Peritoneal Glucose Exposure and Changes in Membrane Solute Transport with Time on Peritoneal Dialysis

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Abstract. Peritoneal solute transport increases with time on treatment in a proportion of peritoneal dialysis (PD) patients, contributing to ultrafiltration failure. Continuous exposure of the peritoneum to hypertonic glucose solutions results in morphologic damage that may have a causative role in changes in peritoneal function. The purpose of this analysis was to establish whether increased exposure to glucose preceded changes in solute transport in a selected group of long-term PD patients. Peritoneal solute transport, residual renal function, peritonitis rate, and peritoneal exposure to glucose were recorded prospectively in a cohort of 303 patients at a single dialysis center. A subgroup of individuals, treated continuously for 5 yr, were identified and defined retrospectively as having either stable or increasing transport status. Of the 22 patients who were treated continuously for 5 yr, 13 had stable solute transport (solute transport at start, 0.67 ± 0.1; at 5 yr, 0.67 ± 0.1), whereas 9 had a sustained increase (solute transport at start, 0.56 ± 0.08; at 5 yr, 0.77 ± 0.09). Compared with the stable patients, those with increasing transport had earlier loss in residual renal function and were exposed to significantly more hypertonic glucose during the first 2 yr of treatment that preceded the increase in solute transport. This was associated with greater achieved ultrafiltration compensating for the reduced urinary volumes in these patients. Further increases in glucose exposure were observed as solute transport continued to rise. Peritonitis, including severity of infection and causative organism, was similar in both groups. In this selected group of long-term survivors on PD, an increase in solute transport with time was preceded by increased peritoneal exposure to hypertonic glucose. This is supportive evidence that hypertonic glucose may play a causative role in alterations in peritoneal membrane function.

Ultrafiltration failure remains an important cause of technical failure in patients who are treated with peritoneal dialysis (PD) (1). The incidence increases with time on treatment (2), in part because it is revealed by loss of residual renal function (RRF) but also because of acquired changes in peritoneal membrane function (3–6). Peritoneal solute transport, the aspect of membrane function that refers to the rate at which low molecular weight solutes cross the peritoneum, can be estimated from the dialysate:plasma ratio of creatinine (D/Pcreat) at the end of a standard 4-h dwell. A high rate of peritoneal transport is the most common explanation for poor ultrafiltration, caused by the rapid absorption of glucose and thus loss of the osmotic gradient early in the dialysis cycle. Usually, patients with high transport have to use hypertonic glucose exchanges in their long dwell period to prevent net reabsorption of fluid. In a proportion of patients, solute transport increases with time on treatment and is the factor most clearly associated with acquired ultrafiltration failure (1).

Exposure to hypertonic glucose dialysis solution, which also contains glucose degradation products that enhance the formation of advanced glycosylation end products (AGE), has long been suspected as a mechanism of peritoneal membrane injury. There is a growing body of circumstantial evidence to support this, including AGE deposition within the membrane (7–9), diabetiform changes in peritoneal blood vessels (10,11), and the finding that sclerosing peritonitis is associated with the use of more hypertonic exchanges (12). In the study by Hendriks et al. (12), the increased use of hypertonic glucose was evident in the first year of treatment. Recent observations in animal models demonstrated neovascular changes typical of diabetes (11), and early reports from the Peritoneal Biopsy Registry have indicated vascular injury indistinguishable from diabetes that worsens with prolonged periods on dialysis (13). It is likely that there is a link between these morphologic findings and the functional changes with time on treatment. The problem in defining a causative role for hypertonic glucose and the acquisition of functional changes in the membrane is complicated by the need to use more hypertonic exchanges as ultrafiltration failure develops. To clarify which comes first, it is desirable to demonstrate that the use of hypertonic glucose exchanges precedes the changes in peritoneal membrane transport characteristics. The present study reports the detailed evolution of peritoneal kinetics, RRF, peritonitis history, and exposure to glucose, gathered prospectively in a cohort subset of long-term PD patients.

