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Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients

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Background. Time on treatment is associated with a greater risk of impaired ultrafiltration (UF) in peritoneal dialysis (PD) patients. In addition to increasing solute transport, a potentially treatable cause of impaired ultrafiltration, cross-sectional studies suggest that there is also reduced osmotic conductance of the membrane. If this were the case then it would be expected that the UF capacity for a given rate of solute transport would change with time. The purpose of this analysis was to establish how solute transport and UF capacity change relative to one another with time on therapy.

Methods. Membrane function, using a standard peritoneal equilibration test, was measured at least annually in a well-characterized, single-center observational cohort of PD patients between 1990 and 2003. Demography included age, gender, original cause of renal failure, body surface area (BSA), validated comorbidity score, residual urine volume and urea clearances, peritoneal urea clearances, and plasma albumin.

Results. Data from 574 new PD patients were available for analysis. Independent demographic factors associated with higher solute transport at baseline were male gender and higher residual urine volume. Throughout time on therapy there was a negative relationship between solute transport and UF capacity and a significant increase and decrease in these parameters, respectively. During the first 12 months of treatment, the increase in solute transport was not associated with the expected fall in UF capacity, a phenomenon that was not explained by informative censoring, but was associated with an increased, albeit weak, correlation with BSA. In contrast, later in treatment there was a disproportionate fall in UF capacity, more accelerated in patients developing UF failure. Early exposure to higher intraperitoneal glucose concentrations, in the context of more comorbidity and relative lack of residual renal function, was associated with more rapid deterioration in membrane function.

Conclusion. Despite a causal link between solute transport and UF capacity of the membrane, due to the effect of the former on the osmotic gradient, there is evidence of their longitudinal dissociation. This implies a change in the structure-function relationship with time on treatment that can, to some extent, be predicted from clinical factors present within the first year of treatment. Dialysis-induced membrane injury must involve at least two processes, for example, increased vascular surface area contact with dialysate combined with changes in hydraulic conductance due to scarring of the vessels and interstitium.

Key words: peritoneal equilibration test, glucose exposure, comorbidity, ultrafiltration failure.

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Impaired peritoneal removal of salt and water, especially in functionally anuric patients, is an important cause of reduced patient and technique survival in peritoneal dialysis (PD) patients [1–3]. Until recently this problem was most clearly identified in continuous ambulatory peritoneal dialysis (CAPD) patients with high peritoneal solute transport characteristics [4–6]. High transport results in impaired ultrafiltration (UF) due to the more rapid absorption of glucose and earlier loss of the osmotic driving force for fluid transport across the peritoneal membrane. This problem can be largely avoided, however, by the use of automated peritoneal dialysis (APD) to enable shortening of dwell length to prevent fluid reabsorption [3, 7], and by using polyglucose solutions during the long dwell period, where they will result in sustained ultrafiltration and improvement in fluid status [8, 9]. Despite these clinical tools, however, there is still evidence that adequate fluid removal remains a clinical problem [3].

Cross-sectional studies have consistently shown that there appears to be more than one mechanism underlying ultrafiltration failure [10, 11]. While high small solute transport remains a common cause, these studies also suggest that the achieved ultrafiltration for a given osmotic gradient appears to be worse, even when other mechanisms, such as fluid reabsorption, are taken into account [12]. This reduction in osmotic conductance of the peritoneum will result in a relative fall in the ultrafiltration capacity for a given level of solute transport, both of which can be measured easily in PD patients by employing the Peritoneal Equilibration Test (PET), as described by Twardowski [13]. The purpose of the present study was to show how these two measures of membrane function evolve longitudinally with time on treatment in a large,

single-center cohort with significant numbers of patients completing up to 7 years of continuous therapy. Specifically, the relationship between these 2 parameters was analyzed to establish if it changes with time on treatment, as would be predicted from the cross-sectional studies, and, if possible, to identify risk factors for the evolution of membrane failure.

METHODS

Study design and patients studied

This was a prospective, single-center cohort study of consecutive new patients commencing peritoneal dialysis from January 1990 until the data were censored in November 2003. Data were collected within the first month of treatment, and then usually at 6 monthly intervals unless prevented by intercurrent illness or subject availability. Data included baseline demography, cause of renal failure, comorbidity, residual renal urine volume and solute clearance, peritoneal solute clearance, and membrane function using the PET. The reason for discontinuing PD was also noted and classified, as described previously [14].

