

Mitigating peritoneal membrane characteristics in modern peritoneal dialysis therapy

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Membrane function at the start of peritoneal dialysis (PD) treatment, measured as solute transport rate and ultrafiltration capacity, varies considerably between individuals. Although this can be correlated to clinical factors such as age and body habitus, this accounts for little of the variance seen. It is increasingly clear, however, that this variability in membrane function does impact on clinical outcomes. Specifically, high solute transport increases mortality risk, independent of other known factors such as age, comorbidity, and residual renal function. High solute transport causes earlier loss of the osmotic gradient when a low molecular weight osmolyte such as glucose is used. This will result in an earlier and lower peak in the ultrafiltration achieved combined with a higher fluid absorption rate once the osmotic gradient is lost. It is therefore quite plausible that the worse clinical outcomes associated with high transport reflect less good ultrafiltration, although other explanations must be considered, including higher peritoneal protein losses and a possible association with systemic inflammation. Strategies now exist to mitigate the effects of high transport on fluid removal. These include optimization of the short dwell lengths using automated PD (APD) combined with icodextrin which will result in sustained ultrafiltration and thus prevention of reabsorption in the long dwell. Survival analysis of APD patients, especially in cohorts in which icodextrin has been used, would suggest that high transport status is not a risk factor, although some of these data are only preliminary. In contrast, low ultrafiltration capacity of the membrane seems to be more important in these patients, especially if anuric. Here the best strategy would seem to be prevention as patients who develop low ultrafiltration capacity are not easily treated on PD. Avoiding excessive hypertonic glucose exposure and preserving residual renal function offers the best available approach.

Kidney International (2006) **70**, S76–S83. doi:10.1038/sj.ki.5001920

KEYWORDS: solute transport; ultrafiltration capacity; patient survival; Stoke PD Study; icodextrin; automated peritoneal dialysis (APD)

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Peritoneal dialysis (PD) has led to a sea change in our appreciation of the peritoneal membrane; it has provided us with insights into host defense mechanisms, the control of inflammation, and capillary physiology while performing a job that it never evolved to do. We are also appreciating more and more the impact that the membrane itself has on the success of dialysis treatment. The demonstration of considerable intrinsic variability in membrane function which is linked to variability in clinical outcomes has led to the recognition that membranes with high small solute transport rates and low ultrafiltration capacity are a problem. The design of dialysis regimens and fluids that can mitigate these problems is hopefully translating into improved clinical outcomes. This review will discuss the evidence supporting this logical argument, make a case that better clinical outcomes are achievable and suggest strategies to prevent membrane damage that might occur with time on therapy.

VARIABILITY IN MEMBRANE FUNCTION

We are all indebted to Twardowski for his simple but seminal observation of the variability within a dialysis population of small solute transport rates and ultrafiltration capacity when he put forward the peritoneal equilibration test.¹ This variability in membrane function, which constitutes a two-fold difference in solute transport and a several-fold difference in net ultrafiltration, has been reproduced many times (Figure 1).^{2–4} The peritoneal equilibration test is only a rudimentary description of membrane function, and in particular the measure of ultrafiltration capacity (defined as the amount of ultrafiltration achieved under standard conditions) represents many aspects of membrane function being a lumped parameter.⁵ Nevertheless, it is a simple test to do and as a result there is now enough observational data in the literature to relate membrane function to clinical characteristics. Perhaps surprisingly, it has been difficult to find any strong clinical correlates with membrane function, which means that it is difficult to predict an individual's membrane characteristics before they commence treatment.

Most studies looking at this issue have concentrated on solute transport rather than ultrafiltration capacity; indeed rather annoyingly studies often fail to report data on this aspect of membrane function. The reasons for this are several, but broadly fall into two categories. First, there is no

doubt that the reproducibility of the ultrafiltration measurement is less good (coefficient of variance typically 25%) than for solute transport (coefficient of variance typically <10%). The reasons for this include variability of drainage and sump volume, variability of inflow volume, and probably some true variability in net ultrafiltration that is a function of the balance in Starling's forces, lymphatic reabsorption, and osmotic conductance for the solute, all of which might vary in the short term. Second, there is a perception that solute transport is the important measure, being the primary determinant of ultrafiltration capacity. Certainly, for small osmolytes such as glucose, transport rate will have an important impact on ultrafiltration, as in high transporters there will be more rapid loss of the osmotic gradient. Nevertheless, as can be seen in Figure 1, the amount of variability in ultrafiltration explained by variability in solute transport is only ~18%; even if we allow for the measurement of ultrafiltration capacity being less precise, it is clear that solute transport is only one, albeit important and easily measured aspect of membrane function.^{3,6}