Materials and Methods

Study Design

The Stoke PD Study was set up in 1990 to examine the long-term relationship among peritoneal membrane function, nutrition, and clin-
ical outcome in PD patients (1). As described previously, dialysis clearances, peritoneal transport, nutritional state, peritonitis exposure, and dialysis regimes were recorded prospectively. The database was censored in early 1998, and the longitudinal changes in nutrition, membrane function, and patient and technique survival were reported (1). The data presented in this study are from a subset of this cohort: individuals who had received PD (continuous ambulatory PD only) continuously for at least 5 yr.

Longitudinal changes in peritoneal solute transport were used to categorize this subset into patients with stable solute transport within 0.1 (group 1) and those with increasing solute transport consistently >0.1 of that on commencing treatment (group 2). Patients from these two groups were then compared for a number of dialysis-related factors, including RRF, glucose exposure, peritonitis rate and severity, achieved ultrafiltration and dialysis dose, and demographic factors. Throughout the study period, the dialysate buffer used was lactate, either 35 or 40 mmol/L.

Peritoneal Equilibration Test

The peritoneal equilibration test, performed as described previously (14,15), was used to estimate solute transport. Patients were tested at least once a year, and usually every 6 mo. When more than one test was performed in a year, the mean value was used for analysis. Briefly, a standard 4-h dwell period was used (first exchange of the day), using a 2.27% glucose concentration 2-L volume exchange. The patient used his or her usual overnight dialysis regime, and both the overnight and test drainage volumes were measured. The D/Pcreat at the completion of the 4-h dwell period is an estimate of low molecular weight solute transport. D/Pcreat correlates well with the mass transfer area coefficient for creatinine but is not identical, because of the variable influence of convection (16). As glucose interferes with the assay for creatinine in a linear fashion, concentrations for both of these solutes are measured at 4 h and the true value for creatinine obtained by subtracting the glucose concentration is multiplied by a correction factor derived locally by our laboratory (0.47). With the use of this method, the 4-h D/Pcreat is a highly reproducible measure of low molecular weight solute transport across a wide range of values (0.45 to 0.9), in the short term (3 mo or less, provided that there has been no clinical event such as peritonitis or surgery), with a coefficient of variation of 4.8%.

Glucose Exposure

Glucose exposure was expressed in two ways. First, the total annual exposure to glucose was calculated from the dialysis regime reported every 6 mo. The product of the volume and the glucose concentration for each exchange was calculated. For example, for an individual who was using 4 × 2 L exchanges (2 × 1.36%, 1 × 2.27%, and 1 × 3.86%), there would be 54.4 + 45.4 + 77.2 = 176.8 g of glucose per day. This is equivalent to 64,532 g of glucose per year. The second method was a simple tally of the number of hypertonic (3.86%) exchanges used per day.

Dialysis Dose (Kt/V)

The dialysis dose was assessed by calculating the weekly Kt/Vurea from the 24-h urinary and dialysate clearance, by direct measurement of urea in urine and each dialysate exchange. The volume of distribution for urea was calculated as 58% of the body weight. Results are expressed as the total weekly Kt/Vurea (peritoneal component) or for the RRF alone.

Peritonitis

Peritonitis was defined as a dialysate white cell count >100 cells/μl, and all episodes were treated empirically with intraperitoneal vancomycin and gentamicin until sensitivities were known. Dialysate white cell count was documented on presentation, day 3, and day 12. Definitions of recurrence, same organism within 30 d, and clusters of episodes within 3 mo were used as described previously (4).

Analytical Methods

Plasma and dialysate concentrations of urea, creatinine, and glucose were determined on an automated discrete random access analyzer (DAX 72, Bayer Instruments, Basingstoke, UK). Urine and dialysate total protein estimations were made using the biuret method. Plasma albumin levels were measured using the Bromcresol green method.

