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MAXIMIZING THE SUCCESS OF PERITONEAL DIALYSIS IN HIGH TRANSPORTERS

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This article reviews the current understanding of high transport status in the peritoneal dialysis population and emphasizes survival can be improved for high transporters. To address the current state of knowledge on high peritoneal membrane transport, the negative impact of an increased peritoneal solute transport rate is first discussed. The potential downside of high transport status, notably on survival outcomes (as supported by registry data and meta-analysis), is highlighted. Based on recent advances and clinical studies, ways of maximizing the success of peritoneal dialysis treatment in high transporters are discussed, and management strategies are proposed.

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KEY WORDS: High transport; automated peritoneal dialysis; icodextrin; mortality; peritoneal equilibration test; peritoneal membrane transport; technique survival; ultrafiltration.

Increasing attention has been drawn to the characterization of peritoneal membrane transport properties ever since the description by Twardowski and colleagues of the peritoneal equilibration test (1) in peritoneal dialysis (PD) patients. In particular, higher peritoneal transport status, as represented by a faster rate of membrane solute transport (higher dialysate-to-plasma creatinine concentration ratio after a 4-hour dwell), is believed to characterize a special group of patients who differ significantly from other populations. The issues to consider include

- the consequences of high peritoneal transport status.
- the way in which high peritoneal membrane transport confers the difference.
- whether the adverse effects be prevented, and if so, how.
- whether guidelines are available.

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CONSEQUENCES AND OUTCOMES OF HIGH PERITONEAL TRANSPORT STATUS

From the perspective of peritoneal membrane, high transport implies a structural or functional alteration of the peritoneum—that is, a larger effective peritoneal surface area or higher intrinsic membrane permeability (for the rapid equilibration of small solutes including creatinine and urea). High transporters are therefore prone to lose the osmotic gradient required for sustained ultrafiltration because of rapid absorption of glucose from the dialysate. As a consequence of this loss of osmotic gradient and subsequent decrease in ultrafiltration capacity, high transporters tend to have greater systemic exposure to glucose than low transporters do. The question then arises whether the change in peritoneal transport status is caused by factors related to long-term dialysis, including factors related to the dialysis fluid, such as low pH, hyperosmolality, and high glucose concentration.

Experimental and clinical evidence is emerging that duration of PD and increased surface area of peritoneal microvessels play a key role in the development of high peritoneal membrane transport. Using tissues from biopsies of the parietal peritoneum, the dialysate-to-plasma ratio of creatinine concentration was shown to be positively correlated with increased vascularization (relative microvessel area): that is, vascularization is higher with longer duration of PD (2).

Longitudinal data are increasing the concern that a change in peritoneal membrane structure or function occurs with time on PD treatment. Increasing solute transport or membrane permeability arises to some extent from dialysis-induced membrane injury because of intraperitoneal exposure to glucose (3,4). The presence

of peritonitis is thought to be another possible cause of these changes in peritoneal transport characteristics (5).

Besides ultrafiltration problems, high transporters face the problem of hypoalbuminemia because of numerous factors, including excessive protein losses in peritoneal effluent, relative hemodilution from suboptimal ultrafiltration, and rapid satiety and appetite suppression from a greater glucose load and the resultant poor protein intake (6). Alternatively, lower albumin in high transporters could indicate a state of chronic inflammation (7,8). Our group previously reported that dialysate protein losses correlated with serum concentrations of C-reactive protein (CRP) and suggested that high transport status is a marker for inflammation (9). Subsequently, we found that an increase in peritoneal albumin excretion correlates with a higher adjusted hazard ratio of developing a cardiovascular event (10). Nevertheless, we recognize that another study did not find consistently elevated CRP and serum interleukin-6 among high transporters as compared with patients in other transport categories (11).

A better way to evaluate the consequence of high peritoneal membrane transport would be to analyze the epidemiology data for incident PD patients with respect to the various categories of transport status at baseline. Despite the known shortcomings of most observational studies, robustness of findings can be enhanced if the sample size is large enough to allow meaningful multivariate statistical analysis that controls for confounding variables.

For instance, in the prospective CANUSA study (12), the relative risk of technique failure or death for high transporters as compared with low transporters was 4.00 (95% confidence interval: 1.40 to 11.48) by the Cox proportional hazards model. In our group's prospective longitudinal study of more than 200 Chinese patients, high and high-average transporters were found to have a slightly lower 2-year actuarial patient survival as compared with low transporters (83.3% vs 90.2%), although the result did not reach statistical significance (13).

