Chapter 3

Pharmacological Preservation of Peritoneal Membrane in Peritoneal Dialysis

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Additional information is available at the end of the chapter

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Abstract

Peritoneal dialysis (PD) is an established renal replacement therapy for renal disease. It is based on the capacity of the peritoneum to act as a semipermeable membrane for the exchange of toxic solutes and water, which is called ultrafiltration capacity. Peritoneal membrane (PM) is lined by a monolayer of mesothelial cells (MCs), which lay on an extracellular matrix bed where other cell types and blood and lymphatic vessels can be found. Long-term exposure to hyperosmotic PD fluids (PDFs), peritonitis or hemoperitoneum causes peritoneal injury by the generation of an inflammatory state. Inflammatory cells and their mediators initiate a cascade of reactions promoting alterations in peritoneal cells, loss of MCs, fibrosis, vasculopathy, and angiogenesis, leading to ultrafiltration failure. Recent studies support that the so-called "mesothelial to mesenchymal transition" process of the MCs runs parallel to the anatomical and functional ridging of PM, which suggests that its inhibition might slow down or stop the PM damage. The fight against PM damage begins with the improvement in PDF biocompatibility. Complementary to this, an alternative approach to preserve the PM might be the use of pharmacological agents or molecular strategies. Here, we explain the existing research models for the development of new therapies and analyze several therapeutic options tested with them.

Keywords: biocompatible fluids, mesothelial to mesenchymal transition, peritoneal membrane failure, inflammation, research models, PD solutions low in GDPs, pharmacotherapy

1. Introduction

Peritoneal dialysis (PD) is an established form of renal replacement therapy that uses the peritoneal membrane (PM) as a semipermeable barrier for the exchange of toxic substances and water [1, 2]. The use of this technique has increased during the last years [2, 3], possibly due to the technique improvement, especially in terms of peritonitis prevention and biocompatibility of the PD fluids (PDFs). Nowadays, PD rivals with hemodialysis (HD) in terms of morbidity, mortality, adequacy, and water balance [4–6].

Peritonitis and ultrafiltration failure (UFF), with a clinical result of extracellular volume overload and an increased cardiovascular risk, are still the major factors contributing to technique dropouts [2, 7, 8]. The systemic and local complications associated with PD are the challenge of clinical and basic researchers, both with the same aim of improving the long-term preservation of the PM function.

Peritoneal deterioration due to PD (endogenous and exogenous factors) starts with the induction of an inflammatory state, what damages the mesothelial layer and afterwards the whole structure of the PM, compromising its integrity and promoting angiogenesis and fibrosis. These alterations are responsible for the UFF that leads to technique malfunction.

The mesothelial cell (MC) monolayer is the first line of contact between the body and the PDF. The inflammatory process generated, combined with the accumulation of glucose-degradation products (GDPs), advance glycation end-products (AGEs), and others, can trigger a process called mesothelial to mesenchymal transition (MMT) [2, 8]. This process consist in the loss of baso-apical and base-lateral polarity of the MCs, which acquire a fibroblastoid phenotype, invade the submesothelium, and synthesize a large amount of extracellular matrix component (EMC) and pro-angiogenic and lymphatic factors [2]. Therefore, given the role of MMT in the deterioration of the PM, this process can be considered a therapeutic target [9].

Different strategies have been tested *ex vivo*, *in vivo*, and *in vitro* targeting different processes to achieve PM amelioration. This chapter updates the knowledge regarding the processes involved in the deterioration of the PM with specially emphasis on the possibility of using drugs capable of preventing or ameliorating peritoneal damage.

2. Understanding peritoneal deterioration: models for research

The three most commonly used methods to study the local and systemic alterations related to PD are the following: the first method is the analysis of cytokines, chemokines, and soluble factors present in PD effluents of patients; the second method is the culture *ex vivo* of cells floating on these effluents (human peritoneal mesothelial cells, from now on called HPMCs; or inflammatory cells) and the use *in vitro* of mesothelial cells extracted from omentum of donors (HOMCs); and the third method is the use of animal models to mimic *in vivo* what happens during the exposition to PD fluids.

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Big efforts have been done to achieve *in vivo* animal models, not only to understand the structure and function of the PM but also to resemble PD treatment in human patients, as it is the best way to analyze all the possible elements implicated. With this purpose, several groups have focused on different species, obtaining interesting models where different parameters can be analyzed. Rats and mice are the preferable animal species for these *in vivo* models due to their reduced size, quick metabolism, and easy handling [10].

Along the following sections, we will go deeper on the studies that have been done with these different methods to understand peritoneal deterioration during PD and to develop therapeutic strategies to protect the peritoneum.

3. Peritoneal alterations suffered during PD

The PM is lined by a single layer of MCs, which lay on a compact zone of connective tissue that contains few fibroblasts, mast cells, macrophages, and vessels [11, 12]. The PM acts in PD as a permeable barrier across which ultrafiltration and solute diffusion take place.

The long-term exposure to hyperosmotic, hyperglycemic, and low pH of PDFs, as well as repeated episodes of bacterial and fungal infections (acute peritonitis) or hemoperitoneum, induces inflammatory and uncontrolled reparative responses, causing injury to the peritoneum [2, 13–16]. In this scenario, the peritoneum becomes progressively denuded of MCs and undergoes fibrosis and neovascularisation. Such structural alterations are considered the major cause of the loss of the peritoneal dialytic capacity (UFF) [2, 8, 17–19].

3.1. Inflammation

The local injury induced by classical glucose-based PD fluids is mediated, at least in part, by the presence of GDPs and by the acidic pH. GDPs through the formation of (AGEs) may stimulate the production of extracellular matrix components (ECMs) as well as the synthesis of profibrotic and angiogenic factors [2, 8]. Both infectious and noninfectious factors activate the immune system orchestrating cellular responses. Inflammatory cells secrete large number of cytokines, growth factors, and chemokines to establish a complex network that feed backs resulting in sustained chronic inflammation, which might trigger the fibrogenic and angiogenic processes associated with the ultrafiltration failure [2, 14, 20–23]. This leads to an increased tendency toward plasma exudations that contain fibrin and coagulation factors. The fibrins in the exudates contribute to the intestinal adhesions and formation of fibrin capsule [19].