The PD population was previously censored in 1995 and 1998, at which time survival analyses and descriptions of longitudinal membrane function were described and published [4, 14]. Between 1990 and 1995 patients were treated with standard CAPD (4 × 2L), with no attempt to increase dialysis dose in response to lost residual renal function. Between 1995 and 1998, patients who had become malnourished on peritoneal dialysis had an increase in delivered peritoneal Kt/V of 25%, resulting in an achieved increase of 18% [15]. Since 1998, an increasing proportion of patients were treated with APD when anuric to achieve clearances (target creatinine clearance of 60L/week/1.73m^2), as described in the European Automated Peritoneal Dialysis Outcome Study [3, 16], and icodextrin was used in patients with solute transport >0.64 with increasing frequency. The relevance of these differences in prescription practice is their influence on peritoneal glucose exposure (see below). With a handful of exceptions, all patients were treated throughout with lactate-buffered (40 mmol), pH 5.2, conventional dialysis solutions.

Demographic and comorbidity data

Comorbidity was documented as described previously and validated by other prospective studies [17–19]. Briefly, 7 comorbid domains are considered, including noncutaneous malignancy, ischemic heart disease, peripheral vascular disease (including cerebro- and renovascular), left ventricular dysfunction (moderate to severe hypokinesia on echocardiogram), diabetes mellitus, systemic collagen vascular disease, and any other condition known to reduce life expectancy. The comorbid score for each patient is simply the number of these domains affected, giving a theoretical maximum of 7 (although >5 has not been observed in our patients). The grade of comorbidity is derived directly from this score. Grade 0 (low risk) is a zero score, grade 1 (medium risk) is a score of 1 or 2, and grade 2 (high risk) a cumulative score of 3 or more.

Measures of solute clearance, membrane function, blood biochemistry, and glucose exposure

Dialysis dose and residual renal function (RRF), peritoneal solute transport, and plasma albumin were measured at baseline and every 6 months while the patients remained on PD as described previously [14]. Briefly, the dialysis dose and RRF was calculated as the weekly Kt/V_{urea} from the 24-hour urinary and dialysate clearance by direct measurement of urea in urine and each dialysate exchange. The volume of distribution for urea was calculated from the Watson formula. The PET was used to measure peritoneal solute transport and ultrafiltration capacity [13]. Briefly, a standard 4-hour dwell period was used (first exchange of the day), using a 2.27% glucose concentration 2-L volume exchange. The patient used their usual overnight dialysis regimen, and both the overnight and test drainage volumes were measured. The dialysate:plasma ratio of creatinine at the completion of the 4-hour dwell period (D/P_{creat}) was used as the estimate of low-molecular-weight solute transport. Using this method, the CV for measurements performed 6 months apart is ~10% [20]. Net ultrafiltration (UF capacity) was calculated from the drained volume, weighed after the flush for the next dialysis exchange was performed. Plasma and dialysate concentrations of urea, creatinine, and glucose were determined on an automated discrete random access analyzer (DAX 72; Bayer Instruments, Basingstoke, UK). Plasma albumin levels were measured using the Bromocresol green method. Peritoneal glucose exposure was calculated by summing the number of exchanges performed multiplied by their concentration. Thus, a patient using 4 × 2L exchanges of 1.36% glucose would obtain a value of 5.44, whereas an APD patient using 6 exchanges, 3 of 1.36%, 2 of 2.27%, and one of 3.86% would be 12.28. This approach to quantifying glucose exposure takes into account both the amount (exchange number) and the concentration differences, but not the difference that might be attributed to exchange length (e.g., 4 overnight exchanges in APD may not be equivalent to the same 4 exchanges delivered over 24 hours in CAPD). However, the numbers of patients on APD during the first year of therapy in this study cohort were very small (baseline $N = 9$, at 6 months $N = 22$, and 12 months $N = 18$), making this very unlikely to be a significant confounding factor.

Table 1. Baseline patient demography

	Male	Female	All patients
Number	317 (55%)	257 (45%)	574
Age in years	58.8 (16.2)	56.6 (15.9)	57.8 (16.1)
Proportion diabetic	19%	20%	20%
Comorbidity score	0.98 (1.1)	0.93 (1.06)	0.96 (1.1)
Comorbidity grade	0.67 (0.69)	0.64 (0.64)	0.66 (0.67)
Plasma albumin *g/L*	36.4 (5.5)	36.8 (5.4)	36.6 (5.5)
Urine volume *mL*	1086 (779)[a]	795 (614)	954 (722)
Weight *kg*	72.7 (15.2)[a]	63.6 (15.7)	68.6 (16.1)
Body surface area m^2	1.82 (0.28)[a]	1.64 (0.22)	1.74 (0.27)
Residual Kt/V	1.16 (1.04)	0.99 (1.08)	1.17 (1.02)
Total Kt/V	2.6 (1.02)	3.4 (1.06)	2.9 (1.11)
Solute transport (D/P_{creat} at 4 hours)	0.67 (0.12)[a]	0.63 (0.12)	0.65 (0.13)
Ultrafiltration capacity *mL*	418 (273)[b]	472 (261)	443 (269)

Different between genders, [a] $P < 0.001$, [b] $P = 0.034$.

