THE MUTUAL RELATIONSHIP BETWEEN PERITONITIS AND PERITONEAL TRANSPORT

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◆ **Background:** Preservation of the peritoneum is required for long-term peritoneal dialysis (PD). We investigated the effect of multiple peritonitis episodes on peritoneal transport.

◆ **Methods:** Prospectively collected data from 479 incident PD patients treated between 1990 and 2010 were analyzed, using strict inclusion criteria: follow-up of at least 3 years with the availability of a Standard Peritoneal Permeability Analysis (SPA) in the first year after start of PD and within the third year of PD, without peritonitis preceding the first SPA. For the purpose of the study, we only included patients who remained peritonitis-free ($n = 28$) or who experienced 3 or more peritonitis episodes ($n = 16$).

◆ **Results:** At baseline the groups were similar with regard to small solute and fluid transport. However, the frequent peritonitis group had lower peritoneal protein clearances compared to the no peritonitis group, resulting in lower dialysate concentrations of proteins: albumin 196.5 mg/L vs 372.5 mg/L, IgG 36.4 mg/L vs 65.0 mg/L, and α -2-macroglobulin (A2M) 1.9 mg/L vs 3.6 mg/L, $p < 0.01$. No differences in serum concentrations were present. A comparison between the transport slopes over time in both groups showed a positive time trend of mass transfer area coefficient (MTAC) creatinine ($p = 0.03$) and glucose absorption ($p = 0.09$) and a negative trend of transcapillary ultrafiltration ($p = 0.06$), when compared to the no peritonitis group. Frequent peritonitis did not affect free water transport.

◆ **Conclusions:** Slow initial peritoneal transport rates of serum proteins result in lower dialysate concentrations, and likely a lower opsonic activity, which is a risk factor for peritonitis. Patients with frequent peritonitis show an increase in small solute transport and a concomitant decrease of ultrafiltration. In long-term peritonitis-free PD patients, small solute transport decreased, while ultrafiltration increased. This suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area without all the structural membrane alterations that may develop after long-term PD.

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Structural and functional integrity of the peritoneum is of crucial importance for successful peritoneal dialysis (PD). However, in some long-term PD patients treatment is associated with morphologic and functional peritoneal alterations (1). It is well-known that acute peritonitis causes temporary changes in peritoneal transport parameters, like increased solute transport and protein loss, leading to ultrafiltration failure. This is observed both during intermittent PD (2) and continuous ambulatory PD (CAPD) (3,4). In CAPD, these phenomena return to normal values within 2 weeks after cure of the infection, parallel to the locally produced vasoactive substances that caused them (5).

Studies on permanent effects of peritonitis on peritoneal transport have shown inconsistent results. Some studies showed no effect (6), while others demonstrated a clear consequence of peritonitis on peritoneal membrane function (7–10). Some researchers only found a change in peritoneal transport after severe peritonitis or after frequent peritonitis episodes (8,9). However, all these studies suffered the lack of a control group representing the natural course.

In a recent study, we investigated the possible effect of the very first peritonitis episode on peritoneal transport characteristics in new PD patients and distinguished

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its effect from the natural course (11). Patients who experienced a first peritonitis episode later remained at a faster transport state compared to patients without peritonitis. In addition, a decrease in macromolecular transport and an increase in its size-selectivity was found. Previously, Del Peso *et al.* showed a decreasing mass transfer area coefficient (MTAC) creatinine and increasing ultrafiltration within the first year after the start of dialysis. Similar to our findings, this was not present in patients who suffered peritonitis (12).

Controversy exists about the impact of frequent peritonitis on peritoneal transport characteristics. Therefore, the aim of the present study was to make a comparison of peritoneal transport characteristics between incident PD patients with more than 3 peritonitis episodes during a follow-up of 3 years, and a control group of similar patients who did not experience any peritonitis episode before and during the same follow-up time.