3.2. Mesothelial to mesenchymal transition (MMT)

MMT is a physiological process necessary for tissue repair. However, in uncontrolled conditions, it is not autoregulated, inducing functional and structural changes in the PM. MMT progression is regulated by complex signaling pathways that can collaborate to accelerate or complete the trans-differentiation: delta-like jagged Notch, receptors for TGF/Smads, integ-

rins, tirosine kinase receptors, inflammation, and hypoxia (**Figure 1**). The list of pathways involved in MMT is in constant growth, and other routes have also been described.

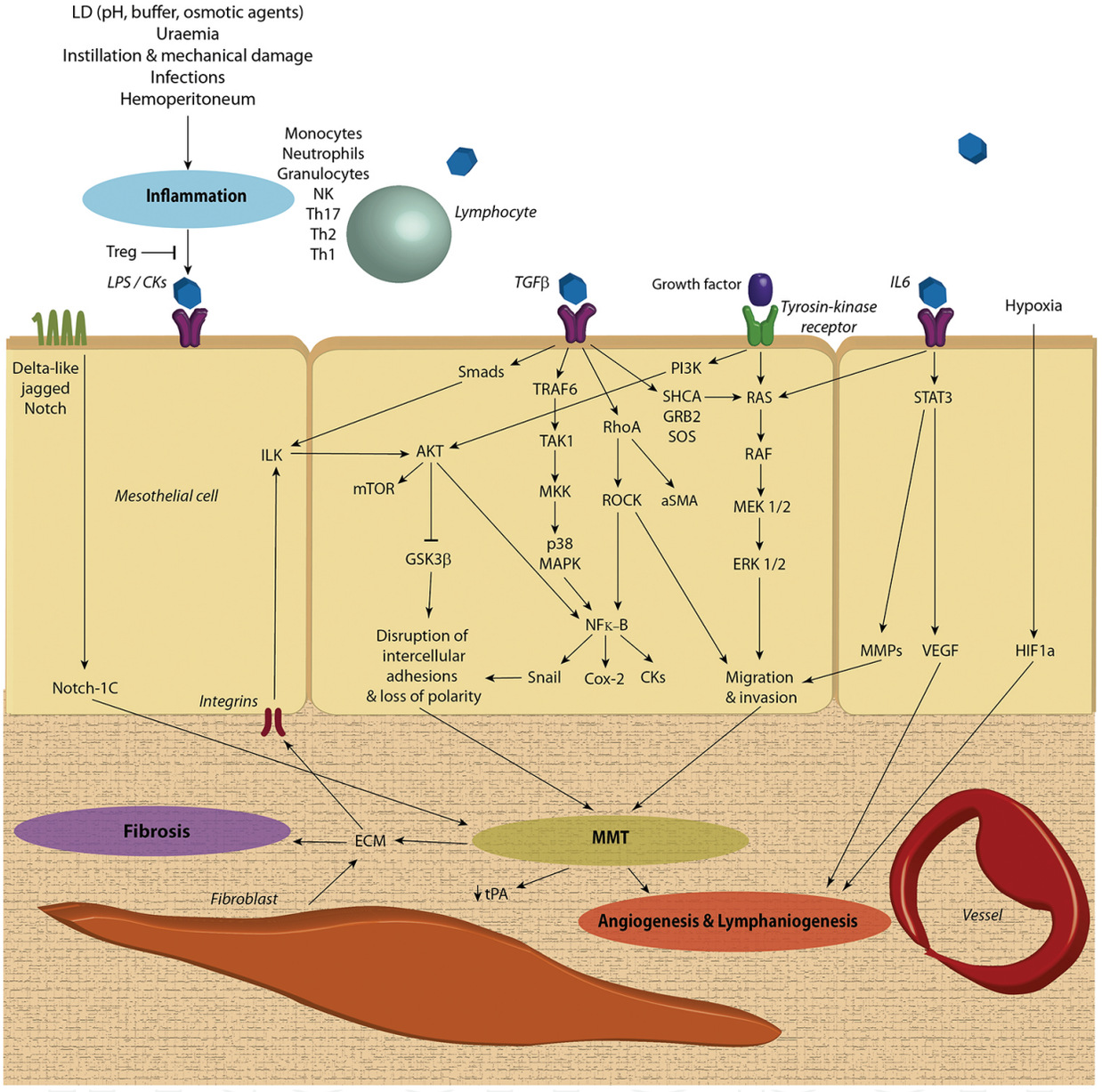

Figure 1. Up to day of the molecular networks that regulate MMT. MMT, mesothelial-to-mesenchymal transition; TGFβ, transforming growth factor-β; TGFβR, TGFβ receptor; MMPs, matrix metalloproteinases; GSK3β, glycogen-synthase kinase-3β; ILK, integrin-linked kinase; MAPK, mitogen-activated protein kinase; RAS–RAF–MEK–ERK pathway, extracellular signal-regulated kinases (MEK: Mitogen-activated protein kinase. ERK: extracellular signal–regulated kinase); NF-kB, nuclear factor-kB; PI3K, phosphatidylinositol 3-kinase; TAK1, TGF-beta activated kinase 1; VEGF, vascular endothelial growth factor; ECM, extracellular matrix; mTOR, mammalian TOR; Notch-IC, intracellular fragment of Notch; COX-2, cyclooxygenase 2; CK, cytokines; Th, T-helper lymphocytes; Treg, T regulatory lymphocytes; SHCA, adaptor protein SRC homology 2 domain–containing-transforming A; GRB2, growth factor receptor–bound protein 2; SOS, son of sevenless; HIF-1α, hypoxia-inducible factor-1α; TRAF6, TNF receptor-associated factor 6; a-SMA, alpha smooth muscle actin; AKT, protein kinase B; RhoA, Ras homolog gene family, member A; ROCK, Rho-associated protein kinase; STAT3, signal transducer and activator of transcription 3; t-PA, tissue plasminogen activator; and LPS, lipopolysaccharide.

