Chapter

Preservation of Peritoneal Membrane Structure and Function in Peritoneal Dialysis

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Abstract

Peritoneal dialysis (PD) is a type of renal replacement therapy which is based on the use of peritoneum, which acts as a semipermeable membrane with diffusion and convection. Long term use can produce structural and functional changes of the membrane by the activation of the resident fibroblasts and infiltrating inflammatory cells, mesothelial to mesenchymal transition, further leading to fibrosis, angiogenesis and ultrafiltration failure. This is due to use of bioincompatible fluids, frequent peritoneal inflammation, uremic milieu and other multiple factors. The peritoneal fibrosis has two parts: fibrosis and inflammation, which induces each other via TGF/SMAD pathway and IL-6 signaling, respectively. The advent of newer biocompatible fluids along with additives has significantly reduced the production of glucose degradation products (GDPs). In addition, the identification of the biomarkers in peritoneal effluent is necessary, which, after being correlated with peritoneal biopsy, may help us to guide future studies and assessment of the efficacy of therapeutic interventions. Various interventions are being tried based on experimental studies from animal models, pharmacology and gene therapy with promising results, with new insights in near future. This article reviews the main aspects associated with the functional and structural alterations related to PD and discusses interventions whereby we may prevent them to preserve the peritoneal membrane.

Keywords: peritoneal dialysis, ultrafiltration, encapsulating peritoneal sclerosis, mesothelial to mesenchymal transition (MMT), VEGF (vascular endothelial growth factors), GDP (glucose degradation products)

1. Introduction

Peritoneal dialysis (PD) is a life-sustaining therapy used by >100,000 patients with ESRD worldwide, accounting for approximately 10 to 15% of the dialysis population [1]. Despite these benefits, only a small number of dialysis patients receive PD, in Europe about 13% and in the USA about 10% and 6% in India [2, 3]. The major obstacles for a successful long-term PD are infections and the deleterious functional alterations in the peritoneal membrane following prolonged exposure to dialysis fluids; which is responsible for increased morbidity and mortality. These alterations, such as progressive fibrosis and vasculogenesis, leading to increased solute transport and ultrafiltration (UF) failure, are seen in more than 50% of patients on PD.

Rippe proposed the existence of three pores of different sizes in peritoneal membrane: a large pore of 100–200 Å corresponding to interendothelial cell clefts allowing transport of large molecular weight solutes; a small pore of 40–60 Å, which allows for transport of water and low molecular weight (LMW)solutes and an ultrasmall pore of 4–6 Å that allows for the passage of only water.

2. The normal peritoneal transport barrier

2.1 Distributed concept of ultrafiltration barrier

The three potential barriers to both solute and water are (1) anatomic peritoneum (2) cellular-interstitial matrix surrounding the blood vessels (3) capillary endothelium. Blood vessels are the main source of UF and the water flow from the capillaries to the interstitium depends on the difference between the capillary luminal pressures and the effective pressure on the interstitial side. The concentration profile occurs due to diffusion of the small solutes via the tissue interstitium along with simultaneous uptake into the capillaries. The largest gradients of osmotic pressure will therefore be across blood vessels closest to the peritoneum.

Figure 1A describes the distributed concept of UF barrier and **Figure 1B** shows changes in membrane [4].

The distributed model proposes that "the influence of a specific capillary on PD transport is the function of that capillary's proximity to mesothelial to the dialysate interface". The proliferation of vessels near the interface increases the "effective" peritoneal surface area; especially during peritonitis and following exposure to high glucose containing fluids.

2.2 Pore matrix concept of endothelial barrier

Flessner [4] has postulated a new concept which says that the large and small pores will be represented as a single entity with the difference in transport characteristics;

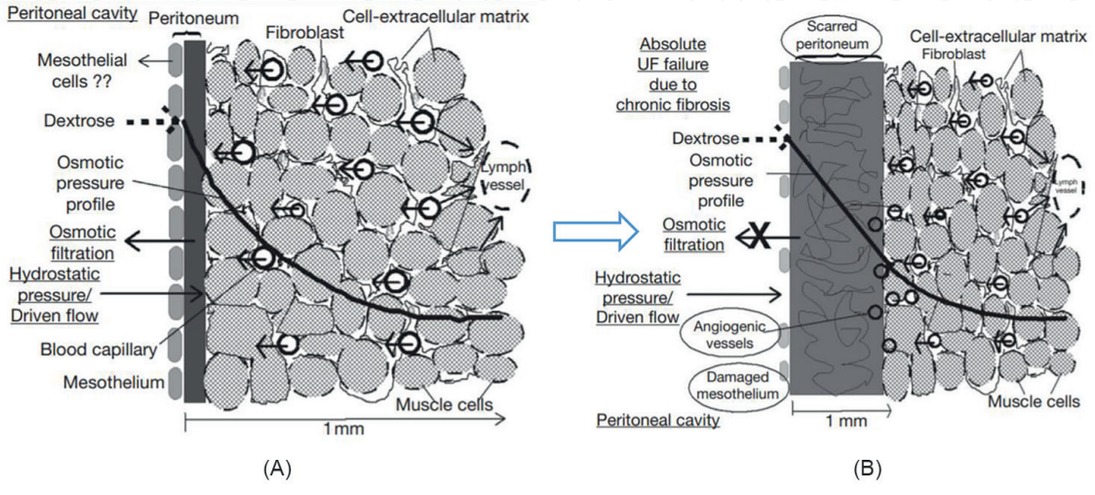

Figure 1.
(A and B) Distributed concept of normal ultrafiltration barrier. Dextrose diffuses from dialysate into tissue and sets up an osmotic pressure profile (thick curved line).

