

Longitudinal membrane function in functionally anuric patients treated with APD: Data from EAPOS on the effects of glucose and icodextrin prescription

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Longitudinal membrane function in functionally anuric patients treated with APD: Data from EAPOS on the effects of glucose and icodextrin prescription.

Background: Peritoneal dialysis is associated with changes in membrane function that can lead eventually to ultrafiltration (UF) failure. Factors driving these changes are thought to include hypertonic glucose exposure, but previously reported associations are confounded by the presence of residual renal function.

Methods: Longitudinal membrane function (solute transport and UF capacity) were measured annually in a prospective cohort of 177 functionally anuric patients as part of the European Automated Peritoneal Dialysis Outcomes Study (EAPOS). Subgroup analysis was performed according to glucose exposure and icodextrin use at baseline.

Results: The whole cohort experienced an increase in solute transport and reduction in UF capacity at 12 and 24 months that could not be explained by informative censoring. These changes were accelerated and more severe in patients using either 2.27% or 3.86% glucose, or those not using icodextrin at baseline. These differences could not be explained by age, comorbidity score, previous time spent on renal replacement, differential dropout from the study, peritonitis rates, or, by definition, residual renal function. Patients using icodextrin at baseline had worse membrane function and were more likely to be diabetic. There was an association between membrane function changes and achieved 24-hour ultrafiltration over the 2-year study period.

Conclusion: Anuric automated peritoneal dialysis (APD) patients experience significant detrimental changes in membrane function over a relatively short time period. Glucose appears to enhance these changes independent of residual renal func-

tion. Icodextrin use in these circumstances is associated with less deterioration in membrane function.

Long-term use of the peritoneal membrane is associated with changes in function that can ultimately lead to ultrafiltration failure [1, 2]. As a cause of treatment failure, this increases with time on therapy, and is associated with increased rates of small solute transport, reduced ultrafiltration capacity, and higher rates of peritoneal fluid absorption [3, 4]. The reduction in ultrafiltration capacity is a consequence of two processes: first, the increase in solute transport, usually defined by the dialysate:plasma ratio of creatinine at four hours, which will result in more rapid glucose absorption, resulting in loss of osmotic gradient. Second, there can be a reduction in the osmotic conductance of the membrane, resulting in less ultrafiltration for a given glucose gradient that is acquired with time on treatment [4, 5]. The main causes of the changes with time on treatment are thought to be repeated episodes of inflammation associated with peritonitis and long-term exposure to bioincompatible dialysate fluid [6, 7]. In particular, hypertonic glucose solutions are implicated due to their hypertonicity, direct effects of glucose toxicity, or associated levels of glucose degradation products (GDPs). Circumstantial evidence supports the role of dialysate glucose exposure in membrane damage, both in morphologic studies of the membrane [8] and longitudinal studies of function [5, 9], but to date these analyses are confounded by the presence of residual renal function. Because loss of function necessitates the greater use of hypertonic glucose, associated changes in membrane function might reflect the effect of worsening uremia.

Key words: ultrafiltration, solute transport, observational cohort study, peritonitis.

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The European Automated Peritoneal Dialysis Outcomes Study (EAPOS) was undertaken in order to establish the efficacy of this treatment modality in functionally anuric patients treated according to previously agreed targets for anemia, several biochemical variables, small solute clearance, and daily ultrafiltration [10, 11]. It demonstrated that good clinical outcomes are possible, and that the most important predictors of survival are age, comorbidity (especially diabetes), and severe malnutrition. In addition, patients who were below the ultrafiltration target at the start of the study (>750 mL/day) proved difficult to get above target throughout the study period, and had a significantly increased mortality. The cause of this excess mortality is not known, but at baseline these individuals were distinguished by their relatively poor ultrafiltration capacity despite equivalent solute transport.

A secondary objective of EAPOS was to examine longitudinal changes in membrane function. This was in part because there is a relative paucity of such information in anuric APD patients in whom exposure to dialysate fluid is very different to continuous ambulatory peritoneal dialysis (CAPD) patients, but also to examine the effects of dialysis prescription on any possible changes without the confounding effect of residual renal function. In addition, the relatively high use of icodextrin in this study was of potential interest.

