Inflammatory Effects of Dialysis Solutions on Peritoneal Membrane in Peritoneal Dialysis Patients

IULIANA ISVORANU[1], ILEANA PERIDE[1,2]*, DANIELA RADULESCU[1,2], ANDREI NICULAE[1,2], RUXANDRA DIANA SINESCU[3,4], IONEL ALEXANDRU CHECHERITA[1,2]

[1]"St. John" Emergency Clinical Hospital, Department of Nephrology and Dialysis, 134 Vitan Barzesti Road, 04122. Bucharest, Romania

[2] "Carol Davila" University of Medicine and Pharmacy Bucharest, Clinical Department No 3, 3-7 Dionisie Lupu Str., 020022, Bucharest, Romania

[3] "Elias" Emergency University Hospital, Department of Plastic Surgery and Reconstructive Microsurgery, 17 Marasti Blvd., 011461, Bucharest, RomaniaBucharest

[4] "Carol Davila" University of Medicine and Pharmacy Bucharest Clinical Department No 11, 3-7 Dionisie Lupu Str., 020022, Bucharest, Romania

In long-term peritoneal dialysis, peritoneal membrane suffers structural and functional changes, being exposed to various proinflammatory insults, which ultimately lead to sclerosis and ultrafiltration failure and require transferring the patients on hemodialysis. Inflammatory status of uremia, recurrent peritonitis episodes, presence of the dialysis catheter and repeatable contact with non-physiological dialysis solutions are all involved in the alterations of peritoneal membrane. This article reviews the harmful effects of the currently used dialysis solutions on the structure and functionality of the peritoneal membrane and presents also the future promises for better alternatives.

Keywords: peritoneal dialysis, dialysis solutions, inflammation, membrane failure

Peritoneal dialysis (PD), a commonly used method of renal replacement therapy, offers several advantages – better hemodynamic stability than hemodialysis, better preservation of residual renal function, no need for vascular access, better control of anemia, increased quality of life and long-term prognosis after kidney transplantation, decreased risk of hepatitis B and C infections, patient's independence *etc* [1-7]. The integrity of peritoneal membrane is mandatory for the efficiency of this method. Numerous literature data show that, in long-term peritoneal dialysis, peritoneal membrane suffers various functional and structural alterations leading to sclerosis and ultimate to membrane failure with need to transfer on hemodialysis [2,8,9].

With time, increased surface area of peritoneum is seen in long-term PD as a consequence of formation of new capillaries in the peritoneum (neoangiogenesis) and increased density of the microvasculature [8-12]. Several researches demonstrated thickening of the basement membrane of mesothelial cells and of the blood vessels in peritoneum in only several month after the beginning of peritoneal dialysis [8,9,11-17]. With more time spent on dialysis, reduplication of the basement membrane had been revealed and the intensity of the process had been proven to be more pronounced in diabetics and in patients with recurrent peritonitis [8-17]. Changes in the basement membrane of blood vessels of peritoneum are associated with fibrosis and hyalinization of the media secondary to increased production of type IV collagen and laminin and with submesothelial fibrosis due to increased interstitial matrix [8-19]. In PD patients, increased levels of proinflammatory cytokines (as interleukin (IL)-1β, IL-6, IL-8), hyaluronan, tumor necrosis factor (TNF-α) and growth factors as transforming growth factor-β1 (TGF-β1) are documented in peritoneal fluids [11,17,20-24].

Membrane failure has multifactorial causality. In uremia, there is an increased inflammatory status which is only partially corrected by dialysis initiation [11,22,23]. Membrane failure itself is followed by hydrosaline retention with secondary bowel oedema and translocation of bacterial gut in the peritoneal fluids and in the blood [24]. The same effect – secondary to intestinal mucosa atrophy – is seen in malnourished patients [25].

Recurrent peritonitis episodes accelerate fibrosis of peritoneal membrane, being the most important cause for switching to hemodialysis [1,8,17,22,26].