Statistical Analyses

Comparison of demographic data between multiple groups was made using ANOVA (parametric) and Kruskal-Wallis (nonparametric variables, e.g., comorbid score). Comparison between groups 1 and 2 of solute transport, glucose exposure, and peritoneal Kt/V was made using an unpaired t test, and for RRF and use of hypertonic exchanges using the Mann-Whitney test. Longitudinal changes in solute transport were tested for using a paired t test.

Results

Of the 303 patients in the cohort study at censor, 67 were at risk with at least 5 yr of follow-up (see Figure 1). Of these 67 patients, 25 were still on PD, 31 had functioning transplants, and 11 had been transferred to permanent hemodialysis. Of the 11 transferred to hemodialysis, 5 had recurrent peritonitis and 6 had ultrafiltration failure. The demographic characteristics of these three survival groups, along with the whole cohort, are shown in Table 1. It can be seen that these three groups, selected by their ability to survive for 5 or more years, do not differ according to their treatment modality at the time of

![Figure 1](image-url)
censor. When compared with the whole population, they are significantly younger and have less total comorbidity.

Of the 25 patients who were on PD for 5 yr at censor, 22 had been on treatment without significant interruption, i.e., period on hemodialysis or with functioning transplant. Of these, 13 had solute transport kinetics that were within 0.1 of that at the start of treatment (group 1) and 9 had a sustained increase of >0.1, equivalent to >15% above baseline (group 2). The demographic details of these two groups at the start of treatment, which did not differ significantly, are shown in Table 1.

The longitudinal changes in solute transport are shown in Figure 2A. It can be seen that the mean solute transport in group 1 is stable throughout the 5-yr period, being 0.67 (±0.1) at the start and 0.67 (±0.08) at 5 yr. In group 2, for the first 2 to 3 yr of treatment the mean solute transport remains relatively low, followed by an increase from 0.56 (±0.08) at the start to 0.78 (±0.09). As would be anticipated from the definition of this group, the increase was statistically significant (P < 0.01). There were no significant differences in plasma albumin or dialysis-delivered Kt/V between groups throughout the study.

The details of peritonitis, including intensity of inflammation, causative organism, and clinical outcome, are summarized in Table 2. It can be seen that the overall severity of the peritonitis record was similar in both groups. If anything, the overall picture is slightly worse for the stable group 1 patients, with a higher peritonitis rate and a tendency to be associated with recognized pathogens.

One of the most important differences between these two patient groups was their RRF, in terms of both urea clearance (Figure 3A) and urine volumes (Figure 3B). Patients in group 2 had less RRF on commencing treatment, and they lost what was remaining at an earlier stage of treatment. Patients who were on this dialysis program before the censor in January 1998 did not have their PD dose increased to compensate for losses in residual renal clearances. It is apparent, however, that they did have their dialysis regimes altered in terms of glucose and thus peritoneal glucose exposure in group 2 patients. The use of hypertonic exchanges is associated with an increased use of hypertonic (3.86% glucose) exchanges in group 2. The use of hypertonic exchanges is summarized in Figure 2, along with the overall resulting glucose exposure to the peritoneum. Seventy percent of the stable group 1 patients used no hypertonic glucose solutions during the first 4 yr of treatment. The greater use of hypertonic glucose and thus peritoneal glucose exposure in group 2 patients preceded the rise in solute transport and continued to increase as solute transport increased.

Discussion

Concern regarding the use of hypertonic glucose in PD solutions has been expressed frequently, but the evidence base demonstrating an adverse clinical outcome from its use is sparse. In one retrospective case-controlled study of patients who were developing sclerosing peritonitis, increased early use of hypertonic glucose was identified as a risk factor (12). Another study of long-term survivors on PD did not find changes in ultrafiltration, but solute transport was not measured, so patients could not be categorized according to their membrane characteristics (17). In our analysis of data collected prospectively, we were able to demonstrate for the first time that clinically significant changes in peritoneal function are associated with an earlier use of hypertonic glucose exchanges. Although an observational study such as this can never prove cause and effect, the data as presented strongly support the view that hypertonic glucose can influence membrane function in the long term. Conversely and of equal importance, we demonstrated long-term functional stability of the membrane in a selected group of patients who were not exposed to hypertonic exchanges.