In Notch and Hedgehog signaling, glioma 1 can induce SNAIL1 expression, and the intracellular domain of Notch can activate SNAIL2 expression, hence downregulating E-cadherin.

The TGFβ/Smads classical pathway is able to activate different routes. One of them starts when the adaptor protein SRC homology 2 domain-containing-transforming A (SHCA) is phosphorilated, creating a docking site for growth factor receptor-bound protein 2 (GRB2) and son of sevenless (SOS), what initiates the RAS-RAF-MEK-ERK MAPK pathway. The p38 MAPK and JNK activation, another TGFβ-induced route, results from the association of TNF receptor-associated factor 6 (TRAF6) with the TGFβ receptor complex, which activates TGFβ-activated kinase 1 (TAK1) and, as a result, p38 MAPK and JNK [24] (see abbreviations in **Figure 1**).

The integrin pathway is able to activate the integrin-linked kinase (ILK), inducing the serine/threonine kinase AKT, which inhibits glycogen synthase kinase (GSK)-3β inducing MMT [24].

Several growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF), can induce epithelial-to-mesenchymal transition (EMT), activating receptor tyrosine kinases (RTKs). The RAS-RAF-MEK-ERK MAPK signaling cascade represents a major pathway that is activated by RTKs in response to growth factors. Once activated, ERK1 and ERK2 MAPK pathway cell motility and invasion are activated [24].

During inflammation and cancer, interleukin (IL)-6 can promote EMT through Janus kinase (JAK)-signal transducer and activator of transcription (STAT)3-induced SNAIL1 expression. Hypoxia in the tumor environment can promote EMT through hypoxia-inducible factor (HIF)-1α [24].

Finally, MCs lose their basoapical and basolateral polarity, acquire migratory capacity to synthesize large amounts of extracellular matrix and angiogenesis through increased synthesis of VEGF (**Figure 1**).

In PD, endogenous and exogenous factors can stimulate the immune system and MCs in the peritoneal cavity to induce MMT by different routes.

3.2.1. Evidence for the involvement of MMT in PM deterioration

Transdifferentiation of MCs *in vivo* has been described in the effluent of PD patients since 2013 [25]. The authors described that soon after PD is initiated, peritoneal MCs showed a progressive loss of epithelial phenotype and acquired myofibroblast characteristics [25]. Effluent-derived MCs can be easily isolated from PD patients using standard methods [25, 26]. It was described that *ex vivo* cultures of effluent-derived MCs showed two main morphologies: epithelioid and nonepithelioid (fibroblast-like). After analyzing several hundred MC cultures with growth capacity, it could be determined that the frequencies of the different effluent-derived MC cultures were approximately 53% for epithelioid phenotype and 44% for nonepithelioid MCs. The prevalence of nonepithelioid MC cultures appeared to be associated with the time the patients have been subjected to PD and with the episodes of acute or recurrent peritonitis or hemoperitoneum [25, 26]. A less frequent cell culture type (less than 6%) with mixed morphologies has also been described [25, 26]. In the course of practicing *ex vivo* cultures of

effluent-derived cells, hypertrophic cells can also be observed occasionally in hypertrophic MCs.

However, the most important evidence of the presence of MMT in both surface and deep (submesothelial) areas comes from studies in peritoneal biopsies of PD patients [27]. The number of transdifferentiated MCs showed a direct correlation with the loss of ultrafiltration, the thickness of the PM, and angiogenesis [27]. Experimentally, it has also been found a positive correlation between the degree of MMT and time in PD [28].

3.3. Peritoneal fibrosis in PD, sclerosis, and EPS

Peritoneal fibrosis (or sclerosis) consists on the deposit of ECM proteins (collagen I, III, V, VI, fibronectin, tenascin) in the interstitium, with increased number of fibroblasts (some of them presenting myofibroblastic characteristics) and inflammatory cell infiltration. Moreover, it is usual to find extracellular accumulation of collagen IV and laminin in the basement membrane, and also proteoglycans, polysaccharides, and glycoproteins [18, 28–31].

Peritoneal fibrosis is a term that includes a wide spectrum of structural alterations, ranging from mild inflammation to severe sclerosing peritonitis and EPS, its most serious and dangerous manifestation [31]. Simple sclerosis (SS), an intermediate stage of peritoneal fibrosis, is the most common lesion found in patients after few months on PD and may represent the beginning of sclerosing peritonitis (SP) [30]. The peritoneal thickness is the most commonly used criteria for differential diagnosis. The normal thickness of human peritoneum is 20 μm [19], but after a few months on PD, it may reach up to 40 μm (SS). The SP is a progressive sclerosis characterized by a dramatic thickening of the peritoneum (up to 4000 μm), accompanied by inflammatory infiltrate, calcification, angiogenesis, and vasodilatation of blood and lymphatic vessels [31, 32].

Fortunately, the frequency of EPS is low (0.5–4.3 cases per 1000 patients per year) [30, 31]. However, its severity and the lack of adequate and proved therapeutic options deserve special attention. The SPS is considered as reversible condition, while EPS still progresses even after the interruption of PD treatment [32] and is characterized by a progressive intra-abdominal inflammatory process that results in bridles and severe fibrous tissue formation, which cover and constrict the viscera leading to obstruction of the intestinal tract.

3.3.1. MMT as initial step for SPS and EPS

Although the pathways to reach EPS from SPS have not been fully established, emerging evidences have indicated that MMT is persistently present in initial and end stages of peritoneal fibrosis [27, 28, 33]. It is not difficult to argue that the MMT leads to peritoneal fibrosis, but the EPS jump is still much discussed [34]. An interesting point is that almost 100% of patients in PD show peritoneal fibrosis or sclerosis, while less than 5% reaches EPS [31, 35, 36], suggesting the presence of another factor that sets the point of no return (**Figure 2**). This factor might be a genetic factor [36, 37]. Different research studies have shown in both, animal models and patients, the presence of MMT in the submesothelium from the early stages to the

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later stages of PD [27, 28, 31]. Moreover, the amount of MMT was closely related to the severity of the damage and anatomical abnormalities in the peritoneal transport.

