Does peritoneal protein transport increase with peritoneal dialysis therapy duration and lead to extracellular water overload in peritoneal dialysis patients?

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Abstract

Background

Faster peritoneal transport status has been associated with adverse outcomes for peritoneal dialysis (PD) patients. Peritoneal protein clearance, through large pores, may be a surrogate marker of local inflammation. We wished to determine whether peritoneal protein transport increased with PD duration or was associated with extracellular water (ECW) expansion.

Methods

We studied the relationships between 4hour Dialysate (D)/Serum (S) protein and ECW excess, using multifrequency bioelectrical impedance assessments, in 103 PD patients with up to four years of prospectively collected peritoneal equilibrium test (PET) results.

Results

4hr PET D/S total protein and creatinine ratios were stable over time (K-W test, p = 0.063 and p = 0.3357 respectively). The initial PET 4hr D/S creatinine and D/S total protein correlated with ECW excess (r = 0.33, p = 0.003, and r = 0.27, p = 0.019 respectively), but thereafter there was no association. CRP and albumin did not correlate with 4hr D/S creatinine or total protein. Serial 4hr D/S total protein and 4hr D/S creatinine correlated all time points (p<0.001).
Conclusions

At the start of PD therapy, over-hydration (ECW excess) was observed with higher 4hr D/S creatinine and 4hr D/S total protein ratios, suggesting initial exposure to PD fluids causes faster transport. Thereafter changes in peritoneal creatinine and total protein transport mirrored each other suggesting that similar factors lead to changes in both small and large pore transport, and there was no sustained increase in larger pore transport with therapy time.

Introduction

The relationships between peritoneal membrane transport characteristics, local and systemic inflammation and patient outcomes remain controversial. Data suggesting that outcome (including mortality) is worse for faster peritoneal transporters treated by continuous ambulatory peritoneal dialysis (CAPD) were reported by the CANUSA study group [1]. This was followed by a large meta-analysis which also observed an association between faster transport status and adverse outcomes, although the use of automated peritoneal dialysis cyclers (APD) appeared to modify this risk [2]. However more recent studies have reported no correlation between faster transporter status and patient or technique survival in peritoneal dialysis (PD) populations using APD [3,4].

Peritoneal membrane transport rate has a number of determinants; including patient size, as this will affect peritoneal surface area and blood supply. Inflammation,
both systemic and locally within the peritoneum, is also likely to increase local blood supply, and faster peritoneal transport has been observed with higher levels of both plasma and dialysate interleukin-6 (IL-6) [5]. In addition genetic polymorphisms resulting in greater IL-6 production may also be associated with faster peritoneal transport [6].

Peritoneal protein clearance depends upon large pore fluid flux, which has been reported to increase with inflammation, patient age, co-morbidities and generalised vascular disease [7,8]. The importance of peritoneal dialysate protein losses, (predominantly albumin) remains unclear. Some groups, including our own, have reported an association with increased patient mortality and PD technique failure [9,10]. However this remains controversial with other studies reporting no such association [11]. These differences between reports may be consequent on different clinical practices in terms of prescribing peritoneal dialysis, as peritoneal protein clearance can be modified by exchange dwell times with shorter dwell times tending to reduce protein losses, particularly for those patients who are slower peritoneal transporters.

Inflammation can lead to endothelial dysfunction [12], with increased capillary permeability and extracellular water (ECW) expansion, although again the latter could be modified by the PD prescription [13]. On the other hand, PD patients may have an expanded ECW, with a lower serum albumin, but this does not necessarily always imply an expanded plasma volume [14,15]. To investigate this further, we wished to explore the relationships between small and large pore transporter status and bioimpedance derived hydration status, and whether these changed over time, as over-hydration due
to increased capillary permeability would link faster transporter status with ECW excess, and provide a potential cause for the increased mortality reported with daily peritoneal protein losses [9].

