to lower mass transfer area coefficients (MTACs) of urea and creatinine and to increase ultrafiltration [2,3]. The effect lasted for up 12 months. More recent studies showed that peritoneal resting was especially effective when applied early after the detection of ultrafiltration failure [4] and with heparinized lavage [5]. Peritoneal resting has been associated with both an increase [6] and a decrease of dialysate glycoprotein cancer antigen 125 (CA125) concentrations [7]. In the other study [8], rats exposed to dialysis fluid for 5 weeks showed a severe angiogenesis in various peritoneal tissues, a profound fibrosis in the parietal peritoneum, a higher number of mast cells and milky spots in the omentum and severe damage to the mesothelial cell layer covering the peritoneum. The 12 weeks peritoneal rest resulted in a significant reduction in blood flow in visceral but not in parietal peritoneum, a reduced degree of fibrosis, normalization of increased mast cell density and recovered mesothelial cell layer.

AA-DS is more biocompatible than glucose-based solutions. Recently it was proven in the rat model of peritoneal dialysis [9]. Daily exposure to glucose-based solution for 5 weeks resulted

in a significant increase in the number of rolling leukocytes in mesenteric venules, whereas instillation of AA-DS did not change the level of leukocyte rolling. Glucose-based solution evoked a significantly higher number of milky spots in the omentum, whereas this response was significantly reduced in animals exposed to AA-DS. These data indicate reduced immune activation with the use of AA-DS. Quantitative morphometric evaluation showed less angiogenesis in the parietal peritoneum after treatment with AA-DS compared to glucose-based solution. Instillation of AA-DS resulted in approximately 50% reduction of fibrosis in the mesentery and approximately 25% reduction in the parietal peritoneum compared to glucose-based solution. As evidenced by electron microscopy, glucose-based solution damaged the mesothelial cell layer, whereas mesothelium was intact after AA-DS treatment.

PG-DS is mentioned as more biocompatible than glucose-based solutions. However, the recent study by Gotloib et al. [10] showed that both osmotic agents, 4.25% glucose and 7.5% icodextrin, substantially restrain the normal process of mesothelial cell repopulation and induce repair by means of connective tissue. The underlying mechanism is most likely sustained oxidative stress.

The 15 new peritoneal dialysis patients were randomized to treatment with either glucose-based or glycerol-based dialysis solutions [11]. No difference between the two groups was found after 1 and 3 months with regard to peritoneal transport kinetics, but dialysate CA-125 concentration was significantly higher in the glycerol-treated patients than in the glucose-treated ones.

Lactate itself exerts harmful effect on human peritoneal mesothelial cells (HPMC) viability. It was shown that 3,4-dideoxyglucosone-3-ene (3,4-DGE) or acidity alone inder the absence of lactate do not decrease HPMC viability. However, combination of acidity and 3,4-DGE markedly decreases viability of HPMC under the existence of lactate [12]. Lactate concentration is the major determinant of polyol pathway activation and sorbitol accumulation in HPMC. Reduction of lactate concentrations might help to limit the negative impact of dialysis solutions on peritoneal membrane and promote its long-term survival [13].

Pyruvate has induced less cytotoxicity to peritoneal macrophages and mesothelial cells than did lactate [14]. That finding can be attributed partly to the lower pH of pyruvate (which makes it a weaker buffer), but also to the ability of pyruvate to scavenge oxygen radicals [15]. Pyruvate also causes less stimulation of intracellular degradation of glucose in the sorbitol pathway [16]. Lactate increases the intracellular NADH/NAD^+ ratio due to inhibition of NAD^+ regeneration. A high NADH/NAD^+ ratio is also called pseudohypoxia [17] and is likely to stimulate the formation of vascular endothelial growth factor (VEGF) [18]. Of many potential mediators produced by mesothelial cells, VEGF was more important than IL-6 in determination of peritoneal solute transport rates in newly started nondiabetic peritoneal dialysis patients [19].

All dialysis solutions not containing glucose have advantage as not stimulating formation of advanced glycation end products (AGEs), which are well known contributors to the peritoneal membrane failure.

Heat sterilization of glucose-based peritoneal solutions increases a variety of GDPs, which directly cause cellular injury in fibroblasts, mesothelial cells and mononuclear cells. Some GDPs, like methylglyoxal, may additionally facilitate the generation of AGEs, causing ultrafiltration failure. Increase in temperature to 37°C during storage for one day (applicable in tropical countries) has minor effect on 3,4-DGE formation. Storage in temperature of 60°C even for one day significantly enhances 3,4-DGE content in dialysis fluid [20].

