

# Time Course of Peritoneal Transport Parameters in Peritoneal Dialysis Patients Who Develop Peritoneal Sclerosis

Denise E. Sampimon,<sup>1</sup> Annemieke M. Coester,<sup>1</sup> Dirk G. Struijk,<sup>1,2</sup> Raymond T. Krediet<sup>1</sup>

*Peritoneal sclerosis (PS) is a severe complication of long-term peritoneal dialysis (PD). We therefore investigated whether longitudinal analysis of solute and fluid transport preceding a diagnosis of PS could predict its development. We reviewed all standard peritoneal permeability analyses (SPAs) performed with 3.86% glucose and completed before a diagnosis of PS in all patients (n = 11) in whom that diagnosis was made in our center between 1995 and 2006. Most patients had 4 SPAs available. A linear mixed-model procedure was used to analyze the trends.*

*Transport of small-solutes showed significant inverse U-shaped trends before a diagnosis of PS. This trend held for the mass transport area coefficients of creatinine, urea, and urate (all  $p < 0.05$ ) and for their dialysate-to-plasma ratios (all  $p < 0.001$ ). Net ultrafiltration and free water transport at 60 minutes showed significant downward linear trends (both  $p \leq 0.01$ ).*

*This U-shaped trend in small-solute transport combined with an ongoing decrease in net ultrafiltration and free water transport might be a warning sign of the development of PS. It underlines the importance of regular assessment of peritoneal function with 3.86% peritoneal equilibration tests in every PD patient—not only those at risk for peritoneal membrane failure.*

## Key words

Solute transport, fluid kinetics, peritoneal sclerosis

## Introduction

Peritoneal sclerosis (PS) is a rare but severe complication of long-term peritoneal dialysis (PD) that can

occur during PD or may develop after discontinuation of PD treatment. Its development is associated with duration of PD treatment and cumulative exposure to glucose and glucose degradation products (GDPs) in PD solutions (1). Clinical symptoms include bowel obstruction, ascites, and blood in the effluent (2). A diagnosis of PS is based on clinical signs and symptoms, confirmed mostly by radiologic findings or laparotomy (2,3). In addition to its clinical symptoms, PS is functionally characterized by impaired ultrafiltration (UF) and fast small-solute transport (4).

Research focusing on early detection of PS is of major importance in the development of strategies to improve the outcome of long-term PD. In the present study, we investigated whether longitudinal analysis of solute and fluid transport could help in predicting a diagnosis of PS.

## Patients and methods

All cases of PS diagnosed at our center between 1995 and 2006 ( $n = 13$ ) were analyzed for this study. The diagnoses of PS were made at our center and were based on the presence of one or a combination of the clinical, radiologic, and macroscopic findings described in the Introduction. Additionally, to show the reliability of the diagnosis of PS, patients were categorized into three groups as outlined by Hendriks *et al.* (2). In category I ( $n = 6$ ), the diagnosis was confirmed by macroscopic examination. In category II ( $n = 4$ ), either one clinical feature was present, or the diagnosis was confirmed macroscopically. In category III ( $n = 3$ ), no definitive macroscopic diagnosis was made, and clinical findings were considered doubtful. Among the category II patients, radiologic findings were convincing for a diagnosis of PS. The patients in category III had both minimal clinical findings and radiologic alterations suggestive of PS. All

From: <sup>1</sup>Department of Internal Medicine, Division of Nephrology, Academic Medical Center, University of Amsterdam, and <sup>2</sup>Dianet Foundation, Amsterdam–Utrecht, Netherlands.

cases were reviewed by two experienced nephrologists who supported the diagnosis in 11 patients and rejected it in the other 2 cases.