**Methods**

We compared 4 hour peritoneal dialysate effluent creatinine and total protein to corresponding serum samples (S) when PD patients attended for routine outpatient peritoneal equilibrium testing (PET) using a standard 22.7 g/l dextrose exchange as part of their routine clinical care. Dialysate (D) creatinine was measured using a kinetic enzymatic method to prevent glucose interference (P module analyzer, Roche Integra, Roche diagnostics, Lewes, UK). Serum and dialysate total protein were measured by a modified biuret method (colorimetric assay based on divalent copper reacting in alkaline solution with protein peptide bonds to form a characteristic purple-coloured biuret complex, measuring increased absorbance at 546 nm), and peritoneal dialysate protein using pyrogallol red which complexes with proteins in an acid environment containing molybdate ions, and measuring absorbance at 600nm. This method is linear up to 2.14 g/L (higher concentration samples were diluted to bring them into range). Serum albumin was measured by bromcresol green method (P module analyzer, Roche Integra, Roche diagnostics, Lewes, UK [16]). C-reactive protein (CRP) was measured using the same assay as the UK National Amlyoid centre, with values reported down to < 1 mg/L, and haemoglobin by an automated counter (Sysmex XN900, Sysmex Corporation, Kobe, Japan) [17]. Multifrequency bioelectrical impedance assessments
were made using a standard protocol (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea), with the dialysate drained out at the end of the PET [18]. Extracellular water volume (ECW) excess or ECW over hydration was estimated according to the method recommended by the European Society for Parenteral and Enteral Nutrition (ESPN) [19], or by the ratio of ECW/total body water (TBW).

Data was available from 103 adult PD patients who had been treated with peritoneal dialysis for a minimum of 12 months and had up to four years of annual peritoneal equilibration tests. Patients with pacemakers and amputees were excluded from MFBIA. These were routine tests performed in stable outpatients and not less than six weeks after completing a three week course of antibiotics for the treatment of any episode of peritonitis. Data was collected between 2003 and 2012, and co-morbidity assessed using the Stoke-Davies score [20].

Statistical Analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Students’ t test was used for parametric and the Mann Whitney U test for nonparametric data, anova or Kruskal Wallis with appropriate correction for multiple analyses where appropriate, and Spearman correlation used for non-parametric data. Statistical analysis was performed using Graph Pad Prism (version 4.0, Graph Pad, San Diego, CA, USA). Statistical significance was taken at or below the 5% level.

Individual consent was waived as all laboratory tests and MFBIA had been performed as part of the routine clinical care of kidney dialysis patients in keeping with the Royal Free Hospital Trust policy and no patient identifiable data was used.

Results

Data on PET and MFBIA was reviewed from 103 consecutive patients initiating peritoneal dialysis who had MFBIA at the time of their initial PET, a median of 2 months from the start of PD training, median time from PD catheter insertion 2.0 (2.0-3.0) months. There were 31 female and 72 male patients, and 18 (17.5%) were diabetic. The mean age at first PET was 56.2 years (range 19 – 86 years). The major ethnic groups were Caucasian 50%, African-Afro-Caribbean 22%, South Asian 18% and East Asian 8%. 24 patients were treated by automated peritoneal dialysis (APD) with no day time exchange, 55 APD with a day time exchange and 24 by continuous ambulatory peritoneal dialysis (CAPD), with 75 (72.8%) using a 7.5% icodextrin exchange, and 34 using 22.7 g/l glucose exchanges. No patient at baseline, or on follow-up, used peritoneal glucose exchanges greater than 22.7 g/l. At baseline the mean haemoglobin
was 113.8 ±13.7g/l, serum albumin 37.8 ±4.6 g/l, sodium 139.2 ±3.9 mmol/l, glucose 7.2 ±4.8mmol/l, urea 17.7±5.2 mmol/l, creatinine 525 ±219 umol/l, median C reactive protein 5.9 (4.5-7.6) mg/l. Residual Kt/Vurea was 1.76 (range 0 - 5.49) and litres of urinary combined mean creatinine and urea cleared 71.8 (range 0 - 248.4) L/week/1.73m². The mean weekly peritoneal Kt/Vurea was 1.21 (range 0.21 - 2.97); with a mean weekly total Kt/Vurea 2.98 (range 1.27 - 6.66). The mean peritoneal creatinine clearance at baseline was 35.7 (range 7.4 - 150.7) L/week/1.73m², giving a mean total creatinine clearance of 104.7 (range 26.6 - 237.4) L/week/1.73m². The mean BMI was 25.8 (range 17.4 - 40.3). The median Stoke Davies co-morbidity score for our cohort was 1. The ratio of extracellular water (ECW) to total body water (TBW) was 0.393 ± 0.012, and mean ECW excess 0.72 ± 0.74 litres.