METHODS

Study design

The design and analysis of primary end points (patient and technique survival) of EAPOS are described in detail elsewhere [10, 11]. Briefly, it was a prospective study of functionally anuric patients (urine volume <100 mL and/or creatinine clearance <1 mL/min/1.73m²) treated with APD undertaken in 28 centers in 14 European countries. One hundred seventy-seven of 204 screened patients were enrolled and followed for two years, or until they stopped peritoneal dialysis. Clinicians were asked to optimize treatment to predefined standards during the first six months, including a solute clearance target of ≥ 60 L/week/1.73m², and a daily ultrafiltration volume of ≥ 750 mL. Clinicians had access to icodextrin, used according to clinical discretion, and standard, pH 5.5, 40 mmol lactate-buffered glucose solutions.

A predefined, secondary end point to the study was peritoneal membrane function, specifically solute transport and ultrafiltration capacity, measured at enrollment and again at 12 and 24 months. Episodes of peritonitis were recorded, as was the use of icodextrin, and the number, volume, and concentration of glucose exchanges. This enables calculation of the average concentration of glucose exposure.

Peritoneal membrane function, solute clearances, comorbidity scoring, and data management

Peritoneal solute transport and ultrafiltration capacity was determined from a standard peritoneal equilibration test, as described previously [12]. Weekly creatinine clearance was calculated from creatinine concentration in plasma, urine, and dialysate, 24-hour urine volume, and 24-hour dialysate volume as described. Residual renal function, when present, was measured as mean of urea and creatinine clearances. Daily ultrafiltration was calculated as the difference between the volume of total dialysate infused (including both night and daytime fluid) and the volume drained over 24 hours for the same period as the solute collection. Comorbidities were counted for each patient to enable calculation of the Stoke comorbidity score [13]. Data management was centralized; peritoneal, urine, and dialysate concentrations of creatinine and all other blood tests were measured in each local laboratory, and results of these and all other demographic data were collated in the central EAPOS office (Baxter Healthcare, Brussels, Belgium), where the PET results and creatinine clearances were calculated.

Statistical analysis

All data are expressed as mean values \pm SD, with the exception of the paired plots of longitudinal membrane function that utilize standard errors. Patients were divided into subgroups according to their dialysis prescription at enrollment. Between-group comparisons at baseline and each time point of the study (e.g., low vs. high glucose exposure, icodextrin use vs. non-use) were made using unpaired *t* tests or Mann-Whitney for non-parametric data. Longitudinal within-group changes in membrane function were analyzed using paired *t* tests. Achieved daily ultrafiltration was nonparametrically distributed so the probability of an increase or decrease over the study period was evaluated using the Wilcoxon signed rank test.

RESULTS

The baseline characteristics of the 177 patients enrolled into EAPOS were as described in detail previously [10]. Briefly, 57% were men, median age was 54 (range 21–91), and 80% were Caucasian, 12% Indo-Asian. The median time on renal replacement was 38 months, and 36% had previously been treated with hemodialysis. Fifteen percent were diabetic, 42% had cardiovascular disease, and solute transport characteristics were relatively high at inclusion: 44 (26%) had low average transport, 80 (46%) high average, and 49 (28%) high transport characteristics as defined by Twardowski [12]. The ultrafiltration capacity for these categories was 412 (± 239), 313 (± 271), and 266 (± 260) mL, respectively. For purposes of this

Table 1. Demographic characteristics according to baseline glucose concentration and icodextrin use

	Low glucose group	High glucose group	Icodextrin group	No icodextrin group
Number	43	134	82	95
Age years	55.3 (18.7)	50.9 (15)	50.7 (16.5)	53.2 (15.6)
Sex ratio M:F	57:43	59:41	58:42	56:44
Body surface area m^2	1.67 (0.2)	1.78 (0.2)	1.77 (0.2)	1.75 (0.2)
Diabetic%	12%	16%	20% ^a	11%
Cumulative comorbid score	0.91 (1.0)	0.8 (1.0)	0.96 (1.1)	0.71 (0.9)
Baseline daily achieved ultrafiltration mL	1218 (678)	1200 (617)	1267 (659)	1029 (585)
Baseline daily achieved creatinine clearance $L/wk/1.73m^2$	65.3 (15.9)	64.5 (15)	65.1 (16.1)	64.4 (14.5)
Average number of previous renal transplants	0.3 (0.5)	0.39 (0.6)	0.43 (0.6)	0.32 (0.6)
Median months on renal replacement	38.1	42.5	44.8	37.7

^a $P = 0.05$, one-tailed nonparametric test compared with patients not using icodextrin.

