REVIEW

Protective measures against ultrafiltration failure in peritoneal dialysis patients

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Ultrafiltration failure in patients undergoing peritoneal dialysis is a condition with an incidence that increases over time. It is related to increased cardiovascular morbidity and mortality and is a major cause of the abandonment of the treatment technique. Because the number of patients undergoing renal replacement therapy is increasing with society aging and because approximately 10% of this population is treated with peritoneal dialysis, this matter is becoming more common in everyday practice for clinicians involved in the care of patients with chronic renal failure. In this review, we summarize the available measures used to prevent and treat ultrafiltration failure and the current state of research in the field, both in the experimental and clinical settings, focusing on the possible clinical applications of recent findings.

KEYWORDS: Peritoneal membrane; Peritoneal dialysis fluids; Peritoneal fibrosis; End-stage renal disease; Ultrafiltration.

INTRODUCTION

Peritoneal dialysis (PD) is an effective therapeutic strategy for managing both acute and chronic kidney disease (CKD) and has been employed as a renal replacement therapy (RRT) modality for CKD for the last five decades.[1] During this time, technical improvements have led to reduced morbidity and mortality rates. In the last decade, better outcomes have been noted with PD, whereas mortality rates have remained stable with hemodialysis (HD).[2] However, the percentage of patients who begin RRT with PD remains approximately 10% worldwide,[3] and although PD and HD should be considered as complementary therapy modalities, PD is not routinely offered to incident patients.

Over the last century, our understanding of the mechanisms involved in solute and fluid transport across the peritoneal membrane (PM) has improved, and this growing knowledge has allowed apparatus development and PD prescription in consonance with peritoneal physiology.[4] "Pore theory,"[5] the most commonly applied description of the dynamics of molecular transport through the PM, basically considers three pore sizes in the walls of sub-mesothelial capillaries through which molecules can travel. A minority of the pores, with diameters of 250 Å, are called large pores and allow the movement of proteins across the PM. Most small solutes can pass through the small pores,

which have diameters of 43 Å. Aquaporin-1 (AQP1) has also been identified in the PM[6] and has been called "ultrapore" or "ultrasmall pore" because only water molecules can move through it. Forty percent of the osmosis during the first 4 hours of a dwell duration is attributed to transport through AQP1. The fluxes through these channels are dependent on the Starling forces that act in the peritoneal cavity and blood compartments, and more recently, importance has been assigned to the distance of each pore from the cavity, which is referred to as the "distributive model."[7]

Because of longer patient survival, PD is used for increasingly long periods. Dysfunctions in the peritoneal transport system have been found to develop over time, with the most prevalent problem being ultrafiltration failure (UFF).

Ultrafiltration failure

UFF, which can be defined as ultrafiltration (UF) of less than 400 mL after a 4-hour dwell duration with a 4.25% dextrose-based peritoneal dialysis fluid (PDF), is a clinical condition that has an increasing incidence with chronic PD duration. Thirty to fifty percent of patients develop UFF after 6 years of PD, and in 24% of cases, changing the RRT modality is required to maintain clinical stability.[8,9]

Signs and symptoms of fluid overload, such as high arterial pressure, pulmonary congestion and a worsening of cardiac function are the usual manifestations of UFF, and a differentiation from the loss of residual renal function (RRF) or dietary noncompliance is necessary. To this end, measuring the UF volume after 4 hours is of great value.[10,11]

Morbidity and mortality rates have been shown to be significantly higher among PD patients with UFF;[12,13] these higher morbidity and mortality rates have been attributed to

excess fluid and its effects on the cardiovascular system, such as arterial hypertension and left ventricular hypertrophy.[14] Atrial natriuretic peptide and brain natriuretic peptide have been studied in PD patients as markers of volume overload, and high levels of each have been linked to an eight-fold increase in mortality relative to patients with low levels.[15] Also important is the correlation between insulin resistance and metabolic syndrome with the fast peritoneal transport,[17] since these metabolic changes can potentially contribute to the development of cardiovascular disease.[16] Therefore, prevention, early identification, and proper clinical management of UFF are crucial elements of cardiovascular risk reduction strategies.