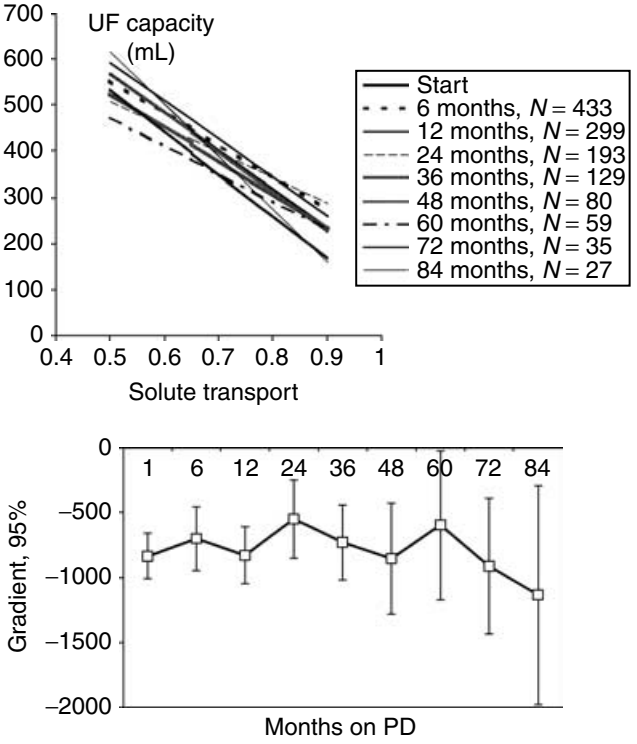

Fig. 1. The upper panel shows the linear best-line fit for the relationship between solute transport and UF capacity at each time-point during the study. The gradients (±95% CI), shown in the lower panel are remarkably similar, but tend to become steeper at 6 and 7 years.

Statistical analysis

At baseline, 6, and 12 months data are expressed as mean values ± SD. After this time period, all patients had measures of membrane function performed at least yearly, in many cases, every 6 months, and in some cases more frequently. If a patient had more than one PET in a 12-month period, this was averaged on an individual basis and then the data expressed for the whole population on an annual basis. Between group comparisons of patients was made using unpaired *t* tests [except when multiple groups were compared, when a one-way analysis of variance (ANOVA) was used], whereas longitudinal changes in membrane function were made with paired *t* tests. Linear correlations were performed using Pearson's test, having first explored the data to check that the relationship was not better described by a nonlinear function. When more that one linear correlation was found, then dominant relationships were explored using multiple regression. Statistical analyses were performed using SPSS, version 12 (Chicago, IL, USA).

RESULTS

Patient demography and baseline membrane function

The demographic details of the 574 patients included in this analysis are summarized in Table 1. The numbers of patients at each time point on PD are shown in the legend of Figure 1. Primary diagnoses of renal failure were glomerulonephritis 22.5%, small kidneys/unknown 19%, diabetic nephropathy 15.8%, reflux nephropathy/interstitial nephritis 8.9%, renovascular disease 7.5%, hypertensive nephropathy 7%, polycystic renal disease 7%, surgical/obstructive 6.3%, myeloma 2.3%, and other 3.2%. Comparison of baseline membrane function between these diagnostic categories revealed no significant differences, with the exception of those with polycystic kidney disease, in whom solute transport was significantly lower (mean value 0.577) compared to most groups (overall mean 0.651). These patients had the least comorbidity of any diagnostic group ($P = 0.001$) and the highest body surface area (BSA, P = NS). It can be seen (Table 1) that men had significantly higher solute transport than women, with an associated reduction in ultrafiltration capacity. Men had a larger urine volume, although when corrected for weight, this was not significant, and the normalized residual urea clearances were not different. At baseline, a number of factors correlated, albeit weakly, with peritoneal solute transport, including age ($r = 0.15$, $P = 0.002$), grade of comorbidity ($r = 0.1$, $P = 0.038$), residual urine volume ($r = 0.11$, $P = 0.018$), and plasma albumin ($r = -0.42$, $P < 0.001$), but not weight, height, BSA, or either total or residual renal urea clearance. On multivariate analysis (see Table 2) only albumin, gender, and residual urine volume remained significant independent covariates, accounting for just 21% of the variability. The only independent covariate to correlate (inversely) with UF capacity at baseline was the peritoneal solute transport.

Cross-sectional relationship of membrane parameters

At each of the time points on treatment (i.e., baseline, every 6 months, and then yearly over a total of 7 years) there was a consistent inverse correlation between solute transport and ultrafiltration capacity. The

Table 2. Multivariate regression of factors associated with baseline peritoneal solute transport

	Standardized β coefficient	*t*	*P* value
Model constant		17.74	<0.001
Age (transport increases with age)	0.076	1.45	0.15
Grade of comorbidity	−0.046	−0.921	0.358
Baseline urine volume (higher transport associated with higher urine volume)	0.148	3.19	0.002
Gender (transport increased in men)	−0.096	−2.1	0.036
Baseline plasma albumin (higher transport associated with lower plasma albumin)	−0.422	−8.9	<0.001

ANOVA for model $P < 0.001$, $R^2 = 0.215$.