Table 2. Numbers of patients, dialysate glucose exposure, dialysate volume, and peritonitis rate at six monthly intervals during the study

	Baseline	6 months	12 months	18 months	24 months
Low glucose group N	43	34 (79%) ^d	24 (56%)	18 (41%)	13 (30%)
Mean percentage glucose exposure	1.36 (0.06) ^{a,c}	1.6 (0.42) ^a	1.54 (0.27) ^a	1.65 (0.49) ^a	1.53 (0.23) ^a
Mean 24-hour dialysate volume L	15.5 (3.9)	16.6 (3.7)	16.4 (3.4)	17.5 (3.5)	16.9 (3.4)
Peritonitis mean rate for 6 months		0.35 (0.5)	0.18 (0.4)	0.22 (0.4)	0.50 (0.6)
High glucose group N	134	103 (77%)	77 (57%)	57 (42%)	44 (33%)
Mean percentage glucose exposure	2.1 (0.45)	2.1 (0.45)	2.1 (0.48)	2.2 (0.5)	2.2 (0.51)
Mean 24-hour dialysate volume L	15.7 (3.3)	16.1 (3.5)	16.5 (3.2)	16.8 (3.3)	16.1 (3.9)
Peritonitis mean rate for 6 months		0.25 (0.4)	0.26 (0.4)	0.29 (0.5)	0.30 (0.6)
Icodextrin group N	82	59 (72%)	48 (59%)	36 (43%)	27 (33%)
Mean percentage glucose exposure	2.1 (0.58)	2.1 (0.55)	2.1 (0.57)	2.1 (0.6)	2.1 (0.61)
Mean 24-hour dialysate volume L	15.6 (3.3)	16.4 (3.6)	16.4 (3.4)	16.7 (3.4)	15.4 (4.3)
Peritonitis mean rate for 6 months		0.35 (0.6)	0.23 (0.4)	0.35 (0.8)	0.40 (0.7)
No icodextrin group N	95	78 (82%)	53 (56%)	39 (41%)	30 (31%)
Mean percentage glucose exposure	1.84 (0.41) ^b	1.89 (0.43)	1.93 (0.43)	2.0 (0.48)	1.91 (0.44) ^c
Mean 24-hour dialysate volume L	15.7 (3.6)	16.2 (3.6)	16.5 (3.1)	17.2 (3.2)	16.8 (3.2)
Peritonitis mean rate for 6 months		0.22 (0.5)	0.24 (0.5)	0.20 (0.5)	0.31 (0.6)
All patients N	177	137 (77%)	101 (57%)	75 (42%)	57 (32%)
Mean percentage glucose exposure	1.95 (0.51)	1.96 (0.49)	1.99 (0.5)	2.04 (0.54)	2.01 (0.53)
Mean 24-hour dialysate volume L	15.7 (3.5)	16.3 (3.6)	16.5 (3.2)	16.9 (3.3)	16.3 (3.8)
Peritonitis mean rate for 6 months		0.28 (0.6)	0.24 (0.5)	0.27 (0.6)	0.35 (0.6)

^aAverage glucose concentration less compared to the high glucose group, $P < 0.001$.

^bAverage glucose concentration less compared to the icodextrin group, $P = 0.003$.

^cAverage glucose concentration increased/decreased compared to six months, paired t test, $P < 0.05$.

^dPercentage of each group remaining in the study at each time point.

analysis, patients were divided according to their glucose prescription and their use of icodextrin at baseline, resulting in four subgroups (two pairs). Low glucose exposure was defined as regimens containing 1.36% only, used by 43 (24%) of patients, whereas 134 patients used at least one 2.27% or 3.86% exchange. Just under half, 82 (46%) of patients were using icodextrin at baseline. These groupings were not, however, mutually exclusive, with 19 patients combining icodextrin with 1.36% glucose only, and 71 using $\geq 2.27\%$ glucose and not using icodextrin. The differences in baseline demography of these groupings are summarized in Table 1, showing that these characteristics were not different, with the exception of the proportion of diabetics according to icodextrin use.

