Peritoneal Membrane Preservation

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Summary: Peritoneal dialysis (PD) is a successfully used method for renal replacement therapy. However, long-term PD may be associated with peritoneal fibrosis and ultrafiltration failure. The key factors linked to their appearance are repeated episodes of inflammation associated with peritonitis and long-term exposure to bioincompatible PD fluids. Different strategies have been proposed to preserve the peritoneal membrane. This article reviews the functional and structural alterations related to PD and strategies whereby we may prevent them to preserve the peritoneal membrane. The use of new, more biocompatible, PD solutions is promising, although further morphologic studies in patients using these solutions are needed. Blockade of the renin-angiotensin-aldosterone system appears to be efficacious and strongly should be considered. Other agents have been proven in experimental studies, but most of them have not yet been tested appropriately in human beings.

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Peritoneal dialysis (PD) is an extensively used method for renal-replacement therapy. However, long-term PD may be associated with ultrafiltration (UF) failure (UFF) or technique failure. UFF has been related to the development of anatomic alterations such as fibrosis, hyalinizing vasculopathy (HV), and angiogenesis.[1] Although the mechanism of peritoneal fibrosis is not completely understood, the main factors that have been linked to its appearance are repeated episodes of inflammation associated with peritonitis and long-term exposure to bioincompatible PD fluids (PDFs).[2,3] Conventional PD solutions contain high concentrations of glucose and glucose degradation products (GDPs) that damage the peritoneal membrane (PM) by inducing local production of inflammatory cytokines that promote chronic inflammation and lead to peritoneal fibrosis.[4] 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.

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PERITONEAL CHARACTERISTICS AT THE BEGINNING OF PD THERAPY

The major factor affecting the structure of the PM in PD patients is the PD solution used during the treatment. The potential contribution of other factors, such as uremia or diabetes, is not well understood.

Anatomically, the peritoneum of non-PD uremic patients shows either complete absence or just mild degrees of morphologic alterations. Some investigators have reported that uremia per se may be responsible for some lesions observed in the PM of PD patients, such as increased submesothelial thickness and HV. In the largest series of peritoneal biopsies reported in uremic patients not on PD, Honda et al[5] described an increase in peritoneal submesothelial thickness compared with controls. Another previous study performed by Williams et al[6] showed similar results. Both studies also described a low prevalence and mild degrees of HV in uremic patients, compared with its absence in controls. These studies, and the study performed by Jiménez-Heffernan et al[7] in autopsies from PD patients with severe peritoneal HV showing an absence of HV in extraperitoneal vessels, suggested that uremia seems to play a secondary role in the anatomic alterations found in PD patients. In addition, diabetes also has been implicated in the pathogenesis of the peritoneal changes observed in uremic patients not on PD. Several studies[5,6,8] have reported a greater prevalence and severity of peritoneal lesions in uremic patients with diabetes. However, these differences disappeared after beginning of PD, suggesting that diabetes does not play an important role in the morphologic lesions found in PD patients.

From a functional point of view, there is great variability in peritoneal transport status at the beginning of PD therapy,[9] but the determining factors are not well established.[10] Several factors have been

related to the different baseline peritoneal features found at starting PD. Some investigators have found genetic factors such as polymorphisms in the interleukin-6 (*IL-6*) gene[11] related to inherent high transport (HT) of small solutes, whereas others have described its association with clinical characteristics (ie, age, sex, comorbidity, residual renal function, and so forth).[12-14]

Davies[15] described that during the first years on PD, the increase of small-solute peritoneal transport is not always accompanied by a decrease in UF capacity. They observed that a disproportionate UF loss related to the increased solute transport is observed during subsequent years. This different behavior in short- and long-term PD stages may be explained by qualitative changes in the PM over time. Moreover, Fernández-Reyes et al[16] have shown that the subsequent outcome of peritoneal function does not depend on the transport at the beginning of PD.