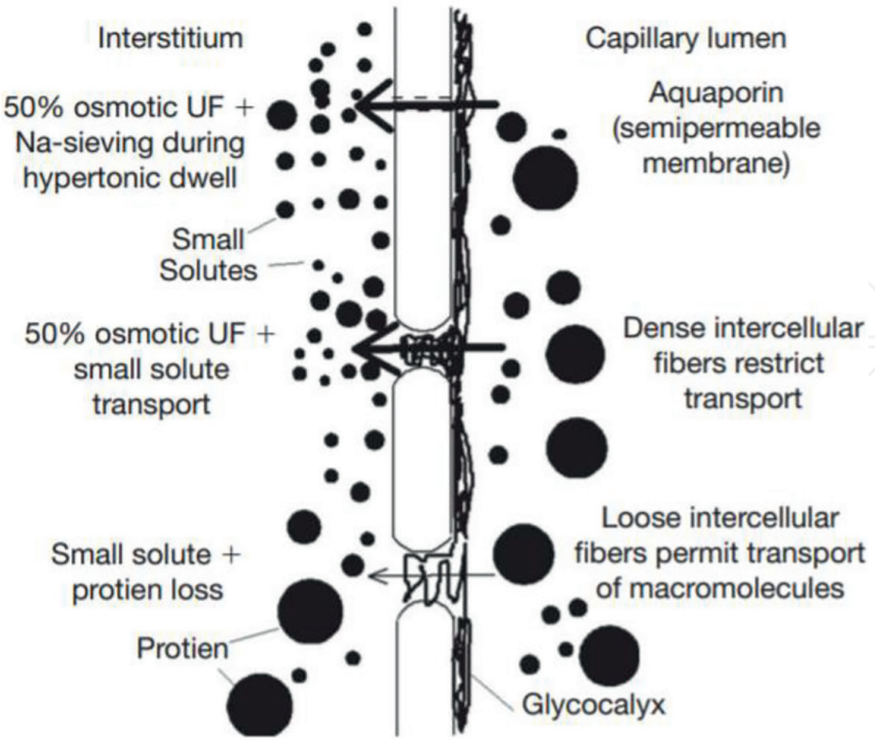

Figure 2.
Pore-matrix concept of endothelial barrier incorporating the luminal glycocalyx [4].

being a function of the density of intercellular glycoprotein matrix; as in **Figure 2**. This additional layer of glycocalyx alters the microenvironment near the true, size-selective boundary.

Moreover, albumin concentration below the glycocalyx but above the tight junction is likely much lower than that in the interstitium. This is because the albumin is unable to diffuse against the ultrafiltrate flow through the gap in the glycocalyx. The glycocalyx density is decreased by perfusion of oxidized LDL, adenosine, ischemia reperfusion injury and TNF-α.

3. Natural history of peritoneal membrane in CAPD

The peritoneal fibrosis has two parts; fibrosis process itself and the inflammation which is promoted by the non-physiologic content of solutions and infections. In the fibrotic process, there is loss of mesothelial cells with fibroblastoid changes leading to mesothelial-to-mesenchymal transition mediated by TGF-ß (Transforming growth factor) and VEGF (Vascular endothelial growth factor) signaling pathways. The inflammation pathway is mediated by the IL-6 (Interleukin-6) and other chemokines. Both the pathways are interlinked to each other and will be potentiating each other.

4. Regulation of peritoneal inflammation and leukocyte trafficking

During acute episodes of peritonitis, there is early activation of proinflammatory cytokines (TNF-, IL-1, and IFN-) and rapid recruitment of neutrophils with subsequent replacement by monocytes. This initial influx of neutrophils is due to the

expression of CXC chemokine, MIP-1/KC, and the release of sIL-6R which facilitates the formation of sIL-6R/IL-6 complexes. These trans-signaling complexes suppress the release of other CXC chemokines, ensuring clearance of neutrophils, and simultaneously promoting the secretion of the CC chemokines, such as monocyte chemoattractant protein 1 (MCP-1) and RANTES, triggering the recruitment of mononuclear leukocytes and regulate the process of apoptosis. The IL-6/sIL-6R signaling also selectively promotes T cell recruitment into the peritoneal membrane through a gp130-dependent, STAT1/3-dependent activation pathway (as shown in **Figure 3**).