Exposure to dialysis solutions with neutral pH and reduced GDPs content has resulted in an increase in the effluent concentration of CA-125 [21-27], in a decrease in dialysate concentration of hyaluronan, irrespective of the buffer used [21,22,27,28], in better preservation of cobblestone-shaped mesothelial cells due to protective effect on their fibroblastoid transition [23], and less formation of AGEs [29,30].

It is commonly accepted that CA-125 levels in dialysate reflect mesothelial cell mass. Therefore, higher CA-125 concentrations indicate better preservation of the peritoneal mesothelium. When two groups of new CAPD patients (one treated with low GDP solution, second treated with high GDP solution) were compared, the low GDP group, using Balance Fresenius Medical Care (Germany), showed higher dialysate CA-125 levels during one year CAPD follow-up (55.4±24.8 vs 8.8±1.7 U/ml at the 1st month – $p=0.000$, 56.7 ± 28.1 vs 22.1±11.5 U/ml at the 6th month – $p=0.000$, 54.2 ± 28.2 vs 24.6±16.5 U/ml at the 12th month – $p=0.000$) [23]. In *ex vivo* studies, dialysate from patients treated with low GDP solution supported growth of mesothelial cells better than that obtained from the same patients on standard dialysis fluid [31]. Additionally, *in vitro* remesothelialization occurred without delay in the presence of low GDP solution but was markedly retarded by standard solution [32]. These facts, taken together, indicate that higher concentration of CA-125 observed with low-GDP solution, may reflect less harmful effects of this solution on mesothelium as compared to conventional fluid.

Glycosaminoglycan (hyaluronan) is a high molecular weight mucopolysaccharide composed of repeating dimmers of N-acetylglucosamine and glucuronic acid. Mesothelial wound healing is associated with local synthesis of hyaluronic acid, therefore lower concentration of hyaluronan in dialysate may indicate less need for remesothelialisation occurring when low-GDP solutions are used instead of standard fluid [21,22,26,28]. The rat studies seem to confirm this hypothesis [33].

The influence of low-GDP solution on chronic peritoneal inflammatory state is not clear. A decrease in dialysate concentration of IL-6 was shown, but simultaneously no influence on dialysate CRP level was observed [24].

Formation of AGEs *in vitro* [29] and in the rat model of peritoneal dialysis [30] occurs faster in the presence of standard dialysis fluid compared to low-GDP solution. The influence of low-GDP fluid on expression of VEGF and microvascular proliferation in the rat is controversial [30,34]. No significant changes in dialysate VEGF in CAPD patients were observed with the use of low-GDP solution [26,27].

Do et al. [23] have introduced scoring system for description of morphology of human peritoneal mesothelial cells: score 1=cobblestone-shaped cells, score 2=mixed, score 3=fibroblas-

toid cell dominant. New CAPD patients treated with low-GDP solution as compared to those using high-GDP solution revealed lower cell scores at the 1st, 6th and 12th months (1.22, 1.22 and 1.56 vs 1.61, 1.75 and 2.14; $p < 0.05$, $p < 0.01$ and $p < 0.01$, respectively), and the significantly lower number of fibroblast dominant cultures at the 12th month (12.5% vs 50% patients, $p<0.05$) [23]. Human peritoneal mesothelial cells can be stained with both cytokeratin and vimentin, whereas typical fibroblasts can be stained with vimentin but not cytokeratin. Do et al. [23] demonstrated that both cobblestone-shaped mesothelial cells and fibroblastoid cells were positively stained with cytokeratin and vimentin. This indicates that fibroblastoid cells originated from epithelium, most likely in a transition from peritoneal mesothelial cells under GDP stress, although they looked like typical fibroblasts in morphology [23]. Selgas et al. [35] suggest that transdifferentiated mesothelial cells are main source of VEGF in PD patients and that an epithelial-to-mesenchymal transition of mesothelial cells is a mechanism responsible for high peritoneal solute transport rate. This transition might be the initiating lesion associated with high transport rate, independent on time on PD [36].

A superior survival was found in patients treated with a neutral pH, low-GDPs solution (Balance, Fresenius Medical Care, Germany) compared to those treated with the conventional fluid. Balance gave mortality rates of 12.2 deaths per 100 patient-years compared with 18.3 deaths per 100 patients-years for the conventional solution. On the other hand, there were no differences between the two groups for technique survival, peritonitis-free survival, or peritonitis rates [37].