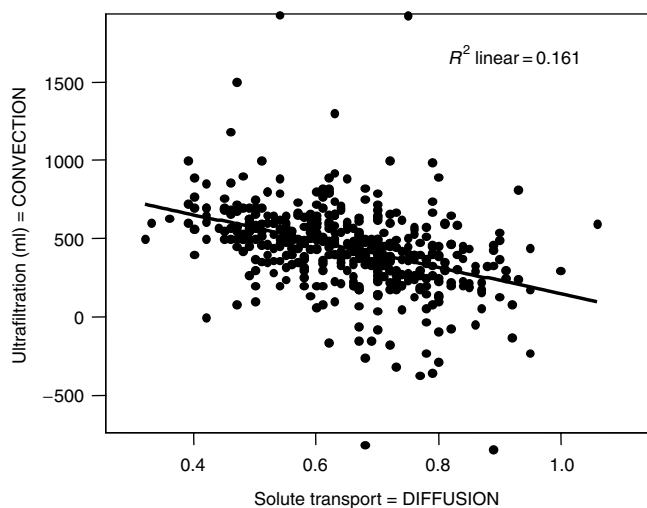


Figure 1 | Solute transport (dialysate:plasma creatinine ratio at 4 h) and ultrafiltration capacity (glucose 2.27%) in 576 consecutive patients commencing PD illustrating the considerable variation in membrane function.³ The regression line indicates the relationship between these two measures of membrane function; high transport is associated with lower ultrafiltration capacity but only accounts for 18% of its variability.

So what are the clinical characteristics that are associated with variability in solute transport at the start of PD? Several studies have looked at this and their findings are summarized in Table 1.^{3,6-10} Before discussing these in detail, two things should be noted. First, in general, although statistically significant relationships are found, they explain relatively little of the variance in solute transport.³ Second, many of the individual correlates disappear on multivariate analysis owing to the fact that they often co-vary with each other. Which one comes out on top sometimes depends on how the multivariate model was constructed and with which different variables. Overall, less than 20% variance in solute transport can be explained. Having said this, looking at Table 1, some patterns do emerge. Men tend to have a larger solute transport rate, which can be accounted for by their higher body surface area. The inverse relationship with body mass index is at first sight surprising until we remember that body surface area and mass index are inversely related. Older age also seems to be associated with higher solute transport that may account for or be due to the tendency for increased comorbidity to be seen in these patients. Finally, race does seem to be important, especially in the Australasian population.⁸ Overall, there is a suggestion that body size and habitus and either age or comorbidity have some effect, albeit modest, on transport status.

MEMBRANE FUNCTION AND CLINICAL OUTCOMES

Concerns that a high peritoneal small solute transport rate might be associated with worse clinical outcomes in PD were first raised in the early 1990s. Initially, relatively small or cross-sectional studies found that high transport was associated with increased peritoneal protein loss and reduced absolute creatinine removal, raising concerns over nutrition.^{11,12} These early studies also found high transport to be associated with more hospital admissions¹² and increased technique failure.¹³ In 1998, the single-center Stoke PD Study^{14,15} and the multicenter CANUSA study,⁷ both prospective cohorts adequately powered to look at mortality, found that high transport was associated with worse patient and technique survival independent of other important predictors, such as age, comorbidity, and residual renal function. Subsequently, a number of other studies have been published which support this observation in either single or

Table 1 | Studies of solute transport in PD

Study	n	Age	Gender	Comorbidity	Race	BMI	BSA	RRF
CAN-USA, Churchill <i>et al.</i> ⁷	606	↑	↑M	↑ diabetic	NS			
Aus-NZ, Rumpsfeld <i>et al.</i> ⁸	3188	↑	(↑M)	(↑ diabetic)	Yes	↓		
UK, Davies ³	574	(↑)	↑M	(↑ CVD)	N/A	NS	(↑)	↑
Madrid, Spain Selgas <i>et al.</i> ⁶	367	NS	NS	NS	N/A			
Korea, Chung <i>et al.</i> ⁹	210	NS	(↑M)	↑ CVD	N/A			
Sweden, Chung <i>et al.</i> ¹⁰	117	NS	NS	NS	N/A		NS	↑
Belgium, Clerbaux <i>et al.</i> ⁵⁵	72	NS	NS	(↑ diabetic) ^a	N/A		↑	NS

BMI, body mass index; BSA, body surface area; CVD, cardiovascular disease; N/A, not applicable; NS, nonsignificant; RRF, residual renal function.