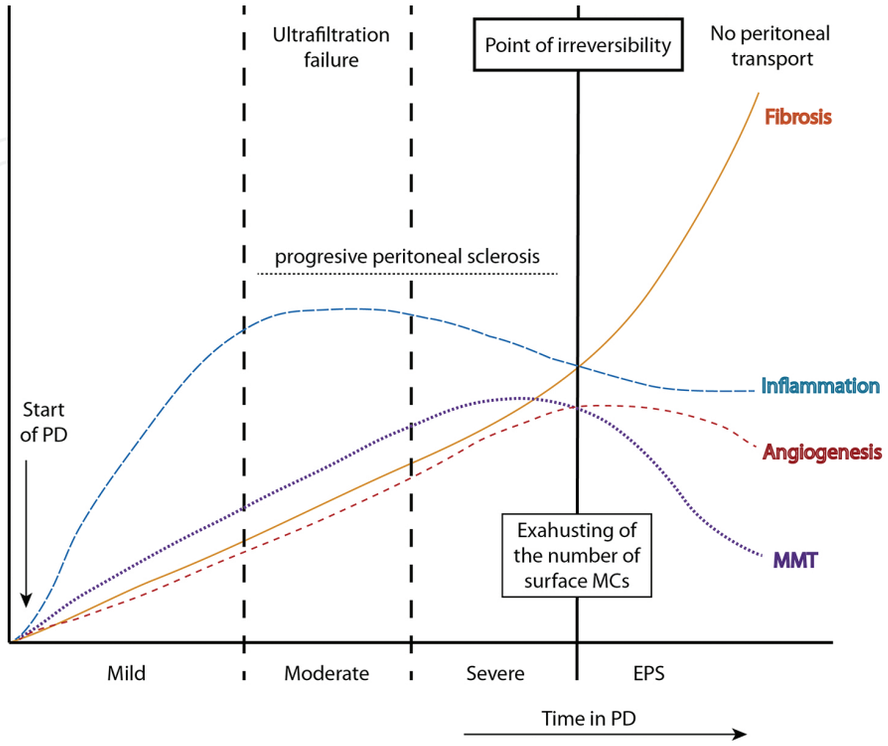

Figure 2. Natural history of morphological and functional changes of the PM in PD.

There are several clinic limitations to perform a peritoneal biopsy study in PD patients looking for traces of MMT through time in PD. Another limitation is that we do not have a realistic model of EPS in vivo. Models of EPS developed through Chlorhexidine exposition [38] do not resemble the natural scene lived by the patients in PD.

Accepting that the MMT is an initial step in the peritoneal deterioration process, we must know the mechanisms governing this process. MMT is a generally reversible process that starts with the disruption of intercellular junctions and loss of polarity, followed by increased migratory, invasive, and fibrogenic capacities. The aim of this process is to heal wounds by promoting the recovery of ancestor capabilities of epithelial cells such as cell migration, production of ECM, and induction of angiogenesis [25, 27].

As a patient begins the PD, the PM starts a deterioration process characterized by peritoneal thickening (fibrosis) and angiogenesis. After a variable time period in PD, the PM develops a PM thickening, which can show a moderate or severe fibrosis degree, and type-I PM UF failure starts. These changes occur in parallel with the induction of MMT, resulting in increased number of transdifferentiated MCs in submesothelium as well as other fibroblastic-like cells derived from bone marrow (CD34+) and Endo-MT. Consequently, the number of MCs monolayer is exhausted, and the peritoneal tissue may initiate an automatic, progressive, and

irreversible process characterized by severe fibrosis, angiogenesis, and peritoneal adhesion formation: EPS.

3.4. Angiogenesis and lymphangiogenesis

Angiogenesis and lymphangiogenesis are phenomena associated with inflammation, MMT, and peritoneal fibrosis. Their relationship is mediated by the production of all VEGF isoforms: VEGF-A is one of the major inducers of angiogenesis, whereas VEGF-C and D of lymphatic vessels [39, 40]. Transdifferentiated MCs are high producers of VEGF, and its levels in effluent and supernatant showed a positive correlation with water and solute peritoneal transport failure. Rapamycin, an mTOR inhibitor, was able to decrease the angiogenesis and specially lymphangiogenesis, maintaining the peritoneal transport in a mice model [41].

4. The search for the Holy Grail: more biocompatible fluids, less deterioration

The so-called "conventional" PD fluids (PDFs) are assumed to be incompatible due to the presence of an acidic pH with glucose as the osmotic agent which, after heat sterilization or extended storage, leads to the formation of extended storage, leads to the formation of GDPs (GDPs). These GDPs themselves act as a wide range of cells inducing inflammatory, angiogenic, and apoptosis processes [42–44], but they also collaborate in the formation of advanced glycation end products (AGEs) and definitely accelerate the PM deterioration [45]. In fact, RAGE (AGE receptor) also plays a pivotal role in inflammation, angiogenesis, and fibrosis of the PM [46]. Moreover, it has been demonstrated that single exposure of MCs to GDPs yields AGEs and a proinflammatory response [42]. Interestingly, the relevance and toxicity of GDPs have been demonstrated to be independent from those of glucose. Igaki et al., demonstrated that the GDP 3-deoxyglucosone (3-DG), and not glucose, accelerates the advanced stage of protein glycation [47].

This knowledge has prompted the search of more biocompatible PD solutions free of GDPs and not-forming AGEs.

Wieslander et al., suggested that separation of the dextrose and buffer components during heat sterilization or storage, could reduce GDP formation [48, 49]. This hypothesis was confirmed later in different studies [50–52]. Kjellstrand et al. demonstrated that a sterilization process at an optimal pH (approximately 3) minimizes GDP formation in glucose-containing fluids [53]. Meanwhile, Erixon et al. confirmed that sterilization of glucose at a pH ranging from 2 to 2.6 reduces levels of several GDPs, such as 3-DG, 5-hydroxymethylfuraldehyde (5-HMF), and 3,4-dideoxyglucosone-3-ene (3,4-DGE) [54]. Moreover, storage of the dextrose component at a pH below 4.0 has been shown to substantially reduce GDP formation [55].

