

Peritoneal Inflammation and High Transport Status

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Current US average annual growth of peritoneal dialysis (PD) is reported to be around 6 to 11% (1). There are wide variations in the utilization of PD in different countries. Similarly, there are wide variations in technique survival among various centers. If death and transplantation are excluded, infectious complications have been the most common reason for transfer out of PD. Over the past two decades, with improved technology and connectology systems, there has been a significant reduction in the rate of infectious complications. Centers with longer PD experience report PD-associated peritonitis rates on an average close to one episode for every six to seven patient years. In parallel, there has been increasing recognition of the importance of adequacy and ultrafiltration capacity. New adequacy guidelines now include, in addition to targets for solute clearances, ultrafiltration capacity recognition and BP control recommendations. There is now an acute awareness of the importance of peritoneal membrane transport characteristics in achieving favorable long-term morbidity and mortality. Factors that determine peritoneal membrane function in an individual are confounded by the coexistence of chronic inflammation due to uremia or other diseases, malnutrition, obesity, advanced cardiovascular diseases with hyperlipidemic state, diabetes, old age, ethnicity, and duration of PD. Recently, high peritoneal transport status in incident PD patients in particular has received increased attention due to poor outcome in some of them. It is as yet unclear what determines such a status in new patients starting PD. Interestingly, some of these high transporters have poor outcome and others do as well as other PD patients. Those with poor outcomes are recognized by the higher prevalence of markers of inflammation, malnourishment, and/or hypoalbuminemia. Studies to address these issues have been inconclusive and often are anecdotal experiences and based on small population studies.

Peritoneal membrane permeability varies widely among individuals and populations (2). The peritoneal equilibration test (PET) is a semiquantitative assessment of peritoneal membrane transport function in patients on PD (3,4). The solute transport rates are assessed by the rates of their equilibration between the peritoneal capillary blood and dialysate. The ratio of solute concentrations in dialysate and plasma (D/P ratio) at specific times (t) during the dwell signifies the extent of solute equi-

libration. This ratio can be determined for any solute that is transported from the capillary blood to the dialysate. Creatinine, urea, electrolytes, phosphate, and proteins are the commonly tested solutes for clinical use. Because glucose is absorbed from the dialysate to blood and is very quickly metabolized, a conventional D/P ratio for glucose is meaningless. Instead, the fraction of glucose absorbed from the dialysate at specific times can be determined by the ratio of dialysate glucose concentrations at specific times (t) to the initial level in the dialysis solution (Dt/D0). The PET also helps measure ultrafiltration and residual volumes (5,6). The PET is a highly reproducible procedure consisting of a standardized 4-h dialysis exchange with a dialysis solution (7). The test permits the comparison of multiple results in a patient over a long period of therapy; in addition, the results between patients within a center and between populations from different geographic locations may be compared. The PET is standardized for various elements (5). In one study, variations in the performance of the preceding exchange before the test, such as utilizing a dry, tidal, or standard exchange, resulted in significantly different results (8). The standardized test for clinical utility measures dialysate creatinine and glucose levels at 0, 2, and 4 h of dwell, and serum levels of creatinine and glucose at any time during the test. The extensive unabridged test, which was originally proposed by Twardowski *et al.*, (5) is used in special clinical situations and as an important research tool. The peritoneal membrane transport classification is based on averages, standard deviations, and minimum and maximum values over 4 h of creatinine D/P and glucose D/D0. Drain volumes correlate positively with dialysate glucose and negatively with D/P creatinine at 4-h dwell times.

Because it is simple and it is easy to understand and to perform, this ratio is the most-used clinical tool for assessment of peritoneal membrane function. Computerization is optional and most centers use simple calculations and graphics to interpret the results. Nevertheless, the test has limitations: It must be done in the dialysis center and it is extremely important to adhere to the standard test regimen (8,9).