Table 2 shows the number of patients, their average dialysate glucose concentration, total dialysate volume, and peritonitis rate at six monthly intervals during follow-

up in each of these categories, as well as for the whole population. It can be seen that the proportion of patients using low versus high glucose concentration fluids, and those using icodextrin as opposed to not doing so at baseline, was similar throughout the study period. Furthermore, the average glucose use remained lower throughout the study in those using low glucose concentrations at baseline. There was a significant increase in the mean glucose concentration in these patients during the first six months of treatment, however, reflecting attempts by clinicians to reach the ultrafiltration targets set in the primary study design. Patients using icodextrin at the start of the study also had a higher average glucose concentration, but this difference disappeared with time due to the increased use of glucose in those patients not using icodextrin. A small number of patients commenced icodextrin during the course of the study ($N = 7$), but no

Table 3. Mean (SD) values for solute transport and UF capacity for all patients in each subgroup and whole study population at each time point

	Baseline	12 months	24 months
Low glucose group <i>N</i>	42	21 (50%)	11 (26%)
Mean solute transport ratio	0.74 (0.11)	0.76 (0.08)	0.8 (0.11) ^c
Ultrafiltration capacity <i>mL</i>	309 (278)	318 (279)	276 (250)
High glucose group <i>N</i>	131	72 (55%)	37 (28%)
Mean solute transport ratio	0.75 (0.12)	0.8 (0.11) ^b	0.82 (0.1) ^b
Ultrafiltration capacity <i>mL</i>	333 (269)	293 (271)	228 (290) ^b
Icodextrin group <i>N</i>	80	44 (55%)	22 (28%)
Mean solute transport ratio	0.76 (0.11) ^a	0.79 (0.11)	0.78 (0.1) ^{a,c}
Ultrafiltration capacity <i>mL</i>	272 (302) ^a	277 (312)	299 (292)
No icodextrin group <i>N</i>	93	49 (52%)	27 (29%)
Mean solute transport ratio	0.73 (0.12)	0.83 (0.1) ^b	0.85 (0.1) ^b
Ultrafiltration capacity <i>mL</i>	374 (232)	318 (228) ^c	188 (264) ^b
All patients <i>N</i>	173	91 (53%)	48 (27%)
Mean solute transport ratio	0.75 (0.11)	0.8 (0.1) ^b	0.82 (0.1) ^b
Ultrafiltration capacity <i>mL</i>	327 (271)	298 (271)	239 (279) ^b

For paired values only, see data represented in Figures 1 through 3.

Between group analysis, different to patients not using icodextrin, ^a $P < 0.02$.

Paired analysis, changed from baseline, ^b $P \leq 0.006$; ^c $P \leq 0.02$.

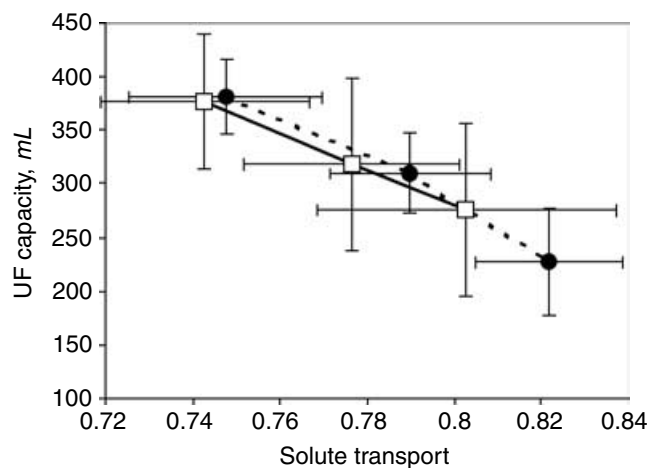


Fig. 2. Longitudinal membrane function according to baseline glucose exposure, patients using 1.36% only (\square), 2.27% or 3.86% (\bullet). As indicated in Figure 1, data points represent paired mean values (\pm SE) for patients remaining throughout the study that move from left to right at baseline, 12 and 24 months. (For longitudinal paired statistics and mean values for all patients at each time point, see Table 3).