Separating patients according to the first PET test (table 1), then faster transporters had lower serum albumin, and greater PET 4 hour D/S total protein ratio, and greater ECW, but there were no differences in serum total protein or CRP, and no differences in patient demographics or comorbidities.

Thereafter serial annual data was available for 101 patients after 12 months, 82 after two years, 70 after 3 years and 38 after 4 years. At the end of the study twenty patients remained treated by peritoneal dialysis (2 APD, 4 CAPD and 14 APD with a day time exchange), twenty had died, thirteen had been transferred to HD and fifty transplanted. Residual renal function declined over time, with most having a urine output of < 100 ml/day by year 3 (median creatinine clearance 0 (0-5.0) ml/min. During the study period the incidence of peritonitis within the centre, was calculated on a
monthly basis and varied from a maximum of one episode per 19 months to a minimum of one episode per 32 months, median one per 26 months.

For the whole group the mean 4 hour PET D/S creatinine remained stable overall over time (Figure 1). The D/S total protein for the whole group was also stable over time (Figure 2). Excluding drop outs, then analysing paired data sets showed that 4 hour PET D/S creatinine was stable over time. For 4 hour PET D/S total protein, there was a significant difference between the initial PET and at four years (Kuskal Walis with Dunn's correction p < 0.05), but not for any other time points.

There was a statistically significant correlation between the PET 4 hour D/S creatinine and the D/S total protein at all-time points (Table 2). We investigated the relationships between changes in 4 hour PET D/S creatinine and D/S total protein with time in individual patients. There was a positive correlation between the change in 4 hour PET D/S creatinine and the change in D/S protein from the initial data to the three year data (Figure 3). This positive relationship was maintained, at all follow ups, even if the interval chosen was the initial and last data collection for each patient regardless of the duration of peritoneal dialysis (r=0.419, p<0.001).

At the start of peritoneal dialysis therapy, the initial ratio of extra-cellular water/total body water (ECW/TBW) and over-hydration correlated with the 4 hour PET D/S creatinine (r = 0.331, p = 0.0031, and Figure 4, respectively). Similarly both the ECW/TBW ratio and the degree of over-hydration also correlated with the 4 hour PET D/S total protein (r = 0.28, p = 0.0137 and r = 0.267, p = 0.0019), respectively. However thereafter, at all subsequent time points there was no statistical correlation
between either the ECW/TBW or litres of ECW over hydration and either the corresponding 4 hour PET D/S creatinine or D/S total protein, nor were there any significant relationships between changes in D/S creatinine or D/S total protein over time and changes in hydration status over the same time period. (supplementary figures 5-8)

The 4 hour PET D/S total protein did not correlate significantly with surrogate markers of systemic inflammation such as serum albumin or CRP at any time point, but did correlate with age ($r = 0.297$, $p = 0.0024$). The 4 hour PET D/S creatinine also correlated weakly with age ($r = 0.217$, $p = 0.0289$). The initial 4 hour D/S creatinine correlated negatively with the serum albumin ($r = -0.358$, $p = 0.0002$); this relationship was maintained with time (at one year $r = -0.417$, $p < 0.0001$; at two years $r = -0.332$, $p = 0.0026$; at three years $r = -0.556$, $p < 0.0001$; at four years $r = -0.347$, $p = 0.0355$). There was no statistical correlation between either the 4 hour PET D/S total protein or the D/S creatinine and either CRP or the Stoke-Davies co-morbidity score or grade.