PATIENTS AND METHODS

PATIENTS

Between 1990 and 2010, all adult patients starting PD in a tertiary-care university hospital were included in the study. Data about peritonitis episodes and peritoneal transport characteristics were collected prospectively in a large database. We compared a Standard Peritoneal permeability Analysis (SPA) in the first year after start of PD ('baseline') and a SPA within the third year of PD ('late'). Patients either had to remain peritonitis-free or experienced 3 or more peritonitis episodes during the 3-year follow-up period. Data were excluded from the analyses, when peritonitis preceded the baseline SPA or when a SPA was performed within the acute phase of 30 days after peritonitis (Figure 1). Patients were treated with Dianeal (Baxter Healthcare S.A., Castlebar, Ireland) between 1990 and 1997, with Dianeal or Physioneal (Baxter Healthcare S.A., Castlebar, Ireland) between

1998 and 2004, and with Physioneal between 2005 and 2010. The use of icodextrin started in 1997.

PERITONITIS

Peritonitis was diagnosed when at least 2 of 3 findings were present: clinical symptoms, effluent cell count > 100 cells/ μ L, and a positive culture of the dialysate. These criteria have been developed by Vas *et al.* (13) and adopted by the current guidelines of the International Society for Peritoneal Dialysis (ISPD) (14). All episodes were treated empirically with a first-generation cephalosporin, which was combined with gentamicin when the patient was clinically ill and needed hospitalization. Antibiotic treatment thereafter could be adjusted according to the resistance of the causative organism. Treatment duration was 1 week after cultures had become negative and cell counts reached less than 100 cells/ μ L. The previously described protocol was published in 1985 and has not been changed since that time (15).

STANDARD PERITONEAL PERMEABILITY ANALYSES (SPA)

Since 1990, a SPA was performed yearly to assess peritoneal transport characteristics (16,17). Only SPAs using solutions containing 3.86% glucose were selected for this study. Standard peritoneal permeability analyses measurements included the MTAC of creatinine, the percentage of glucose absorption and peritoneal clearances of serum proteins β -2-microglobulin (B2M), albumin, IgG and α -2-macroglobulin (A2M). The restriction coefficient to macromolecules (RC) was calculated from these clearances (18). It represents the size-selectivity of the peritoneal membrane, i.e. the average large pore radius. In addition, parameters of fluid transport were determined: transcapillary ultrafiltration, effective lymphatic absorption, and free water transport (19). All calculations were performed as previously described by Pannekeet *et al.* (16) and Smit *et al.* (19,20).

STATISTICAL ANALYSES

An independent Student *t*-test, Mann-Whitney (continuous data) or chi-square test (categorical data) was used to assess differences in baseline clinical characteristics and baseline SPA measurements between the group without peritonitis and the frequent peritonitis group. To compare baseline and late measurements in individual patients, a paired sample *t*-test or Wilcoxon signed ranks test (dependent on the distribution of

Figure 1 — Study design. *The “late” SPA was never done within 30 days after an episode of acute peritonitis. PD = peritoneal dialysis; SPA = standard peritoneal permeability analysis.

the data) was used. Results are expressed as mean values and standard deviations, or as median values with interquartile range. Crude and adjusted linear mixed models were performed to differentiate between changes in peritoneal transport characteristics caused by frequent peritonitis episodes, from the possible effects caused by PD duration itself. Adjustments were made for age and diabetes. Results are expressed as crude and adjusted slope differences and 95% confidence intervals (CIs). Data analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

SENSITIVITY ANALYSES

Adjusted linear mixed models were used to investigate whether the time period of start of PD, the number of peritonitis episodes, or the severity of peritonitis modified the effect of peritonitis on peritoneal transport. For this purpose only, a group with 1 or 2 peritonitis episodes (intermediate) was added. The patient cohort was stratified by the time period PD was started: time period 1990 to 2000 or 2000 to 2010. Severe peritonitis was specified as 1 or more peritonitis episodes with a leukocyte count $> 1,090$ cells/mm³ on day 3 or > 100 cells/mm³ on day 5 of the peritonitis episode and compared to a reference group of less severe peritonitis. Results are expressed as adjusted slope differences and 95% CIs. A separate analysis could not be done for the kind of dialysis solution used, because of the small number of patients in the various subgroups.