CHANGES DURING EARLY PD STAGES

Peritoneal function commonly changes over time, but few studies have analyzed its evolution during the first years of PD. Some of them[17,18] have observed an increase in small-solute transport during the first months on PD, whereas others described functional stability until 18[19] or 24 months.[20] In addition, some investigators have reported a tendency to regression toward the mean of both small-solute and water transport during the first 1 to 2 years in PD patients using conventional PD solutions. Lo et al[21] found that the evolution during the first years of PD depends on the starting point; patients with HT showed a tendency to decrease, whereas low transporters experienced an increase in small-solute transport. Del Peso et al[22] found similar results in a series of 249 PD patients. The interpretation of these variable behaviors is diverse: some investigators[17] have suggested that an initial increase in peritoneal permeability could be caused by an irritative response to bioincompatible PD solutions. Other investigators have related the initial HT to the presence of peritoneal inflammation.[18] It is important to note that in the presence of repeated or severe episodes of peritonitis, or increased exposure to glucose PD solutions, HT did not reverse during the early years on PD.[3,16,23]

Recently, new PD solutions have been developed that have a neutral pH and low content of GDPs. The evolution of peritoneal function with the use of these more biocompatible solutions still is unclear.[24] Until now, few studies have compared functional differences with both conventional and biocompatible solutions. Williams et al,[25] in the Euro-Balance Trial, reported that the use of low-GDP PD solutions was associated with low UF capacity and HT. Previously, Selgas et al[26] observed similar results in a group of patients using bicarbonate PD solutions. In contrast, other groups did not confirm these findings.[27] More recently, a systematic review of several clinical trials found no significant differences in water and small-solute transport with both types of solutions.[24]

Morphologic analysis of the PM during PD treatment could allow us to correlate anatomic lesions with functional changes; ideally, this should be performed in longitudinal studies. However, a peritoneal biopsy is an invasive technique that cannot be used systematically. Studies that correlate peritoneal anatomy and function therefore are scant and most of them have been performed in patients with PM problems, mainly UFF. Only a few small series have analyzed peritoneal tissue from patients without peritoneal functional alterations.

During the first years on PD, patients without peritoneal dysfunction do not show significant histologic changes of the peritoneal membrane. The most frequent lesion found is loss of the mesothelial layer with reduplication of the peritoneal basement membrane. Another frequently observed change is an increase in thickness of the submesothelial region caused by an increase of extracellular matrix, usually accompanied by a low number of cells.[28] Epithelial-to-mesenchymal transition (EMT) of mesothelial cells (MCs), defined as the presence in the submesothelial region of fibroblast cells of mesothelial origin (cytokeratin and α-smooth actin–positive cells), first was described by Yáñez-Mo et al[29] in peritoneal biopsy specimens from PD patients. Animal models have shown that EMT of MCs is one of the starting lesions of the fibrotic process in the peritoneum.[30]

At the vascular level, the most frequent lesion found is HV, owing to reduplication of the submesothelial basal membrane. It is associated with time on PD and with the presence of fibrosis, and it is found more frequently in long-term PD patients. Glucose and its derivates are the main factors involved in its pathogenesis.[7,31] In addition, an increase in the peritoneal vascular area has been described in some PD patients, which can explain a decrease in UF capacity, as a result of an increase in peritoneal permeability.[32] In seven patients on PD for up to 2 years, Mateijsen et al[33] reported the presence of mild fibrosis in all patients. Williams et al,[6] in a larger series of 58 patients, found HV lesions in 29% of patients, mostly of mild degree. More recently, in a series of 35 patients, Del Peso et al[34] found increased submesothelial thickness in almost half of them, in situ evidence of EMT in 20%, and mild to moderate HV in up to 20%. They described that HT at early PD stages was related to the presence of EMT on peritoneal biopsy. In addition, this study showed that angiogenesis is not necessarily associated with short-term PD.