The ratio of ECW/TBW remained stable over time, being $0.389 \pm 0.013$ after 12 months, $0.392 \pm 0.010$ after 24 months, $0.392 \pm 0.009$ after 36 months, and finally $0.392 \pm 0.128$. Similarly ECW excess was estimated as $0.52 \pm 0.61$ L after 12 months, $0.73 \pm 0.51$ L after 24 months, $0.84 \pm 1.72$ L after 36 months and finally $0.67 \pm 0.62$ L, and there was no association between changes in peritoneal protein transport and ECW excess over time.

As the majority of patients were transplanted on follow-up, we compared patient outcomes. As expected transplanted patients were younger compared to those
who died (48.5±14.3 vs 65.7±13.5 years, p<0.05), and had less co-morbidity (Davies grade 0/1/2: 30/19/1 vs 3/13/4, X²=27.7, p<0.001), and fewer diabetics (20% vs 50%, X²=11.3, p=0.01), and had lower ECW/TBW ratio (0.39±0.01 vs 0.40±0.02, p<0.05). However there were no differences in PD modality, use of icodextrin. 22.7 g/l glucose or physioneal usage, or standard PET test results. The 4 hr PET D/S total protein, and the ratio of D/S total protein to creatinine were higher in those transferred to haemodialysis than those who were transplanted (0.021±0.009 vs 0.008±0.006, and 0.023±0.009 vs 0.011±0.001, p<0.05 respectively), but there were no differences with those patients who died.

38 patients continued on peritoneal dialysis and had serial data for more than 4 years. When peritoneal creatinine and protein transporter status (PET results), serum total protein and 24 hour peritoneal protein losses at enrolment were compared with those of the other patients at enrolment, no differences (supplemental table 1) were found.

Discussion

Previous studies, typically based on CAPD cohorts, have reported an association between faster transporter status and both PD technique failure and mortality [1,2], whereas other observational studies have linked faster transporter status to patient co-morbidity and ECW over hydration [8, 21]. However other reports have not shown the same associations between faster transporter status and outcomes [3], or ECW
volume overload [22], but instead have noted associations between inflammation as assessed by increased serum CRP and reduced serum albumin concentrations and ECW excess [23]. As such we looked at the association between the standard 4 hour PET D/S creatinine and total protein ratios, as markers of small and large pore fluxes, and MFBIA derived volume assessments in a cohort of peritoneal dialysis patients over time, to ascertain whether ECW over hydration was driven by increased large pore fluxes.

At the start of peritoneal dialysis we found that there was a significant correlation between both the initial 4 hour PET D/S creatinine and the D/S total protein and ECW over-hydration, and a negative correlation with serum albumin, consistent with the hypothesis that over-hydration may be related to faster peritoneal transporter status secondary to generalised or local inflammation [5] and so help to explain the association reported between fast transporter status and peritoneal dialysis technique failure and worse patient outcomes [1,12]. Our results on total protein transport and hydration status support an earlier study which reported an initial relationship between peritoneal albumin and creatinine transport [11]. This latter study also noted an association between peritoneal albumin transport and increased co-morbidity, however there were differences between this study and ours both in terms of patient co-morbidity and peritoneal membrane testing [11]. Increased peritoneal protein and creatinine transporter status could be secondary to local peritoneal inflammation following exposure to hypertonic low pH lactate based peritoneal dialysis fluids which was still present at the time of the first PET, and then with time either
there was adaptation to the effect of peritoneal dialysates or changes made in the peritoneal dialysis prescription adjusted for the membrane properties designed to reduce patient over-hydration [13,24]. However there were no differences in peritoneal dialysis modality, or usage of 22.7 g/l glucose dialysates or physioneal, although more faster transporters used icodextrin. We did not find any association with either small pore or large pore transport and CRP or ECW over hydration on repeat testing of peritoneal membrane function. However there was a negative correlation between the 4 hour D/S creatinine and serum albumin at all-time points, whereas there was no such association with 4 hour D/S total protein at any time point. As lower serum albumin concentrations are associated with adverse outcomes, supporting previous studies [11], this would support a link between faster small solute transport and PD technique failure and patient mortality [1,2]. The question arises as to why there was no association with ECW as serum albumin concentrations are recognised to be affected by hydration status, and residual renal function. However MFBIA results were available to the clinicians and as such changes in PD prescription to adapt to loss of residual renal function could have abrogated ECW expansion [25], as not all peritoneal dialysis patients become volume overloaded when residual renal function is lost [26]. In addition, in keeping with the majority of UK laboratories we used the bromocresol green method to measure serum albumin, which may be less reliable in patients with lower serum albumin levels due to interactions with the plasma globulin fraction [27]. This may potentially explain the lack of association between 4 hour D/S total protein and serum albumin.
In our cohort 4 hour D/S creatinine remained stable, whereas other reports have suggested a progressive increase in D/S creatinine with duration of PD therapy [28]. Although this increasing D/S transporter status has been linked to previous peritonitis episodes [29], and changes in peritoneal membrane predisposing to encapsulating peritoneal sclerosis [30], it is now recognised that small pore transporter status does not increase in all PD patients over time [31]. Similarly we found that for the whole group then over time peritoneal large pore flux, as determined by 4 hour PET D/S total protein also remained stable, in keeping with previous reports [8,31], suggesting that there was no progressive change in the peritoneal membrane “leakiness” to larger molecules during the period of treatment with PD. If anything 4 hour D/S protein was lower after 4 years, which may been due to a residual inflammatory effect due to the initial exposure to peritoneal dialysis fluids at the time of the first PET test.