RESULTS

POPULATION CHARACTERISTICS

Between 1990 and 2010, 479 adult patients started PD in our center. Of these patients, 435 patients were excluded. More than half of the patients had an insufficient time of follow-up on PD, 31% had missing SPA data, 3% had an episode of peritonitis before the first SPA and 5% had only 1 or 2 episodes of peritonitis. Eventually, 44 patients were included in the analysis, 28 patients who remained peritonitis-free and 16 patients who experienced 3 or more episodes of peritonitis (Figure 2). The baseline characteristics are summarized in Table 1. Both groups were similar at baseline with respect to age, percentage of males, distribution of causes of end-stage renal disease (ESRD), the Davies comorbidity score, treatment modality and time period of start of PD. No differences in baseline characteristics (age, sex, and cause of ESRD) were found between the excluded and included patients in this study.

Figure 2 — Flow chart patient selection. The reasons for insufficient follow-up include death, transplantation, or transfer to hemodialysis. PD = peritoneal dialysis; SPA = standard peritoneal permeability analysis.

CHANGE IN PERITONEAL TRANSPORT STATUS FROM BASELINE TO LATE PER GROUP

Table 2 shows a comparison of baseline and late peritoneal transport parameters per group. The no peritonitis group, in which the natural time course is reflected, showed a significant decrease from baseline to late in PD treatment for MTAC creatinine ($p = 0.01$) and glucose absorption ($p = 0.03$), accompanied by an increasing trend for transcapillary ultrafiltration ($p = 0.09$). No differences were observed for the protein clearances, effective lymphatic absorption, or free water transport. In contrast, only a significant increase was found for the clearance of albumin in the frequent peritonitis group.

COMPARISON OF BASELINE AND LATE PERITONEAL TRANSPORT STATUS BETWEEN THE GROUPS

A comparison between the no peritonitis group and the frequent peritonitis group at the baseline SPA and at the late SPA is shown in Table 2. Median time on PD to the baseline SPA was 5 months in the no peritonitis group and 4 months in the frequent peritonitis group, $p = 0.11$. Median time to a late SPA was 39 months in both groups, $p = 0.72$. The median time between a baseline SPA and a late SPA was 35 months in the group without peritonitis and 36 months in the frequent peritonitis group, $p = 0.28$.

No differences between the no peritonitis group and the frequent peritonitis group were observed at baseline for small solute transport, transcapillary ultrafiltration, lymphatic absorption, and free water transport. However, at baseline, peritoneal clearances of the serum proteins albumin ($p = 0.02$), IgG ($p = 0.01$),

TABLE 1
Baseline Characteristics of the Patients

	No peritonitis	Frequent peritonitis	<i>p</i> value
Number of patients	28	16	
Sex (M:F)	14:14	10:6	0.42
Mean age (yrs) at start PD	55±14	50±14	0.34
Time period of start PD (1990–2000 : 2000–2010)	14:14	10:6	0.42
Diabetes	11	4	0.34
Cause of ESRD			0.81
Renal vascular disease	3	5	
Diabetic nephropathy	9	4	
Glomerulonephritis	6	2	
Other	10	5	
Davies comorbidity score (%)			0.20
0 comorbidities	29	38	
1–2 comorbidities	54	63	
≥ 3 comorbidities	18	0	
Treatment modality (APD:CAPD)	6:22	5:11	0.47
Residual GFR at baseline, estimated by serum β-2-microglobulin (mg/L)	19.4±8.2	23.8±7.9	0.11
Time from start PD to baseline SPA in months (median [IQR])	5 (4–6)	4 (3–6)	0.11
Time from start PD to late SPA in months (median [IQR])	39 (32–41)	39 (33–41)	0.72
Time between baseline and late SPA (median [IQR])	35 (26–36)	36 (27–37)	0.28

PD = peritoneal dialysis; ESRD = end-stage renal disease; APD = automated peritoneal dialysis; CAPD = continuous ambulatory PD; GFR = glomerular filtration rate; SPA = standard peritoneal permeability analysis; IQR = interquartile range.