More recent studies, notably the registry-based analysis of incident PD patients in Australia and New Zealand, confirmed that high peritoneal transport status is a highly significant risk factor for both technique failure and death (14). Further, subgroup analyses (14) of the data from the Australia and New Zealand Dialysis and Transplant Association (ANZDATA) registry showed that high transport status was independently predictive of death-censored technique failure for patients on continuous ambulatory peritoneal dialysis (CAPD), but not for those on automated PD (APD). And another large multivariate analysis noted that high peritoneal transport predicted mortality in adult PD patients, but that its role seemed to be related to the presence of diabetes mellitus (15).

The relevance of high transport status has been highlighted by a recent meta-analysis (16), in which 19 studies were pooled to generate a summary relative risk for mortality of 1.15 (95% confidence interval: 1.07 to 1.23) for every 0.1 increase in the dialysate-to-plasma ratio of creatinine concentration ($p < 0.001$). After adjustment for age, diabetes, and albumin, high transporters (as compared with low transporters) were estimated to have a 77% higher risk for mortality. A similar relationship trend was noted between transport status and technique failure, although that relationship did not reach statistical significance. Meta–regression analysis demonstrated that the proportion of patients who were on continuous cycling PD within a particular study is inversely proportional to the mortality risk ($p = 0.05$), in keeping with the data from Australia and New Zealand (14,16).

WAYS TO TACKLE HIGH PERITONEAL TRANSPORT STATUS

In theory, because the osmotic gradient is dissipated after excessive dwell time, high transporters require short dwell times to maximize small-solute clearance and net ultrafiltration. Whether APD or continuous cycling PD is beneficial in the setting of high transport has been studied only in relatively small trials, just one of which randomly assigned high-transport patients prospectively to the CAPD and APD modalities (17). That trial was beset with problems from a high attrition rate (26%), and was underpowered to detect differences in clinical outcome between CAPD and APD.

Even when prospective interventional data is lacking, the tacit assumption is that the shorter dialysis dwells of APD minimize the negative impact on ultrafiltration of rapid glucose reabsorption among high transporters (18). Use of short-dwell therapy at night, often called nocturnal intermittent PD (NIPD), also allows high transporters to keep a dry abdomen during the day, thereby potentially minimizing protein losses not attributable to glucose absorption.

The use and effectiveness of APD in high transporters needs to be interpreted with recent observational evidence in mind. Although high-transport PD patients are seemingly at a survival disadvantage, such associations are confined to patients on CAPD, and do not appear to affect those on APD (14,16). Those observations thus provide support for the idea that APD is more appropriate for patients with high transport status.

Despite the advantages of shortened cycle length with APD in high transporters, some important caveats remain. Use of APD with a "dry day" (NIPD), may differ from the use of continuous cycling PD in terms of treatment outcomes simply because the peritoneal cavity is empty between the intermittent cycler treatments of the former option. In a small cross-over clinical trial involving 11 high and high-average transporters, a change from CAPD to NIPD was accompanied by a substantial decline in serum CRP and significantly better ultrafiltration. Those beneficial effects tended to be reversed after a switch from NIPD to CCPD (19).

Taken at face value, that finding seems to accord reasonably well with the hypothesis that the reduction in contact time between dextrose dialysis fluid and the peritoneal membrane is the main advantage of APD. However, loss of the beneficial effect on systemic inflammation after a switch to CCPD from NIPD was not accompanied by a change in dialysate proinflammatory cytokine levels (19). An alternative explanation for the decrease in systemic inflammation may be the better volume control achieved with NIPD.

What are the implications, if any, of these results for the clinical management of high transporters?

Perhaps APD (to be precise, NIPD) is justified in high transporters so as to achieve better clinical outcomes—although the key would be to aim for satisfactory volume control (19,20). Notwithstanding the practical advantages of using NIPD, several alternative strategies for high transporters deserve comment. Among them, icodextrin-containing PD solution represents one of the most promising additions to the expanding armamentarium of technologies to achieve volume control in high transporters (21,22). Icodextrin, a high molecular weight glucose polymer, substitutes for glucose as the osmotic agent in dialysate and provides sustained ultrafiltration through colloid osmosis. It offers the twin advantages of reduced absorption of glucose and increased ultrafiltration as compared with conventional hypertonic glucose–containing solutions. Interestingly, high transport status predicts a more favorable ultrafiltration response to icodextrin (22,23).

In one prospective study on PD patients with refractory fluid overload, the increase in ultrafiltration volume after an icodextrin exchange correlated positively with the dialysate-to-plasma creatinine concentration ratio after a 4-hour dwell in a peritoneal equilibration test (22). The findings of greatest ultrafiltration response to icodextrin among high transporters are in keeping with biologic plausibility—specifically, a larger number of small pores in the peritoneal membrane of those patients. A more pronounced improvement in ultrafiltration volumes in patients with high-average or high peritoneal membrane transport status, as confirmed in stable PD patients without ultrafiltration failure (23,24), provides support for the recommendation from the International Society of Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis to consider icodextrin for the long dwell in high transporters with ultrafiltration failure (21).