The presence of the intraperitoneal catheter is a strong stimulus for intraperitoneal inflammation immediately after implantation [12]. In long-term, the peritoneal catheters promote inflammation as bacterial biofilms are often developing on them [12,22].

Repeatable exposure of peritoneal cells to the non-physiologic dialysis fluid is a permanent insult for the peritoneal membrane even in the absence of other proinflammatory stimuli. This article focuses on the proinflammatory effects of peritoneal dialysis fluids in chronic peritoneal dialysis.

Composition of peritoneal dialysis fluids

Peritoneal dialysis solutions are sterile aqueous mixtures (Table 1) structurally designed to serve the goals of dialysis: restoration of electrolyte and acid-base balance, ultrafiltration of excess fluid and removal of uremic toxins and foreign substances.

As a result, they contain various concentrations of sodium, chloride, calcium, magnesium – usually in concentrations similar to those of plasma, except potassium which is absent; depending the patient's calcium metabolism alterations, several concentrations of calcium may be available [1,12,27-31] (table 1).

* *email: ileana_peride@yahoo.com*

All authors had equal contribution.

	Conventional composition			Icodextrin composition
§Glucose (g/dL)	1.5	2.5	4.25	0
Icodextrin (g/dL)	0	0	0	7.5
Sodium (mmol/L)	132	132	132	132
Calcium (mEq/L)	2.5 – 3.5	2.5 – 3.5	2.5 – 3.5	3.5
Magnesium (mEq/L)	0.5 – 1.5	0.5 – 1.5	0.5 – 1.5	0.5
Chloride (mmol/L)	102	102	102	96
Lactate (mEq/L)	35 – 40	35 – 40	35 – 40	40
Potassium (mmol/L)	0	0	0	0
HCO_3^- (mmol/L)	0	0	0	0
HPO_4^- (mmol/L)	0	0	0	0
pH	5.2 – 5.5	5.2 – 5.5	5.2 – 5.5	5.2
Osmolarity (mOsm/kg)	347	413	486	282 – 286

Table 1
PERITONEAL DIALYSIS FLUID COMPOSITION

§There are two forms available of glucose: monohydrate ($C_6H_{12}O_6H_2O$) and anhydrous ($C_6H_{12}O_6$) [34]; both can be used in peritoneal dialysis solutions, with the equivalence presented in Table 2 [35].

Monohydrate glucose (g/dL)	Anhydrous glucose (g/dL)
1.5	1.36
2.5	2.27
4.25	3.86

Table 2
THE EQUIVALANCE BETWEEN MONOHYDRATE AND ANHYDROUS GLUCOSE

In currently and widely available peritoneal dialysis solution, for the correction of uremic acidosis, lactate is used as buffer [1,27] (table 1). In single-bag solutions, bicarbonate may precipitate in the presence of calcium (forming calcium carbonate); therefore, lactate is used instead [1,27]. In newer, but more expensive solutions, having bags with two compartments, it is used as buffer either only bicarbonate or a mixture of lactate and bicarbonate [1,27,32,33].

In PD, ultrafiltration is achieved using glucose as osmotic agent. For this purpose, various concentrations of glucose are available, varying from manufacturer to manufacturer [1,12,27-31] (table 1). There are two forms available for glucose: monohydrate ($C_6H_{12}O_6H_2O$) and anhydrous ($C_6H_{12}O_6$) [34]; both can be used in peritoneal dialysis solutions (table 2) [35]. The osmolarity of these solutions is generally high and depend mainly of glucose concentration; it ranges from 347mOsm/kg in solutions with a concentration of glucose of g/dL to 486mOsm/kg in those solutions with a concentration of glucose of 4.5 g/dL (table 1) [1,12,27-31].

Alternative available osmotic agents for ultrafiltration in peritoneal dialysis are icodextrin and amino acids. Icodextrin is a polymer of glucose with an average molecular weight of 17 kDA; solutions containing icodextrin have electrolyte concentrations close to glucose-containing solutions (table 1), but osmolarity is lower [1,27-31,36]. Amino acids-containing solutions are an alternative for malnourished patients; they contain a concentration of 1.1% amino acids and have also a lower osmolarity [1,25,27,37].