The most consistent change observed in peritoneal tissues of a patient on PD is an increase in the sub-mesothelial thickness associated with peritoneal fibrosis.

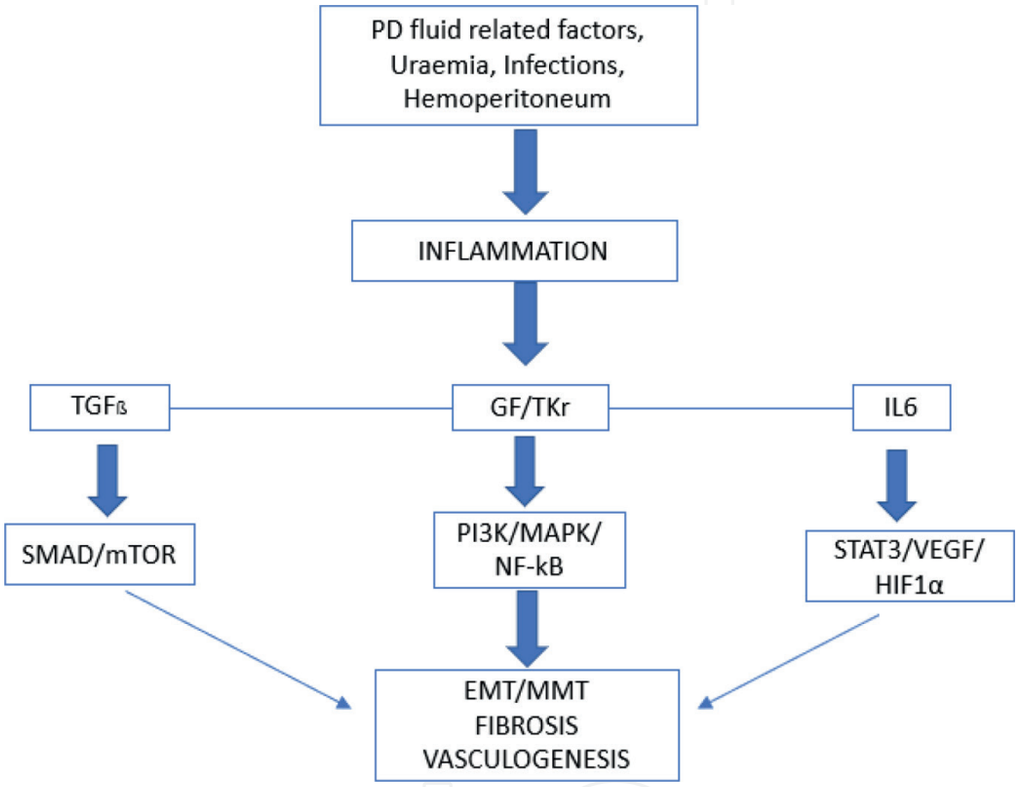

Figure 3.
Molecular network that regulate EMT [5]. Courtesy: Gonzalez 2016. Abbreviations: TGF ß—Transforming growth factor ß; GF—growth factor; TKr—Tyrosine kinase receptor; IL-6—interleukin 6; and EMT/MMT—Epithelial/Mesothelial to mesenchymal transition.

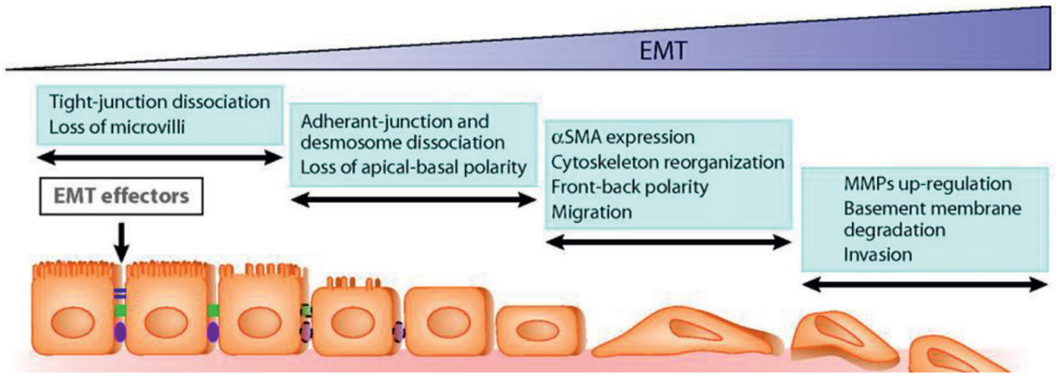

Figure 4.
Key events during EMT (Courtesy: [6]).