NS, no significant association found when examined for. Associations shown in brackets indicate present on univariate analysis only.

^aIn this study, a positive association was also found with the use of angiotensin-converting enzyme (ACE) inhibitors which may reflect a relationship with comorbidity.

multivariate analysis.^{9,16} A few studies have not found an association; however, in some cases this is likely to be due to being under powered,^{17,18} or an association was found on univariate analysis only¹⁹⁻²¹ or to be associated with morbidity but not mortality.²² Two large studies have failed to find an association; in both cases, there were potential reasons for this, including a largely prevalent patient population,²³ non-standard methods of measuring membrane function, and a non-prospective study design.²⁴ Most recently, analysis from the ANZDATA registry, by far the largest study published to date, has confirmed the association of high transport rates with increased mortality and technique failure.²⁵

It is worth emphasizing that solute transport is a continuous variable, even though it is often discussed as if discrete and categorical – a data presentation device that goes back to Twardowski's original description. This can lead to the erroneous view that the problem is essentially confined to high transport category patients. It is clear from the comparative 2-year mortality figures presented in Table 2 that the differential effect of transport on survival occurs across its whole range. Indeed, it might be more productive to consider what is good about being a low transport patient rather than bad about high transport. It would also appear from Table 2 that the degree of the effect is lessening with time. The possible reasons for this will be discussed later.

Is the ultrafiltration capacity of the membrane also important? As we saw, when discussing the data in Figure 1, transport and ultrafiltration capacity are linked and so it is often difficult to demonstrate that the latter is independently associated with clinical outcomes. Patients with severe ultrafiltration failure, however, do not just have high solute transport. They also exhibit reduced osmotic conductance of the peritoneal membrane – a measure of the efficiency by which glucose induces ultrafiltration.^{26,27} This might occur either because the membrane is less permeable to the flow of water or because the glucose is less efficient as an osmotic agent in inducing ultrafiltration, for example, owing to impaired aquaporin function or dissipation of the glucose gradient by the fibrosed interstitium.

Whatever the mechanism, is it true to say that ultrafiltration capacity of the membrane can influence patient outcomes, independent of solute transport, other than in those patients with severe ultrafiltration failure? The first and

only study to suggest that this is the case is the European Automated Peritoneal Dialysis Outcomes Study (EAPOS), a prospective cohort of anuric patients treated with automated PD (APD).²⁸ This study is unique in that its design included the pre-setting of a daily ultrafiltration target, namely 750 ml. It found that patients below this target at baseline had an increased mortality, independent of age, comorbidity, and nutritional status, and that these patients never achieved the level of ultrafiltration throughout the study period enjoyed by those above target. Interestingly, solute transport was not a predictor of survival in this study, but the main factor explaining the reduced ultrafiltration was a reduced ultrafiltration capacity independent of transport status. The finding that overall daily ultrafiltration was a predictor of survival has since been confirmed by the NECOSAD study of anuric patients²⁹ and was previously shown to be important in Turkish PD patients, independent of residual urine volume.³⁰

Taken together, these observational studies suggest that peritoneal membrane function does influence survival; whereas the data is stronger for solute transport, an independent role for ultrafiltration capacity, over and above that determined by solute transport, is apparent.

UNDERSTANDING THE PROBLEM OF HIGH SOLUTE TRANSPORT

So why is high solute transport a problem? Is it a direct result of membrane characteristics on the treatment process itself or is it a proxy effect due to an association with another, important predictor of survival? The strongest case for the latter explanation is that membrane transport status is a surrogate measure for inflammation and that this is the reason for the increased mortality.

