THE FIRST PERITONITIS EPISODE ALTERS THE NATURAL COURSE OF PERITONEAL MEMBRANE CHARACTERISTICS IN PERITONEAL DIALYSIS PATIENTS

Anouk T.N. van Diepen,*[1] Sadie van Esch,*[1,2] Dirk G. Struijk,[1,3] and Raymond T. Krediet[1]

Division of Nephrology,[1] Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Nephrology Department and Internal Medicine,[2] St Elisabeth Hospital, Tilburg,
The Netherlands; and Dianet,[3] Amsterdam-Utrecht, The Netherlands

♦ *Objective:* Little or no evidence is available on the impact of the first peritonitis episode on peritoneal transport characteristics. The objective of this study was to investigate the importance of the very first peritonitis episode and distinguish its effect from the natural course by comparison of peritoneal transport before and after infection.

♦ *Participants:* We analyzed prospectively collected data from 541 incident peritoneal dialysis (PD) patients, aged > 18 years, between 1990 and 2010. Standard Peritoneal Permeability Analyses (SPA) within the year before and within the year after (but not within 30 days) the first peritonitis were compared. In a control group without peritonitis, SPAs within the first and second year of PD were compared.

♦ *Main outcome measurements:* SPA data included the mass transfer area coefficient of creatinine, glucose absorption and peritoneal clearances of β-2-microglobulin (b2m), albumin, IgG and α-2-macroglobulin (a2m). From these clearances, the restriction coefficient to macromolecules (RC) was calculated. Also, parameters of fluid transport were determined: transcapillary ultrafiltration rate (TCUFR), lymphatic absorption (ELAR), and free water transport. Crude and adjusted linear mixed models were used to compare the slopes of peritoneal transport parameters in the peritonitis group to the control group. Adjustments were made for age, sex and diabetes.

♦ *Results:* Of 541 patients, 367 experienced a first peritonitis episode within a median time of 12 months after the start of PD. Of these, 92 peritonitis episodes were preceded and followed by a SPA within one year. Forty-five patients without peritonitis were included in the control group. Logistic reasons (peritonitis group: 48% vs control group: 83%) and switch to hemodialysis (peritonitis group: 22% vs control group: 3%) were the main causes of missing SPA data post-peritonitis and post-control. When comparing the slopes of peritoneal transport parameters in the peritonitis group and the control group, a first peritonitis episode was associated with faster small solute transport (glucose absorption, *p* = 0.03) and a concomitant lower TCUFR (*p* = 0.03). In addition, a discreet decrease in macromolecular transport was seen in the peritonitis group: mean difference in post- and pre-peritonitis values: IgG: -8 µL/min (*p* = 0.01), a2m: -4 µL/min (*p* = 0.02), albumin: -10 µL/min (*p* = 0.04). Accordingly, the RC to macromolecules increased after peritonitis: 0.09, *p* = 0.04.

♦ *Conclusions:* The very first peritonitis episode alters the natural course of peritoneal membrane characteristics. The most likely explanation might be that cured peritoneal infection later causes long-lasting alterations in peritoneal transport state.

Preservation of peritoneal membrane quality in peritoneal dialysis (PD) patients is required to maintain these patients on PD. Both morphological and functional peritoneal alterations are a consequence of long-term PD treatment (1–3). Exposure to glucose and glucose degradation products (4) and the occurrence of peritonitis (5,6) are proinflammatory stimuli that may cause alterations. Both morphological and functional changes may result in discontinuation of chronic PD treatment (7).

Peritonitis has been hypothesized to be an important cause of peritoneal transport alterations by inflammatory damage. However, only few studies determined the importance of cumulative peritonitis among long-term PD patients by measurements of transport kinetics, and reported inconsistent results. A few studies have shown a

Correspondence to: Anouk T.N. van Diepen, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, PO Box 226601100DD, Amsterdam, The Netherlands.
a.t.vandiepen@amc.uva.nl

* Both authors contributed equally.

temporary effect of peritonitis on small solute transport and net ultrafiltration, which recovered after the acute phase (8,9). Others identified a sustained effect of recurrent or severe peritonitis on peritoneal transport characteristics (10–13). In contrast, some authors found no association between the occurrence of peritonitis and peritoneal transport status (14–16) when peritonitis was treated properly (15) or adjustments for time on PD were made (16). Studies investigating the effects of a single, but not the first, peritonitis episode reported equivocal results (8,9,11,17–19).

Little or no evidence is available on the impact of the very first peritonitis episode on peritoneal transport characteristics. It is unknown whether the first episode of peritonitis causes permanent peritoneal membrane damage or has only a temporary and reversible effect.