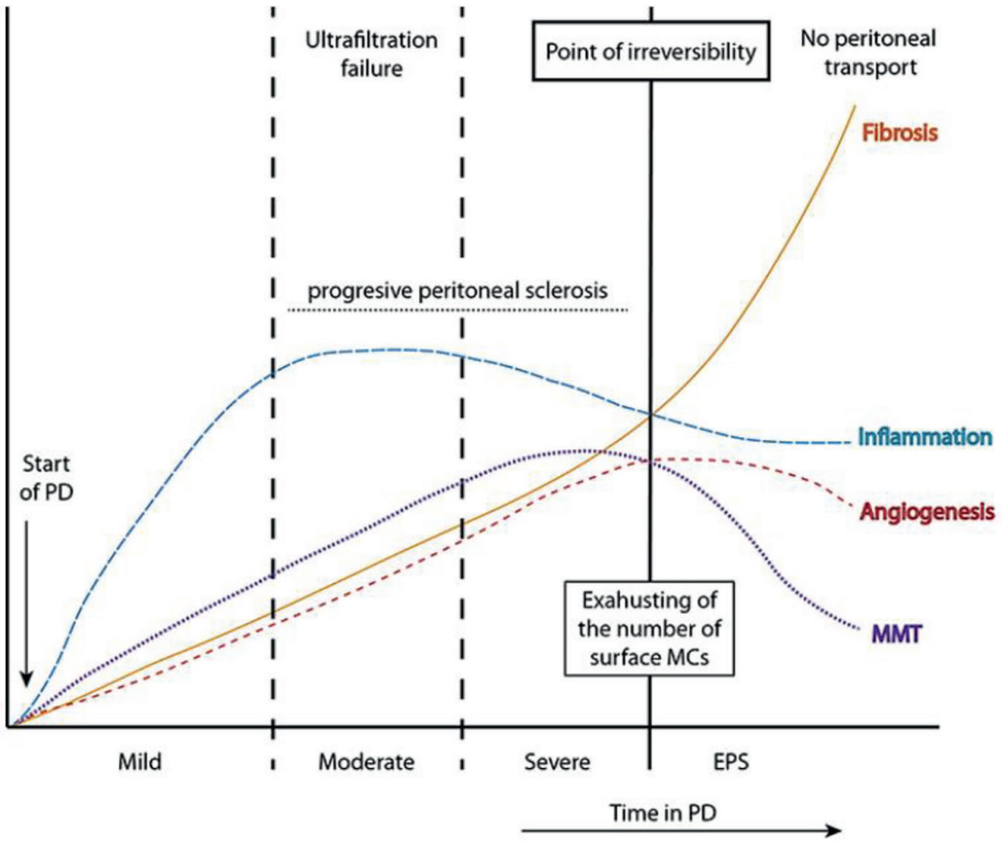

Figure 5.
Natural history of peritoneal membrane changes (Courtesy: [5]).

The use of non-physiologic PD solutions along with uremic milieu, has led to the production of advanced glycation end products (AGEs) in peritoneal tissues which induces vasculogenesis and fibrosis. The interaction between fibrosis and angiogenesis may occur at the level of inducing cytokines; TGF-ß leading to SMAD pathway and inflammatory cytokines induce VEGF and angiogenesis; this is how EMT (epithelial to mesenchymal transition)/MMT (mesothelial to mesenchymal transition) occurs (shown in **Figure 4**).

There are two pathologic types of PD related fibrosis. Most common type is simple peritoneal sclerosis which is seen in almost all patients. The other one is Encapsulating peritoneal fibrosis (EPS) that evolves rapidly with intense fibrosis and inflammation leading to life threatening visceral encapsulation (as shown in **Figure 5**).

5. Consequences of peritoneal fibrosis

The peritoneum is an acellular, avascular layer of tissue. Significant scarring of the peritoneum is often present after 6 or more years of CAPD. Solute transport is rapid across this avascular, acellular layer and uptake into abnormal blood capillaries is rapid. However, with the loss of the interstitial cell matrix and the increase in the distance of the blood capillaries from the peritoneum, the water transport to peritoneal cavity will be nearly zero [4]. Immunolocalization of collagen 1α-1 revealed that this protein was predominantly expressed in the sub-mesothelial compact zone of EPS peritoneal samples, whereas non-EPS patients exhibited diffuse and homogeneous Col1a-1 staining.

For more advanced peritoneal conditions with potential EPS development, EPS-prone states [7] is defined by (i) PD duration >3 years (ii) history of recurrent ± severe peritonitis (iii) presence of acquired UF failure or high-fast membrane transport (iv) high exposure to high GDP PD fluids, (v) repeated hemoperitoneum.

6. Risk factors for peritoneal membrane damage

A. Diabetes: In diabetes there will be upregulation of vascular endothelial growth factor (VEGF), driven by local hypoxia induced by vasculopathy of the microvasculature and also due to increased GDPs. They also have lower lumen-to-vessel diameter ratios and higher postcapillary venule diameters.

B. Uraemia: There will be increased expression of several proteoglycan components (versican, matrix metalloproteinase-2 [MMP-2] and hyaluronan) in patients with uraemia along with upregulation of AGE receptors (RAGE). It has been shown that presence of the C allele of RAGE protects against peritoneal fibrosis.

C. Dietary salt intake: There will be upregulation of TGF-β1 and IL-6 expression in the peritoneal membrane, resulting in an enhanced EMT; in addition, to an increase in peritoneal small solute transport leading to UF failure.