Treatment of CAPD patients with combination of AA-DS, PG-DS and bicarbonate/lactate-buffered glucose-based solution for 30 weeks resulted in higher CA-125 dialysate concentration compared to standard fluid [38]. However, this low-glucose and low-GDPs regimen was not able to prevent the decrease of dialysate CA-125 level, observed after 6 weeks of dialysis follow-up. It indicates that advanced studies should be continued to improve biocompatibility of peritoneal solutions.

Preventing or diminishing harmful effects of dialysis solutions

Interventions with drugs for the preservation of the peritoneum have been studied, but such interventions have never been applied for a large scale. Drug therapy is still experimental – and to some extent disappointing [1].

Phosphatidylcholine, given intraperitoneally during CAPD, increased ultrafiltration in patients with ultrafiltration failure and with normal ultrafiltration [39,40-42]. The most likely mechanism is an effect on lymphatic absorption of fluids [43], either by direct uptake in the subdiaphragmatic lymphatics [44] or by an effect on the glycocalyx that inhibits transmesothelial transport. Phosphatidylcholine has never been employed in day-to-day clinical practice because it is extremely difficult to dissolve in dialysis solution and oral administration is not effective [45].

Intraperitoneal hyaluronan effects were examined in peritoneal dialysis patients [45,47] and in rats [48,49]. In peritoneal dialysis patients, solute (sodium, urea, creatinine, albumin, glucose) clearances, dialysate to plasma ratios and MTACs were similar with or without hyaluronan [47]. In rats, clearance of urea was higher with hyaluronan [49]. In other studies, intraperitoneal administration of glycosaminoglycan in CAPD patients was associated with reduced peritoneal protein loss [46]. In some studies hyaluronan decreased peritoneal fluid absorption [49,50] or at least net ultrafiltration tended to be slightly higher during treatment with solution containing hyaluronan compared to control treatment [47]. Recently, Flessner et al. [51] concluded that the hyaluronan concentration in the visceral peritoneal interstitium does not significantly contribute to the barrier for water flow to or from the visceral space surrounding the peritoneal cavity. Hyaluronan also revealed protective effect against peritoneal injury during repeated exposure to hypertonic dialysis solutions or 0.9% saline in rats [48,52,53]. Explanation of this finding includes suppression of the release of active oxygen from peritoneal macrophages by hyaluronan [54], which also acts as a free-radical scavenger [55].

In rats exposed to dialysis fluid supplemented with N-acetylglucosamine, peritoneal permeability to creatinine and proteins was reduced when compared to animals dialyzed with glucose solution. This effect was related to accumulation of glycosaminoglycans in the peritoneal interstitium [56,57]. Synthesis of hyaluronan by mesothelial cells was significantly increased in the presence of N-acetylglucosamine [58]. Tissue content of hyaluronic acid was increased in rats receiving N-acetylglucosamine intraperitoneally as compared to animals treated with glucose or mannitol based dialysis solutions. However, submesothelial thickness showed an increase in all rat groups [59].

In rats low molecular weight heparin – dalteparin – improved peritoneal ultrafiltration acutely due to reductions in peritoneal transport of small solutes. It is speculated that this effect may be related to the anti-inflammatory effects of dalteparin, reducing the vasodilatation normally occurring at the beginning of peritoneal dialysis dwells [60]. Using intraperitoneal dalteparin in long-term peritoneal dialysis patients, an increase in the peritoneal restriction coefficient to macromolecules was found [61]. Recent studies [62] showed that an increase in ultrafiltration caused by low molecular weight heparin was associated with inhibition of formation of thrombin and blockade of C5a activity.

Peritoneal fibrosis, and particularly peritoneal sclerosis, constitutes some of the most disastrous complications of peritoneal dialysis [63]. In the view of the good results obtained with tamoxifen for the treatment of retroperitoneal fibrosis, in 1992 Diaz-Buxo et al. [64] suggested for the first time its use in peritoneal dialysis patients. Tamoxifen inhibits protein kinase C, a mediator of cellular proliferation, and possibly inhibits other growth factors (epidermal growth factor and calmodulin). Nine of 23 patients, diagnosed with peritoneal sclerosis, were treated with tamoxifen (20 mg BID for a period of 14.5 ± 7 months) and 14 patients served as controls [65]. None treated patient did not develop encapsulating peritoneal sclerosis (EPS) and overall mortality rate was 22%, whereas in non-treated group 4 patients developed EPS and 71% died ($p=0.03$).