Nowadays, different PDFs have been developed, and their use has been widespread in different countries. Many investigations have been developed to discover new osmotic agents to substitute glucose with the finality of avoiding the formation of GDPs and AGEs. Even the

glucose-containing PDFs of new generation are now more biocompatible, thanks to the fact that they are prepared as bags with separated chambers that allow the sterilization and storage of the glucose at a low pH, mixing them at the very moment of the instillation in the patient's body. The beneficial effects on peritoneal status are amply documented [56].

In this line, it is important to analyze the impact that the different options of PDFs have on the peritoneal damage related to PD treatment. As commented before, chronic PDF exposition leads to inflammation, phenotype alteration with mesenchymal transition of different cell types (bone marrow-derived mesothelial and endothelial cells), angiogenesis, fibrosis, ultrafiltration failure, and in some cases EPS development. The evidences found *ex vivo*, *in vitro* and *in vivo* with both animal models and human patients in the most commonly used PDFs nowadays are discussed later.

4.1. Glucose as the osmotic agent

4.1.1. Lactate alone-buffered fluids

StaySafe from Fresenius Medical Care and Dianeal from Baxter are the so-called "conventional PDFs," and they are prepared on a single-chamber PD bag, therefore, presenting a higher amount of GDPs. Balance and Gambro (Fresenius Medical Care) are developed with a double-chamber bag to permit a lower formation of GDPs (although still presence).

4.1.2. Bicarbonate-buffered fluids

Bicavera from Fresenius Medical Care is buffered with bicarbonate alone, while Physioneal from Baxter is formulated with a mix of lactate and bicarbonate as buffers.

Effluent MCs grown *ex vivo* from patients treated with bicarbonate/low-GDP BicaVera fluid showed a tendency to maintain an epithelial phenotype, with lower production of pro-inflammatory cytokines and chemokines than was seen with MCs from patients treated with a lactate-buffered conventional PDF [57].

In an *in vitro* study conducted by Grossin et al., HOMCs exposure to BicaVera resulted in higher cell proliferation compared to lactate-buffered PDFs such as Balance and StaySafe (at the same glucose concentration), due to their higher viability (as oncosis was demonstrated to be significantly lower). BicaVera, containing lower amounts of GDPs, stimulated less AGE formation and VEGF production than Balance or StaySafe. No effect of lactate on TGFβ expression related to potential polyol pathway stimulation could be demonstrated [58].

Bicavera also showed decreased PM inflammation and fibrosis compared with a conventional PDF (StaySafe) in an *in vivo* mice model [59].

Meanwhile, Physioneal has also showed improved results in terms of PM preservation comparing to conventional PDFs. *Ex vivo*, PDF-induced VEGF, and procollagen III N-terminal peptide (PIIINP) secretion were more prominent in the conventional PDF Dianeal and less prominent in Physioneal. This study also shows that high glucose plays an important role in VEGF secretion comparing to low glucose concentrations, and that GDPs may play important

roles in VEGF production by HPMC. Moreover, glucose above 50 mmol/L increased TGFβ1 expression in HPMC [43].

In vivo, newly formed vessels and total number of transmigrated neutrophils were higher in Dianeal-treated rats than in Physioneal-treated rats [60].

A recent study from Kumar et al. suggests that glucose-based PDFs may increase the risk and severity of *Staphylococcus aureus* peritonitis, a serious complication for chronic PD patients, as these fluids showed inhibited complement host defenses [61]. For this reason and the fact that it is not possible to absolutely eliminate GPD formation in glucose-containing PDFs, the interest of developing other osmotic agents has been raised in recent times.

4.2. Amino acids as the osmotic agent

4.2.1. Nutrineal

Chan et al. compared the effects *ex vivo* on MCs of dialysate obtained from 4-hour dwells with amino acids (AA)-based and glucose-based PDFs and found that ultrastructure and viability of cells were better preserved and cell proliferation less reduced during AA treatment, although IL-6 secretion by cultured MCs increased [62].

In an experimental *in vivo* study, mesothelial damage and vascular changes could be avoided in rabbits when AAs were used instead of glucose as osmotic agent in dialysis solutions [63]. The enhanced biocompatibility of AA-based PDFs is likely based on both the reduction in glucose load, leading to the less formation of GDP and AGE and the more physiological pH of AA.

The use of glucose-free PDFs, especially AA, seems to preserve MC mass and host defense [64]. Martikainer et al. suggested that an activation of systemic and peritoneal inflammation (measured as increased C-reactive protein levels in serum and inflammatory markers such as IL-6 and TNF-α in dialysate) may appear during the use of icodextrin and to a lesser extent during the use of AA [64]. This circumstance could be due to a better cell preservation rate. In fact, Brulez et al. found better preservation of macrophage function during the use of AA than during the use of 2.27% glucose-based solution [65].

4.3. Icodextrin as the osmotic agent

Icodextrin (ICO) is a starch-derived, water-soluble, high-molecular weight glucose polymer (dextrin) that is used as a colloid osmotic agent. Its mean molecular weight is 16,800 Da, and water transport occurs because of the difference in colloidal osmotic pressure. ICO is slowly absorbed into the circulation, and ultrafiltration can be obtained even in a long-term dwell [66].

Currently, very scarce information on the effect of long-term ICO use on the PM is available. In favor of icodextrin, omentum-derived human peritoneal MCs cultured with Icodextrin grew and proliferated adequately [67], and this osmotic agent did not induce upregulation of Snail or Cox-2 as did the PD solution rich in GDPs [59]. Unpublished data by Gallardo et al. using a technique called trans-epithelial electrical resistance (TEER) found that Icodextrin had lower

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water intercellular transport resistance than dextrose (4.25%) in the MDCK cell line monolayer (**Figure 3**). TEER is an easily quantifiable method to measure the intercellular tight junctions and is a marker of health of monolayer cells. As commented before, the MC monolayer is the first barrier exposed and affected by PDFs, and it can also be used as a marker of solute and water peritoneal transport [68].