TABLE 2
Comparison of Baseline and Late Peritoneal Transport Parameters Between the Group Without Peritonitis
and the Group With Frequent Peritonitis Episodes

	Baseline SPA		Late SPA	
	No peritonitis	Frequent peritonitis	No peritonitis	Frequent peritonitis
SPA measurement	Mean±SD	Mean±SD	Mean±SD	Mean±SD
MTAC creatinine (mL/min)	11.8±4.1	10.0±3.2	10.0±3.2 ^b	11.5±3.2
Glucose absorption (%)	64±10	61±10	59±9 ^b	64±86
Clearance				
B2M (mL/min)	1.2±0.5	1.0±0.4	1.1±0.3	1.2±0.4
Albumin (mL/min)	0.11±0.05	0.07±0.03 ^a	0.10±0.04	0.10±0.04 ^c
IgG (μL/min)	59±30	36±16 ^a	56±34	54±25
A2M (μL/min)	23±20	11±7 ^a	19±23	15±10
Restriction coefficient	2.39±0.32	2.64±0.34 ^a	2.48±0.35	2.64±0.52
ELAR (mL/min)	1.53±0.75	1.48±0.55	1.65±0.85	1.14±0.62 ^a
TCUFR (mL/min)	3.0±1.56	3.91±1.50	3.52±1.50	3.56±1.31
Free water transport 0–60 min (mL)	123.3±65.0	141.5±62.4	131.9±85.4	135.7±55.4

SPA = standard peritoneal permeability analysis; SD = standard deviation; MTAC = mass transfer area coefficient; B2M = β-2-microglobulin; IgG = Immunoglobulin G; A2M = α-2-macroglobulin; ELAR = effective lymphatic absorption rate; TCUFR = transcapillary ultrafiltration rate.

^a Significantly different (*p*<0.05) between no peritonitis and frequent peritonitis group, either at baseline or after 3 years.

^b Significantly lower than the baseline SPA of the no peritonitis group.

^c Significantly higher than the baseline SPA of the frequent peritonitis group.

and A2M ($p = 0.02$) were significantly lower in the frequent peritonitis group compared with the no peritonitis group, with a concomitant higher restriction coefficient to macromolecules. No differences were present in the plasma concentrations of these proteins to explain the difference in clearances between the groups at baseline. However, the dialysate concentrations of the macromolecules at baseline were significantly ($p < 0.01$) lower in the frequent peritonitis group compared to the no peritonitis group, median: albumin 196.5 mg/L vs 372.5 mg/L, IgG 36.4 mg/L vs 65.0 mg/L, and A2M 1.9 mg/L vs 3.6 mg/L. No significant increase of dialysate IgG was found in the group without peritonitis (Figure 3, panel A), while in the frequent peritonitis group an increase was present from baseline to late in PD treatment (Figure 3, panel B, $p = 0.04$). Late in PD treatment, the differences in dialysate concentrations of serum proteins between the groups were no longer present.

Comparison of late SPA measurements between the groups showed only a significantly lower effective lymphatic absorption ($p = 0.04$) in the frequent peritonitis group.

THE EFFECT OF FREQUENT PERITONITIS EPISODES COMPARED TO THE NATURAL COURSE

A comparison between the slope of peritoneal transport characteristics in the frequent peritonitis group and the

group without peritonitis was made. Table 3 shows crude and adjusted slope differences. This is further illustrated in Figure 4. After frequent peritonitis episodes, patients had a positive time course of MTAC creatinine and glucose absorption, leading to an increase, when compared to patients without peritonitis (MTAC creatinine: adjusted slope difference: 3.04, 95% CI: 0.40 – 5.67, $p = 0.03$; glucose absorption: adjusted slope difference: 6, 95% CI: -1 – 14, $p = 0.09$). This was accompanied by a negative time course of transcapillary ultrafiltration, leading to a decrease (adjusted slope difference: -0.81, 95% CI: -1.63 – 0.02, $p = 0.06$), when compared to the group without peritonitis. Also, patients in the frequent peritonitis group had a positive time course of the protein clearances B2M and albumin, leading to an increase in comparison with the patients without peritonitis (B2M: adjusted slope difference: 0.30, 95% CI: -0.003 – 0.60, $p = 0.05$; albumin: adjusted slope difference: 0.04, 95% CI: 0.005 – 0.07, $p = 0.02$). Frequent peritonitis episodes did not significantly affect the time course of IgG and A2M clearances, lymphatic absorption and free water transport.

SENSITIVITY ANALYSES

Sensitivity analyses showed no effect of the time period of patient inclusion, nor of the number of peritonitis episodes (supplemental data), or their severity

Figure 3 — Scatter plots for individual dialysate IgG concentrations. Panel A and B: Dialysate IgG for patients without peritonitis (panel A) and patients with frequent peritonitis episodes (panel B) at baseline and late in PD treatment. At baseline, the dialysate concentrations of dialysate IgG were significantly ($p < 0.01$) lower in the frequent peritonitis group compared to the no peritonitis group. The dots represent individual patients, the lines represent the median and IQR. IgG = Immunoglobulin G; PD = peritoneal dialysis; IQR = interquartile range.