At each time point we found a correlation between 4 hour PET small pore and large pore transport. Some studies based on albumin measurements have suggested that peritoneal surface area may increase with duration of PD therapy, so that there could be some divergence between small and large pore transport [8,32]. However in our study for individual patients changes in the 4 hour PET D/S creatinine were associated with similar changes in the same direction for the D/S total protein. There are some major differences between our study and these reports, in that we had a high usage of icodextrin, and were much less reliant on hypertonic glucose exchanges, with no patients using glucose concentrations in excess of 22.7 g/l glucose dialysates. As
such this combination may have resulted in less ECW volume expansion [33] and reduced exposure to glucose and glucose degradation products. Secondly we measured total protein, whereas previous studies relied on the peritoneal albumin measurements [8,32]. Although there may potentially be differences between total protein and albumin peritoneal transport, it is more likely that studies which have measured peritoneal dialysate effluent albumin as a surrogate of protein transport could well be confounded by the bromocresol green method, which is recognised to be less accurate at lower albumin concentrations, and is prone to interactions with the globulin protein fraction [27].

The D/S creatinine is determined by the number of small pores, a function of capillary surface area. This may be related to local inflammation within the peritoneal space. The D/S protein is thought also to be related to inflammation; large pore “leakiness” might be determined by either local or systemic inflammation [10]. Our observation that D/S protein so closely paralleled the D/S creatinine suggests that the same factors are affecting both parameters. One explanation for this could be that local mediators affect both the small and large pore permeability in the peritoneum. Changes in permeability would be expected to lead to an expansion in ECW, rather than expansion in plasma volume [15,34], and as such would lead to reports of both increased peritoneal protein and creatinine transport being linked to PD technique failure and patient mortality [1,2,10,32]. However we found no association between peritoneal protein transport and ECW excess over time.
In any observational longitudinal study there will be the inevitable question of whether results can be biased due to a survivor effect, as patients drop out from follow up. In the UK where there is an active kidney transplant program, as expected younger patients and those with less co-morbidity were more likely to be transplanted. On the other hand patients who died did not have faster peritoneal transport for protein or creatinine. As such the observation that there was no change in peritoneal protein to creatinine transport over time would provide further support for our findings. Additionally we did not find differences in enrolment peritoneal transport status for creatinine or protein for those patients who remained on peritoneal dialysis for more than 4 years and those who did not. The majority of our patients used 7.5% icodextrin dialysate and no patient received glucose dialysates of more than 22.7 g/l, and although we cannot exclude an effect due to dialysates, we feel that this is unlikely, as there were no differences in peritoneal protein transport between the different treatment modalities.