All PS patients had undergone standard peritoneal permeability analyses (SPAs) before the diagnosis of PS. Patients were included in the study when at least 2 of their prior SPAs were available, with a separation interval between them of at least 6 months. The number of SPAs ranged from 2 to 4, but for most patients ( $n = 7$ ), 4 SPAs were available. The median interval between these SPAs was, on average, 1 year. The median interval from the last SPA to a diagnosis of PS was 12 months (range: 7–16); from the second-to-last SPA, it was 23 months (range: 20–28); from the third-to-last, it was 34 months (range: 29–40); and from the fourth SPA preceding the diagnosis, it was 48 months (range: 44–55). This spacing allowed us to express the time points at which the SPAs were performed as years before the diagnosis of PS.

At the time of diagnosis, the median PD duration in the study patients was 87 months (range: 46–150). Median age was 30 years (range: 18–72). Of the 11 evaluable patients, 9 had UF failure at the time of PS diagnosis. We defined UF failure as UF less than 400 mL in 4 hours during a 3.86% glucose SPA (5). Almost all of the patients used 7.5% icodextrin or 3.86% glucose solutions and had multiple abdominal surgeries and peritonitis episodes in their medical history (Table 1).

#### *Procedure for SPA*

The SPAs were performed based on 4-hour dwells with 3.86% glucose-based dialysis solution (Physioneal or Dianeal; Baxter Healthcare SA, Castlebar, Ireland) as previously described (6,7). Measurements of total dextran concentration in effluent and of sodium, small solutes, and proteins in plasma and effluent were also performed.

#### *Calculations*

Solute and fluid transport parameters were calculated as previously described (7,8). Transport of small solutes was calculated (8) as mass transfer area coefficients (MTACs) and dialysate-to-plasma (D/P) ratios. The solute concentrations in serum were corrected for plasma water (9). Net UF was calculated as the difference between the intraperitoneal volume (IPV) at the end of the dwell and the initially infused IPV.

Changes in IPV result from transcapillary ultrafiltration (TCUF) and fluid absorption. We used the intraperitoneally administered volume marker dextran 70 to assess TCUF and changes in IPV during the dwell (6,7). The TCUF comprises both free water transport (FWT) and small-pore water transport (SPT). The SPT is always accompanied by convective transport. Therefore, FWT was calculated by subtracting TCUF coupled to sodium (SPT) from TCUF as previously described (7). A diffusion correction for sodium seiving was applied using the MTAC of urate (10). The contribution of FWT was examined after 60 minutes and was expressed as an absolute value.

#### *Statistics*

Data are presented as medians and ranges. A linear mixed model procedure was used to analyze the trends in peritoneal solute transport and fluid kinetics. The pairwise comparisons in this trend analysis were adjusted with a Bonferroni correction for multiple comparisons.

#### **Results**

Peritoneal small-solute transport showed significant inverse U-shaped trends before the diagnosis of PS. Figure 1, left panel, shows this pattern for the MTAC of creatinine, the MTAC of urea ( $p = 0.01$ ), and the MTAC of urate ( $p = 0.02$ ). The increase in this inverse U-shape from the fourth to the second year before the diagnosis of PS was significant for all three solutes ( $p < 0.05$ ). At 1 year before the diagnosis of PS, this increase attenuated and even showed a decrease, but the decrease did not reach statistical significance.

Given that the increasing peritoneal small-solute transport in long-term PD most likely reflects a more permanent increase in vascular surface area, an ongoing linear increase would be expected. Therefore, for every patient, we produced a linear extrapolation (estimated MTAC) for the SPA immediately before the PS diagnosis, based on the results obtained in the earlier SPAs. Using a Kruskal–Wallis test, we observed a significant difference between the actual and extrapolated MTACs for all small solutes ( $p = 0.003$ ). Glucose absorption (Figure 1, right panel) and D/P ratios of the small solutes showed the same significant U-shaped trends (all  $p < 0.001$ ).