To some extent this argument depends on what is meant by an inflamed membrane. If we mean a membrane with relatively increased blood flow or an increased number of perfused capillaries in contact with dialysis fluid then this could well result in a higher small solute transport rate.³¹ High transport at the start of PD is associated with functionally relevant interleukin-6 polymorphisms³² and in selected patients an early increase in solute transport has been linked to local interleukin-6 production.³³ However, this set of circumstances may not depend on increased local production of proinflammatory cytokines but could be driven by other factors such as tissue hypoxia causing local production of vascular endothelial growth factor,³⁴ amplified longitudinally by certain vascular endothelial growth factor genotypes,³⁵ explaining the weak or absent correlation between transport, inflammation, and comorbidity.³⁶ Also, the anatomical area of membrane in contact with dialysis fluid does matter, as evidenced by the clinical data linking transport rate to body size and habitus already discussed, combined with observations that increased fill volume is associated with greater contact area on computerized tomography scan and higher solute transport.³⁷

The cardinal feature of inflammation is increased permeability of the microvasculature to proteins; whereas this will

Table 2 | Proportion of patients surviving at 2 years according to small solute transport category

Transport category	n	Low	Low-average	High-average	High
Davies <i>et al.</i> ¹⁵	303	86	87	75	58
Churchill <i>et al.</i> ⁷	608	91	90	72	71
Wang <i>et al.</i> ⁶⁶	46	100	90	85	64
Hung <i>et al.</i> ⁶⁷	50	100	62.6	48.4	46.2
Chung <i>et al.</i> ⁹	213	←-----79.5-----→			57.1
Szeto <i>et al.</i> ²²	58	90	←-----83.3-----→		
Rumpsfeld <i>et al.</i> ^{a,25}	3702	83.5	83.5	82.5	81.5

^aPercentages derived from plots of adjusted data.

also result in increased blood flow and thus faster small solute transport, it does not follow that high transport rates always mean inflammation. The difficulty here is in distinguishing solute transport from membrane permeability with sufficient ease as to make large-scale studies a practical possibility. One approach is to use the Personal Dialysis Capacity test, which uses the three-pore model of the membrane to distinguish between small solute transport – expressed as the area parameter – and the peritoneal protein losses as a measure of large pore leakiness.^{38,39} Using this method at least two studies have suggested that membrane permeability and not membrane area is a better predictor of mortality^{40,41} and a further study has found dialysate albumin concentration to be a predictor of cardiovascular events.⁴² Even this approach has its problems, however, as there is coupling between membrane area and protein losses in part owing to assumptions in the Personal Dialysis Capacity model,³⁸ but also because albumin, the predominant protein in dialysate effluent, is able to pass through small and large pores, the relative amount being dependent on convection.⁴³ Nevertheless, it is increasingly clear that solute transport, as measured by the rate of creatinine equilibration, is not simply a measure of membrane inflammation. This, combined with the fact that several of the studies linking solute transport to survival have already taken into account in their multivariate analyses the main clinical factors associated with inflammation (age, comorbidity, body habitus, and residual renal function), would suggest that this is not necessarily how high solute transport is exerting its malign influence.

The alternative is that the worse outcomes associated with high transport relate to how these membranes function as a dialysis organ. Even this is not straightforward. There can be no doubt that the efficiency of ultrafiltration achieved using low molecular weight osmolytes such as glucose is reduced and this, combined with a more rapid absorption of fluid from the peritoneal cavity, will result in worse salt and water removal.^{5,27} The main thesis of this review is that this is the most important mechanism, so this will be discussed in more detail shortly. It is necessary to recognize at this stage that other explanations need to be considered. As already discussed, larger membranes are associated with increased protein losses, especially albumin, whether they are inflamed or not. This is a substantial contributor to the low plasma albumin seen in PD patients that is likely to result in clinical problems including nutritional challenge and the compartmentalization of fluid distribution. A low plasma albumin is one of the strongest predictors of extracellular fluid expansion seen in PD patients.^{44,45} It should also be remembered that ultrafiltration can still be maintained in high transport patients if high dialysate glucose concentrations are prescribed. This in turn may have detrimental systemic effects that are the mechanism of increased mortality or technique failure rather than as a result of reduced ultrafiltration.