7. Genetic factors

A. IL-6 POLYMORPHISM: There can be G and C allele variant IL-6 polymorphism. IL-6 level is linked to peritoneal small solute transport and to albumin leakage. Those with GC or CC genotype had much higher IL-6 levels in their serum and in the drained dialysate than did patients with a GG genotype, along with upregulation of IL-6mRNA in the membrane [8].

B. eNOS: eNOS genotype aa or ab (versus bb) was an independent predictor of reduced peritoneal membrane transport rate [9].

C. Receptor for AGE: Numata et al. observed that a polymorphism of RAGE, the presence of the C allele in RAGE –429 T/C, were not present in patients with EPS [10]. Anti-RAGE antibodies also prevented the AGE associated upregulation of TGF-β1.

D. Il-1β: polymorphism has shown increased infection rate (lower with T/T vs. C/T & T/T) [11].

E. IL-1RN: polymorphism was an independent predictor of technique survival.

F. CCL18: Increased expression of CCL18 was associated with functional deficiency, increased fibrosis and atherosclerosis.

The risk factors for the peritoneal membrane damage are summarized in **Figure 6**.

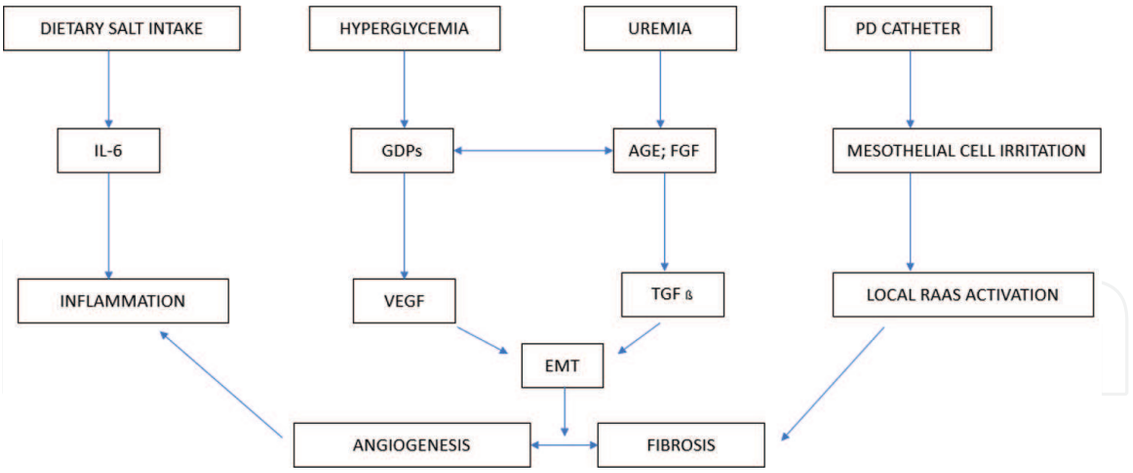

Figure 6.
Factors affecting peritoneal membrane degradation. Abbreviations: IL-6—Interleukin-6; VEGF—vascular endothelial growth factor; TGF—Transforming growth factor; and RAAS—renin angiotensin aldosterone system. Courtesy: Pletinck et al. [12].

8. Diagnosis of peritoneal fibrosis

A. Effluent biomarkers: Nowadays, early detection of membrane damage can be done with biomarkers. Some of them are CA-125, IL-6 and PAI-1. A low effluent level of CA 125 has recently been found as a prognosis factor for the membrane damage [13]. Cases of plasminogen activator inhibitor and CCL18, in peritoneal effluent are also associated with the prognosis of the membrane [14]. Other biomarkers are VEGF, MMP-2, TGF-ß, CTGF, TNF-α.

B. Histopathology: is the gold standard. The biopsy findings if using bioincompatible fluids were mesothelial layer disappearance, thickening of the sub-mesothelial compact zone, hyalinizing vasculopathy, angiogenesis, along with co-expression of α-smooth muscle actin and cytokeratin. The biopsy findings in those who used biocompatible fluids were associated with more well-preserved MC layer (56% vs. 26%), mild thickening with less dense sub-mesothelial compact zone (47% vs. 69%) and an absence of hyalinizing vasculopathy (4% vs. 30%) [15].

9. Conventional PD fluids

First generation Fluids: contain 35–40 mM lactate buffer with an acidic pH of 5.5. The low pH will be aggravating the detrimental effects of the high lactate on peritoneal mesothelium. During heat sterilization and storage, more of (GDPs) (e.g., formaldehyde, acetaldehyde, glyoxal, methylglyoxal, 5-hydroxymethylfurfural (5-HMF), 3-Deoxyglucosone (3-DG) and 3,4-dideoxyglucosone3-ene (3,4-DGE)) are formed, leading to membrane damage (shown in **Figure** 7).

Second generation Fluids: The buffers (such as lactate ± bicarbonate) are in separate chamber and are kept in very low pH to prevent formation of GDPs. Prior to use, they are mixed to a pH of 7–7.5 and are administered. They are detailed below.

