Peritoneal fast transport in incident peritoneal dialysis patients is not consistently associated with systemic inflammation

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Abstract

Background. The determinants of peritoneal fast transport status at the beginning of peritoneal dialysis (PD) are still under debate. The relationship between fast transport status and inflammation or co-morbidity, and its impact on patient survival are not fully elucidated. Our objective was to investigate if fast transport status in incident patients is associated with markers of inflammation and atherosclerosis, and its relationship to patient survival.

Methods. Seventy-three incident patients on PD performed a 3.86% peritoneal equilibrium test (PET) at 4.7±2.7 months after starting PD. Doppler carotid wall intima-media thickness (IMT) and the presence of carotid plaque were used as markers of atherosclerosis. C-reactive protein (CRP) and serum interleukin-6 (IL-6) were evaluated as markers of systemic inflammation. Baseline plasma levels of albumin, homocysteine, lipoprotein (a) [Lp(a)] and other lipid parameters were measured. Body mass index and residual renal function (RRF) were calculated. Patients were classified with the Davies co-morbidity score.

Results. The dialysate–plasma creatinine ratio (D/P creatinine) was 0.75±0.10; 26% were fast transporters (D/P ≥0.85). In comparison with other transport categories, these had similar age, body mass index and RRF, and did not present a higher co-morbidity score than non-fast transporters. IMT did not significantly differ between groups. By multiple regression analysis, baseline peritoneal small solute transport was not related to systemic inflammation biomarkers. Fast transporters did not present higher levels of CRP or serum IL-6. Plasma levels of lipids, Lp(a), calcium × phosphorus product and albumin also did not differ between groups. Similar results were obtained when patients were grouped according to mass transfer area coefficient for creatinine. Patients with more than two co-morbidities had lower levels of plasma albumin (3.6±0.58 vs 3.9±0.9 g/dl, P=0.054), significantly higher median levels of serum IL-6 (19.3 vs 9.2 pg/ml, P=0.003) and wider IMT (0.90±0.36 vs 0.65±0.28 mm, P=0.017). Multivariate analysis confirmed that baseline peritoneal transport was not a significant determinant of patient survival (P=0.848), while the co-morbidity score remained significant (hazard ratio = 3.48, 95% confidence interval = 1.29–9.38, P=0.014).

Conclusion. Initial fast transport was not associated with systemic inflammation and atherosclerosis. In a population with preserved RRF and absence of baseline serious co-morbidity, it was not predictive of worse prognosis. Other determinants of early peritoneal fast transport deserve investigation.

Keywords: inflammation; peritoneal transport; survival

Introduction

Hyperpermeability of the peritoneal membrane, defined as fast or high transport by the peritoneal equilibration test (PET [1]), can develop during long-term peritoneal dialysis (PD) [2,3], but may also be present from the start of dialysis [4]. Studies in the latter group of patients have reported an association with increased mortality [5,6], decreased technique survival [7] or a combination of both [8].

The association of a fast transport status with decreased technique survival can be explained because the resulting inadequate ultrafiltration usually leads to transfer from continuous PD to automated PD or haemodialysis when residual urine volume has decreased. However, the reason for the higher mortality reported in earlier studies has not been clarified.
Pathogenic effects of a high peritoneal transport status have been documented [9], but poor outcome was not confirmed by all [10–12]. Some studies [13–15] reported an over-representation of a fast peritoneal transport status in patients with co-morbidity. It has been suggested that a chronic inflammatory status might determine baseline peritoneal transport [16]. As inflammation is associated with hyperaemia, it can be hypothesized that concomitant peritoneal hyperaemia leading to an increase in the effective vascular-peritoneal surface area (the number of effectively perfused capillaries) might explain the relationship between co-morbidity and peritoneal transport status. Acute systemic inflammation is indeed associated with a temporary increase in the peritoneal solute transport rate in PD patients [17]. However, a causal relationship between inflammation and basal peritoneal transport is doubtful and was not supported in more recent investigations [18,19].