The objective of this study was to investigate the importance of the first peritonitis episode in chronic PD patients by comparison of peritoneal membrane characteristics before and after the infection. To distinguish possible effects from those induced by the duration of PD, a control group without peritonitis was included.

SUBJECTS AND METHODS

We analyzed prospectively collected data from 541 incident PD patients, aged > 18 years old, receiving dialysis in a tertiary-care university hospital between January 1990 and July 2010. A peritonitis group and a control group were formed. The peritonitis group included patients experiencing a first peritonitis episode and with a Standard Peritoneal Permeability Analysis (SPA) within the year before (pre-peritonitis SPA) and the next one within the year (but not within 30 days) after their first peritonitis episode (post-peritonitis SPA). The post-peritonitis SPA was performed before the occurrence of a second peritonitis episode. The control group included patients without peritonitis and with a SPA within the first year (pre-control SPA) and within the second year (post-control SPA) after the start of PD. Pre- and post-peritoneal transport measurements were compared.

PERITONITIS

All peritonitis episodes during PD treatment were documented. Peritonitis was diagnosed, according to the criteria developed by Vas *et al.* (20), when at least 2 of 3 findings were present: abdominal pain, cloudy effluent with ≥ 100 white blood cells/μL and 50% polymorphonuclear cells and/or positive microbiological culture of the dialysate. These criteria have been endorsed by the International Society for Peritoneal Dialysis in the current PD-related

infection guidelines (21). Detailed information including leukocyte counts, microbiology and start and stop dates of peritonitis episodes was collected.

STANDARD PERITONEAL PERMEABILITY ANALYSES

Since 1990, a yearly SPA was routinely performed to examine peritoneal transport characteristics (22,23). Only SPAs using solutions containing 3.86% glucose were selected for this study. SPA measurements included the mass transfer area coefficient (MTAC) of creatinine, glucose absorption and peritoneal clearances of the following serum proteins: β-2-microglobulin (b2m), albumin, IgG, and α-2-macroglobulin (a2m). From these clearances, the restriction coefficient to macromolecules (RC) was calculated (24). In addition, parameters of fluid transport were determined in a SPA: transcapillary ultrafiltration, effective lymphatic absorption and free water transport (25). The complete SPA procedure and all calculations have thoroughly been described previously by Pannekeet *et al.* (22) and Smit *et al.* (23,25). From 1997, the measurement and calculation of the biomarker cancer antigen 125 (CA-125) and its appearance rates were incorporated in the SPA.

STATISTICAL ANALYSES

Differences in baseline characteristics between the peritonitis and control group were tested with an unpaired Student's *t*-test, Mann-Whitney (continuous data) or chi-square test (categorical data). An independent sample *t*-test or Mann-Whitney U test (dependent on the distribution of the data) was used to assess differences between cases and controls on baseline (pre-measurements) and after either the peritonitis or after one year to investigate the natural course (post-measurements). A paired sample *t*-test or Wilcoxon signed ranks test (dependent on distribution of the data) was performed comparing pre- and post-SPA data. Results are expressed as mean values and standard deviations. Crude and adjusted linear mixed models were performed to distinguish changes within peritoneal transport characteristics, caused by the initial peritonitis episode from those related to the natural course. Adjustments were made for age, sex, and diabetes. Results are expressed as crude and adjusted slope differences and 95% confidence intervals (CIs). Data analyses were performed using SPSS 20.0.

SENSITIVITY ANALYSES

Adjusted linear mixed models were used to investigate whether peritonitis' characteristics such as timing,

causative microorganisms or severity modified the effect of the first peritonitis on peritoneal transport. Early peritonitis was defined as < 1 year after the start of PD and compared to a reference group of late peritonitis, defined as ≥ 1 year after start of PD. Severe peritonitis was defined as a leukocyte count > 1,090 cells/mm^3 on day 3 or > 100 cells/mm^3 on day 5 of the peritonitis episode and compared to a reference group of less severe peritonitis. Causative microorganisms were dichotomized in gram-positive microorganisms (not coagulase-negative staphylococci) and compared to a reference group that consists of all other causative microorganisms. Results are expressed as adjusted slope differences and 95% confidence intervals (CIs).