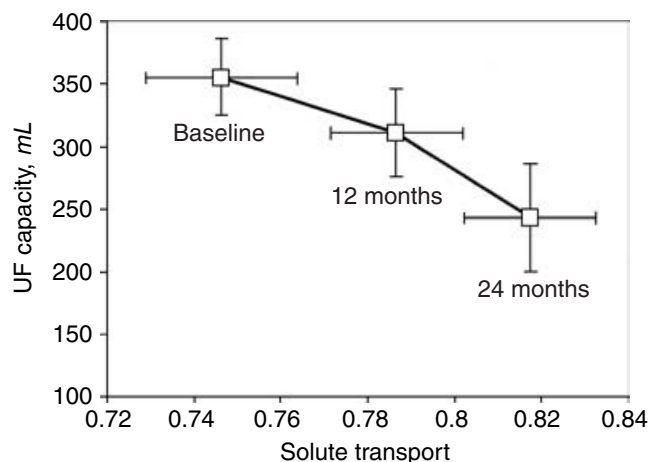


Fig. 1 Longitudinal membrane function for the whole patient cohort. Each data point represents the mean values (\pm SE) for the patients who remained in the study for the full two years. (For longitudinal paired statistics and mean values for all patients at each time point, see Table 3).

patients stopped using it. There were no significant differences between any of the groups or time periods in the peritonitis rate throughout the study.

Table 3 (for all patients at each time point) and Figures 1 to 4 (paired data only) summarize the actual membrane characteristics at baseline, 12, and 24 months, again for the above subgroupings, as well as for the patient group as a whole. It can be seen that baseline membrane function for those using icodextrin from start of the study was different, with higher solute transport and reduced ultrafiltration capacity when compared to those not using this product. There were no differences in membrane function according to glucose usage at baseline. For the patient group as a whole, there was a significant increase

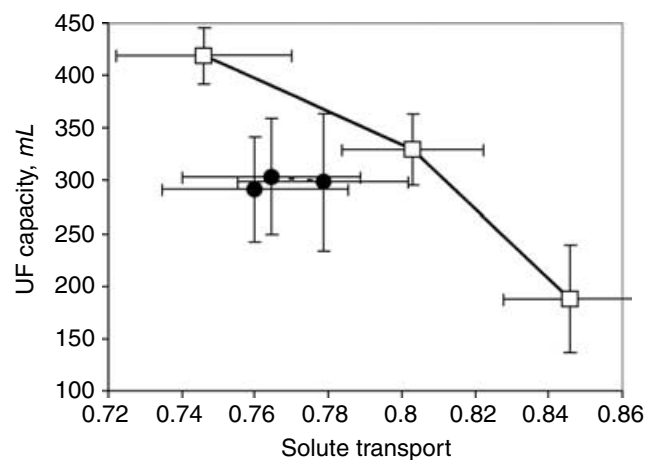


Fig. 3 Longitudinal membrane function according to baseline use of icodextrin (\bullet) or no icodextrin (\square). As indicated in Figure 1, data points represent paired mean values (\pm SE) for patients remaining throughout the study that move from left to right at baseline, 12 and 24 months. (For longitudinal paired statistics and mean values for all patients at each time point, see Table 3).

in solute transport during the course of the study that was already apparent by one year. Ultrafiltration capacity decreased during the study and, as can be seen in Figure 1, this was especially marked during the second year, where the data points represent values for the paired data only. When patients were divided according to their baseline glucose concentration (Table 3, Fig. 2), both groups had an increase in solute transport, although this was more marked and occurred earlier in the patients using $\geq 2.27\%$ solutions. This group also had a significant fall in ultrafiltration capacity by 24 months. Longitudinal changes in membrane function were least apparent in the patients

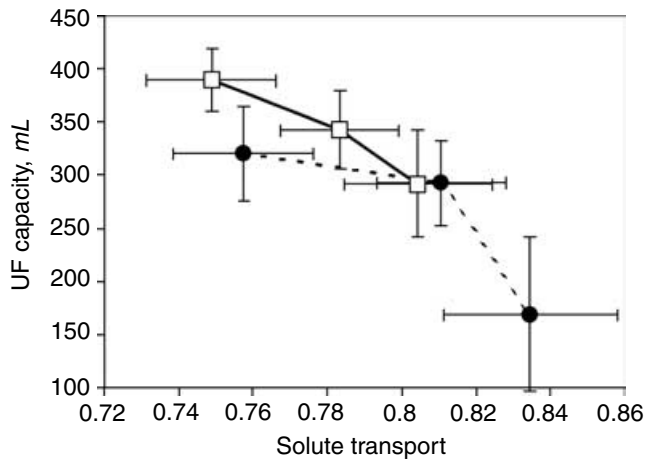


Fig. 4. Longitudinal membrane function according to whether patients experienced no peritonitis (□) or one or more episodes (●). As indicated in Figure 1, data points represent paired mean values (\pm SE) for patients remaining throughout the study that move from left to right at baseline, 12 and 24 months. Significant changes longitudinal changes occur in both groups, and appear more rapid and severe in the peritonitis group, but between group comparisons are not statistically significant.