TABLE 3
Comparison of the Rate of Change in Transport Parameters Between the Frequent Peritonitis Group ($n=16$) and the No Peritonitis Group ($n=28$)

SPA measurement	Crude slope difference (95% CI)	<i>p</i> value	Adjusted* slope difference (95% CI)	<i>p</i> value
MTAC creatinine (mL/min)	3.47 (1.01–5.93)	0.01	3.04 (0.40–5.67)	0.03
Glucose absorption (%)	8 (0.2–15)	0.04	6 (–1–14)	0.09
Clearance				
B2M (mL/min)	0.31 (0.02–0.60)	0.04	0.30 (–0.003–0.60)	0.05
Albumin (mL/min)	0.04 (0.006–0.06)	0.02	0.04 (0.005–0.07)	0.02
IgG (μL/min)	20.9 (–1.1–42.9)	0.06	20.3 (–2.5–43.1)	0.08
A2M (μL/min)	7.9 (–4.9–20.7)	0.22	8.6 (–4.8–21.9)	0.20
Restriction coefficient	–0.08 (–0.41–0.24)	0.60	–0.06 (–0.40–0.28)	0.73
ELAR (mL/min)	–0.45 (–1.03–0.14)	0.13	–0.44 (–1.04–0.16)	0.14
TCUFR (mL/min)	–0.80 (–1.61– –0.0001)	0.05	–0.81 (–1.63–0.02)	0.06
Free water transport 0–60min (mL)	–16.4 (–82.0–49.3)	0.62	1.63 (–65.0–68.2)	0.96

SPA = standard peritoneal permeability analysis; CI = confidence interval; MTAC = mass transfer area coefficient; B2M = β -2-microglobulin; IgG = Immunoglobulin G; A2M = α -2-macroglobulin; ELAR = effective lymphatic absorption rate; TCUFR = transcapillary ultrafiltration rate.

Linear mixed models were performed with the group without peritonitis as the reference group.

* Adjusted for age and diabetes.

Figure 4 — SPA parameters for the no peritonitis group and the frequent peritonitis group, at baseline and late in PD treatment. Baseline values were set to 100%. MTAC creatinine (closed circles), glucose absorption (open circles), TCUFR (closed squares), and the restriction coefficient (closed triangles) are given. When comparing the slopes of the transport parameters between the no peritonitis and the frequent peritonitis group, frequent peritonitis was associated with the development of a faster small solute transport (MTAC creatinine $p = 0.03$, glucose absorption $p = 0.09$) and a concomitant lower TCUFR ($p = 0.06$). No difference in the rate of change of the restriction coefficient was found ($p = 0.73$). SPA = standard peritoneal permeability analysis; TCUFR = transcapillary ultrafiltration rate; MTAC = mass transfer area coefficient.

on the time course of peritoneal transport. The intermediate peritonitis group had a time course very similar to that in the no peritonitis group. Severe peritonitis episodes showed a similar association to that of mild peritonitis with peritoneal transport, as shown in Table 4.

DISCUSSION

In the present study, we found that patients who experienced frequent episodes of peritonitis during a 3-year follow-up period had lower peritoneal clearances of serum proteins at the start of PD treatment,

TABLE 4
Peritonitis Group Stratified by Peritonitis Severity

SPA measurement	Adjusted* slope difference (95% CI)	p value
MTAC creatinine (mL/min)	-0.43 (-6.04–5.18)	0.87
Glucose absorption (%)	1 (-17–19)	0.93
TCUFR (mL/min)	-0.43 (-2.01–1.14)	0.56

SPA = standard peritoneal permeability analysis; CI = confidence interval; MTAC creatinine = mass transfer area coefficient of creatinine; TCUFR = transcapillary ultrafiltration rate.

Adjusted linear mixed models were performed.