Hitherto, data to inform the clinician about a long-term patient and technique survival benefit of icodextrin in high transporters were inadequate. However, studies of clinical outcomes provide important clues to the potential effect of this newer PD solution. Table 1 summarizes the major clinical interventional studies targeted specifically toward PD populations with high (and high-average) transport. To date, two randomized controlled trials have evaluated the use of icodextrin in high transporters—one in Europe (25) and another in the United States (26). Both studies demonstrated that use of icodextrin for the long dwell results in highly statistically significant and clinically meaningful improvements in net ultrafiltration, as compared with the ultrafiltration achieved using conventional dextrose-based solutions. Furthermore, icodextrin was observed to provide a sustained reduction in body weight (largely attributable to lower extracellular fluid volume) in the absence of detrimental effects on residual renal function (25).

AREAS OF UNCERTAINTY

Although most authorities recommend NIPD for high transporters (6,18,27), no reliable data are available on the issue of adequate solute clearance. Whether manual daytime exchanges are the best strategy remains controversial. Data from controlled studies to guide the optimal treatment of patients who have lost residual renal function and who are thus unable to achieve adequate clearance with a "dry day" on NIPD are lacking. Clinical experience suggests that such patients may benefit from "resting" the peritoneal membrane by temporary transfer to hemodialysis.

Recently, another new strategy—a high nightly dialysate flow and added manual daytime exchange instead of the conventional low-flow APD treatment regimen—was evaluated in a randomized controlled clinical trial (28) and proved to significantly increase peritoneal creatinine and urea clearances. Interestingly, this improved effect on clearances was shown, in a subgroup analysis, to be most marked in higher-transport patients (28).

Further studies are needed not only to resolve the uncertainty about prescription of dialysis method, but

TABLE 1
Published Interventional Studies Targeted at Peritoneal Dialysis Patients with High Transport Status

Reference	Intervention	Patients (*n*)	Duration of study	Clinical outcome measures
Bro *et al.*, 1999 (17)	APD (versus CAPD)	12:13	6 Months	No difference in hospitalization rates
Cueto–Manzano *et al.*, 2006 (19)	Crossover from CAPD to NIPD and then to CCPD	11	12 Months	Better ultrafiltration (increase from 380 mL on CAPD to 2640 mL on NIPD, $p<0.05$) and trend toward improved blood pressure with NIPD
Davies *et al.*, 2003 (25)	Icodextrin in the long dwell (versus 2.27% glucose)	28:22	6 Months	Better ultrafiltration (increase of 399.0 mL after 3 months, $p<0.05$) and total sodium losses ($p<0.05$); sustained reduction in weight or extracellular fluid volume
Finkelstein *et al.*, 2005 (26)	Icodextrin (versus 4.25% dextrose solution)	47:45	2 Weeks	Better net ultrafiltration (unchanged from baseline in control group, but increased from 141.6 mL to 540.2 mL at week 2 in icodextrin group, $p<0.001$)and significantly less incidence of negative net ultrafiltration ($p<0.0001$)

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; NIPD = nocturnal intermittent peritoneal dialysis; CCPD = continuous cycling peritoneal dialysis.

also to guide the choice of PD solution. Interest in the use of more "biocompatible" PD solutions for high transporters has been increasing. One point that deserves emphasis relates to a small study that showed a preferential reduction in effluent matrix metalloproteinase-2 among high transporters after a switch from conventional lactate-buffered to neutral-pH PD solution (29). This improvement (decrease in a marker of peritoneal damage) was not seen in patients with a lower peritoneal transport status. The reductions in the formation of advanced glycation end-products and glucose degradation products and the use of amino acids in newer generations of PD solutions are attractive, particularly in the context of high transporters with high mortality rates. As is often the case in dialysis, the putative advantages brought about by technologic advances need to be validated in better-designed clinical studies, preferably with emphasis on long-term patient and peritoneal outcomes.

CONCLUSIONS

Although high-transport PD patients are seemingly at a survival disadvantage, realistic expectations of improved strategies to better manage such patients are becoming relevant. However, to truly understand the long-term benefits of the new strategies, large-scale observational data and (preferably) randomized controlled studies with long follow-up are needed. Reductions in cardiovascular morbidity and mortality (a major problem in chronic PD patients) may be another potential benefit of this progress (30).

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