using icodextrin from the start of the study (Table 3, Fig. 3). They had no changes in ultrafiltration capacity, and a relatively small but significant increase in solute transport, such that their mean value was less than their comparator group at 12 months—the inverse of the situation at the beginning of the study. As might be expected from the above, those patients with regimens that excluded icodextrin but used higher glucose concentrations had the most marked changes in longitudinal membrane function. Solute transport at baseline: 0.74, 24 months: 0.84, $P < 0.001$, and ultrafiltration capacity at baseline: 437 mL, 24 months: 196 mL, $P = 0.006$. In the converse group (i.e., icodextrin and 1.36% glucose only), membrane function was unaltered, solute transport at baseline: 0.72, 24 months: 0.73, NS, and ultrafiltration capacity at baseline: 405 mL, 24 months: 414 mL, NS, although numbers were very small.

The influence of peritonitis rate on longitudinal membrane changes was also investigated. When comparing patients who had no peritonitis with those who had at least one episode, it appears that the latter group had more rapid changes in membrane function, but this was not statistically significant (see Fig. 4).

The relationship of these four groupings to changes in achieved daily ultrafiltration was also explored. It can be seen from Table 4 that there was a tendency in all four groups for the daily ultrafiltration volume to be less at the end of the study than at baseline, in keeping with previous analyses. This was more marked, and statistically significant in the groups who had more detrimental changes in membrane function.

Table 4. Proportion of patients whose net achieved daily ultrafiltration increased or decreased between baseline and the end of the study

	Number with increasing daily ultrafiltration during study	Number with decreasing daily ultrafiltration during study	<i>P</i> value ^a
Low glucose group	5 (38%)	8 (62%)	0.55
High glucose group	11 (27%)	29 (73%)	0.002
Icodextrin group	9 (34%)	17 (66%)	0.10
No icodextrin group	7 (26%)	20 (74%)	0.008

^aWilcoxon signed rank test.

DISCUSSION

This is the first detailed description of longitudinal changes in membrane function occurring in functionally anuric patients treated with automated peritoneal dialysis. It is also the largest study describing longitudinal membrane changes in patients using icodextrin. The non-randomized nature of the study design combined with variability in the clinician attempts to reach the pre-agreed ultrafiltration target of 750 mL per day need to be taken into account in interpreting data. Nevertheless, it confirms previous longitudinal studies showing that solute transport increases and ultrafiltration capacity decreases with time on treatment [1, 5, 7, 14], and supports the evidence that hypertonic glucose exposure accelerates this process independently of residual renal function loss. Icodextrin would appear at least to be a safe solution in these circumstances, and potentially seems to be of benefit.

Most studies with sufficient numbers and a prospective design, thus reducing selection bias, have indicated that peritoneal solute transport increases with time on treatment [1, 5, 7, 14]. This is associated with a reduction in the peritoneal ultrafiltration capacity and an increased risk of ultrafiltration failure with time on treatment. The reason for the drop in UF capacity is in part explained by the more rapid absorption of the glucose during the dwell, although there is increasing evidence that the hydraulic conductance of the membrane is also affected due to intrinsic changes in the peritoneal membrane [4, 7]. The observations of the present study support these concepts in that increasing solute transport was associated with an expected fall in ultrafiltration capacity, which tended to be disproportionately large, especially in the second year of the study. In an observational study such as this it is always important to consider that the findings are a function of informative censoring. This is very unlikely to be the explanation of the findings presented here because a reduction in ultrafiltration capacity is more likely to lead to patient withdrawal, especially in view of the study design that encouraged clinicians to achieve a minimum daily ultrafiltration. Previous analysis of this study showed that patients not achieving >750

mL of daily ultrafiltration at baseline had a significantly higher death rate, were less likely to achieve target ultrafiltration throughout the study, and had worse peritoneal ultrafiltration capacity (but not solute transport) at baseline. If anything, therefore, this observational study has underestimated the severity of membrane changes with time because patients with the worst ultrafiltration capacity will have left the study earlier.