Icodextrin: is an osmotic agent (Mol.wt-16,800 Da) derived from the starch, used in long night dwell with very low GDP, since they are absorbed into the

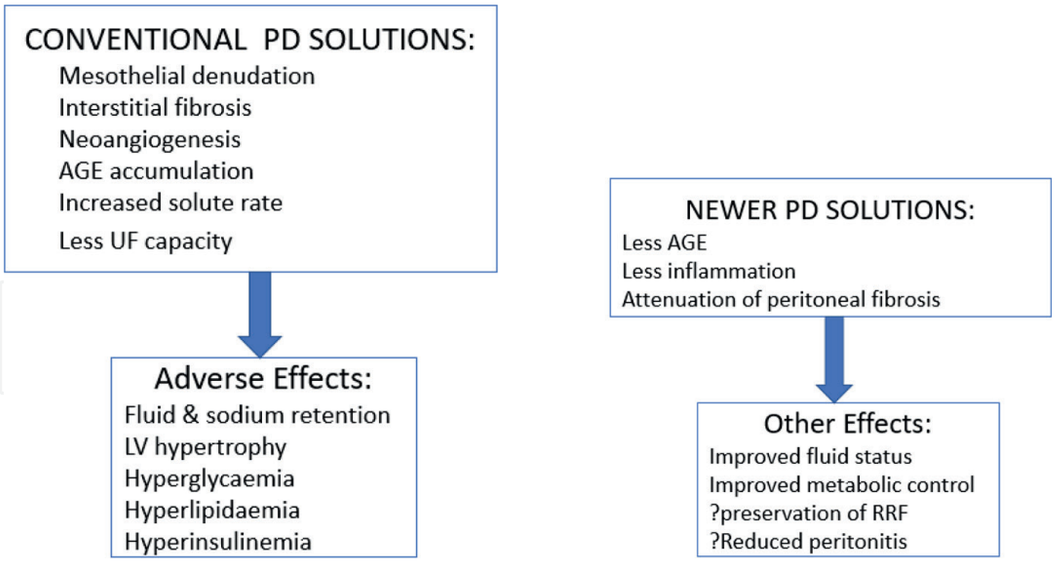

Figure 7.
Potential beneficial effects of newer peritoneal dialysis solutions [16]. (Courtesy: Garcia nature reviews 2012). Abbreviations: RRF—residual renal function; LV—left ventricle; and AGE—advanced glycosylated end products).

circulation, with no sodium sieving. It has an UF capacity comparable to 4.25% dextrose fluid. Despite this, acidic PD fluid has been associated with increased local and systemic inflammation with increased permeability and IL-6. Even though this reaction is reaction, long term exposure may irreversibly change peritoneal morphology. The ISPD guidelines recommends use of icodextrin in high transporters for better volume control.

Amino acid solutions: A bag of 1.1% 21 amino acid PD fluid used in one exchange a day provide 22gm of amino acids (2/3rd essential & 1/3rd nonessential) which is 25% of daily requirement and generate an UF equal to 2 L 1.5% dextrose. It has an acidic pH of 6.6 with very low GDPs and low VEGF. For optimized nutrition of malnourished patients and to prevent increased serum nitrogen levels and metabolic acidosis, they should be applied at a ratio of 1:4 with glucose-containing PD fluids [17]. Nutrineal in one exchange with icodextrin (Extraneal) and Physioneal (Baxter) for other exchange as a regimen (NEPP regimen) has shown to preserve mesothelial integrity but with increased VEGF.

10. Newer PD fluids

1. Trio gambrosol- tri compartment with two small chambers with 50% glucose and last chamber with calcium, magnesium, chloride & lactate.

2. Physioneal- two chamber with chamber A containing glucose in 1.5%, 2.5%, 4.5% at a pH of 2.1 along with calcium & magnesium salts and chamber B with buffer lactate & bicarbonate at a pH 9.0. Volume of chambers in 3:1 ratio and solutions in both chamber mixed prior infusion, at least 1.6 L instilled during each infusion (to avoid accidental infusion of buffer only chamber and alkalosis)

3. Balance- double chamber with glucose & electrolyte and other with buffer in equal volumes.

Fluid	pH	Buffer	GDP (μmol/L)	Osmotic agent
Icodextrin	5.8	Lactate	45	7.5% polyglucose
Amino acid	6.6	Lactate		1.1% amino acid
Trio Gambro	6.3	Lactate	65	Dextrose
Physioneal	7.4	Bicarbonate+lactate	253	Dextrose
Balance	7.0	Lactate	42	Dextrose
Bicavera	7.4	Bicarbonate	42	Dextrose
Delflex NpH	7.0	Lactate+bicarbonate	70	Dextrose

Table 1.
Newer PD fluids and constituents.

4. Bicavera-double chamber which has used bicarbonate as buffer used along with glucose containing calcium& magnesium chloride. This is the only PD fluid which used bicarbonate alone as buffer.