UFF generally develops as the result of one or more of the following phenomena: a significant increase in the peritoneal vascular surface area, a decrease in the osmotic conductance of the PM, increased lymphatic absorption, and the reduction of the peritoneal surface area by scars or adhesions.[18]

Uremia,[19] infectious peritonitis,[20] high glucose concentrations in PDF,[21] glucose degradation products (GDPs) formed during heat sterilization,[22] and the generation of advanced glycation end-products (AGEs)[23] have all been implicated in UFF development. These factors are primarily related to chronic and acute inflammation of the peritoneum,[24] which in turn leads to local neoangiogenesis, vasculopathy, the epithelial-to-mesenchymal transition (EMT) of mesothelial cells[25] and collagen deposition in the compact submesothelial zone with subsequent PM thickening.[26] These morphological changes translate clinically into faster small-solute transport with rapid vanishing of the osmotic gradient between the blood and the cavity and diminished osmotic conductance of the membrane, meaning that there is less osmosis even though a gradient is present. Both effects are associated with a functional decline in the peritoneum as a dialyzing membrane. There is evidence that the decrease in the peritoneal osmotic conductance is related to AQP1 dysfunction[27] and that the acceleration of small-solute transfer is related to the thickening of the collagen layer and high vascular density.

A rare, though dramatic, clinical condition also associated with the loss of dialyzing and UF capacity is known as sclerosing peritonitis, encapsulating sclerosing peritonitis (ESP) or abdominal cocoon. One possible explanation for the development of this condition is a ''two-hit'' model, in which a denuded, thickened PM resulting from long-term PD undergoes a second inflammatory insult.[28] These second stimuli, even when very slight, could trigger the development of ESP in a severely damaged peritoneum, while a less-damaged membrane would likely require more potent stimuli. The most characteristic feature of ESP is the formation of a peritoneal capsule as the result of the deposition and organization of fibrin, which are likely the key events in ESP's pathogenesis. The fibrin seems to derive from increased plasma exudation from the peritoneal microvessels, and the adhesion of the peritoneum causes serious intestinal immobility, thus resulting in ileus.[29]

However, some researchers believe this condition to be a separate nosological entity as opposed to a further stage of progressive peritoneal damage caused by bio-incompatible PDFs.[30] These researchers argue that the different natural history, the association with autoimmune diseases[31] and the frequent occurrence in individuals not being treated with PD and even in other species favor this hypothesis. In addition, animal models for these conditions require different aggressors to be simulated.[32] In this hypothesis, PD would act as a risk factor, not as the etiologic agent of the condition.

This review focuses on the established clinical measures and ongoing research on the possible interventions aimed at preventing the gradual degeneration of PM related to chronic PD.

UFF prevention

Peritonitis. Because peritonitis episodes are consistently related to the loss of UF capacity,[33] adequate prevention and early treatment are essential to the success of the technique. It is believed that compliance with the antiseptic routine is related to a reduction in the number of infectious episodes,[34] which consequently results in lower dropout rates.

Specific measures to reduce the incidence of peritonitis begin with catheter insertion. These measures include positioning the tip downward, not using stitches to close the exit site wound and using prophylactic intravenous antibiotics, all of which have been shown to decrease infection.[35,36]

Over the long term, hand washing is crucial for the prevention of contamination; the training nurse is the most important professional for this activity. There is evidence that, in addition to hand washing, topical prophylaxis with mupirocin[37,38] or gentamycin[39] reduces peritonitis rates. Because exit site infections are also related to peritoneal cavity infections, early and aggressive treatment of exit site lesions and infections should be started as soon as the first signs appear and should be maintained until the lesion or infection has been resolved.[40]

Avoiding contamination from other sources through antibiotic prophylaxis is also recommended when invasive procedures are performed and when there is another intra-abdominal source of contamination.

Liquid and salt balance. It is prudent to frequently remind PD patients of the importance of fluid and salt restriction because the ability of the kidneys to reach a neutral sodium balance is diminished with the loss of RRF.

