ULTRAFI LTRATION FAILURE IN PERITONEAL DIALYSIS PATIENTS

C hanges in peritoneal transport may occur at any stage of peritoneal dialysis (PD), but are particularly common in patients treated for several years. In almost all prospective studies of patients treated with PD for 4 years or more, a tendency toward decreasing ultrafiltration (UF) capacity, as well as increasing small solute transport, is evident (1). In an epidemiological study from The Netherlands in the present issue of Peritoneal Dialysis International (PDI), Smit et al. studied the prevalence of ultrafiltration failure (UFF) in patients treated with PD for more than 4 years, and examined the peritoneal transport characteristics of these patients (2). The authors defined UFF as a net UF of less than 400 mL at the end of a 4-hour dwell with 3.86%/4.25% glucose solution, the definition proposed by the International Society for Peritoneal Dialysis committee on UFF (3).

The authors tried to define the peritoneal transport patterns of patients with UFF and classify why UF was poor among those patients. They suggest that three different transport patterns (and in particular, various combinations of the three) underlie the poor UF in the majority of the studied patients: (a) a large vascular surface area (as assessed by a high mass transfer area coefficient for creatinine or a high glucose absorption), (b) a decreased dip in dialysate-to-plasma ratio (D/P) of sodium, and (c) an increased fluid absorption rate (denoted by the authors as a high effective lymphatic absorption rate). As this third mechanism of UFF, and in particular the question of whether a high tracer disappearance rate represents mainly lymphatic absorption or, more likely, mainly fluid absorption into adjacent tissues (4), has recently been extensively discussed in PDI (5,6), we will focus on the first two suggested causes of UFF.

The authors confirm that increased transport of small solutes with rapid glucose absorption is the most common mechanism observed in PD patients with UFF, as reported previously (1,7–10). This suggests a large vascular surface area in these patients. However, consistent with previous reports (9,11), Smit et al. found no difference in the clearances of macromolecules (2). A large vascular surface area should also result in increased transport of macromolecules; therefore, interpretation of increased small solute clearances still requires some caution. One speculation is that the expansion of the submesothelial compact zone observed in many long-term PD patients (12) may be more pronounced in patients with increased vascular surface, and that transport of macromolecules through the expanded interstitium of the submesothelial compact zone may be retarded.

The authors regard a decreased dip in D/P sodium as indicative of one specific cause of UFF, that is, poor aquaporin function. However, if the UF rate is very low, regardless of the cause of the UFF, there will be little or no decrease in D/P sodium, as there is minimal dilution of the sodium concentration in the dialysate by ultrafiltrate, precisely because there is so little UF. Computer simulations have demonstrated that sodium sieving will always be markedly reduced when UF is poor, even if aquaporin function is normal (13). Consequently, the absence of a dip in D/P sodium is, in many cases, only a consequence of low UF and not a marker of a specific cause of UFF. Therefore, it is not completely valid to use a decreased dip in D/P sodium to define one cause of UFF.

In many patients with UFF, the osmotic gradient cannot induce water flow as effectively as in patients with normal UF capacity (14,15), indicating decreased osmotic conductance or reduced osmotic efficiency of glucose, that is, the UF flow induced by one unit of osmotic gradient across the peritoneal membrane (15,16). Reduced osmotic conductance has been suggested to be due to decreased transcellular water transport or deficient aquaporin-mediated UF (7,17). However, although this is a theoretical possibility, it is still not established and we do not have the ability to distinguish between deficiencies in aquaporin and interstitial water convection, as these processes are in series in the membrane. In fact, aquaporin expression was reported to be normal in one long-term PD patient with poor UF and reduced sodium dip, attributed to impaired transcellular water transport (18). Therefore, further research is needed to establish the pathophysiological mechanisms behind the reduced osmotic conductance in PD patients with poor UF. In the interim, it is preferable to denote this mechanism of UFF as simply “reduced osmotic conductance.”