Pearson correlation coefficient for this relationship was –0.401 at baseline and varied between –0.24 and –0.51, but was always statistically significant, the *P* value depending on the number of observations, but ranging between 0.042 and <0.0001. The linear regression lines obtained at each time point are summarized in Figure 1, where it can be seen that the gradient remains stable for the first few years of treatment, but appears steeper after 5 years (not significant). In each case, fitting of the data with non-linear functions did not improve the goodness of fit.

Longitudinal relationship of membrane parameters

Solute transport increased significantly in the 6 months following commencement of peritoneal dialysis, a trend that continued throughout the course of treatment (see Fig. 2). Conversely, ultrafiltration capacity declined with time on treatment, but only after 12 months on therapy. When the longitudinal relationship between changing solute transport and UF capacity is plotted together (see Fig. 3), on the background of the relationship between these parameters determined from cross-sectional analysis above (as shown in Fig. 1), it can be seen that their relative change to each other in time is not exactly as predicted. The early increase in solute transport is not associated with a fall in UF capacity as anticipated. Later on, the fall in UF capacity is disproportionately large for a given rise in solute transport. This would suggest that the earlier changes in membrane function differ qualitatively from those occurring later in treatment.

Analysis of early changes in membrane function

Further analysis of factors potentially associated with the early increase in solute transport was undertaken. In contrast to baseline, at 12 months there was a weak but significant correlation between solute transport and BSA ($r = 0.14$, $P = 0.025$). On multiple regression analysis (see Table 3), this was not an independent covariate if gender was kept in the model. If gender was dropped from the model, BSA remained a significant positive correlate ($P = 0.009$), with very little change in the overall predictive power of the model ($R^2 = 0.11$). Another important difference between the models described in Tables 2 and 3 is that by 12 months, higher solute transport is associated with a lower urine volume, whereas the inverse was

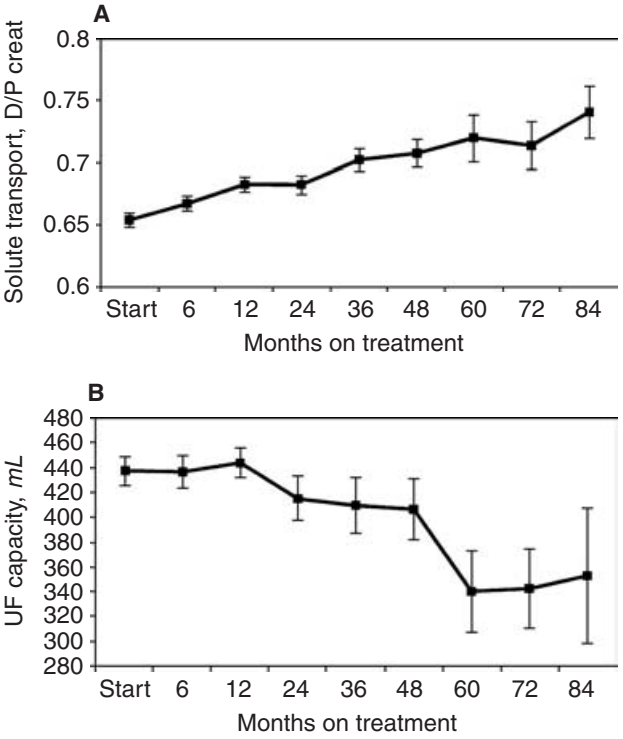

Fig. 2. Longitudinal changes in solute transport (*A*) and UF capacity (*B*) for the whole cohort. A significant increase in solute transport was seen by 6 months and for each subsequent time point, $P = 0.008$ to < 0.001. A reduction in UF capacity occurred at 24 months and beyond, $P = 0.047$ to <0.001. For numbers of patients at each time point, see legend to Figure 1.