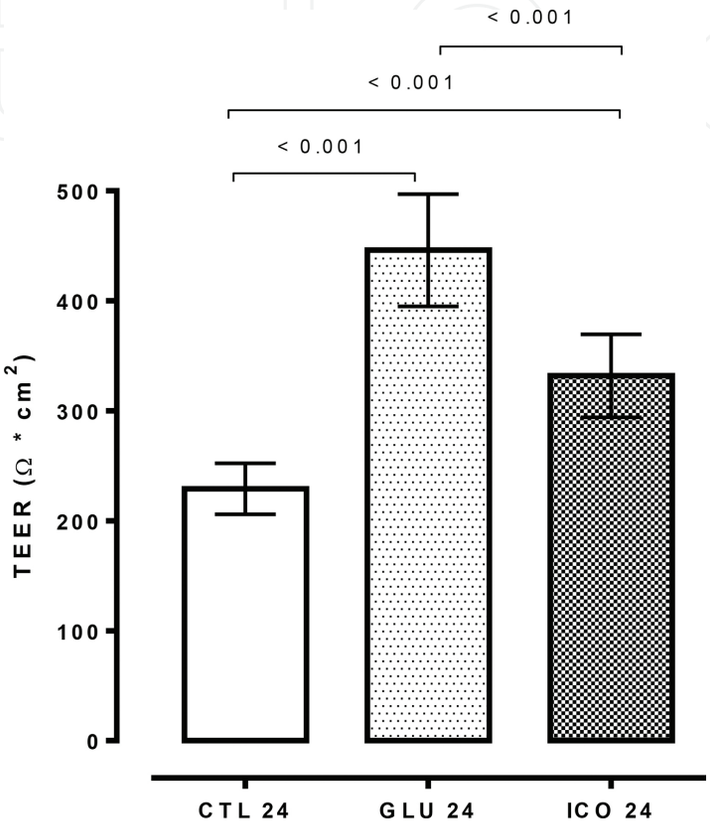

Figure 3. Applications of trans-epithelial electrical resistance (TEER) in the measurement of cellular health and PD solution biocompatibility. Results are expressed as ohms per square centimeter [74, 75]. Columns in the figure express means ± standard deviations.

Clinically, Paniagua et al. suggested that ICO treatment is superior to dextrose treatment, allowing a better metabolic control and improved extracellular fluid volume control in diabetic patients in PD [69].

The positive effects of Icodextrin also include improvement in the atherogenic lipoprotein profile, fasting glucemia, insulin resistance, and hypertension [66]. Icodextrin also improves the viability of the PM as demonstrated by Davis et al. [70].

However, because PD uses the biologic membrane as a dialytic membrane, impairment of the peritoneum by exposure to PDF is inevitable, and Icodextrin has also shown negative effects on the PM. This osmotic agent has been related to an induced peritoneal inflammation, increased peritoneal permeability and levels of IL-6 and other inflammatory molecules in effluent. The reaction was transient, but long-term exposure to Icodextrin may irreversibly change peritoneal morphology [71, 72].

Other side effects related to the use of ICO such as allergic skin reactions and aseptic peritonitis have been reported [73].

TEER changes were analysed in MDCK cell monolayers cultured during 24 hours with PD solutions, dextrose 4.24% (GLU 24), and icodextrin 7.5% (ICO 24), compared with control (CTL). Dextrose increased the TEER more than icodextrin, What is associated with upregulation of intercellular tight junction-related molecules. This phenomenon may be related to loss of peritoneal transport capacity at long-medium term in peritoneal dialysis patients.

MDCK-II cultures were obtained from the American Type Culture Collection (MDCK, CCL-34) and maintained in DMEM supplemented (CDMEM) with 10% bovine serum and 10,000 U/mg/ml of penicillin/streptomycin. Cells were harvested with trypsin EDTA, cultured on Transwell permeable supports at approximately 2 × 105 cells/cm^2 (Corning Costar), and maintained for 3 days in CDMEM. The concentration of serum was complemented with PDFs, glucose (GLU), or icodextrin (ICO), the last 24 hours before TEER measures. The medium for MDCK cell control was CDMEM alone. The degree of tight junctions permeability to ionic solutes was assessed by measuring the TEER of the cells grown on Transwell permeable supports using an EVOM (Epithelial Volt Hom Meter; World Precision Instruments). TEER was measured before and after PDF exposition. Final values were obtained by subtracting the resistance of the bathing solution and an empty support.

5. The new hope: pharmacological interventions to treat and prevent peritoneal damage

As a completely biocompatible PDF will be difficult to achieve, glucose-based PDFs are still needed, and more biocompatible PDFs are expensive, using drugs is a valuable alternative [76]. An advantage of drugs is that they might be administered orally or intraperitoneally, but most of the experiments developed till now are performed in animal models. The challenge for future years is to demonstrate through clinical trials if results in animals are reproducible in humans. New research studies on this line should preferably focus on the potential benefits for the peritoneum of drugs that may serve multiple purposes for PD patients [76].

PD treatment-associated damage can be induced by different factors such as hemoperitoneum, peritonitis episodes, mechanical injury due to the infusion process or the distension of the tissue, and the bioincompatible composition of the PDF, with a nonphysiological pH and osmotic agents that generate an inflammatory response (glucose, GDPs, and AGEs). More biocompatible fluids (low GDP solutions) reduce the peritoneal impact of the treatment but do not solve the problem completely. As the first line of contact between the body and the PDF, MCs are a key target for pharmacological actions. Some drugs have demonstrated the capacity to reduce MMT, such as BMP7, Tamoxifen, TAK1 inhibitors, and Vitamin D receptor activators, among others.

On the other hand, MCs might suffer a mesenchymal transition. Endothelial and bone marrow-derived cells also contribute to the generation of cells with fibroblastoid phenotype [77]. The

migratory capacity of transdifferentiated cells can be diminished using anti-VEGF or NRP1 antibodies, as well as with drugs like Tamoxifen. Moreover, it is possible to reduce the increased fibrinolytic capacity of these cells with Tamoxifen, Nebivolol, and heparin.