Compared to other longitudinal studies of membrane function, the changes observed here appeared to be more rapid than might be anticipated. This may reflect two things: first, the fact that most patients had been on renal replacement for some time, typically more than three years, and thus had time to acquire membrane damage. Their average peritoneal transport was relatively high at the start of the study and uremia itself might contribute to changes in the peritoneal membrane. Second, APD is a treatment associated with use of larger dialysate volumes over the 24-hour period and shorter exchanges of dialysate, resulting in more frequent changes in intraperitoneal pH and greater exposure to lactate, hypertonic glucose, and GDPs.

The principle difficulty in demonstrating a link between glucose exposure and membrane function changes in previous observational studies has been that of sorting out cause and effect. Clearly, worse membrane function dictates the use of more hypertonic glucose. Equally, if the patient has lost residual renal function, then more ultrafiltration will be required. The demonstration, in either selected [9] or unselected patients [5], that increased use of hypertonic glucose precedes changes in membrane function go some way toward addressing the first of these concerns, but the increased use of glucose in these circumstances was due to loss in residual renal function. This still leaves the criticism that membrane change was driven by progressive uremia, possibly due to associated membrane inflammation [15], rather than exposure to glucose itself, or its harmful associates, such as GDPs. The importance of the present study is that residual renal function is eliminated as a confounding factor, and patients were treated to a common standard in terms of small solute clearance. In comparing the groups avoiding or using hypertonic glucose at the start of the study, there are no clear differences at baseline, and the relative proportion in each group remained in the study at each of the six monthly time points, again making informative censoring an unlikely explanation of the differences in membrane function that were observed. As with previous studies, exposure to higher concentrations of glucose appears to be associated with accelerated changes in membrane function, although it remains possible that some unidentified but causative selection factor is associated with the use of higher glucose concentrations at baseline in this study.

Patients using icodextrin at the start of the study had less marked changes in longitudinal membrane function

when compared to those who were not. This difference appears to be independent of age, treatment time, or peritonitis during the study period, and occurred despite the fact that they had worse membrane function at the beginning, an observation compatible with the appropriate clinical use of this product [16]. This group of patients was more likely to be diabetic, again reflecting appropriate clinical practice. There is no reason to think that diabetics are less prone to worsening changes in membrane function. If anything, patients with multiple comorbidities, frequently diabetic, have more marked changes in membrane function [17]. In the absence of any other explanation this study would suggest that icodextrin is beneficial under these circumstances. There is some debate as to the relative benefits of icodextrin in terms of its biocompatibility, although on balance its properties are favorable. It is iso-osmolar with plasma, but has a relatively low pH of 5.1. It avoids the use of glucose, and contains reduced levels of GDPs compared to conventional solutions [18, 19]. Furthermore, it possibly enhances peritoneal removal of advanced glycation end products [20], and both in vivo and ex vivo studies of cellular toxicity have generally been favorable [21]. There has been concern that its use is associated with sterile or allergic peritonitis, although this was not apparent in this study [22]. Some concerns have been raised regarding dysplastic change in mesothelial cells associated with lipid peroxidation in animal models of icodextrin exposure, although the relevance of these findings remains unclear, and have not yet been observed in the human, where there is no intraperitoneal amylase [23]. Bearing in mind the nonrandomized nature of this study and, thus, the potential for unmeasured confounding effects, it would appear that the use of icodextrin in anuric APD patients is supported by these observations of relatively preserved membrane function in addition to other clinical indications for its use.

CONCLUSION

Finally, we were interested to see if the variable changes in membrane function according to prescription translated into differences in achieved daily ultrafiltration. One of the important findings of EAPOS was a modest but highly significant fall in achieved ultrafiltration during the course of the study that cannot be explained by informative censoring, reduced use of hypertonic glucose, or icodextrin [10]. This trend was seen in each of the subgroups analyzed but was proportionately more likely and more statistically significant in either those using more hypertonic glucose or not using icodextrin. It would seem, therefore, that these changes in membrane function are more than of simple theoretical concern; rather that they may lead either to changes in fluid status or a need for more strict fluid restriction in APD patients with time on treatment. There is clearly a need for longitudinal studies

of the newer biocompatible dialysis solutions in APD patients to establish their role in membrane preservation.