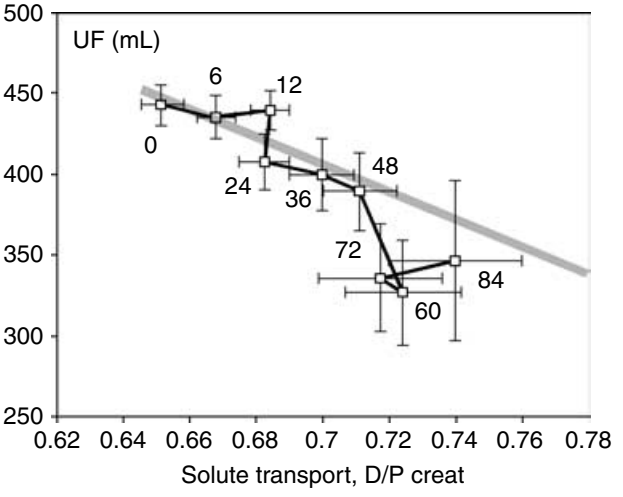

Fig. 3. The actual mean values (SE bars) for solute transport and UF capacity at each time point (baseline, 6 months, and then yearly over 7 years, indicated as months) are shown superimposed upon the mean linear regression line (see Figure 1 for individual lines and numbers of patients at each time point). There is relative preservation of UF capacity early during treatment that later reduces disproportionately.

Table 3. Multivariate regression of factors associated with peritoneal solute transport measured at 12 months

	Standardized β coefficient	*t*	*P* value
Model constant		10.5	<0.001
Age (transport increases with age)	0.028	0.4	0.689
Grade of comorbidity	0.057	0.823	0.411
Urine volume at 12 months (higher transport associated with lower urine volume)	−0.139	−2.25	0.025
Gender (transport higher in men)	−0.166	−2.45	0.016
Body surface area	0.091	1.35	0.18
Plasma albumin at 12 months (increased transport associated with lower plasma albumin)	−0.233	−3.7	0.001

ANOVA for model $P < 0.001$, $R^2 = 0.136$.

true for baseline solute transport. The weak relationship of solute transport to grade of comorbidity was present at 6 and 12 months, reflecting the differences at baseline, such that solute transport appears to increase in parallel independent of the comorbid load.

Patients were divided into 2 groups according to whether they had a significant increase (Δ D/P$_{creat}$ $\geq$0.1) or decrease (Δ D/P$_{creat}$ ≥ -0.1) in solute transport during the first year of treatment. Defined in this way, 3 times as many patients experienced a significant rise in transport ($N = 91$) compared to those in whom it was reduced ($N = 30$), whereas the relative proportions having an increase or decrease in transport of <0.1 were almost identical. In comparing these 2 groups there was no difference in age, gender split, patient size, prevalence of diabetes, grade, or score of comorbidity at baseline (see Table 4). Those experiencing an increase in solute transport had significantly higher plasma albumin and lower residual urine volume at baseline, and, as would be expected, had lower transport and higher UF capacity at the start of treatment and vice versa. Indeed the 2 groups appear to swap over at 6 months, at which time they have identical mean solute transport and UF capacities, suggesting that the relationship between these parameters is not fundamentally different in these 2 patients groups. The differences in albumin, therefore, are likely to reflect the phenomenon of regression to mean, as there is a negative relationship between solute transport and plasma albumin at each time point due to increased peritoneal protein clearance. Multiple regression, excluding albumin because of this problem with autocorrelation, but including glucose exposure, indicated that only one factor, baseline urine volume, was predictive of changes in solute transport, such that lower volume was associated with an increase ($P = 0.004$), although the overall significance of the model was borderline (ANOVA, $P = 0.07$) with an R^2 value of 0.038.

Because the relative preservation of ultrafiltration compared to the changes in solute transport do not appear to be related to the early changes in membrane function, the possibility that it was due to informative censoring was considered. If patients with relatively poor UF capacity for a given solute transport are more likely to leave PD due to either death or transfer, then this could result in an apparent improvement in UF capacity; 14.5% of patients left PD during the first 12 months of treatment due either to death or technical failure. Compared to those remaining on PD, baseline UF capacity was identical (443.2 vs. 442.7 mL), despite slightly higher solute transport characteristics on the early failure group (0.688 vs. 0.64, $P = 0.01$), commensurate with the apparent link with age and comorbidity. If anything, therefore, those patients leaving the dialysis program due to death or technique failure during the first year of treatment had relatively higher UF capacity than would be expected for their solute transport, indicating that preservation of UF capacity at 12 months was not simply a function of informative censoring.

Table 4. Comparison between patients with an early and significant increase or decrease in solute transport of clinical parameters measured at baseline, 6, and 12 months