Proinflammatory effects of PD solutions

Numerous literature data report that PD solutions are associated with increased peritoneal inflammation and progressive fibrosis. Excessive intraperitoneal glucose, production of glucose degradation products (GDP) and advanced glycation end products (AGEs), dialysate *p*H, hyperosmolarity or icodextrin metabolites produce all various inflammatory reactions leading in the end to membrane failure [8,27].

Glucose. Excessive exposure of peritoneal cells to hyperglycemic milieu determines changes similar with those in diabetic nephropathy: thickening of the basement membrane of mesothelial cells and of the vascular cells in capillary of the peritoneum [8-24].

Prolonged contact with to high concentrations of glucose stimulates peritoneal mesothelial cells to increase production of transforming growth factor (TGF)-β1 [8-24, 38], by upregulation of both TGF-β receptors, type I and type II, in these cells [8-24,39].

Besides TGF-β1, excessive glucose in dialysate stimulates production of vascular endothelial growth factors (VEGFs) which promote neoangiogenesis and mesothelial fibrosis [8-24,40].

Absorption of glucose from peritoneal fluids is often seen in PD patients leading to obesity and increased production from adipocyte of various adipokines (adiponectin, leptin) proven to promote systemic and peritoneal inflammation [41,42].

Glucose degradation products (GDP). Methylglyoxal ($CH_3C(O)CHO$), glyoxal (OCHCHO), and 3-deoxy-glucosone are glucose degradation products produced in peritoneal fluids during the process of heat sterilization [43](fig.) 1, 2 and 3.

These carbonyl compounds are proven to induce proliferation and fibrosis of peritoneal membrane [8,43-45] and they have greater affinity than glucose for proteins in producing advanced glycation end-products (AGEs) [8,43,46].

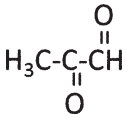

Fig. 1.
Methylglyoxal
($CH_3C(O)CHO$)

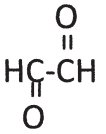

Fig. 2.
Glyoxal (OCHCHO)

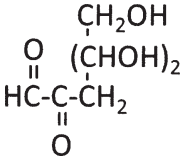

Fig. 3.
3-deoxyglucosone

In experimental studies, GDP were associated with increased VEGF expression in mesothelial and endothelial cells in peritoneum, contributing to neoangiogenesis [8,45]; there is evidence that there is an increased local production of VEGFs as a result of high levels of GDP, especially after prolonged storage of the PD solutions [8,53].

Advanced glycation end products (AGEs). As it happens in blood in diabetes mellitus, in PD fluids also, excessive glucose and especially glucose degradation products bind non-enzymatically with proteins, free amino groups and lipids and lead to increased production of AGEs [8,54,55]. Intraperitoneal accumulation of AGEs, especially of pentosidine ($C_{17}H_{26}N_6O_4$), is noted in PD patients [8,56,57]. These high levels decrease after transferring the patient on glucose-free dialysate [8,58].

As a consequence of increased absorption of glucose across the peritoneal membrane in blood, in PD patients, even nondiabetics, increased production of AGEs is seen also in systemic circulation [8,59]. This process in accelerated whenever there is an increased oxidative stress, as it is noted in uremia [8,11,12]. Circulating AGEs are normally excreted by the kidney, but, in the condition of decreased glomerular filtration rate, they accumulate in the serum [8,60].

AGEs accumulate in the mesothelium and submesothelial cells, in the interstitium and in the vessel walls of peritoneum and, by inducing overexpression of endothelial nitric oxide synthase in the peritoneal membrane, they stimulate vascular proliferation and neoangiogenesis [8,61,62]. Acting on their specific receptors, RAGE, AGEs stimulate oxidative stress as a consequence of generation of oxygen-derived free radicals in the peritoneal membrane and they determine increased permeability, increased production of TGF-b1 and accumulation of collagen type IV [63,64]. Increased glucose in dialysate and also uremia itself stimulate upregulation of RAGE in the peritoneal membrane cells [65].