Our understanding of the mechanisms of ultrafiltration has been greatly enhanced by mathematical modeling, in

particular that achieved by application of the three-pore model.⁴³ The superiority of this approach is demonstrated by its ability to predict an additional pathway of water transport, now known to be via aquaporins, and at the same time explain fluid transport achieved by dispersed polyglucose dialysis solutions such as icodextrin.^{46,47} The description of fluid transport through these different pathways during a typical 3.86% glucose exchange is shown in Figure 2. Despite low efficiency when compared to aquaporins, substantial fluid transport occurs through the small pores, the area of which is proportional to small solute transport rates. It can be seen that in the first part of the dwell, when the osmotic gradient is able to drive net water transport into the peritoneal cavity, that a little over half of the ultrafiltration occurs through the small pores. Theoretically in this initial phase of the dwell, fluid transport could be greater in high transport patients and this has been confirmed experimentally.⁴⁸ This advantage is short-lived, however, as with the

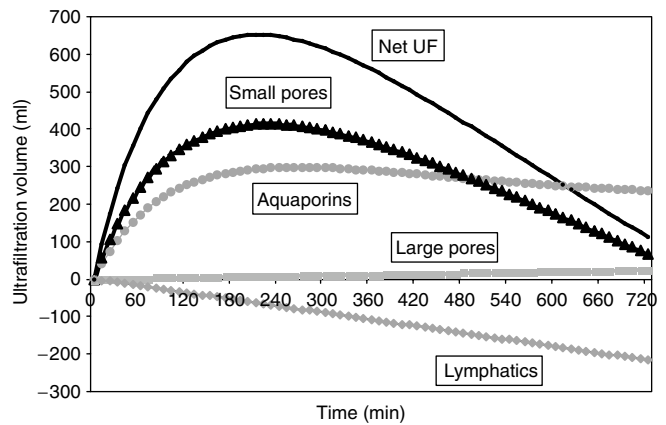


Figure 2 | Computer simulation of ultrafiltration pathways across the peritoneal membrane for glucose 3.86%. Once the osmotic gradient has dissipated, at ~240 min, fluid reabsorption will occur through small pores as well as lymphatics. As solute transport equates to the small pore area, high transport membranes will reabsorb more fluid.

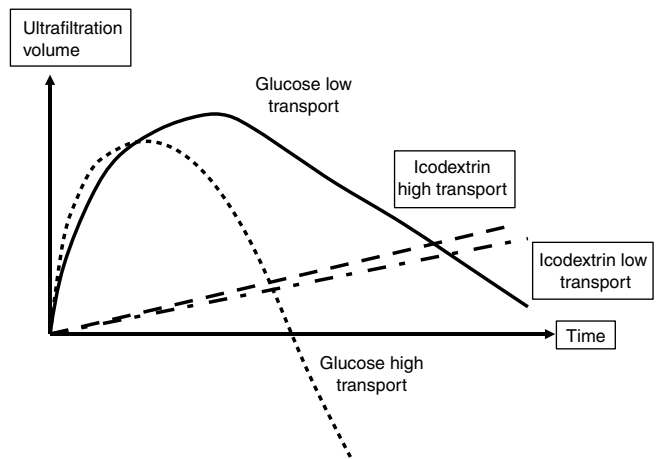


Figure 3 | A diagrammatic representation of the change in ultrafiltration profile associated with high transport status seen with glucose and icodextrin.

more rapid absorption of glucose there will be earlier loss of the osmotic gradient leading to a lower peak of ultrafiltration and an earlier transition to the reabsorptive phase of the dialysis cycle. Subsequently, it can be seen that the model predicts fluid reabsorption via the small pores once the osmotic gradient has dissipated, driven by Starling's forces: the model would predict that this fluid reabsorption will be faster in high transport patients, again confirmed by observations in our own unpublished studies. The overall effect of transport status on the ultrafiltration cycle using glucose is summarized in Figure 3.

MITIGATING THE PROBLEM OF HIGH SOLUTE TRANSPORT

Referring to Figure 3, it is fairly clear that two different but complementary strategies will be required to address the problem of high transport: the use of short dwell exchanges to ensure that the peritoneal cavity is drained at the point of optimal ultrafiltration and the use of a dialysis solution that will prevent the process of fluid reabsorption by counterbalancing Starling's forces. The former strategy is achieved by adopting APD, enabling short exchanges to occur overnight, and the latter by using icodextrin.