A large study [20] reported recently that a higher peritoneal transport status was not independently predicted by diabetes, other co-morbid diseases or residual renal function. The baseline dialysate–plasma creatinine ratio (D/P creatinine) also had no effect on patient or technique survival in a multicentre study of automated PD anuric patients [21].

Therefore, the diversity of peritoneal transport characteristics in different populations and controversial data concerning its determinants deserve more investigation. The validity of baseline peritoneal transport as an independent predictor of patient survival is questionable.

The aim of the present study was to investigate whether peritoneal hyperpermeability in incident PD patients was associated with inflammation, atherosclerosis or co-morbidity, and its impact on patient survival.

Patients and methods

Seventy-three incident PD patients (27 male, 46 female), aged 48 ± 16 years, were evaluated in a prospective observational study. Twenty (27%) patients were diabetic, 17 (23%) presented clinical ischaemic heart disease, five (6%) had a previous cerebrovascular event and nine (12%) had peripheral vascular disease. Patients were subjected to a basal PET with a 3.86% solution, at 4.7 ± 2.7 months after starting on PD. Mean D2/3P1 creatinine was 0.75 ± 0.10. Patients were categorized, according to Twardowski et al. [1], as high transporters (D/P ≥ mean ± SD, n = 19) and non-high transporters (n = 54). High and non-high transporters were then stratified using Davies’s co-morbidity scores [22].

To characterize peritoneal small solute transport further, the mass transfer area coefficient (MTAC) for creatinine was calculated with the simplified Garred method, validated for clinical purposes [23–25]. Median MTAC creatinine was 9.3 ml/min [interquartile range (IQR) 6.6–13.1 ml/min]. Additional analysis was done to compare patients according to the level of MTAC creatinine (higher than vs lower than the median).

In search of markers of atherosclerosis, right and left carotid arteries were examined with a G.E. Logic 500 MD duplex scanner (7.5 MHz probe). All scanings were performed by the same trained sonographer. Intima-media thickness (IMT) was defined as the distance between the leading edge of the lumen–intima echo and the leading edge of the media–adventitia echo, measured 10 mm proximal to the common carotid artery bifurcation. A carotid plaque was reported if localized IMT > 1 mm and at least a 100% increase in thickness compared with adjacent wall segments was present.

Body mass index (BMI) and serum albumin were measured. Serum albumin was measured with the bromocresol green method. Residual renal function (RRF) was calculated from 24 h urine with the media of creatinine and urea clearances.

C-reactive protein (CRP) was used as an inflammatory marker. It was measured by nephelometry with a high sensitivity assay (Boehringer analyzer II; normal values: CRP < 0.5 mg/dl).

Serum interleukin-6 (IL-6) was additionally measured in 42 patients for whom samples were available. These patients were similar in terms of peritoneal permeability (D/P creatinine, MTAC creatinine), age, gender, RRF, plasma albumin and co-morbidity score compared with the remaining cohort (n = 31). A commercially available immunoenzymometric assay (IL-6 Easia; Biosource Europe SA, Nivelles, Belgium) was used.

Metabolic and humoral cardiovascular risk factors included: homocysteine, lipoprotein (a) [Lp(a)], other lipid parameters and calcium × phosphorus product (Ca × P).

Total cholesterol, triglycerides and high-density lipoprotein cholesterol were assayed enzymatically by colorimetric methods (Olympus). Low-density lipoprotein cholesterol was calculated using the Friedwald’s formula, and very low-density lipoprotein cholesterol was obtained by dividing the serum triglycerides level by 5. The plasma Lp(a) concentration was quantified by an immunoturbidimetric assay from Boehringer-Mannheim, using the automatic analyser Olympus AU 800 [Lp(a) normal values: < 30 mg/dl]. Total fasting homocysteine levels were determined by a fluorescence polarization immunoassay on an automated IMx analyzer from Abbott laboratories (Axis Biochemical’s ASA, Oslo, Norway) (reference values of homocysteine ranged from 5 to 15 μmol/l).

Statistical analysis

Normality of data distribution was tested by the Kolmogorov–Smirnov test. Pearson’s correlation was then used to assess the relationship between continuous variables with normal distribution.