Increased production of AGEs is also associated with overexpression of VGEF leading to neoangiogenesis [8,66].

Several studies found a direct relationship between the levels of AGEs in the structures of peritoneal membrane, the degree of functional alterations and the time spent on dialysis: higher permeability for various solvates [8,61], severe interstitial fibrosis or extensive sclerosis of vessels [8,67]. These pathologic findings were all associated with membrane ultrafiltration insufficiency and hydrosaline retention [8].

Although excessive glucose in the dialysate is first incriminated in increased intraperitoneal production of AGEs, there are clearly numerous unknown data regarding the genesis of AGEs, because increased levels of intraperitoneal AGEs had been noted in short time after beginning dialysis, even when the patients didn't need high-glucose dialysates [8,68].

pH of dialysate. Lactate used as a buffer in PD is absorbed in blood and converted in bicarbonate in the liver. Lactate is a powerful stimulus for production of FGF (Fibroblast growth factor) which is involved in peritoneal fibrosis. Secondary to lactate blood absorption, instillation of dialysate in the peritoneal cavity is followed by a rapid acidification of the fluid, leading to decreased phagocytosis capacity of neutrophils and reduced viability of mesothelial cells [12-24,27-29,31,69]. Amino acids-containing solutions are proven to accentuate systemic and local acidosis, therefore they have also a deleterious effect on cells viability [1,27-29,31].

Icodextrin. Icodextrin-containing dialysate was considered initially an innovation and a salvage solution for patients with ultrafiltration problems and with excessive needs for high-glucose containing PD fluids. Several studies demonstrated less production of GDP and AGEs with icodextrin [8,27,70,71].

Yet, some researches associated long-term use of icodextrin-based solutions with development of encapsulated peritoneal sclerosis, an extremely severe complication with worst prognosis [72]. Moreover, in long-term follow-up, icodextrin-containing dialysate did not associate with better prevention of membrane failure when compared with classic glucose-based solutions [8,27,73].

Newer PD solutions and future prospectives for prevention dialysate-induced peritoneal inflammation. Non-glucose-based dialysates had been introduced in the last years; besides those with icodextrin and amino acids, there are also available solutions containing glycerol [27]. These solutions are associated with less formation of GDP or AGEs [8,27,71,74], but the osmotic power of none of them can be compared with that of glucose [8,27].

PD dialysates with neutral pH, with lactate-buffered or bicarbonate (± lactate)-buffered and with low GDP (as a consequence of separate sterilization of glucose at low *p*H) had been designed also [8,27,75]. These solutions are associated with better preservation of residual urine output, but no supplementary benefits – in terms of prolonging functionality of peritoneal membrane, peritonitis rate or patients' survival – were proven [27,76].

Solutions using bicarbonate as buffer are linked to decreased markers of peritoneal membrane viability (as cancer antigen-125 = CA-125) in some reports [1,32,33,77].

Promising alternatives in preserving long-term viability of the peritoneal membrane and in reducing proinflammatory insults come from several studies which reports favorable effects of pyruvate, *N*-acetylglucosamine, hyaluronic acid, citrate, or low-molecular-weight heparin when these substances are mixed with peritoneal fluids [1,27,78,79].

Conclusions

Standard glucose-based peritoneal dialysis solutions cheaper and available in the majority of dialysis centers represent a permanent proinflammatory injury on peritoneal membrane, leading to fibrosis, neoangiogenesis and ultimate to membrane ultrafiltration failure. Newer non-glucose-containing solutions, bicarbonate-buffered solutions or low *p*H solutions seem to affect less the peritoneal membrane, but they are more expensive and the studies performed so far did not prove significant differences in prevention of membrane failure. Several promising alternatives are yet in research stage and need to be validated in more extensive studies in order to be used in clinical practice.

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