In PD, sodium removal occurs through diffusive transport with glucose-based solutions. When icodextrin is employed, convective transport contributes to global sodium loss as well.[41] In the initial phase of the glucose-based fluid dwell, the osmotic gradient is maximal, and intense osmotic water transport occurs through the ultra-small pores (AQP1), leading to sodium sieving. Sodium sieving is a consequence of the exclusive traffic of water free of solutes, leaving significant sodium loss restricted to the later phase of the dwell.[4] The shorter the prescribed dwells are, the more important sodium retention becomes. Clinically, patients treated with automated peritoneal dialysis (APD) tend to lose less sodium than patients treated with chronic ambulatory peritoneal dialysis (CAPD) due to the short night dwells.[42,43] For APD patients, sodium restriction is even more important in achieving sodium and fluid balance. With icodextrin, the removal of salt through convection can be enhanced because with every 100 mL of UF, approximately 0.9 mg of sodium chloride is removed.[44]

In individuals who respond, who are generally those with residual clearance, the use of high-dose loop diuretics may help in achieving dry weight through an increase in renal fluid and sodium excretion without an additional increase in the glucose load – a measure that does not interfere in RRF.[45,46]

Initial and continuous counseling regarding the importance of complying with the dietary restrictions and adjusting these recommendations according to RRF loss over time may allow the prescription of fewer anti-hypertensive drugs[47] and a lower glucose concentration to promote adequate osmosis and maintain dry weight. To ensure an objective approach to patient management, the reassessment of dietary intake and the renal component of Kt/V (RRF) should be routine practice.

Dialysis fluids. In most countries, glucose is the primary osmotic agent used in PD. It has been demonstrated that glucose acts as a promoter of angiogenesis and fibrosis in the peritoneal cavity in a manner similar to that seen in damaged end-organs in diabetes.[48,49] The greater the necessity to promote UF, which is related to the RRF and fluid and salt ingestion, the bigger the required glucose load. Also important is the baseline small-solute transfer rate of an individual patient, which influences the glucose load prescribed by the nephrologist.[10] As the speed of solute transport and the dissipation of the osmotic gradient increase, the amount of glucose required to obtain adequate fluid balance also increases. Avoiding unnecessary glucose overload in the cavity is recommended during long-term follow-up to prolong the modality lifespan.

Alternatives to glucose have been researched in the last decade, and the glucose polymer icodextrin is already routinely available in some countries. It is an isosmolar compound that promotes UF through colloid osmosis, and its use is currently restricted to 1-2 daily exchanges to avoid systemic accumulation.[50] In general, it is prescribed for the longest dwell, which is the night dwell in CAPD and the day dwell in APD. A slower decline in peritoneal function over time has been demonstrated with icodextrin than with high glucose concentrations.

The avoidance of glucose-based PDF also helps minimize the exposure of the membrane to GDPs and AGEs, which are also associated with a fast transport profile and UFF. GDPs are toxic to mesothelial cells and lead to the faster formation of AGEs in the membrane than glucose does.[51] Fluids with neutral pH and low GDP content lead to an increase in effluent cancer antigen 125 (CA-125), a mesothelial cell mass marker in PD, indicating preservation of the mesothelium.[52] Minimizing AGEs is also of interest, but it should be remembered that the PDF is not the only source of these molecules; the uremic serum is a site of AGE formation as well, but the peritoneal accumulation of AGEs can be reduced if PDFs with lower glucose concentration are prescribed.

An alternative is to prescribe purely bicarbonate-buffered low-GDP fluids, which seem to improve peritoneal membrane integrity, as indirectly evaluated using human peritoneal mesothelial cell (HPMC) culture;[53] preserve host defense mechanisms as shown in animal models;[54] and provide a better effluent marker profile, with lower levels of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) levels in patients.[55] However, these fluids are not widely available. Additionally, these fluids seem to have a positive effect on RRF, but it is not yet possible to foresee

how the PM of patients will respond over the long term with chronic exposure to these new solutions.