Other pathologic effects in the peritoneum related to PD are fibrosis, angiogenesis, and lymphangiogenesis. There are an increasing number of drugs able to act against different processes at the same time, ameliorating peritoneal damage and protecting from PM failure.

5.1. Immunomodulatory strategies

5.1.1. COX-2 inhibition

An *ex vivo* study with MCs drained from peritoneal effluent revealed that nonepithelioid cells (that had undergone MMT) express higher levels of COX-2 than epithelioid MCs. The mass transfer coefficient for creatinine, an indicator of UF capacity, correlated with MC phenotype and with COX-2 levels. Although COX-2 was shown to be upregulated during MMT of MCs, COX-2 inhibition was not able to prevent MMT *in vitro*. In mice and rats *in vivo* models of PD, COX-2 inhibition with orally administered Celecoxib decreased peritoneal inflammation, angiogenesis, and fibrosis and preserved PM function [59, 78].

5.1.2. Modulating specifically Th17/T regulatory responses

It has been recently shown that Th17-mediated and, more specifically, IL-17-mediated inflammatory responses play an important role in PM damage [79]. In fact, pharmacologic treatments modulating Th17 response and/or enhancing regulatory T-cell response ameliorated peritoneal fibrosis and preserved PM function.

Peroxisome-proliferator activated receptor (PPAR)-γ agonist Rosiglitazone was shown to protect PM from PDF damage (diminishing the accumulation of AGEs, preserving the mesothelium, decreasing the number of invading MCs, reducing fibrosis and angiogenesis, and improving peritoneal function in an *in vivo* mice model). This effect was associated with augmented levels of the anti-inflammatory cytokine IL-10 (T regulatory-associated cytokine) and increased recruitment of regulatory T cells [80]. Other protective mechanism was the inhibition of Th17 differentiation through a Stat3 cascade blockade, which results in a down-regulation of RORγt and a decrease in IL-17 production [81]. However, the side effects of rosiglitazone have limited its use around the world [82]. New PPAR modulating agents could be promising.

Meanwhile, the activation of immunological regulatory mechanisms by vitamin D receptor (VDR) signaling could also prevent or reduce fibrosis, as observed in an *in vivo* mice model of peritoneal exposure to PDF with Paricalcitol, a VDR activator. The treatment reduced peritoneal IL-17 levels and increased the presence of T cells with a regulatory phenotype, which strongly correlated with a significantly lower peritoneal fibrotic response [83].

It has been recently demonstrated that the leukocyte antigen CD69 controls fibrosis by regulating Th17 response, so it represents a new, yet unexplored, therapeutic target [84].

5.2. To preserve the mesothelium

5.2.1. To restore the cytoprotective stress proteome

Exposure of MCs to PDFs results in cytoprotective cellular stress responses that counteract with PDF-induced damage. The cellular stress responses may be inadequate in PD due to deficient levels of glutamine, resulting in increased vulnerability against PDF cytotoxicity. Adding pharmacological doses of Alanyl-Glutamine to PDF restored the cytoprotective stress proteome, resulting in improved resistance of MCs to exposure to PDF [85].

5.2.2. To act on the TGFβ signaling pathway

TGFβ was revealed as a master molecule in the pathogenesis of peritoneal damage in a mice PD model [77]. The strategy employed on this study blocked MMT, endo-MT, fibrosis, and angiogenesis. However, TGFβ regulates many immune, inflammatory, and tissue repair functions, so these data should be taken with caution. TGFβ signaling pathways involved in MMT provide more specific strategies for the preservation of peritoneal membrane with fewer side effects (**Figure 4**). In this context, the endogenous factors, such as HGF and BMP-7, have been demonstrated to block MMT *in vitro*. In addition, intraperitoneal administration of these proteins prevented and reverted peritoneal damage in experimental *in vivo* animal models [86–88]. It is important to note that the use of BMP-7 may be difficult in the clinical practice because of its high price and its association with ossification [89]. Likewise, regulating inflammatory factors that activate TGFβ, such as Celecoxib, could be an option.

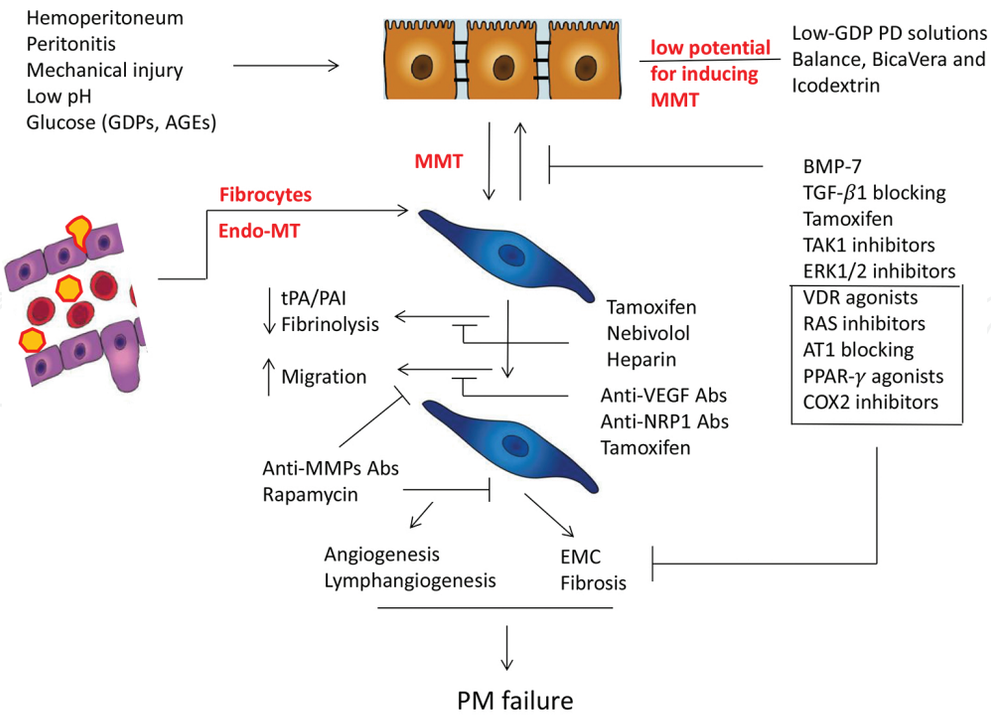

Figure 4. Pharmacological amelioration of PD-induced PM damage.