The value of using APD in the management of higher transport patients has long been recognized. Apart from optimizing the drainage time of the peritoneal cavity, there is the added advantage in this situation of minimizing the potential effects of sodium sieving. One consequence of using short dialysis exchange times is that these will result in good water removal via the aquaporins pathway but insufficient time for sodium to equilibrate. The predictions of relative water versus sodium removal by the three-pore model under various conditions have been confirmed, and as predicted the discrepancy is significantly less in higher transport membranes.⁴⁹ It is not clear at this stage whether this effect of sodium sieving in APD patients results in a clear clinical problem, although it should be remembered this remains an issue for all PD patients who have been demonstrated as a group to be thirsty.⁵⁰ There is evidence, however, that APD mitigates the effects of high transport. Solute transport appears to be less important as a predictor of outcomes in APD patients when compared to continuous ambulatory PD patients. In EAPOS, it was ultrafiltration capacity not solute transport that was the membrane characteristic associated with low baseline ultrafiltration and increased mortality risk.^{28,51} In a subgroup analysis of the ANZDATA study, the increased risk of solute transport was seen in continuous ambulatory PD but not APD patients.²⁵

The problem with APD is that it still leaves the long daytime dwell to be managed. This is not resolved easily with a dry day policy, unless there is sufficient urine volume to enable satisfactory fluid and solute removal, as there is always going to be absorption of any dialysate remaining in the cavity. Indeed, the day dwell volume may be substantially longer in APD patients when compared to the overnight dwell in continuous ambulatory PD resulting in even more fluid reabsorption. Icodextrin resolves this problem by

enabling a slow but linear ultrafiltration combined with almost complete prevention of fluid reabsorption (Figure 3). As icodextrin is essentially iso-osmolar to plasma, this is thought to be due to a modest oncotic pressure gradient that is sustained owing to its relatively slow absorption and metabolism during the dwell period which more than counterbalances Starling's forces. Many randomized studies have demonstrated that icodextrin results in sustained ultrafiltration between 9 and 14 h, with benefits over glucose solutions of all strengths that are greater the higher the solute transport.⁵²⁻⁵⁶ This improved ultrafiltration also translates into better body composition with a prevention of weight gain, at least in part that due to increased fat weight, and a

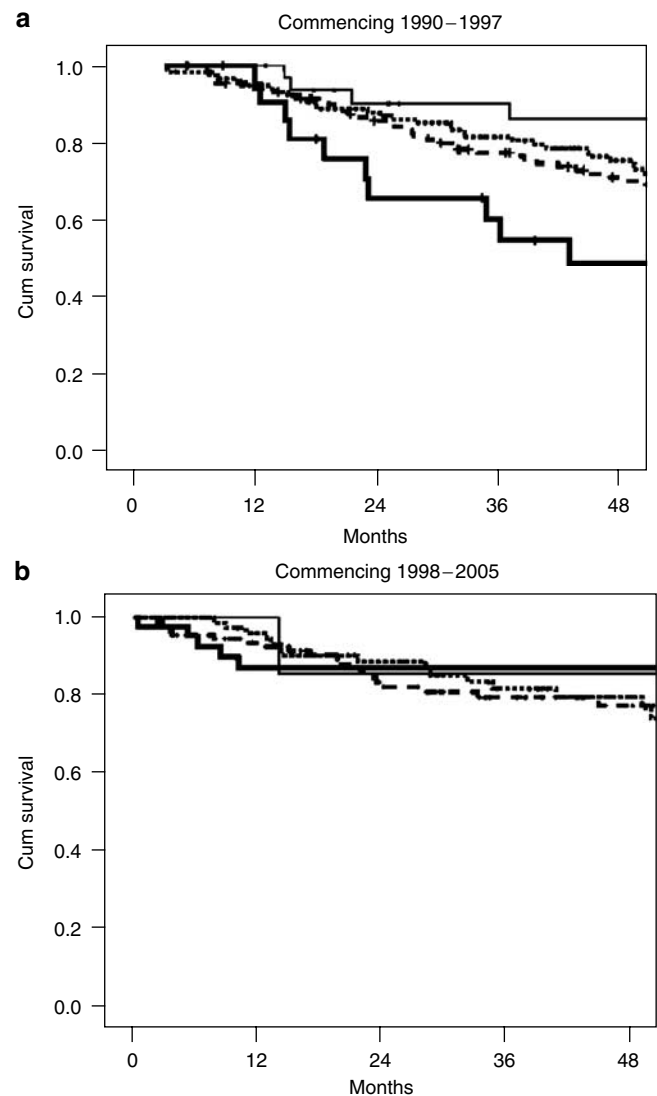


Figure 4 | Survival on PD (patients censored at transplant or transfer to hemodialysis), according to transport category at the start of treatment in two cohorts commencing between (a) 1990-1997, $n = 320$ and (b) 1998-2005, $n = 300$. Low (—), Low average (· · · ·), High average (---) and High (—). In the first cohort, transport category was significantly ($P = 0.009$) associated with survival, whereas in the second this was not the case due to an improvement in the survival of high transport patients.