Oxidative stress. Many links have been identified between oxidative stress and the activation of fibrogenic and angiogenic pathways, mostly through TGF-β and VEGF. The expression of growth factors induced by GDPs, such as methylglyoxal and acetaldehyde, have been successfully blocked in *in vitro* and *in vivo* studies by the antioxidant agents N-acetylcysteine (NAC)[56] and catalase.[57] Our group has also shown that NAC prevents PM thickening *in vivo*[58]. GDPs are precursors of AGEs, which also induce the production of cellular reactive oxygen species (ROS),[59,60] and ROS in turn promote AGE formation and thus signal amplification.[61] In the PM, GDPs, and AGEs play an essential role in chronic inflammation when glucose-based fluids are employed, and it has been found that NAC and angiotensin receptor antagonists (ARBs) prevent PDF-induced collagen I and heat shock protein accumulation in the omentum, results that strongly suggest that ROS are major mediators of peritoneal fibrosis.[62]

In addition, cyclooxygenase-2 inhibitors[63] and peroxisome proliferator-activated receptor-γ (PPAR-γ) antagonists[64] have been tested in HPMC studies and in animal studies to determine the ability of these drugs to prevent the connection between inflammatory stimuli and profibrotic pathways; positive results have been reported.

The final goal is the translation of these results into clinical practice. In patients, NAC, angiotensin-converting enzyme inhibitors (ACEis) and ARBs have been tested, and the results are discussed in the following sections.

Fibrosis. TGF-β1 is the most important cytokine involved in peritoneal fibrosis, and its synthesis in peritoneal mesothelial cells and the synthesis of its receptors are stimulated by bio-incompatible PDFs.[65,66,67] Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), which are released during peritonitis episodes, also contribute to peritoneal fibrogenesis, probably through the induction of EMT,[68] which is a phenomenon experiencing growing interest amongst recent publications. Other cytokines, such as TGF-β2, TGF-β3, platelet-derived growth factor, fibroblast growth factor-2, and connective tissue growth factor[69] are involved, together with plasminogen activator inhibitor-1,[70] in the initiation of fibrosis. There is also evidence that angiotensin II induces fibronectin expression in mesothelial cells via extracellular-signal-regulated kinase 1 (ERK-1), ERK2 and mitogen-activated protein kinase (MAPK)[71,72] and that it takes part in the membrane's cellular immune response.[73]

In experiments with cultured HPMCs and animal models, attempts to block fibrosis through interference with these factors have been made, with variable results. Among the tested interventions, positive results for fibrosis and EMT prevention were achieved with bone morphogenic protein-7,[74] emodin,[75] mammalian target of rapamycin inhibitors,[76] pentoxifylline,[77] diltiazem,[78] tranilast,[79] and dipyridamole.[80] In collaboration with Spanish colleagues, we have tested the beta-blocker nebivolol *in vivo* and have achieved success in reducing fibrogenesis and neoangiogenesis, in the PM.[81] The adenovirus-mediated gene transfer of decorin has also been tested and was shown to reduce peritoneal collagen content in an animal model of PD.[82]

In addition to the prevention of fibrogenesis, collagen turnover is becoming an object of scrutiny in PD. The matrix metalloproteinases 2 and 9 (MMPs) are gelatinases involved in the regulation of inflammation and in the degradation of

the extracellular matrix, and thus they facilitate the migration of cells in processes such as EMT. When in excess, MMP activity may impair wound healing.[83] ACEis have been studied in this context and have shown direct anti-MMP-2 activity in PD by binding to its active site and forming complexes in the drained effluent.[84] This activity could possibly blunt EMT.

These experiments have been extremely useful in further improving our understanding of UFF pathogenesis independent of the clinical application of the specific drug employed. Comprehension of the involved mechanisms has been essential in adapting PD to peritoneal physiology and in determining which drugs could be beneficial to patients with signs of fibrosis progression and PM degeneration in PD.

Angiogenesis. The inhibition of angiogenesis has been tested *in vitro* and *in vivo* in different scenarios, such as wound healing,[85] carcinoma metastasis,[86] and PD.[82] Inhibition has been achieved with anti-proliferative agents such as angiostatin and anti-VEGF antibodies.[87] In the context of wound healing, slower or incomplete tissue repair has been found to be a consequence of this inhibition.[88] In carcinomas, the results have been positive, and anti-VEGF antibodies are already clinically available as adjuvant drugs to inhibit the growth and metastases of a variety of tumors.