Comparisons between high and non-high transporters for continuous variables were made with non-parametric techniques because of the different sizes of the compared groups. Group data are expressed as median (IQR), and differences between medians were analysed by Mann–Whitney U-test. Frequencies of categorical variables were compared by χ²-test or Fisher exact test.

A multiple regression analysis was done to examine the relationship between inflammation and baseline peritoneal transport. Statistical significance thresholds required for inclusion and exclusion at each stepwise run were set at
significant.

**Results**

D$_4$/P$_4$ creatinine ranged from 0.54 to 0.96, with a mean level of 0.75±0.10. Demographic and laboratory data, and co-morbidity scores of the patients are presented in Table 1. The magnitude of RRF was not significantly different between high transporters and non-high transporters. No significant differences were found in co-morbidity in high transporters vs non-high transporters (10.5 vs 27.8%, P = 0.207) (Table 1).

In the subgroup of 42 patients from whom serum IL-6 was available, the median (IQR) level of this marker was 11.1 (4.6–17.8) pg/ml. Twenty-one patients had serum IL-6 levels higher than the median. Peritoneal solute transport did not differ significantly between the groups, categorized according to the median level of serum IL-6 (>the median vs ≤median level): MTAC 8.2 ± 4.4 vs 10.7 ± 6.3 ml/min, P = 0.16; D/P creatinine 0.73 ± 0.10 vs 0.76 ± 0.11, P = 0.38, respectively.

Median levels of serum albumin, CRP and serum IL-6 were not significantly different in high and non-high transporters (Table 2). Plasma levels of lipids, including Lp(a), homocysteine, parathyroid hormone, calcium × phosphorus product and IMT did not differ between groups. Similar results were obtained when patients were grouped according to MTAC for creatinine (analysis not shown).

Baseline peritoneal small solute transport (D$_4$/P$_4$ creatinine, MTAC creatinine) was not significantly correlated with markers of systemic inflammation, with either IL-6 (P = 0.273) or CRP (P = 0.804).

A multivariate analysis was performed to examine the relationship between inflammation and baseline peritoneal transport. Baseline D/P creatinine, or MTAC in a subsequent and similar analysis, was the dependent variable and all potential clinically relevant variables were examined, namely serum IL-6, CRP, plasma levels of lipids, including Lp(a), homocysteine, parathyroid hormone, calcium × phosphorus product and co-morbidity score. The presence of diabetes mellitus, clinical ischaemic heart disease, peripheral vascular disease and a previous cerebrovascular event were also tested.

Each variable was included one by one as independent variables (continuous or categorical). Except for homocysteine, none of the remaining variables was significantly related to D/P creatinine or MTAC. Even so, a multivariate analysis was performed, and all the variables were tested. Models with two, three, four, five and six variables were studied, in several combinations. We verified again that, except for homocysteine, none of the remaining variables was significantly related to D/P creatinine or MTAC.

Patients with more than two co-morbidities had lower levels of plasma albumin (3.6 ± 0.58 vs 3.9 ± 0.49 g/dl, P = 0.054), significantly higher median levels of serum IL-6 [19.3 (14–37.5) vs 9.2 (4–14.4) pg/ml, P = 0.003] and wider IMT (0.90 ± 0.36 vs 0.65 ± 0.28 mm, P = 0.017).

Baseline peritoneal fast transport did not show an impact on patient survival: fast transporters had 92, 77 and 77% of cumulative survival vs 98, 85 and 79% in non-fast transporters at 1, 2 and 3 years, respectively, P = 0.84 (Figure 1).

| Table 1. Demographic characteristics, RRF and co-morbidity score in the studied population |
|---------------------------------|----------|----------|
| **High transporters** (n = 19) | **Non-high transporters** (n = 54) | |
| Age (years) 39 (30–61) | 49 (37–64) | |
| Gender (M/F) 4/15 | 23/31 | |
| Diabetes mellitus (Yes) 6 (31.6%) | 14 (25.9%) | |
| Interval (start PD to PET; months) 4 (2–7) | 4.2 (2.5–6) | |
| BMI (kg/m$^2$) 22.9 (21.7–25.3) | 23.3 (21.2–26.1) | |
| RRF (ml/min/1.73 m$^2$) 4.4 (3.0–7.9) | 4.0 (3.0–5.0) | |
| Co-morbidity (Davies score ≥2) 2 (10.5%) | 15 (27.7%) | |

Values are given as median (interquartile range) for continuous variables and as n (%) for categorical variables.