reduction in extracellular fluid volume.^{54,57,58} Indeed, some care has to be taken to avoid too rapid volume depletion in some cases that might jeopardize residual renal function.⁵⁹

There is currently no randomized evidence that the combined approach of using APD and icodextrin in high transport results in an improvement of patient or technique survival. There was a high penetration of icodextrin use (45%) in EAPOS; patients using it at the start of the study had worse membrane function as determined by higher solute transport and less good ultrafiltration capacity and yet they achieved as good daily ultrafiltration as those not on icodextrin.^{28,51,60,61} Furthermore, in these patients there was no detectable adverse effect of solute transport on achieved daily ultrafiltration, whereas for the remaining patients high transport was negatively correlated despite the use of APD. Icodextrin did not have an independent beneficial effect on survival in EAPOS but it clearly had an additional beneficial effect and was of value to patients with worse membrane function.

In 1998, following clear demonstration of adverse outcomes associated with high transport in the Stoke PD Study,^{14,15} we adopted important changes in management of our PD patients. These included routine use of APD in anuric patients and the avoidance of dialysis exchanges which result in net fluid reabsorption by use of APD and when available icodextrin. Whereas before 1998 solute transport category was significantly associated with survival on PD in the prospective cohort commencing PD between 1990 and 1997 ($P=0.009$), this ceased to be the case in the 1998–2005 cohort, with the best improvement in survival being seen in high transport patients (Figure 4). This preliminary observation supports the view that it is possible to mitigate the problem of high solute transport, but requires further rigorous analysis, peer review, and similar findings in other studies before it can be safely concluded that the problem is solved.

MITIGATING LONG-TERM MEMBRANE DAMAGE

Whereas we now have good strategies for dealing with high transport, it is clear that the ultrafiltration capacity of the membrane, for a given transport status, remains an issue. This might be intrinsic to the membranes characteristics from the start of treatment, for reasons that are poorly understood, or reflect progressive membrane damage with time on therapy. There is mounting evidence from cross-sectional and longitudinal studies that ultrafiltration failure and changes in membrane function do not only reflect an increase in solute transport but also a reduction in the osmotic conductance – essentially a reduced efficiency of the membrane.^{3,48,62} Indeed, as discussed above, it would seem that the clinical importance of this aspect of membrane function only becomes apparent once strategies to address high solute transport have been used. Precisely why membranes lose osmotic conductance is not known, although theoretical explanations could include loss of aquaporin function, effects of a thickened interstitium on

glucose gradients, and reduction in the hydraulic conductance of the membrane owing to scarring and fibrosis.

At present, there is no therapeutic answer to low ultrafiltration capacity owing to reduced osmotic conductance. Mitigation of this problem must rely on prevention for the time being. There is evidence that acquisition of this problem is more likely to occur in patients utilizing more hypertonic glucose exchanges associated with more rapid loss of residual renal function.^{3,61,63} Again the exact mechanism is not known although there is evidence for glucose degradation product injury as well as damage from exposure to hypertonic glucose itself.⁶⁴ It is to be hoped that use of the newer biocompatible low glucose degradation product solutions will prevent its occurrence although there is no long-term data on membrane function confirming this at present. There is observational evidence that use of icodextrin in anuric APD patients over 2 years is associated with less chance of worsening ultrafiltration capacity⁶¹ and this combined with avoidance of hypertonic glucose solutions, where possible using non-glucose-containing solutions, would seem a logical strategy.

ACKNOWLEDGMENTS

I am grateful to the co-investigators of EAPOS, the European Icodextrin Study Group and to the clinical colleagues and peritoneal dialysis team in my own unit for their support. Thanks to Daniele Venturoli and Bengt Rippe for their explanations of the three-pore model and to Figure 2.

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