* Adjusted for age and diabetes. Severe peritonitis ($n=9$) was defined as one or more peritonitis episodes with a leukocyte count $> 1,090$ cells/mm³ on day 3 or >100 cells/mm³ on day 5 of the peritonitis episode compared to a reference group of less severe peritonitis ($n=7$).

compared to patients without peritonitis. A concomitant higher restriction coefficient to these macromolecules in the frequent peritonitis group was found. Peritoneal transport of macromolecules from the circulation to the dialysate is size-selectively restricted by the intrinsic permeability of the peritoneal membrane (20,21). As a consequence, their MTACs or clearances are determined both by the effective peritoneal surface area (the total number of intercellular pores) and by the intrinsic peritoneal permeability (the large pore radius). The latter can be expressed as the peritoneal restriction coefficient, thus the higher the restriction coefficient, the lower the permeability to macromolecules. Peritoneal MTACs of solutes can be used as an indicator for the effective peritoneal surface area, provided that their transport is not hampered by the intrinsic permeability of the membrane, which is the case for small solutes, including B2M (22,23). In the present study, no difference in B2M clearance between the no peritonitis and frequent peritonitis group was found at baseline. However, differences were found in the clearances of larger proteins, like albumin, IgG, and A2M, indicating that rather than a lower effective surface area, a lower intrinsic permeability of the peritoneal membrane is the cause of this observation. As a consequence, this led to lower dialysate concentrations of albumin, IgG and A2M.

Evidence suggests that cytokines, such as interleukin-6 (IL-6), growth factors like vascular endothelial growth factor, together with the release of nitric oxide by endothelial cells, play an important role in the regulation of vascular density and permeability within the peritoneum. Zemel *et al.* reported local production of IL-6 within the

peritoneal cavity in stable CAPD patients without peritonitis (24). Dialysate IL-6 was related to permeability characteristics of the peritoneal membrane, because elevated levels of IL-6 were associated with an increased intrinsic permeability and higher IgG clearances. Pecoits-Filho *et al.* found relationships between dialysate IL-6 and peritoneal albumin clearances (25). The possibility of IL-6 as a determinant of differences in peritoneal membrane transport characteristics at the start of PD is further supported by the finding of Gillerot *et al.* who identified the -174 G/C polymorphism of IL-6 as an independent predictor of solute transport. In that study, dialysate IL-6 concentrations were higher at the start of PD in patients harboring the CC and GC genotypes compared with the GG genotype (26). It may be that some patients at the start of PD have low dialysate IL-6 concentrations leading to a decreased large pore size, with decreased permeability of the peritoneal membrane and low dialysate protein levels as a consequence. However, effluent IL-6 concentrations were not available in the present study. In our analysis, the frequent peritonitis group was the group with lower dialysate IgG levels at the start of PD, compared to the no peritonitis group. Others found that baseline values of peritoneal protein leakage, estimated by peritoneal total protein clearance, were independent predictors of peritonitis. However, unlike our study, analysis of individual proteins in PD effluent was not performed and total protein losses were measured in 24-hour effluent (27,28). In contrast, Zemel *et al.* did not find a correlation between dialysate IgG concentration and overall peritonitis incidence (29), but in this study dialysate IgG was determined at any moment during PD.

It is known that for most pathogens, opsonization is essential for efficient phagocytosis. This is dependent on the concentration of specific IgG and/or alternate pathway complement components. *In vitro* studies have shown that dialysate IgG is involved in the opsonization of bacteria (30–32). We hypothesize that slow initial peritoneal transport rates of serum proteins result in lower dialysate concentrations of IgG, and likely a lower opsonic activity, which is a risk factor for peritonitis. This is supported by the findings of Lamperi *et al.* (33). These authors found a significant correlation between the opsonization capacity for bacteria and IgG concentrations in peritoneal effluent. Moreover, they reported an inverse correlation between the opsonic capacity of effluent and the number of episodes of peritonitis. Intraperitoneal immunoglobulin treatment raised the dialysate opsonization capacity and lowered peritonitis incidence in patients with a previously high incidence of peritonitis. In another study, these authors demonstrated that for patients in whom the immunoglobulin

therapy did not reduce the peritonitis incidence, only transient increases in the dialysate IgG and opsonic activity levels were present. This was due to a defective number of peritoneal macrophages Fc receptors, and consequently, a decreased binding capacity of IgG (34).