The rat studies indicate that angiotensin II blockade may be a potential means of preventing fibrosis of the peritoneal mem-

brane [66,67]. Duman et al. [66,67] found that, in rats receiving high glucose dialysis solutions for 4 weeks, simultaneous administration of enalapril significantly reduced the thickness of submesothelial connective tissue, produced fewer adhesions, and was associated with lower concentration of tumor growth factor-β (TGF-β). Studies on cultured HPMC additionally showed that TGF-β1 induced by high glucose is controlled by angiotensin-converting enzyme inhibition and angiotensin II receptor blocker [68].

In rats dexamethasone has a diminishing effect on the fibroproliferative phase of non-inflammatory TGF-β-induced peritoneal fibrosis [69]. Rapamycin, an antirejection agent that has potential antifibrotic and anti-angiogenic activity, used intraperitoneally in a rodent model of TGF-β1-induced peritoneal fibrosis and angiogenesis, did not have significant benefit on the morphological changes in the peritoneum [70].

The high glucose concentrations of the dialysis solutions may saturate physiological glucose metabolism pathways and stimulate the polyol pathway, which probably contributes in the development of fibrosis and angiogenesis during peritoneal dialysis. In this pathway of intracellular glucose metabolism, glucose is reduced to sorbitol by aldose reductase, coupled with oxidation of NADPH to $NADP^+$. Sorbitol is then oxidized to fructose by sorbitol dehydrogenase, coupled with reduction of NAD^+ to NADH. Possible mechanisms of polyol pathway-linked functional abnormalities include osmotic stress due to intracellular accumulation of sorbitol, an increased NADH/NAD^+ ratio leading to pseudohypoxia, and enhancement of the formation of AGEs by fructose. Inhibition of the polyol pathway in rats by administration of zopolrestat, a newly developed inhibitor of aldose reductase activity, resulted in less fibrosis and fewer peritoneal vessels than in rats dialyzed with 3.86% glucose-containing fluid without zopolrestat [71].

An antioxidant, sodium sulfite, is an additive commonly used for food preservation. It was able to suppress AGEs formation in rats with normal renal function, eliminating oxidative stress caused by methylglyoxal. It is presumed that sodium sulfite reacts with methylglyoxal to form chemically inactive substances. Sodium sulfite was administered intraperitoneally to rats once a day for 5 consecutive days together with methylglyoxal. Other group of rats was given methylglyoxal alone. Prominent hypervascularity and intense immunostaining of anti-AGE antibodies were noted in methylglyoxal-treated rats, whereas the macroscopic alterations were suppressed in the rats that had been treated with sodium sulfite [72].

The potential use of AGEs inhibitors and breakers as salvage therapy for peritoneal membrane failure was also considered in studies with pimagedine, which has been shown to inhibit the formation of AGEs and to slow the progression of nephropathy in animal models [73].

Decreasing infection rate and its harmful consequences

Severe or repeated episodes of peritonitis are particularly damaging to the peritoneal membrane. The short-term, single episodes had no significant effect on membrane permeability or ultrafiltration, while recurrences or clusters of infection caused an increase in membrane permeability and reductions in ultrafiltration. Thus, prevention of infectious complications of peritoneal dialysis, especially peritonitis, is a great challenge for every dialysis unit. Proper patient' education and regular use of mupirocin at the exit site exert an important role in diminishing peritonitis rate. Use of prophylactic antibiotics at the time of catheter insertion has also been shown to reduce the incidence of early peritonitis [74]. Accepted rate of peritonitis is 1 episode per 18 patient-months [75].

In the rat model of peritoneal dialysis it was shown that hyaluronan modifies inflammatory response and peritoneal permeability during peritonitis [48,53,76]. There are no studies confirming this beneficial effect in humans.

It was shown that also acute systemic inflammation influences the peritoneal membrane function, increasing small solute transport rate. Possible mechanisms linking inflammation and peritoneal transport include enhancement of vascular superoxide formation leading to modification of endothelial junctional elements (advanced oxidation protein products formation), IL-6 increased generation influencing D/P of creatinine and a direct effect of C-reative protein on vascular permeability [77]. This finding may contribute to explanation of reasons of damage of the peritoneal membrane over dialysis duration in patients without peritonitis, but showing episodes of systemic inflammation. Thus, to protect the peritoneal membrane one also has to pay attention for avoiding systemic inflammation.

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