RESULTS

POPULATION CHARACTERISTICS

Between January 1990 and July 2010, 541 incident PD patients aged 18 and older received dialysis in our department. Of these patients, 367 experienced at least one episode of peritonitis. Of these episodes, 92 were preceded and followed by a SPA within one year and could be selected for inclusion in the peritonitis group. Of the patients without a peritonitis episode, 45 were eligible for inclusion in the control group (Figure 1). Logistic reasons

were the main cause for missing SPA data after the first peritonitis episode (48%) and in the controls (83%). In addition, in the peritonitis group, switch to hemodialyis (22%), death (22%), and receiving a transplant (8%) within one year after the first peritonitis episode accounted for the rest of the missing SPA data. In the control group, only a minority of missing post-SPA data could be explained by patients who changed modality (3%), died (7%), or received a transplant (7%) within the second year of PD treatment. The baseline characteristics of the study population are summarized in Table 1. The peritonitis and control group were similar at baseline with respect to age, percentage of males and diabetics and the distribution of causes of end-stage renal disease. No differences in baseline characteristics were observed when patients included in the present study were compared to all patients eligible for the study.

PRE- AND POST-SPA MEASUREMENTS

Pre- and post-SPA measurements were compared in the peritonitis and in the control group. Results are shown in Table 2. Median time on PD to pre- measurements was 5.1 months in the peritonitis group and 4.1 months in the control group ($p = 0.10$). The median time to post-measurements was 17.8 months in the peritonitis group and 16.6 months in the control group ($p = 0.38$). The mean
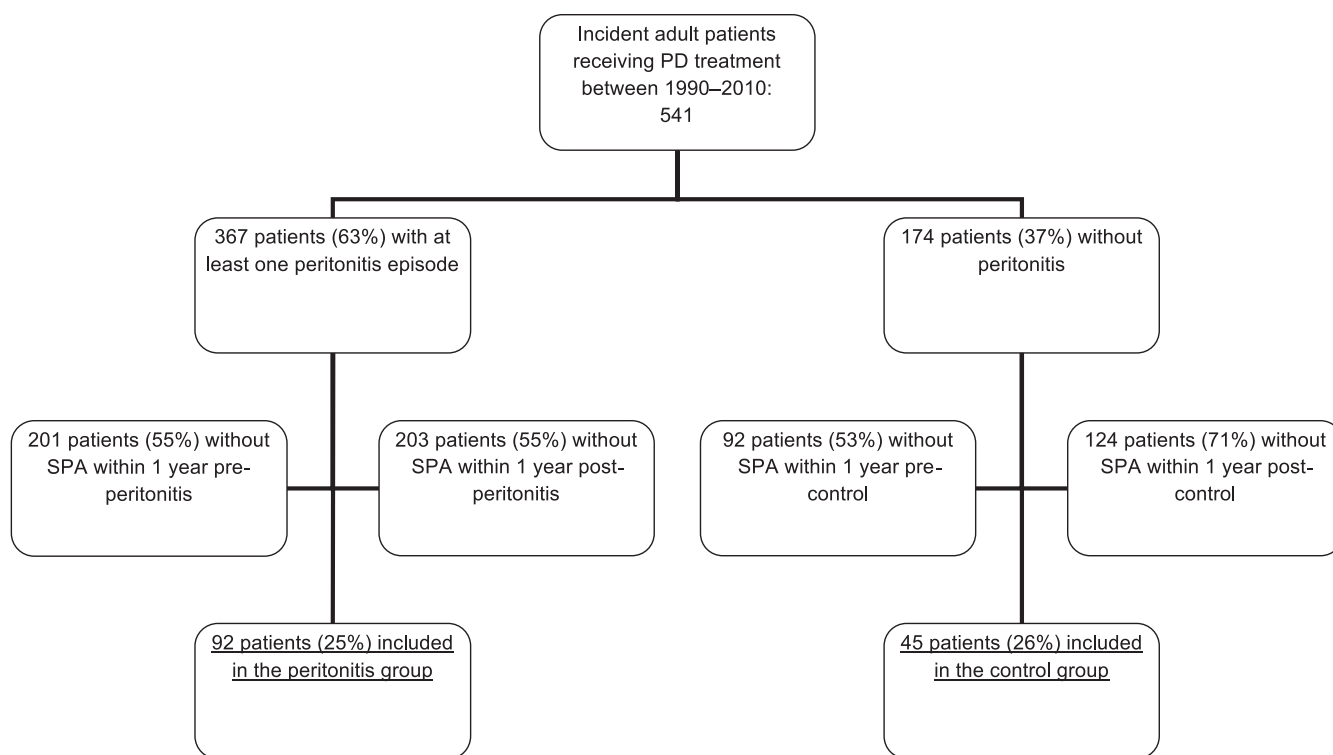

Figure 1 – Flow chart of patient selection in peritonitis and control group. PD = peritoneal dialysis; SPA = standard peritoneal permeability analysis.