Our data is consistent with that of other groups who have demonstrated a stable 4 hour PET D/S albumin and extends the data on relationships between D/S total protein and D/S creatinine with time on peritoneal dialysis. In summary, the stability of the D/S total protein over time argues against the hypothesis that continued exposure to peritoneal dialysates causes progressive increase in peritoneal large pore transport. The early association of D/S total protein with over-hydration suggests that over-hydration might be a consequence of a local inflammatory state when patients were first exposed to peritoneal dialysates; however this effect did not
persist over time. The close association with the D/S creatinine suggests that common factors affect both small and large pore function.

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The data contained in this paper has not been previously published in whole or part form.
References


Figure 1 shows the 4 hour peritoneal dialysis equilibrium test D/S creatinine data at yearly intervals. Data presented as median and interquartile range (whiskers indicate range). p=0.3 by Kruskal Wallis.

Figure 2 shows the 4 hour peritoneal dialysis equilibrium test D/S total protein data at yearly intervals. Data presented as median and interquartile range (whiskers indicate range). p=0.89 by Kruskal Wallis.

Figure 3: Changes in 4 hour peritoneal dialysis equilibrium test D/S creatinine and D/S total protein over 3 years in 70 individual patients. Spearman correlation r= 0.425, p=0.0015.

Figure 4: correlation between the initial 4 hour peritoneal dialysis equilibrium test D/S creatinine and extracellular water over-hydration r=0.333, p=0.0033.

Supplementary figures

Figure 5: change in extracellular water to total body water ratio compared to change in dialysate to serum creatinine ratio at 12 months

Figure 6: change in extracellular water to total body water ratio compared to change in dialysate to serum creatinine ratio at 24 months

Figure 7: change in extracellular water to total body water ratio compared to change in dialysate to serum creatinine ratio at 36 months

Figure 8: change in extracellular water to total body water ratio compared to change in dialysate to serum creatinine ratio at 48 months
Table 1. Patient characteristics and biochemical results at time of 1st PET test. Results as number, mean ±SD, or median (interquartile range) or percentage. Davies co-morbidity grade (Davies grade), C reactive protein (CRP), serum total protein (serum TP), dialysate (D) and serum (S), peritoneal equilibration test (PET). Extra cellular water(ECW), total body water (TBW). Final patient outcomes. p values Chi square with correction for small numbers or by annova testing with post hoc correction vs fast transporters.

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<th>Fast average</th>
<th>Fast</th>
<th>p value</th>
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Table 2: Table of correlation analysis between 4 hour peritoneal dialysis equilibrium testing dialysate to peritoneal ratios for creatinine and total protein at baseline, and subsequent years 1, 2, 3, and 4. Number of patients at each time point (n).
Supplemental Table 1: Data from the initial peritoneal dialysis equilibration testing (PET) and peritoneal dialysis adequacy assessments from the 38 patients who remained on peritoneal dialysis after 4 years (4-year survivors) and the other peritoneal dialysis patients. PET samples (4 hour), adequacy samples (24 hour), Dialysate (D), Serum (S), Data expressed as mean ± SD. p=not significant for all variables.

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<td>0.72 ± 0.15</td>
</tr>
<tr>
<td>4 hour D/S total protein</td>
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<tr>
<td>4 hour D/S total protein/D/S creatinine</td>
<td>0.012 ± 0.005</td>
<td>0.014 ± 0.008</td>
</tr>
<tr>
<td>4 hour D total protein g/L</td>
<td>0.57 ± 0.21</td>
<td>0.68 ± 0.48</td>
</tr>
<tr>
<td>Serum protein g/L</td>
<td>68.2 ± 7.9</td>
<td>67.2 ± 5.8</td>
</tr>
<tr>
<td>24 hour D total protein g</td>
<td>5.46 ± 3.24</td>
<td>5.33 ± 2.35</td>
</tr>
<tr>
<td>Peritoneal protein clearance ml/24 h</td>
<td>82.41 ± 56.1</td>
<td>80.5 ± 39.2</td>
</tr>
</tbody>
</table>