	Increase in solute transport $N = 91$	Decrease in solute transport $N = 30$
Age *years*	56.1 ± 16.8	56.6 ± 17.3
Height *cm*	163.3 ± 19.6	161.1 ± 11.2
Grade of comorbidity	0.64 ± 0.62	0.59 ± 0.73
Residual Kt/V$_{urea}$ (baseline)	0.97 ± 0.77	1.33 ± 0.97[a]
Residual Kt/V$_{urea}$ (6 months)	0.66 ± 0.69	0.83 ± 1.0
Residual Kt/V$_{urea}$ (12 months)	0.52 ± 0.69	0.75 ± 1.0
Total Kt/V$_{urea}$ (baseline)	2.82 ± 0.9	3.10 ± 1.0
Total Kt/V$_{urea}$ (6 months)	2.52 ± 0.84	2.75 ± 0.93
Total Kt/V$_{urea}$ (12 months)	2.32 ± 0.91	2.72 ± 1.1
Solute transport (baseline)	0.54 ± 0.09	0.77 ± 0.08[f]
Solute transport (6 months)	0.65 ± 0.1	0.68 ± 0.1
Solute transport (12 months)	0.71 ± 0.1	0.62 ± 0.09[f]
UF capacity (baseline) *mL*	532 ± 209	267 ± 307[f]
UF capacity (6 months) *mL*	411 ± 196	404 ± 237
UF capacity (12 months) *mL*	394 ± 241	463 ± 230
Plasma albumin (baseline) *g/L*	38.5 ± 5.0	35.7 ± 5.5[b]
Plasma albumin (6 months) *g/L*	36.6 ± 4.6	36.7 ± 4.4
Plasma albumin (12 months) *g/L*	36.0 ± 5.1	36.8 ± 4.6
Urine volume (baseline) *mL*	761 ± 512	1134 ± 828[c]
Urine volume (6 months) *mL*	626 ± 562	786 ± 781
Urine volume (12 months) *mL*	540 ± 624	571 ± 794
Average glucose exposure (baseline)	6.51 ± 1.97	7.68 ± 3.2[d]
Average glucose exposure (6 months)	7.78 ± 2.6	6.98 ± 1.7
Average glucose exposure (12 months)	8.12 ± 2.7	7.09 ± 2.06[e]

Between group unpaired *t* test: [a]$P = 0.059$; [b]$P < 0.02$; [c]$P = 0.004$; [d]$P = 0.067$; [e]$P = 0.079$; [f]$P < 0.001$.

Analysis of late changes in membrane function

The disproportionate fall in UF capacity seen later in the course of PD, in particular, beyond 4 years, was more exaggerated in patients who developed ultrafiltration failure. Of the 192 observed technical failures in PD, 48 (25%) had ultrafiltration failure as the primary reason for switching to hemodialysis. It can be seen from

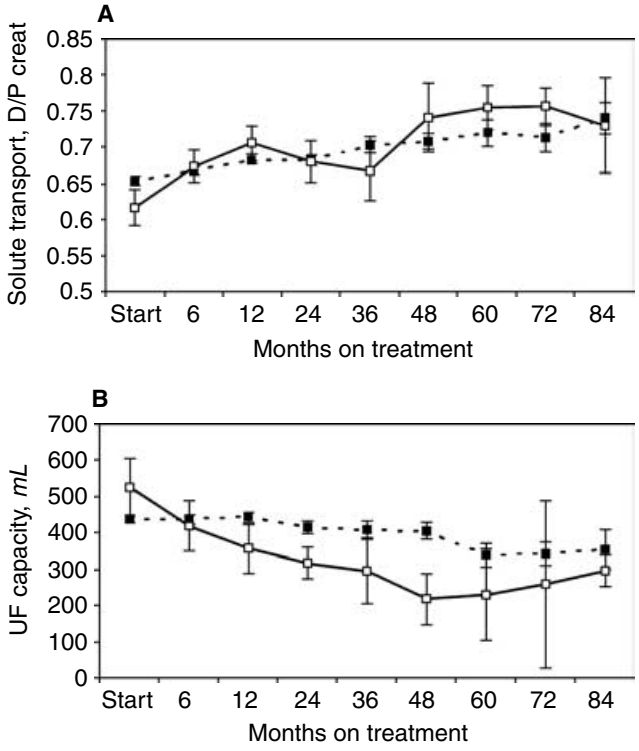

Fig. 4. Longitudinal changes in solute transport (*A*) and UF capacity (*B*) for the patients who subsequently developed UF failure (□) and the remainder of the cohort (■). Despite better membrane function at the start of treatment, the rate of increase in solute transport tends to be faster with significantly worse UF capacity at 24 and 48 months, $P < 0.05$.

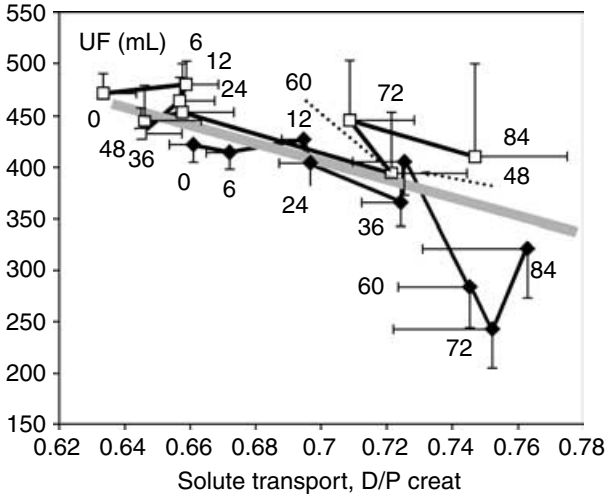

Fig. 5. In this case two lines are plotted, that for patients with low (□) and high (◆) intraperitoneal glucose exposure during the first 12 months of dialysis treatment. At each time point, the latter group has higher solute transport and less UF capacity, but in those exposed to low glucose concentrations, membrane function is stable for the first 4 years of therapy, and UF capacity never becomes disproportionately low. See Figure 3 for description of this graph format.