Whereas the data for this study were collected prospectively, achieved peritoneal ultrafiltration in Figure 3 indicate that the loss in urine volume was compensated for by an increase in ultrafiltration. It is of interest that both groups had remarkably similar total fluid losses, which were sustained throughout the 5-yr treatment period.

These differences in achieved peritoneal ultrafiltration were associated with an increased use of hypertonic (3.86% glucose) exchanges in group 2. The use of hypertonic exchanges is summarized in Figure 2, along with the overall resulting glucose exposure to the peritoneum. Seventy percent of the stable group 1 patients used no hypertonic glucose solutions during the first 4yr of treatment. The greater use of hypertonic glucose and thus peritoneal glucose exposure in group 2 patients preceded the rise in solute transport and continued to increase as solute transport increased.

Table 1. Demographics of whole PD population compared with those who survived at least 5 yr according to treatment modality at censora

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Whole PD Population (n = 303)</th>
<th>Surviving at Least 5 Yr at Censor</th>
<th>On PD 5 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 25)</td>
<td>(n = 30)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54b ± 2.1</td>
<td>48.7 ± 6.4</td>
<td>43.1 ± 6.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>55%</td>
<td>52%</td>
<td>61%</td>
</tr>
<tr>
<td>Diabetes mellitus (% patients)</td>
<td>48 (15.8%)</td>
<td>3 (12%)</td>
<td>2 (6.6%)</td>
</tr>
<tr>
<td>Plasma albumin (g/L) on starting PD</td>
<td>36.6 ± 0.7</td>
<td>40 ± 1.7</td>
<td>38.3 ± 2.6</td>
</tr>
<tr>
<td>Solute transport on starting PD</td>
<td>0.63 ± 0.016</td>
<td>0.57 ± 0.06</td>
<td>0.62 ± 0.06</td>
</tr>
</tbody>
</table>

a PD, peritoneal dialysis.

b P < 0.05 compared with subgroups that survived 5 yr, ANOVA or Kruskal-Wallis test.

c Unpaired t test or Mann-Whitney U test comparing groups 1 and 2.
the categorization of patients into those with stable as opposed to increasing solute transport had to be made in retrospect. The definition of stable solute transport, a D/P_{creat} remaining within 0.1 (approximately 15%) of that at the start of treatment, was chosen to account for the reproducibility of the test (4.8%) (15) and the observation that changes within this range are rarely of clinical significance. Modest fluctuations in solute transport did occur in stable patients during the 5-yr period of treatment, but none had a significant trend with time. The observation that patients who experienced changes in solute transport had an increase rather than a decrease with time reflects the general trend of the whole patient cohort and the experience of other authors (3).

Peritonitis was reported previously to alter membrane function (4,18). It was important, therefore, to examine closely the peritonitis record in these two patient groups. Changes in membrane function related to peritonitis are associated with recurrent clusters of infection and usually occur during the first 2 yr of treatment (4). These patients had, by definition, avoided excessive peritonitis, which remains the principal cause for treatment dropout. It seems unlikely, therefore, that peritoneal infection is the explanation for the difference in these patient groups.

The principal difference between these two patient groups was their RRF. It is unlikely that renal function has a direct effect on solute transport. There is no relationship between peritoneal transport status and RRF at the beginning of PD treatment, and their influence on patient and technique survival is independent (1,19,20). If anything, there is a selection advantage of low solute transport on long-term survival on PD, which is most apparent in those who lose RRF early. Indeed, this is probably the explanation of the observation in this analysis that patients who had increasing transport (group 2) had persistently lower solute transport during the first 2 to 3 yr of treatment.