In this issue of *CJASN*, Van Biesen and colleagues used the Peritoneal Dialysis Capacity (PDC) test to analyze data in all new 135 patients starting PD at the University Hospital, Ghent, UK, during a 6-yr period starting January 1998 (10). PDC describes the peritoneal membrane characteristics by three parameters: The area parameter (A0/dX), which is equivalent to D/P of PET; the fluid reabsorption rate (JvR) from the abdominal cavity to blood after the glucose equilibrium has been

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achieved; and large pore fluid flux (JvL). The test uses a computerized mathematical model based on the three-pore model of Rippe (11). The authors classified their study patients into two groups according to composite interpretation of large pore flux and A0/dX. In essence, this model identified patients with large pore flow higher than expected for the given A0/dX. Based on the PET 4-h D/P creatinine (D/Pcr), they identified 19 patients as high transporters at a cut off of D/Pcr at 0.76, a level much lower than the 0.81 in the original study by Twardowski *et al.* (5). The PDC classified “fast transporters” as being older, with a higher C-reactive protein (CRP) with a lower serum albumin. There was a correlation between JvL and CRP, but not between D/Pcr at 4 h and CRP. A higher JvL was independently predicted by inflammation and A0/dX. After multivariate analysis for demographics, higher pore flow patients had a higher mortality than those who had a normal JvL. D/Pcr was not related to mortality in the analysis.

In the original PET series by Twardowski *et al.*, approximately two thirds of patients had average transport rates (5). The remaining one third consisted almost equally of high and low transporters. This distribution, however, may not be observed in all patient populations (12). There appears to be an association between initial peritoneal transport status and certain clinical features, particularly age. This was best studied in a report of 3188 patients from Australia and New Zealand who initiated PD between 1991 and 2002 and underwent a baseline PET within the first six months (13). Upon multivariate analysis, a high transporter was associated with increased age (odds ratio of 1.08 for each 10 yr, 95% confidence interval of 1.03 to 1.13) and ethnicity (odds ratio 1.48 for Maori and Pacific Islander racial origin, 95% confidence interval of 1.13 to 1.94). By comparison, this finding was not associated with gender, diabetes and other comorbid conditions, smoking, previous hemodialysis therapy or transplantation, or residual renal function. A similar association between increasing age and high transporter status at dialysis initiation was noted in a second, smaller study from Spain (14).

The results of the study by Van Biesen *et al.* (10) must be viewed in light of this study's limited use of PET methodology, specifically its reliance on only D/Pcr and largely ignoring other aspects of PET that were originally described by Twardowski (5) and subsequently altered by the International Society for Peritoneal Dialysis Ad Hoc Committee in the “Modified PET” (15). As designed in Van Biesen's study, PDC was better able to discriminate inflammation as causing leaky membrane than PET. However, similar information could have been obtained with modified PET. Assessment of sodium sieving during the study period is an important aspect of PET that has been largely ignored in this study. Since the adoption of modified PET, glucose concentration has been increased to 4.25% when assessing for ultrafiltration capacity. The use of higher glucose solution during PET allows more accurate measure of sodium sieving, and thereby assessment of aquaporin-induced free water transport. Obtaining such information during a modified PET, three causes of low ultrafiltration can be discriminated: (1) High solute absorption is associated with rapid dissipation of osmotic agent and thereby reduced ultrafiltration volume. So-

dium sieving is present but occurs early in the dwell. It can be caused by acute infection and/or inflammation, and in long-term PD patients, possibly is secondary to exposure to a high glucose load. (2) High absorption PD fluid through lymphatic can also reduce the net drained volume. In this case, the sodium sieving is present and solute transport is unchanged, but is associated with low drain volume. (3) Aquaporin deficiency, seen largely in long-term PD patients, is associated with impaired free water generation and sodium sieving will be absent. Frequently, multiple causes are present in an individual, and an estimate of each of these components can be determined with modified PET.

Although the article by Van Biesen *et al.* is an important addition to our understanding the peritoneal physiology of water and solute transport, it is premature to suggest that PET is unable to discriminate the causes of low ultrafiltration. The contribution of this study in recognizing enhanced large pore flux is invaluable. However, further studies comparing larger number of patients with modified PET and PDC may help delineate the role and limitations of each test.

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See related article, “The Personal Dialysis Capacity Test Is Superior to the Peritoneal Equilibration Test to Discriminate Inflammation as the Cause of Fast Transport Status in Peritoneal Dialysis Patients,” on pages 269–274.