*P* Statistically non-significant (*P* > 0.05) for all these variables.

| Table 2. Comparisons between high and non-high transporters for continuous parameters showed no significant differences |
|---------------------------------|----------|----------|
| **High transporters** | **Non-high transporters** | |
| Median (IQR) | Median (IQR) | |
| Albumin (g/dl) | 3.9 (3.4–4.3) | 3.9 (3.6–4.2) |
| CRP (mg/dl) | 0.24 (0.12–1.15) | 0.52 (0.14–1.15) |
| IL-6 (pg/ml) | 9.3 (7–17.5) | 11.8 (4–18.6) |
| Ca × P | 51.8 (42–56.3) | 46.5 (38.6–54.3) |
| Parathyroid hormone (pg/ml) | 204 (108–488) | 224 (120–466) |
| Total cholesterol (mg/dl) | 190 (165–234) | 197 (164–239) |
| LDL cholesterol (mg/dl) | 116 (104–147) | 122 (92–151) |
| HDL cholesterol (mg/dl) | 44 (35–51) | 44 (38–80) |
| Triglycerides (mg/dl) | 165 (129–220) | 175 (126–197) |
| Lp(a) (mg/dl) | 37 (11–65) | 45.7 (16–104) |
| Homocysteine (μmol/l) | 20 (16–27) | 18.2 (14.3–22.7) |
| IMT (mm) | 0.6 (0.50–0.67) | 0.6 (0.5–0.8) |

*P* Statistically non-significant (*P* > 0.05) for all these variables.
Patient survival was negatively influenced by co-morbidity score: patients with a co-morbidity score < 2 had a cumulative survival of 98, 89 and 85 vs 93, 64 and 55% in patients with a co-morbidity score ≥ 2, at 1, 2 and 3 years, \( P = 0.006 \) (Figure 2).

By Kaplan–Meier survival analysis, elevated levels of serum IL-6 were a significant predictor of mortality (Figure 3). Differences in survival between patients with elevated vs low serum IL-6 levels (higher vs lower median IL-6 levels) were compared using the log rank test. Eight patients died in the group with IL-6 levels higher than the median, while no fatal event occurred in the group with IL-6 equal to or below the median levels of IL-6 \( (P = 0.0019) \).

The Cox proportional hazards method was then used to evaluate the influence of baseline peritoneal hyperpermeability on patient survival of PD patients when combined with the co-morbidity score or markers of inflammation evaluated, namely CRP and IL-6. Because inclusion of covariates with high degrees of collinearity may inflate the variance of the model, inclusion of the co-morbidity score in the model was done separately from the inclusion of IL-6 and CRP. Including baseline peritoneal transport and co-morbidity score in the same model confirmed that baseline peritoneal transport \( (D/P_4 \text{ creatinine} > 0.85) \) was not a significant predictor of mortality in PD patients \( (HR = 1.13; 95\% \ CI = 0.31–4.14; \ P = 0.848) \), while a co-morbidity score > 2 remained a significant and independent marker of poor outcome \( (HR = 3.48; 95\% \ CI = 1.29–9.38; \ P = 0.014) \) (Table 3). After excluding the morbidity score from the model and including IL-6, or CRP, with baseline peritoneal transport, neither of the two inflammation markers was predictive of mortality.

Similar conclusions were obtained when MTAC creatinine was used as a measure of peritoneal small solute transport.

**Discussion**

This study showed that baseline peritoneal fast transport was not associated with markers of systemic inflammation; neither was predictive of worse patient survival in incident PD patients. Our results are in accordance with recent investigations [19–21].

It has been speculated that peritoneal hyperpermeability in the beginning of PD might impact on patient mortality due to serious associated co-morbidity, such as underlying atherosclerosis [26] and chronic inflammatory status [16], or insufficient management of fluid load and humoral abnormalities [27]. However, controversial data came from relevant recent studies [20,21].