time between a pre-SPA and a post-SPA was 11.9 months in the peritonitis group and 12.6 months in the control group, which was not different ($p = 0.19$). No differences were found between pre-peritonitis and pre-control group SPAs. In the peritonitis group, no significant decrease of

TABLE 1
Baseline Characteristics of the Patients

| Characteristic | Patients included in the present study | | |
	Peritonitis group	Control group	*p*-value
Patients (*n*)	92	45	
Age start dialysis (median range)	51 (21–78)	55 (25–78)	0.30
Male (%)	49	60	0.25
Diabetes (%)	24	22	0.77
Cause of ESRD (%)			0.85
Renal vascular disease	16	18	
Diabetic nephropathy	23	19	
Glomerulonephritis	16	16	
Other	44	48	

ESRD = end-stage renal disease.
No significant differences between the included and excluded peritonitis group; no significant differences between the included and excluded controls.

low molecular weight solute transport was found, while in the control group a decrease was present ($p < 0.001$). A concomitant increase in transcapillary ultrafiltration ($p = 0.04$), lymphatic absorption ($p = 0.01$) and decrease in the percentage of free water transport ($p = 0.01$) was seen in the control group, while this was absent in the peritonitis group. A discreet, but significant, decrease in the transport of macromolecules was found after the first peritonitis episode. The mean differences between post- and pre-peritonitis values were IgG: -8 µL/min ($p = 0.01$), a2m: -4 µL/min ($p = 0.02$), albumin: -10 µL/min ($p = 0.04$). Also, the RC increased after peritonitis: 0.09, $p = 0.04$. These significant differences in macromolecular transport and the RC were not observed in the control group. Finally, the CA-125 appearance rates after the first peritonitis episode were significantly lower compared to the control group ($p < 0.001$).

THE EFFECT OF THE FIRST PERITONITIS EPISODE COMPARED TO THE NATURAL COURSE

A comparison between the slope of peritoneal transport parameters in the peritonitis group and the control group was made. Crude and adjusted slope differences are shown in Table 3. After a first peritonitis episode, patients had a positive time course of glucose absorption, leading to an increase (adjusted slope difference: 5, 95% CI: 1 – 9; $p = 0.03$) and a negative time course of

TABLE 2
Comparison of Pre- and Post-Peritoneal Transport Status in the Peritonitis and Control Group

| SPA measurement | *n*=92 | | | *n*=45 | | |
	Pre-peritonitis SPA Mean±SD	Post-peritonitis SPA Mean±SD	*p*-value	Pre-control SPA Mean±SD	Post-control SPA Mean±SD	*p*-value
MTAC creatinine (mL/min)[a]	10.7±3.6	10.2±3.0	0.27	11.8±4.3	10.1±3.3	<0.001
Glucose absorption (%)[a]	64±11	61±10	0.11	65±11	58±10	<0.001
B2m clearance (mL/min)[b]	1.2±0.5	1.1±0.4	0.09	1.3±0.5	1.1±0.4[d]	0.01
Albumin clearance (mL/min)[b]	0.10±0.05	0.09± 0.04	0.04	0.10±0.04	0.09±0.04	0.23
IgG clearance (µL/min)[b]	57±34	51±28	0.01	62±32	51±24	0.02
A2m clearance (µL/min)[b]	21±16	20±33	0.02	24±19	21±12	0.44
Restriction coefficient[a]	2.41±0.38	2.50±0.34	0.04	2.41±0.34	2.38±0.30	0.60
ELAR (mL/min)[b]	1.57±1.03	1.55±0.96	0.67	1.79±0.93	1.42±0.77	0.01
TCUFR (mL/min)[b]	3.51±1.57	3.32±1.37	0.35	3.36±1.41	3.79±1.31	0.04
Free water transport (%)[a]	31.6±12.1	28.8±19.8	0.82	29.1±12.6	28.9±17.7	0.01
Appearance rate CA-125 (U/min)[ac]	129.4±85.3	105.9±70.1[d]	0.07	153.7±105.0	172.3±119.4	0.83

SPA = standard peritoneal permeability analysis; SD = standard deviation; MTAC creatinine = mass transfer area coefficient of creatinine; ELAR = effective lymphatic absorption rate; TCUFR = transcapillary ultrafiltration rate.
[a] Paired sample *t*-test;
[b] Paired Wilcoxon signed ranks test. Mean and standard deviations are given.
[c] CA-125 measurements from 1997.
[d] Significantly lower than the post-control SPA.