The factors that determine solute transport are complex. The distributed model, which describes the diffusive transport across the peritoneal membrane for molecules the size of creatinine, defines three major factors (21,22). These include the area of the peritoneum in contact with dialysate, the diffusive mass transport through the capillary wall, and the diffusive mass transport through the interstitium. It is not known which of these factors is responsible for the changes seen in solute transport with time on dialysis. It is tempting to speculate that the diabetiform changes, particularly new vessel formation that has been described, cause an increase in solute transport by

**Figure 2.** Longitudinal changes in peritoneal solute transport (A) and peritoneal glucose exposure (B) in those patients defined as having stable solute transport (group 1, □; n = 13) and increasing solute transport (group 2, ■; n = 9) with time on treatment. *, P < 0.05 when comparing groups (unpaired t test). C shows use of hypertonic exchanges.

<table>
<thead>
<tr>
<th>Number</th>
<th>Start</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 1</td>
<td>.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Group 2</td>
<td>.081</td>
<td>.025</td>
<td>.034</td>
<td>.023</td>
<td>.06</td>
<td>.074</td>
</tr>
</tbody>
</table>

**Table 2.** Summary of peritonitis record in stable (group 1) and increasing peritoneal transport (group 2) patients

<table>
<thead>
<tr>
<th>Peritonitis Details</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of episodes</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>Peritonitis rate (mo)</td>
<td>1 in 14.7</td>
<td>1 in 22.5</td>
</tr>
<tr>
<td>PD fluid WCC^a (cells/µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at presentation (median)</td>
<td>960</td>
<td>455</td>
</tr>
<tr>
<td>at day 3 (median)</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>at day 12 (median)</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>culture-negative episodes</td>
<td>21 (40%)</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>coagulase-negative staphylococci</td>
<td>18 (35%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td>4 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td>7 (13%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>isolated episodes</td>
<td>29 (54%)</td>
<td>18 (75%)</td>
</tr>
<tr>
<td>response to treatment (proportion cured with single course of antibiotics)</td>
<td>37 (70%)</td>
<td>21 (87%)</td>
</tr>
</tbody>
</table>

^a WCC, white cell count.
augmenting mass transport through the capillary wall. For a molecule such as creatinine, which passes relatively freely through intercellular pores, the capillary surface area will influence solute transport (23). If solute transport increases disproportionately to the peritoneal ultrafiltration coefficient, then ultrafiltration failure will ensue. The case, therefore, that the long-term use of glucose as the primary component to dialysis fluid is detrimental to the peritoneal membrane is growing. The in vitro toxicity of glucose to cellular components (24), the demonstration of AGE deposition in the peritoneal membrane consequent on their enhanced formation from glucose degradation products (7,9), and the findings of advanced vascular changes typical of diabetes in peritoneal biopsy samples are concerning (13). To these must now be added functional changes in the peritoneal membrane, both in the present study and from the observation that glucose-free dialysis results in a modest reduction in solute transport (10).

It should be remembered, however, that even low-strength glucose solutions (1.36%) are far from being physiologic. Another way of expressing the data presented in this study is that it was not possible to demonstrate functional changes in the peritoneal membrane over 5 yr of exposure, provided hypertonic exchanges (3.86%) were avoided. This is encouraging for the continued use of glucose as the predominant low molecular weight osmotic agent in dialysis fluid. It also suggests that it is the extreme hypertonicity of 3.86% solutions that is the problem, and this may be true of other osmotic agents. This will need to be kept in mind during the development and testing of alternatives to hypertonic glucose solutions.

In summary, in a selected group of patients, we demonstrated that the early use of hypertonic glucose exchanges is associated with subsequent increases in solute transport. The possibility that hypertonic glucose, perhaps through its effects on the peritoneal capillary vessels, can alter membrane function is supported. This reinforces the need for the development of alternative hypertonic dialysis solutions. Equally, the use of 1.36% glucose solutions over 5 yr was associated with stable membrane function.

Acknowledgments

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