Concerning the relationship with inflammation, a single cross-sectional [28] study involving 40 patients documented a positive correlation between D/P creatinine and serum and effluent IL-6, a sensitive marker of inflammation. Recently, a multicentre study [29]
Fig. 2. Co-morbidity score impacted negatively on patient cumulative survival (group 0 = co-morbidity score < 2, n = 56, eight events; group 1 = co-morbidity score ≥2, n = 17, eight events, P = 0.006) follow-up given in months.

Fig. 3. Serum IL-6 impacted negatively on patient cumulative survival (group 0 = IL-6 < median level, n = 21, no events; group 1 = IL-6 ≥ median level, n = 21, eight events, P = 0.0019) follow-up given in months.
Table 3. Cox proportional hazard regression model

<table>
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<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>P</th>
<th>Risk</th>
<th>95% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4/P4 creatinine &gt;0.85</td>
<td>1.225</td>
<td>0.504</td>
<td>0.848</td>
<td>1.134</td>
<td>0.311</td>
</tr>
<tr>
<td>Co-morbidity score &gt;2</td>
<td>1.575</td>
<td>2.518</td>
<td>0.014</td>
<td>3.476</td>
<td>1.289</td>
</tr>
</tbody>
</table>

Method: ‘Enter’.

demonstrated an influence of certain genetic and clinical factors on the baseline peritoneal permeability: fast transporters had higher age, higher proportion of diabetic patients, and higher prevalence of high-grade co-morbidity and cardiovascular disease. Peritoneal fast transport in this population was associated with −174 GC and CC IL-6 polymorphism and higher levels of IL-6; this inflammation biomarker was only available in 56 patients from the studied cohort. This association, however, was not reproduced in other populations [18–20,30] certainly due to different epidemiological characteristics. It was reported recently that a fast peritoneal transport status in incident non-diabetic PD patients was not related to co-morbidity nor higher levels of serum IL-6 [19]. In our study, higher age, diabetes and co-morbidity were not over-represented in fast transporters, nor did they show higher lipid levels, higher IMT or lower albumin and BMI, surrogate markers of cardiovascular disease and malnutrition. In this population, markers of inflammation such as CRP and serum IL-6 were not increased in baseline fast transporters.

On the other hand, multivariate analysis demonstrated that, while baseline fast transport did not impact on patient survival, higher co-morbidity did. In agreement with our study, Passadakis et al. [10] also did not find differences comparing the survival curves of high transporters and patients of other transport types. Chung et al. [13] were able to document poorer patient survival only in patients who, besides a hyper-permeable peritoneum, had higher co-morbidity scores. The authors contended that the severity of the underlying co-morbidity was likely to influence the prognosis more strongly than PET categorization. Davies et al. [14] also failed to document peritoneal transport as an independent predictor of patient survival, but co-morbidity was clearly a determining factor.

A protective factor in our incident population could also have been preserved RRF. A strong association between low RRF and inflammation has been shown [31], both with an impact on outcomes. Although the authors recognize the limitations of the present study due to the single-centre enrolled population, with a small number of patients with extensive co-morbidity, the results are supported by other studies. A multivariate analysis in a large study [20] revealed that higher peritoneal transport status was not independently predicted by diabetes, other co-morbid diseases or RRF. Another representative study reported a reduction of D/P creatinine at 1 year after the start of PD [32], which also questions the causal relationship of systemic inflammation and baseline peritoneal transport.

All these studies suggest that other determinants for peritoneal transport may exist in non-infamed patients: baseline hypermeability was shown to be associated with higher levels of vasoactive mediators produced by the mesothelium [18,19], certainly a more benign determinant of increased effective capillary surface at the beginning of PD.

It can be concluded that a fast peritoneal transport status in incident PD patients without an associated serious co-morbid condition cannot be explained by inflammation and does not impact negatively on patient survival. Other mechanisms of early peritoneal fast transport should be clarified, since patients with high peritoneal transport present as a heterogeneous group that is not always associated with worse outcomes.

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Conflict of interest statement. None declared.

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