Significant U-shaped trends were also present for the larger solutes  $\beta_2$ -microglobulin ( $p < 0.001$ ) and immunoglobulin-G ( $p = 0.05$ ), but not for albumin

TABLE I Clinical characteristics of all patients who developed peritoneal sclerosis (PS)

Patient	Primary kidney disease	PD fluid use		Abdominal surgeries (n)	Total peritonitis episodes	Peritoneal sclerosis category	Outcome
		Icodextrin	3.86% Glucose				
1	Alport disease	Yes	Yes	8	4	I	Died
2	Hypertensive nephropathy	Yes	Yes	2	17	I	Hemodialysis
3	Polycystic kidney disease	Yes	Yes	5	3	I	Died from PS
4	Glomerulonephritis	Yes	No	5	2	II	Renal transplant
5	Hypertensive nephropathy	Yes	Yes	2	4	I	Died from PS
6	Glomerulonephritis	No	Yes	9	0	I	Renal transplant
7	Reflux nephropathy	Yes	Yes	3	3	II	Died
8	Polycystic kidney disease	Yes	Yes	4	0	II	Renal transplant
9	Chronic interstitial nephritis	Yes	Yes	2	4	I	Died
10	Reflux nephropathy	Yes	Yes	5	3	II	Hemodialysis
11	Glomerulonephritis	No	Yes	4	6	III	Hemodialysis

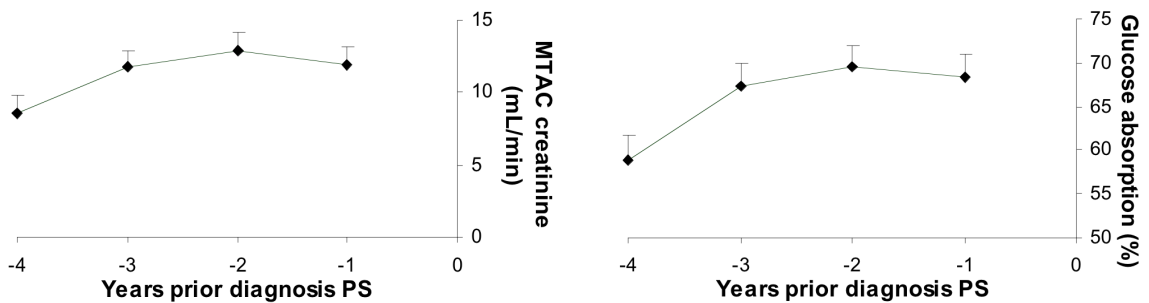


FIGURE 1 Trends in small-solute transport are given for the mass transfer area coefficient (MTAC) of creatinine (left panel) and peritoneal glucose absorption (right panel). Time point 0 indicates the diagnosis of peritoneal sclerosis (PS). For both solutes, we found significant ( $p = 0.01$ ) inverse U-shaped trends.

( $p = 0.6$ ) or  $\alpha_2$ -macroglobulin ( $p = 0.2$ ). As was the case with the small solutes, clearances of immunoglobulin-G and  $\alpha_2$ -macroglobulin showed an increasing trend, reaching a maximum value 2 years before the diagnosis of PS. No such trend was seen with  $\beta_2$ -microglobulin and albumin, which had already reached their maximum values at 3 years before the PS diagnosis.

Net UF at the time of the last SPA before diagnosis of PS was 124 mL (range: -113 to 594 mL). Net UF (Figure 2, left panel) and FWT at 60 minutes (Fig-

ure 2, right panel) showed significant downward linear trends.

**Discussion**

In the present study, patients with PS fulfilled the previously formulated PS criteria (1). In contrast with many other studies, extensive longitudinal assessments of peritoneal function were available in this population, permitting a longitudinal analysis of the evolution of various peritoneal transport parameters.