Agents	Mechanisms	References
Anti-fibrotic agents		
(AcSDKP) Tetrapeptide	TGF-β inhibition	[92]
Pentoxifylline	Inhibition of ECM production	[93]
Dipyrodamole	Inhibition of TGF-β production	[94]
Emodin	Inhibition of ECM production	[95]
Simvastatin	Increases fibrinolytic activity	[96]
Anti-angiogenic agents		
Anecortave acetate	Inhibits VEGF production	[97]
Pegaptanib	Inhibits VEGF-VEGFR-binding	[98]
anti-VEGFRII	Blocks receptor VEGFRII	[99]
TNP-470	Decreases VEGF expression	[100]
Inhibition of EMT		
Rho/ROCK-inhibitor (Y-27632)	TGF-β/Samds inhibitors	[101]
Antioxidant agent	NF-κB inhibition	[102]
Notch inhibitors	Inhibit the induction of snail and repression of VE-cadherin	[103]
JNK inhibitors (PS600125)	Inhibition of both ZEB and Rho pathway	[104]
CBR1 antagonists	TGF-β/Samds inhibitors	[105]

AcSDKP, *N*-Acetyl-seryl-aspartyl-lysyl-proline.

Table 1. Potential MMT modulators untested in PD.

Other molecular strategies able to block MMT include ILK, RhoA-ROCK, and Akt-mediated signaling cascade inhibitors. These strategies have not been demonstrated yet in PD. **Table 1** shows agents capable of modulating MMT or its deleterious effects that have not yet been tested in association with PD.

5.3. Anti-fibrotic agents

Rapamycin, an mTOR inhibitor may diminish IL-17 production. The mTOR activation induces HIF-1 and RORγt and subsequently IL-17 and IL-23 production. Thus, Rapamicin may provide anti-inflammatory and antifibrotic effects and possibly an anti-MMT action, as demonstrated by different groups [106, 107]. Its anti-fibrotic effect is mediated by an increase in arrested MCs and a decrease in MCs dividing DNA [41]. The problem of this drug is the possibility of delayed tissue healing, so its use can be limited to specific moments in the evolution of patients with peritoneal damage.

Other drugs with anti-fibrotic effect include immunosuppressants, simvastatin, pentoxifylline, dipyridamole, diltiacen pyridoxine, tranilast, tamoxifen, statin, and emodin (**Table 1**).

Tamoxifen is a synthetic modulator of the estrogen receptor and is the only agent that has a clinical trial demonstrating its effectiveness in preventing the PM fibrosis or stopping the EPS

when it is established [108]. Tamoxifen inhibited MMT in MCs treated with TGFβ in a PD mice model. It significantly reduced PM thickness, angiogenesis, invasion of the compact zone by mesenchymal MCs, improved the fibrinolytic capacity (increasing tPA), and peritoneal function. Tamoxifen also reduced the effluent levels of VEGF and leptin [28].

5.4. To act at vascular level

5.4.1. Renin-angiotensin system inhibition

RAS targeting with intraperitoneal or oral enalapril, valsartan, or lisinopril reduced peritoneal thickening and loss of ultrafiltration induced by 4 weeks of daily hypertonic PDF exposure in rats [109, 110].

5.4.2. Anti-angiogenic and anti-lymphangiogenic agents

Guba et al. published that Rapamycin decreased the synthesis of VEGF by endothelial cells [111]. *In vivo* exposure to PDF in a mice model, significant reduction in VEGF in PD effluent and in the number of both peritoneal blood and lymph vessels was founded [41].

5.5. Anti-fibrinolytic agents

Fibrinolytic capacity of MCs is mediated by a complex balance between pro-fibrinolytic (PAI) and anti-fibrinolytic (tPA, uPA). When fibrinolytic capacity decreases (increased PAI and/or decrease tPA), there is a tendency to peritoneal fibrosis and adhesion MMT as the tPA increases the secretion of HGF [109]. Experimentally, tamoxifen [28], nebivolol [112] and heparin [90] increased fibrinolytic capacity associated with tPA levels increase.

5.6. Anti-migration agents

Another way to prevent the deleterious effects of MMT is inhibiting transdifferentiated MC migration. Tamoxifen was demonstrated to inhibit human peritoneal MC migration *in vitro* through inhibition of MMP2 [28]. Although it has not been studied in peritoneal human MCs, anti-MMPs antibodies/peptides are also able to inhibit the cell migration [91].

6. Conclusion

Infectious and noninfectious PD-related factors activate the immune system resulting in a sustained inflammatory state that might trigger the structural and functional alterations associated with PD failure, such as MMT, End-MT, fibrosis, angiogenesis, lymphangiogenesis, SPS, and EPS. The methods used nowadays to study the alterations related to PD include the analysis of soluble factors present in the effluents and the use of cultured cells and animal models (which are the best approach to study all the elements implicated). Thanks to the different studies developed in the last decades employing these methods, the challenge of peritoneal amelioration has been deeply studied. New more biocompatible fluids had been

shown to improve peritoneal status, but still there is no way to completely avoid peritoneal deterioration, so the use of drugs is a valuable option. Among the different available strategies, immunomodulation and mesothelial preservation presented promising results. Given the connection among MMT, SPS, and EPS, MMT should be considered as a therapeutic target to preserve the PM failure in PD. The use of anti-fibrotic, anti-angiogenic, anti-fibrinolytic, and anti-migratory agents could also represent interesting therapeutic alternatives.

In conclusion, the therapeutic strategies to preserve the peritoneum during PD should aim to improve the biocompatibility of PDFs as well as modulate the inflammation and MMT and their deleterious effects such as fibrosis, angiogenesis, lymphangiogenesis, cell migration, and fibrinolytic capacity alterations.

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