Figure 4 that these individuals had relatively good membrane function, in particular, UF capacity, on commencing PD compared to their peers, indicating this was an acquired problem with membrane function in the majority of cases. They experienced a similar or more accelerated rise in solute transport with time on treatment, and a disproportionately large fall in UF capacity.

For the whole population, these later changes in membrane function were analyzed according to the average use of glucose during the first year of dialysis therapy. In patients using an average daily cumulative glucose concentration load of 6% or less (which reflects typically a regimen that uses the lowest glucose concentrations throughout the day), membrane function was almost unchanged for the first 4 years of treatment. In contrast, those using higher glucose concentrations had a much more rapid increase in solute transport that was associated with a disproportionate fall in the UF capacity (see Fig. 5). At baseline, these patients had higher solute transport (0.66 vs. 0.63, $P = 0.025$) and worse UF capacity (421 vs. 471 mL, $P = 0.054$), were older (59.9 vs. 53.2, $P < 0.001$), had more comorbid conditions (1.1 vs. 0.67, $P < 0.001$) and, most important of all, less residual urine volume (832 vs. 1138 mL, $P < 0.001$) that persisted over the next 5 years (typically, half the urine volume at each time point).

DISCUSSION

The purpose of this analysis was to provide a comprehensive description of longitudinal changes in 2 easily measured aspects of membrane function, solute transport and ultrafiltration capacity, concentrating in particular on their changing relationship with time. The previous observations that solute transport tends to increase, and UF capacity decrease, with time on therapy were endorsed [21–23]. However, the relatively large numbers of patients in the study and the prolonged period of follow-up enabled demonstration that the relationship between these 2 parameters changes qualitatively with time on treatment. Early increases in solute transport are not associated with the expected fall in UF capacity, whereas later on, this becomes disproportionate, especially in those individuals with clinical evidence of ultrafiltration failure, or the early use of hypertonic glucose associated with loss of residual renal function.

Baseline membrane function

There is a large degree of variability on peritoneal membrane function at the start of treatment between patients, and yet, it is difficult to see what accounts for this. Despite the inclusion of a number of clinical variables in both univariate and multivariate analysis, only ~20% of the variability in solute transport can be accounted for, and for most variables this is negligible (e.g., age accounts

for about 2%). Some of this might be due to the lack of precision in measuring solute transport, although this is quite reproducible with a coefficient of variation less than 10%. This cannot be said for UF capacity, where the CV is closer to 50% of the net UF volume. This may well explain the lack of correlation between any of the clinical factors, with the exception of the well-described relationship with solute transport. However, it must also be remembered that UF capacity is a measurement that lumps together many aspects of membrane function, including fluid reabsorption by lymphatics and other pathways combined with osmotic conductance of the membrane across both inter- and transcellular pores, none of which are measured in this study.

The finding that solute transport tends to be higher in older patients with more comorbidity is similar to observations made in other population studies [5, 17, 24]. Few studies have included multivariate analysis of this issue, however, and it would appear that when other factors are included, namely, gender, urine volume, and plasma albumin, that they disappear, although age remains important in one large study of Australasian patients [25]. It could be argued that albumin should not be included in this model as it is not a true baseline value, but rather a consequence of starting dialysis, resulting from increased albumin clearance in those with high solute transport. Whether this is included or not, however, the other factors (gender and residual urine volume at baseline) remained significant. The relationship with urine volume was unexpected, and may reflect a tendency to commence PD earlier in patients with worse comorbidity. This may result in a better correlation in the multivariate model than with grade of comorbidity due to the more continuous nature of this covariate. It has, however, been suggested that solute transport is increased due to uremia at baseline, per se, linked perhaps by inflammation [26]. Unfortunately, this study did not include an independent measure of inflammation, such as C-reactive protein (CRP) or interleukin-6 (IL-6).