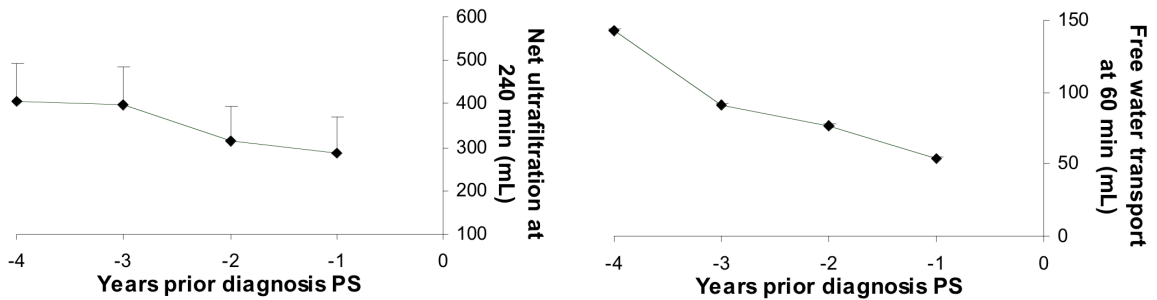


FIGURE 2 Trends for fluid transport are given for net ultrafiltration (left panel) and free water transport at 60 minutes (right panel). Time point 0 indicates the diagnosis of peritoneal sclerosis (PS). For both fluid transport indicators, significant ( $p \leq 0.01$ ) downward linear trends were found.

The trends in transport that we observed are in line with the general assumption that peritoneal solute transport increases and UF capacity decreases with the duration of PD treatment, suggesting development of an increased peritoneal surface area (11). However, predicting which patients will develop marked peritoneal membrane failure remains difficult, because of a parallel increase in the inpatient variability in transport parameters with duration of PD (11) and as judged from the large range in PD duration seen in our PS patients. We therefore investigated whether longitudinal analysis of solute and fluid transport preceding a diagnosis of PS could help to predict its development.

Peritoneal small-solute transport showed a significant inverse U-shaped trend, with maximum values being reached at 2 years before the diagnosis of PS. The increase in this trend suggests an increasing peritoneal surface area because of neoangiogenesis (11), a more permanent peritoneal membrane alteration. The subsequent decrease in small-solute transport 1 year before the PS diagnosis was not significantly different from the maximum value noted at 2 years before the PS diagnosis. A low incidence of PS (1) meant that only a small number of patients were available for the study, which is the most likely reason for an absence of statistically significant results.

The attenuation in the trend of peritoneal solute transport was more significant when expressed as the difference between the actual and estimated peritoneal small-solute transport at 1 year before the PS diagnosis. A hypothesis for this deviation from the

established trend of solute transport is speculative, but it could be that fibrotic abnormalities in peritoneal interstitial tissue are involved. Whether the peritoneum and the dialysate in the peritoneal cavity contribute to the problem is unknown. Also, extensive loss of the mesothelium may diminish the synthesis and release of vasoactive substances. Studies are required to distinguish between these possibilities.

Net UF and FWT at 60 minutes both showed significant downward linear trends with the development of PS. Given the inverse U-shaped trend in peritoneal small-solute transport, a mirror image for net UF and FWT would have been expected. A smaller peritoneal vascular surface area leads to less-rapid dissipation of glucose as the osmotic agent, which was indeed shown by decreased glucose absorption 1 year before the PS diagnosis. That situation would result in higher FWT and net UF. Our finding of the opposite case suggests a specific impairment of peritoneal water transport. Whether that impairment is attributable to aquaporin-1 dysfunction or to more diffuse alterations in the peritoneal interstitial tissues is currently unknown.

Because the SPAs were conducted at fixed intervals to correct for duration of PD, we think that our findings regarding the time course of peritoneal transport are specific for the development of PS. These findings include a combination of blunting or even a reversal of a previous upward trend in peritoneal small-solute transport combined with an ongoing decrease in UF and FWT. The case history described by Verger *et al.* (12) fits this concept.

### Conclusions

A U-shaped trend toward a decrease in small-solute transport combined with an ongoing decrease in net UF and FWT at 60 minutes might be a warning sign for the development of PS. This finding underlines the importance of regular assessment of peritoneal function with 3.86% peritoneal equilibration tests in every PD patient—not just for those at risk of peritoneal membrane failure.

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#### Corresponding author:

Annemieke M. Coester, MD, Academic Medical Center, University of Amsterdam, Department of Internal Medicine, Division of Nephrology, A01-114, PO Box 22700, Amsterdam 1100 DE Netherlands.

#### E-mail:

a.m.coester@amc.uva.nl