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APPENDIX

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REFERENCES

- HEIMBURGER O, WANG T, LINDHOLM B: Alterations in water and solute transport with time on peritoneal dialysis. *Perit Dial Int* 19(Suppl 2):S83-90, 1999
- DAVIES SJ, PHILLIPS L, GRIFFITHS AM, et al: What really happens to people on long-term peritoneal dialysis? *Kidney Int* 54:2207-2217, 1998
- HEIMBURGER O, WANIEWSKI J, WERYNSKI A, et al: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kidney Int* 38:495-506, 1990
- SMIT W, SCHOUTEN N, VAN DEN BERG JW, et al: Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis: A cross-sectional study. *Perit Dial Int* 24:562-570, 2004
- DAVIES SJ: Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int* 67:, 2004 (in press)
- SELGAS R, BAJO MA, FERNANDEZ-REYES MJ, et al: An analysis of adequacy of dialysis in a selected population on CAPD over 3 years: The influence of urea and creatinine kinetics. Functional longevity of the human peritoneum: How long is continuous peritoneal dialysis possible? Results of a prospective medium long-term study. *Am J Kidney Dis* 23:64-73, 1994
- DAVIES SJ, BRYAN J, PHILLIPS L, RUSSELL GI: Longitudinal changes in peritoneal kinetics: The effects of peritoneal dialysis and peritonitis. *Nephrol Dial Transplant* 11:498-506, 1996
- WILLIAMS JD, CRAIG KJ, TOPLEY N, et al: Morphologic changes in the peritoneal membrane of patients with renal disease. *J Am Soc Nephrol* 13:470-479, 2002
- DAVIES SJ, PHILLIPS L, NAISH PF, RUSSELL GI: Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol* 12:1046-1051, 2001
- BROWN EA, DAVIES SJ, RUTHERFORD P, et al: Survival of functionally anuric patients on automated peritoneal dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 14:2948-2957, 2003
- BROWN EA, DAVIES SJ, HEIMBURGER O, et al: Adequacy targets can be met in anuric patients by automated peritoneal dialysis: Baseline data from EAPOS. *Perit Dial Int* 21:S133-137, 2001
- TWARDOWSKI ZJ, NOLPH KD, KHANNA R, et al: Peritoneal Equilibration Test. *Perit Dial Bull* 7:138-147, 1987
- DAVIES SJ: Assessment of comorbidity in peritoneal dialysis patients. *Contrib Nephrol* 140:98-103, 2003
- STRUIJK DG, KREDIET RT, KOOMEN GCM, et al: A prospective study of peritoneal transport in CAPD patients. *Kidney Int* 45:1739-1744, 1994
- CHUNG SH, HEIMBURGER O, STENVINKEL P, et al: Influence of peritoneal transport rate, inflammation, and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. *Perit Dial Int* 23:174-183, 2003
- WILKIE ME, PLANT MJ, EDWARDS L, BROWN CB: Icodextrin 7.5% dialysate solution (glucose polymer) in patients with ultrafiltration failure: Extension of CAPD technique survival. *Perit Dial Int* 17:84-87, 1997
- DAVIES SJ, PHILLIPS L, NAISH PF, RUSSELL G: Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival. *Nephrol Dial Transplant* 17:1085-1092, 2002
- BARRE DE, CHEN C, COOKER L, MOBERLY JB: Decreased in vitro formation of AGEs with extraneal solution compared to dextrose-containing peritoneal dialysis solutions. *Adv Perit Dial* 15:12-16, 1999
- COOKER LA, HOLMES CJ, HOFF CM: Biocompatibility of icodextrin. *Kidney Int* (Suppl):S34-45, 2002
- UEDA Y, MIYATA T, GOFFIN E, et al: Effect of dwell time on carbonyl stress using icodextrin and amino acid peritoneal dialysis fluids. *Kidney Int* 58:2518-2524, 2000
- POSTHUMA N, TER WEE PM, DONKER AJ, et al: Assessment of the effectiveness, safety, and biocompatibility of icodextrin in automated peritoneal dialysis. The Dextrin in APD in Amsterdam (DIANA) Group. *Perit Dial Int* 20:S106-113, 2000
- TINTILLIER M, POCHEM JM, CHRISTOPHE JL, et al: Transient sterile chemical peritonitis with icodextrin: Clinical presentation, prevalence, and literature review. *Perit Dial Int* 22:534-537, 2002
- GOTLOIB L, WAJSBROT V, SHOSTAK A: Mesothelial dysplastic changes and lipid peroxidation induced by 7.5% icodextrin. *Nephron* 92:142-155, 2002