Osmotic conductance may be estimated from a simple mathematical model using a linear relationship between volume changes and the osmotic gra-
dient (15,16), and in this way several assumptions may be avoided. Smit et al. used a different approach, estimating osmotic conductance using the three-pore model. This approach involves several assumptions and the results may be a little more complex to interpret and result in some theoretical problems. For example, if a decreased sodium dip were due to water channel dysfunction, then the number of (functional) ultrasmall pores would be low compared to patients with normal UF. The fractional UF coefficient ($\alpha_c$) for ultrasmall pores should be lower, as the fraction of UF passing through the aquaporins is lower, and the respective fractional UF coefficients for small and large pores should be higher in these patients than in patients with normal UF, with all other parameters being similar. It may be difficult to take this into account in the modeling of individual patients (13). Having assumed that the fractional contribution (alphas) of different types of pores to the fluid transport characteristics ($L_P$ and sigma) are the same for normal patients and patients with UFF, Smit et al. fitted the radius of small and large pores to get the best description of the data (2). As a result, they obtained significantly different reflection coefficients for the two groups of patients, with decreased reflection coefficients and, therefore, also osmotic conductance for the patients with UFF. The values of the obtained pore radii were not reported, but one may guess that the radii of the small pores were higher in the patients with UFF than in the normal patients. Therefore, the explanation of the finding of decreased osmotic conductance may be increased radius of small pores, indicating changes in the capillary wall structure rather than loss of aquaporins, as their fractional UF coefficient was kept constant during the fitting procedure for all patients.

This problem illustrates well how complex and sophisticated the application of the three-pore model may be, and that many possible explanations of the same phenomenon are offered by this and other models that have many parameters available for manipulation during the fitting procedure. For this reason, the application of the simplest possible membrane models should always be the first step in the evaluation of the data. In particular, osmotic conductance may be obtained by simple fitting of dialysis fluid volume to the cumulative osmolality gradient (15,16). Further analysis should, however, include interpretation of the transport coefficients using the models that describe the structure of the “peritoneal membrane” more adequately than the “black box” models.

Although the authors defined UFF from the results of a peritoneal equilibration test, they found a prevalence of UFF that is remarkably similar to the incidence our group previously reported, using a more clinical definition, in patients treated with PD for more than 4 years (9). However, our criterion for UFF, which was the inability to reach dry weight using three or more hypertonic 3.86% glucose solution exchanges per day, may have defined more severely affected patients, and the populations in the two studies may not be completely comparable. Furthermore, the interpretation of most studies looking at changes in peritoneal transport with time, and in particular of cross-sectional studies like that of Smit et al., should be cautious because of the potential for methodological fallacy due to dropout of patients with “inadequate” peritoneal transport. Thus, high and low transporters may fail PD due to insufficient fluid removal and inadequate small solute clearances, respectively, leading to selection or survivor bias. Despite this limitation, the Smit study clearly demonstrates that decreased UF capacity is common in patients treated with PD for more than 4 years.

The causative factors and pathogenetic mechanisms behind these alterations in transport are not well established, although both the effect of peritonitis (19) and the bioincompatibility of the PD solutions have been widely discussed. Numerous studies have demonstrated the bioincompatibility of conventional PD solutions in vitro, and features such as hyperosmolarity, acidity, use of lactate as a buffer, and the high content of glucose and reactive carbonyls have been suspected as causes of changes in peritoneal solute and fluid transport (20,21). However, there are few clinical data demonstrating such a relationship. Until recently, almost all standard PD solutions have had similar composition and bioincompatibility, and so little is still known about which factors cause long-term changes in peritoneal membrane structure and function, or which basic mechanisms are involved in the evolution of these alterations. Hopefully, the growing use of new more biocompatible solutions will result in a decreased incidence of membrane failure and UFF. The study by Smit et al. clearly demonstrates the need for much more research in this area.

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