In vivo, systemic angiogenesis inhibition has been related to different clinically undesirable effects, which differ according to the developmental phase. In adults, one of the most prominent unwanted events is the worsening of or *de novo* proteinuria,[89,90] which can lead to additional loss of RRF. In retinal vascular proliferative diseases, however, where AGEs stimulate the expression of VEGF mRNA,[91] anti-VEGF agents are used locally with success.[92] The possibility of using locally active agents without systemic side effects is an attractive idea in the management of progressively accelerating small-solute transport because VEGF activation is thought to play an essential role in the observed membrane damage[93] and because the preservation of RRF is related to survival in dialysis patients.[94] Experimental protocols are currently under development.

Captopril, enalapril and losartan have also been studied in HPMC culture and have been shown to lead to a decrease in VEGF production after exposure to TNF-α and IL-1.[95] In humans, a retrospective analysis comparing small-solute transport in 36 patients receiving an ACEis or ARBs with that in 30 controls revealed that in the treated group, small-solute transport decreased over 2 years of follow-up, whereas transport increased among controls.[96] Although the available evidence is not considered strong, as discussed in a recent meta-analysis,[97,98] the use of either ACEis or ARBs in PD patients is commonly advocated to preserve RRF and prevent cardiovascular events.

Most of the experimental protocols targeting the vascular component of UFF pathogenesis are focused on its prevention, and important answers concerning the reversal of established excessive vascularization are still lacking.

UFF reversal

A few strategies have led to recovery from UFF, including membrane rest involving four weeks of hemodialysis, with which positive results have been obtained in recently diagnosed cases.[99,100] In addition, in cases of UFF associated with beta-blockers, where scant tissue damage is observed, the reversal of the dysfunction has been described with the discontinuation of the drug.[101] However, reversal is not guaranteed in severe cases of UFF in which histological damage is clear or when the diagnosis is only made at later stages. A delayed diagnosis can be common in patients with significant RRF who can maintain adequate fluid balance without being dependent on peritoneal clearance. In cases of established tissue damage, such as diffuse fibrosis and significant established neoangiogenesis, no satisfactory clinical or pharmacological intervention has been found.

Mesothelial cell transplantation has been studied as another possibility for promoting PM repair, as these cells play a central role in local inflammatory responses, in the regulation of peritoneal microcirculation and in maintaining the balance between fibrin deposition and degradation.[102] A few studies have been published evaluating this intervention in animals and in humans,[103,104,105] but activation of the PM, with prolonged inflammation and increased thickness in the early post-transplant phase, has been noticed.[106] Whether this activation is a result of the cell culturing conditions or of the transplant itself has yet to be established; therefore, the applicability of this technique is not yet clear.

Another possible intervention for the future could be the transplantation of bone marrow-derived cells because markers indicative of their implantation were detected in the PM 7-42 days after their intraperitoneal injection; however, this result is very preliminary, and it is not possible to define the role of bone marrow-derived cells in the context of membrane failure.[107]

CONCLUSION

In the near future, it is possible that new pharmacological interventions aiming to minimize the occurrence of UFF will emerge as a result of ongoing worldwide research in this field because many of the processes involved in the progression of damage have been unveiled. However, few strategies are available to date. ACEis or BRAs are already frequently prescribed to the PD population in an attempt to preserve RRF and prevent UFF, regardless of the limited available evidence supporting their use. It is desirable to avoid the current bio-incompatible PDFs, which allow immediate control of fluid overload but accelerate the degeneration of the membrane; thus, more compatible fluids must be made available. Adequate training, nutritional advice and surveillance, and patient compliance to the diet and to sterile techniques are already feasible procedures and should be monitored on a routine basis as part of PD preservation strategies.

Collectively, the cited studies show that many distinct parallel event chains can ultimately lead to the fast transporter phenotype and that it is probably necessary to simultaneously block different triggers to effectively minimize inflammation and its local consequences. Beyond considering one factor as the defining step, the balance between the activation of pro- and anti-inflammatory pathways seems to define the final phenotype.

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