5. Delflex Neutral pH- Only FDA approved neutral pH PD fluid. GDP levels are 55, 70, 95 μmol/L depending on 1.5%, 2.5%, 4.5% glucose content (**Table 1**).

The Euro-Balance trial, demonstrated improved residual renal function together with decreased peritoneal UF with the pH neutral, low GDP fluid, as compared to the first generation, acidic high GDP solution [18]. The BalANZ trial has shown a lower risk of anuria and lower ultrafiltration and higher solute clearance rates with the use of low GDP fluid during the first 9 months of PD. Peritonitis incidence and severity were reduced in the BalANZ trial [19]. The TRIO trial comparing biocompatible solution (Gambrosol Trio) to standard PD fluid (Dianeal) showed contrasting results with slower rated of GFR decline but with higher peritonitis rate.

11. Novel PD fluid protoypes

The introduction of novel osmotic agents, is a promising way to improve the biocompatibility (**Figure 8**).

1. The addition of 3.5% taurine-based PD fluid achieved equivalent ultrafiltration as glucose-based PD fluid and induced less mesothelial and fibroblast cell proliferation(rat model) [20]

2. Hyperbranched polyglycerol containing PD fluid achieved similar solute and water transport and induced less peritoneal membrane damage (rat model)but data on metabolism are lacking [21]

3. By the addition of dipeptide alanyl-glutamine to first- and second-generation PD fluid improved mesothelial cell stress response and cell survival with reduced peritoneal fibrosis [22]. A phase 3 trial is needed.

4. Addition of L-carnitine to acidic, glucose PD fluids resulted in superior ultrafiltration and improved insulin sensitivity [23].

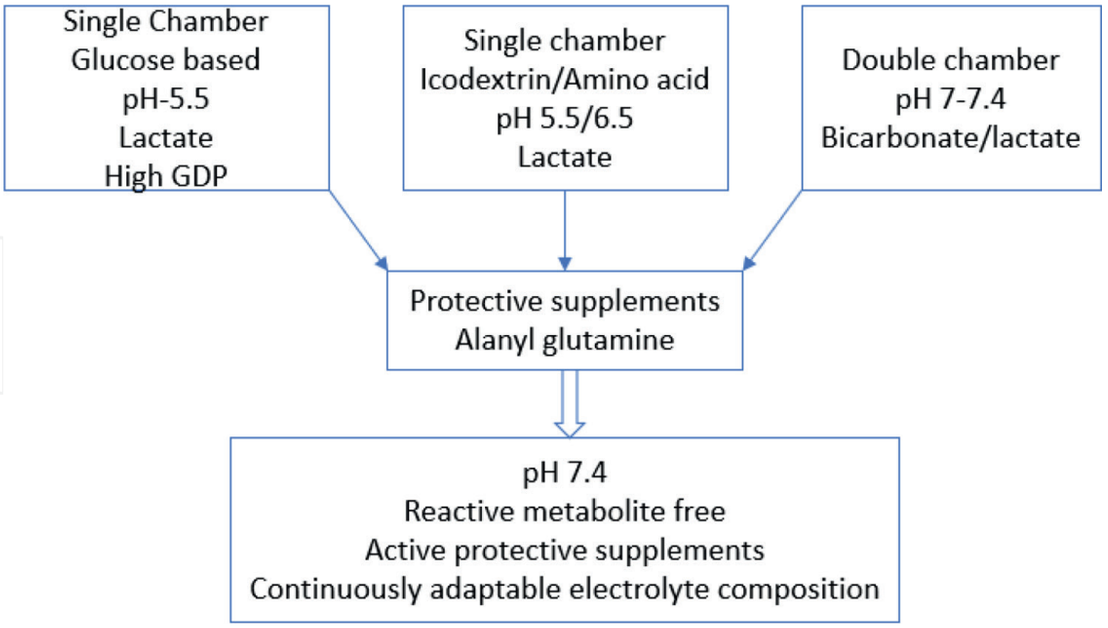

Figure 8.
Novel PD fluid prototypes.

Other preventive strategies:

Peritoneal resting: especially for high solute transport with Type 1 UF failure because this partially reverses some of the functional alterations of peritoneal transport. De souse et al. [24] found decreased D/P creatinine with increased UF capacity, after 4 weeks of peritoneal resting.

12. Newer agents to ameliorate membrane damage

1. Inhibitors of the RAAS system: The mesenchymal cells can locally activate RAAS; in autocrine and paracrine fashion. The administration of RAAS inhibitors results in blockage of the TGF-β, fibronectin and VEGF. Koleysnk et al. [21] and Jing et al. [25], found that ACE inhibitors appeared to have a slower rate of decline in ultrafiltration and residual function, effectively protect against peritoneal fibrosis in long-term peritoneal dialysis.

2. Hyaluronic acid: Preservation of hyaluronan concentration in PD effluent is deemed to be a marker of preservation of peritoneal integrity. It has protective role against abrasion and infection, through the initiation of increased synthesis of growth factors.

