SHOULD PERITONEAL RESTING BE ADVISED IN ULTRAFILTRATION FAILURE ASSOCIATED WITH A FAST PERITONEAL SOLUTE TRANSPORT STATUS?

The development of overhydration in peritoneal dialysis (PD) patients after they have lost urine production is probably the main cardiovascular risk factor for death during long-term dialysis (1). Inability to remove excess fluid from the body by dialysis—ultrafiltration failure—is the most important cause. When ultrafiltration failure is present in long-term PD patients, it is the functional manifestation of severe morphologic alterations in the tissues that form the peritoneal membrane (2). Two pathophysiologic mechanisms are involved: first, extensive absorption of the intraperitoneal (i.p.) administered glucose, leading to a rapid decrease of the osmotic gradient, and second, a reduced osmotic conductance to glucose (3). It is currently unlikely that the morphologic changes can be influenced by therapeutic interventions, making this form of ultrafiltration failure a process for which only symptomatic treatment, such as with icodextrin, is possible (4).

Patients can also have ultrafiltration failure shortly after the initiation of PD. This is often not recognized clinically, because urine production saves them from becoming overhydrated. The diagnosis requires a standardized test, like a modified peritoneal equilibration test (PET), in which the presence of ultrafiltration failure is defined by the 3 × 4 criterion: < 400 mL net ultrafiltration (UF) after a 4-h exchange with a 3.86/4.25% dialysis solution (5). It can be caused by the existence of a high lymphatic absorption rate (6) or, much more frequently, by the presence of a fast peritoneal transport status, leading to a rapid disappearance of the osmotic gradient. The incidence of an initial fast transport status varies from 1% in Hong Kong (7) to 16% in Australia and New Zealand (8). A potential cause may be low-grade inflammation, as evidenced by high dialysate concentrations of interleukin-6 (IL-6), because this cytokine has mainly proinflammatory effects in PD (9,10). But high effluent concentrations of vascular endothelial growth factor (VEGF) and the mesothelial cell marker cancer antigen 125 (CA 125) have also been described in incident patients with a fast peritoneal transport status (11). A cross-sectional study performed in stable non-diabetic PD patients without any previous or current peritonitis episode showed that the mass transfer area coefficient (MTAC) of creatinine was not related to comorbidity, but

showed significant relationships with effluent CA 125 and VEGF (12). Linear regression analysis adjusting for potential confounders confirmed that VEGF influenced the association between MTAC creatinine and CA 125, while IL-6 weakened this association only marginally. *In vitro* and *ex vivo* studies have shown that CA 125 and VEGF are constitutively produced by peritoneal mesothelial cells (13,14), while IL-6 needs an inflammatory trigger (15).

The above findings suggest that a large mesothelial cell mass or a high mesothelial turnover rate can be present in early stages of PD treatment, causing fast solute transport rates of small solutes and therefore impaired ultrafiltration. The presence of endothelial-to-mesenchymal transition (EMT) of mesothelial cells may be the responsible mechanism. Its occurrence in PD patients was first described in 2003 based on histology and effluent cell cultures (16). Both epitheloid and non-epitheloid mesothelial cells synthesize CA 125 (17) and VEGF production is even greater in non-epitheloid than in epitheloid cells (18). These markers are associated with fast peritoneal solute transport rates in early PD (12). A cross-sectional study from Madrid showed the presence of EMT in 17% of peritoneal biopsies obtained during the first 2 years of PD treatment in 35 stable patients (19). Those with the the highest MTAC creatinine had the highest prevalence of EMT. These data confirm that EMT is an early event in PD that is probably self-limiting, the functional consequences of which have never been established for long-term PD. Exposure to dialysis solutions is the most likely culprit for EMT. Therefore, the process may be influenced by discontinuation of PD.

Temporary discontinuation of PD has been used since 1991 by the Madrid group in patients with ultrafiltration failure (20). The authors reported good results, but had no knowledge of the various mechanisms summarized in the above sections and how peritoneal resting could influence these. It never became popular outside the Iberian peninsula. In the current issue of *Peritoneal Dialysis International*, the group of Selgas *et al.* presents their 25 years' experience with peritoneal resting for ultrafiltration failure (21). Although the definition of ultrafiltration failure has changed over time, which is unavoidable with such a long inclusion time, all patients had this complication and were not just overhydrated.

Furthermore, a control group with temporary discontinuation of PD was also analyzed. Some of the results are striking. First, only 35 patients could be included in a quarter of a century. This suggests that not all patients with ultrafiltration failure qualified for inclusion, or that ultrafiltration failure was a rather infrequent event. Second, peritoneal resting was only effective in the 20 patients in whom it was applied within 6 months after the diagnosis. The duration of PD for the whole group ranged from 18 to 60 months, but no information is given on PD duration in the group where it was effective. If it were shorter than in the other patients, this would support the contention of the authors that peritoneal resting is especially effective in the presence of ultrafiltration failure due to EMT. However, this theory is not supported by effluent concentrations of CA 125 and VEGF for instance.

The question of whether or not peritoneal resting should be applied in all patients with early ultrafiltration failure is not solved by the currently published study. Temporary transfer to hemodialysis requires vascular access, which is usually by a central venous line. Also, possible effects of hemodialysis for 1 month on residual renal function have not been published. More importantly, early fast solute transport usually improves spontaneously with PD duration (22). The time-course of EMT is not known, because longitudinal observations are not available and the hypothesis that it may be an early stage in the later development of peritoneal fibrosis, vasculopathy and neoangiogenesis is pure speculation. More research is required on the mechanisms and natural time-course of early ultrafiltration failure before it can be recommended for general use in ultrafiltration failure.

DISCLOSURES

The author has no financial conflicts of interest to declare.

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