After 3 years of PD, the differences in dialysate concentrations of macromolecules between the no peritonitis group and the frequent peritonitis group were no longer present. Several studies reported increased dialysate levels of cytokines and eicosanoids during peritonitis (35,36), leading to an increase of the effective surface area of the peritoneum, increased protein clearances and a concomitant decreased restriction coefficient (5). It may be that after several episodes of peritonitis, these effects are not only temporary, but also partly sustained, which explains the observation that after 3 years of PD, the dialysate concentrations of macromolecules are equal between the 2 groups.

In the present study, patients with frequent peritonitis episodes showed an increase in small solute transport and a decrease of ultrafiltration, which was not found in peritonitis-free patients. The latter group, in which the natural time course of peritoneal transport is reflected, showed a significant decrease from baseline to late in PD treatment for MTAC creatinine and glucose absorption, accompanied by an increasing trend for transcapillary ultrafiltration. This is in contrast with previous studies showing an increase in small solute transport and glucose absorption with time on PD (37–40). Apparently, this does not apply to patients without peritonitis, or patients with only 1 or 2 peritonitis episodes. Therefore, the detrimental effects on the time course of peritoneal transport are only evident in patients with frequent peritonitis episodes. Several studies found no correlation between peritonitis and changes in peritoneal transport (41–43), probably due to the short observation time, a sub-optimal assessment of peritoneal function or by inclusion of patients with a limited number of peritonitis episodes. In concordance with our findings, Davies *et al.* showed that frequent peritonitis episodes were associated with significant increases in D/P creatinine and reductions in ultrafiltration volume (8). This was also found in a more recent study by Fernández-Reyes *et al.* (44). It suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area. Our observation that frequent peritonitis episodes had no significant effect on the time course of the restriction coefficient to macromolecules suggests that the increase in the effective peritoneal surface area may develop without the concomitant fibrotic structural membrane alterations that may develop after long-term PD.

The present study has some limitations. First, the

study population represents a selective group of patients. Because PD is associated with a high drop-out rate due to technique failure, transplantation, or death, 53% of the original cohort of patients could not be included because of an insufficient follow-up, mainly due to transplantation or death. Obviously, patients with a more severe peritonitis episode were more at risk to be lost to follow-up. However, this selection procedure will lead to the loss of more patients with altered solute transport and ultrafiltration failure, making the observation of this study more clinically relevant. Moreover, there were no differences in patient characteristics between both groups at baseline. In addition, it can be speculated that the lower peritoneal clearance of macromolecules found in the frequent peritonitis group at baseline is due to informative censoring, as recently pointed out by Yu *et al.* (10). These authors refer to studies in which a high protein clearance at baseline is an independent predictor of survival, which may result in the potential confounding of longitudinal data due to earlier dropout of patients with high protein clearances. However, in a larger study with a longer observation period no association between protein clearance and survival was found (45). Second, dialysate concentrations of cytokines and growth factors could not be determined, as discussed above. Nevertheless, previous studies clearly demonstrated the role of IL-6 in peritoneal protein transport (25,26). Thirdly, in our dialysis unit the type of dialysis solution has been changed over the years. Although we could not analyze possible effects of these changes, the sensitivity analysis comparing the 2 time periods gives no indication for this. One of the strengths of this study is the use of the SPA instead of the peritoneal equilibration test (PET), which provides additional information on pathways of fluid transport and includes the peritoneal clearances of several serum proteins from which the restriction coefficient to macromolecules can be calculated (46). Moreover, very strict inclusion criteria were used: a SPA within the first year and within the third year of PD had to be available, without peritonitis preceding the first SPA. A group without peritonitis and a group with frequent peritonitis were formed. Because of this, we were able to distinguish between changes in peritoneal transport due to frequent peritonitis episodes and changes caused by PD duration itself.

CONCLUSIONS

The present study has demonstrated that patients with frequent peritonitis episodes had an increase in small solute transport and a decrease of ultrafiltration, which was not found in patients without peritonitis. This

suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area without all the structural fibrotic membrane alterations that may develop after long-term PD. In addition, compared to patients without peritonitis, patients who experienced frequent episodes of peritonitis had lower peritoneal clearances of serum proteins at the start of PD. These lower clearances result in lower dialysate concentrations of IgG and likely a lower opsonic activity, which is a risk factor for peritonitis.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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