3. I.P. Tinzaparin & Bemiparin: Del peso et al. [26] showed an improvement in UF capacity

4. Paricalcitol: VDR activator reduced IL-17 and increased Tregs leading to antifibrotic and anti-inflammatory effects.

5. Rapamycin: mTOR inhibitors diminish IL-17 and decreases fibrosis with anti-MMT action but delayed healing, limiting its use in specific situations. It also decreases synthesis of VEGF

6. Tamoxifen: Estrogen receptor modulator, which inhibit MMT, reduces membrane thickness, invasion of the compact zone by mesenchymal mesothelial cells leading to reduced peritoneal MC migration and improved fibrinolytic capacity. A Dutch study showed a decreased mortality among patients with EPS after treatment with Tamoxifen.

7. Nebivolol & Heparin (IP): increases fibrinolytic capacity associated with increased tPA levels. Apart from anticoagulation, heparin also has anti-inflammatory, immunomodulatory, antiangiogenic, antiproliferative, antifibrotic properties. Low-molecular-weight heparins can also inhibit VEGF and fibroblast growth factor activity.

8. Benfotiamine: A derivative of thiamine, has been associated with decreased AGE and decreased oxidation by increasing transketolase [27].

9. Pyridoxamine: beneficial role against UF failure; by reduction in accumulation of AGEs and the expression of angiogenic cytokines leading to decreased transport rates for small solutes and reduced blood vessel density [28].

10. NSAIDs: In a rat model, oral administration of celecoxib drastically reduced prostaglandin E2, angiogenesis and lymph angiogenesis [29] and preserved ultrafiltration. Liu et al. observed that selective COX inhibition resulted in blunting of TGF-β production by mesothelial cells when exposed to high glucose concentrations and resulted in reduction of fibrosis and blunted ultrafiltration failure. No data on oral administration.

11. Sulodexide: consists of 80% LMW heparin and 20% heparan sulphate. Apart from anticoagulation, it has immunomodulating, anti-inflammatory and antiproliferative, and anti-angiogenic properties. Oral sulodexide inhibits either VEGF directly by binding to it or by inhibiting its interaction with receptor.

12. PPAR Y agonist: Rosiglitazone, decreases AGE and fibrosis but the adverse effects have limited its use. The anti-inflammatory properties were mediated by an increase in peritoneal levels of IL-10 along with recruitment of CD4+ CD25+ FoxP3+ cellsD3+ lymphocytes.

13. Tranilast: proposed to have some effects on peritoneal MCs, being the therapeutic potential for the treatment of peritoneal fibrosis [30]

The potential MMT modulators untested in PD are depicted in **Table 2**:

A study in a rat model, by using the stem cells demonstrated that the xenografts of human umbilical mesenchymal stem cells prevented the PD-induced membrane alterations [31].

By the advent of the proteomics and functional genomics analysis of the MC and the EMT, these fine biomarkers can be used for the accurate follow-up of the progressive peritoneal membrane deterioration. They also will identify the master molecules which governs the mesenchymal transition of MC. These molecular profiles of the EMT process in future might become an excellent tool to test the biocompatibility of newer PD fluids. Although further studies are needed, it is expected that increasing knowledge will provide a novel approach for therapeutic benefits in the treatment of peritoneal fibrosis, thus maintaining the peritoneal membrane for an extended period in PD patients.

Antifibrotic agents	**Mechanism of action**
1) Tetrapeptide	TGF ß inhibition
2) Dipyridamole	TGF ß inhibition
3) Pentoxyfylline	Inhibition of ECM production
4) Emodin	Inhibition of ECM production
5) Simvastatin	Increases fibrinolytic activity
Antiangiogenic	
1) Anecortave acetate	Inhibits VEGF production
2) Pegaptanib	Inhibits VEGF-VEGFR binding
3) Anti-VEGFRII	Blocks receptor VEGFRII
4) TNP 470	Decreases VEGF expression
Inhibition of EMT	
1) Rho-ROCK inhibitor (Y27632)	TGF-β/Smads inhibitors
2) Anti-oxidant agent	NF-κB inhibition
3) Notch inhibitors	Inhibit the induction of snail and repression of VE-cadherin
4) JNK inhibitors (PS600125)	Inhibition of both ZEB and Rho pathway
5) CBR1 antagonists	TGF-β/Smads inhibitors

Courtesy: Gonzalez 2016.

Table 2.
Potential MMT modulators untested IN PD:

Conflicts of interest

None.

Disclosures

None.

Source of funding

Nil.

Abbreviations

AGE	advanced glycation end products
EMT	epithelial to mesenchymal transition
EPS	encapsulating peritoneal sclerosis
GDP	glucose degradation product
IL-6	interleukin 6
LMW	low molecular weight

MC	mesothelial cells
MMT	mesothelial to mesenchymal transition
PD	peritoneal dialysis
RAGE	receptor for AGE
RANTES	regulated on activation, normal T cell expressed and secreted
RRF	residual renal function
STAT	signal transducer and activator of transcription
TGF	transforming growth factor
UF	ultrafiltration
VEGF	vascular endothelial growth factor

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