The observation that men tend to have higher solute transport, independent of age and comorbidity, is best explained by their relatively larger size compared to women. Interestingly, if the initial solute transport is corrected for BSA, then this gender difference completely disappears (0.445 ± 0.83 $D/P_{creatinine}$ ratio/m^2 in men vs. 0.445 ± 0.82 in women). In Australasians, men also tended to have higher transport, although no analysis of BSA was made in this study [25]. Both the 3-pore and distributed models of membrane function predict that the rate of solute transport would be increased when a larger membrane surface area is in contact with dialysate, albeit that it is the effective vascular area rather than the anatomic membrane area that is important. In this context, the observation that the patients with polycystic kidneys have the lowest solute transport but highest mean BSA (1.83 m^2) illustrates the complexity of these associations. They had less comorbidity, which partly explains the low transport, but it may also be that there is relatively less peritoneal contact area with dialysate due to distortion of the peritoneal cavity by the presence of their enlarged kidneys.

Early changes in membrane function

As reported previously, there was an early increase in peritoneal solute transport during the first year of treatment that was already apparent by 6 months [21]. This has not been a universal finding [27], however, and some authors have suggested that the early changes in membrane function reflect a regression to the mean, rather than a clear trend [28]. This study, through its relatively large numbers, indicates that both phenomena are in fact occurring. As indicated above, the reproducibility of this measure means that a change in the D/P creatinine ratio of less than 0.1 cannot be considered as significant. This was confirmed in the present analysis, as patients experiencing a change in ratio of less than 0.1 were equally likely to go in either direction. When the analysis was confined to patients with a larger change (>0.1), then this was 3 times more likely to be an increase. There is, therefore, considerable noise in the data, but a clear tendency to increase transport that will not be apparent in studies of smaller patient numbers.

It is of considerable interest that this early rise in solute transport is not associated with a fall in UF capacity. This is not due to lack of study power, as the expected relationship appears after 12 months when patient numbers are smaller. Likewise, it does not appear to be due to informative censoring. The possibility that it was due to inherent differences in membrane function in those patients whose membranes changed significantly during the first year of therapy, in either direction, also seems unlikely because both of these groups experienced appropriate changes in UF capacity for their given alteration in transport status. Rather, it seems to have been a general phenomenon across the whole patient cohort. The finding of a stronger relationship, albeit still a weak one, between transport and body surface area at 12 months, dominated in the multiple regression by gender (a major determinant of BSA), raises the possibility that the area relationship between solute transport and peritoneal contact has become more apparent. It is possible to envisage that an early increase in contact area might result in an increase in ultrafiltration. While a large surface area will increase the rate of loss of the osmotic gradient, it could at the same time increase the ultrafiltration coefficient of the membrane, which is determined by the liquid permeability (Lp) area (S) product, LpS. If Lp was unaffected in the early stages of PD, then an increase in S could result in an increase in LpS that counterbalanced the effect of increased

glucose absorption, giving an overall preservation of osmotic conductance, as has been demonstrated in computer models of membrane function [29].

Late changes in membrane function

In contrast to these early changes, but by the same token, it would appear that later on in the treatment the converse it true (i.e., that there is a relative reduction in osmotic conductance that is disproportionate to the changes in solute transport). This was more exaggerated in patients who subsequently went on to develop clinical ultrafiltration failure, in keeping with cross-sectional studies that have indicated that in addition to high solute transport there is at least one other cause of poor UF capacity [11]. The precise mechanism is unclear, but appears to affect free water transport disproportionately, either by reducing membrane Lp, or by influencing the reflection coefficient for glucose, especially across aquaporins. The current longitudinal study establishes that this is clearly an acquired problem, as these patients had normal, or even better, membrane function at the start of treatment. It is interesting to speculate what these functional changes mean in the context of the recently documented long-term morphologic changes to the peritoneal membrane. In particular, the changes of membrane thickening and vascular sclerosis observed in the Peritoneal Biopsy Registry might be responsible for the disproportionate fall in UF capacity [30].

CONCLUSION

The main risk factors associated with this change in membrane function were already identifiable within the first year of treatment. Increased early exposure of the membrane to glucose was associated with a faster increase in solute transport, even allowing for the higher value at baseline, and almost exclusively with the late disproportionate fall in UF capacity. This is in keeping with previous observations of solute transport [31], including a selected group of long-term PD patients from this cohort published previously [32]. As in this previous report, it is not possible to dissect out the different risk factors for changing membrane function from each other as they coexist. It can be said, however, that in patients who start life on PD with less efficient membranes, who are also older with more comorbidity and, perhaps most importantly, lose their residual renal function early, thus necessitating greater use of hypertonic exchanges, there is a significantly greater risk of developing longitudinal detrimental changes in membrane function. Peritonitis could be added to this list of risk factors, not analyzed in the current study due to its considerable complexity, but previously shown in a subgroup of these patients [21] and in other studies to be a contributory factor [33–35]. This study effectively predates the use of the newer, biocompatible dialysis solutions. It does, however, provide further evidence for their need in hopefully preventing membrane damage, or at least delaying it, in the future.

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