TABLE 3
Comparison of the Rate of Change in the Transport Parameter in the Peritonitis Group (*n*=92)
Compared to the Control Group (*n*=45)

SPA measurement	Crude slope difference (95% confidence interval)	*p*-value	Adjusted[a] slope difference (95% confidence interval)	*p*-value
MTAC creatinine (mL/min)	1.27 (-0.16–2.71)	0.08	1.10 (-0.34–2.53)	0.13
Glucose absorption (%)	5 (1–9)	0.02	5 (1–9)	0.03
B2m clearance (mL/min)	0.06 (-0.13–0.25)	0.52	0.06 (-14–0.25)	0.57
Albumine clearance (mL/min)	-0.01 (-0.02–0.02)	0.76	-0.01 (-0.02–0.01)	0.70
IgG clearance (μL/min)	3 (-10–16)	0.65	3 (-11–17)	0.69
A2m clearance (μL/min)	-1 (-7–5)	0.70	-2 (-9–4)	0.53
Restriction coefficient	0.10 (-0.04–0.24)	0.16	0.14 (-0.01–0.27)	0.06
ELAR (mL/min)	0.36 (-0.05–0.77)	0.08	0.30 (-0.11–72)	0.15
TCUFR (mL/min)	-0.59 (-1.09– -0.09)	0.02	-0.58 (-1.09– -0.07)	0.03
Free water transport (%)	-5.9 (-12.7–0.9)	0.09	-5.2 (-12.1–1.7)	0.14
Appearance rate CA-125 (U/min)[b]	-2.53 (-7.39–2.33)	0.30	-2.81 (-7.71–2.09)	0.26

SPA = standard peritoneal permeability analysis; MTAC creatinine = mass transfer area coefficient of creatinine; ELAR = effective lymphatic absorption rate; TCUFR = transcapillary ultrafiltration rate; CA = cancer antigen.
Linear mixed models were performed with the control group as the reference group.
[a] Adjusted for age, sex, and diabetes.
[b] CA-125 measurements from 1997.

transcapillary ultrafiltration, leading to a decrease (adjusted slope difference: -0.58, 95% CI: -1.09 to -0.07; *p* = 0.03), when compared to the controls. The very first peritonitis episode did not significantly affect protein clearances and its restriction coefficient, lymphatic absorption, free water transport, and the CA-125 appearance rate. However, all parameters followed the direction of an enhanced transport state after the first peritonitis episode compared to the natural course.

TIMING, SEVERITY, AND CAUSATIVE MICROORGANISM

Several characteristics of a peritonitis episode theoretically can modify the effect on peritoneal transport (Table 4). Sensitivity analyses were performed to investigate whether the time of occurrence after the start of PD, its causative microorganisms, and the severity of the episodes were potential modifiers (Table 5). The timing of the first peritonitis episode did not alter the association with peritoneal transport. A severe first peritonitis was associated with decreased lymphatic absorption (adjusted slope difference: -0.76, 95% CI: -1.40 to -0.11; *p* = 0.02) when compared to less severe peritonitis, but not with other parameters of fluid transport. A first peritonitis episode caused by gram-positive microorganisms (not coagulase-negative staphylococci) was associated with enhanced transport of low molecular weight solutes and a concomitant increased lymphatic absorption (adjusted slope

TABLE 4
Characteristics of the Peritonitis Episodes (*n*=92)

Characteristic	Value
Months after the start of PD (median; IQR)	12 (7–24)
Peritonitis in the first year (%)	53
Peritonitis in the second year (%)	24
Peritonitis in the third year or later (%)	22
Severity (*n* [%])	
Leukocyte count>1090 cells/mm³ day 3	8 (9)
Leukocyte count>100 cells/mm³ day 5	13 (14)
> 1090 cells/mm³ day 3 or >100 cells/mm³ day 5	16 (17)
Causative microorganism (*n* [%])	
Gram-positive	53 (58)
Gram-negative	14 (15)
Culture-negative	8 (9)
Other	17 (18)

PD = peritoneal dialysis; IQR = interquartile range.

difference: 0.59, 95% CI: 0.06 – 1.12; *p* = 0.03) compared to peritonitis episodes caused by other microorganisms.

DISCUSSION

The results of the present study show that after the recovery from the very first peritonitis episode, patients

TABLE 5
The Adjusted Slope Differences Per Peritonitis Group Stratified by Characteristics of the Peritonitis Episode[a]

SPA measurement	Peritonitis group stratified by timing of peritonitis[b] Adjusted[e] slope difference (95% CI)	*p*-value	Peritonitis group stratified by severity of peritonitis[c] Adjusted[e] slope difference (95% CI)	*p*-value	Peritonitis group stratified by microorganism of peritonitis[d] Adjusted[e] slope difference (95% CI)	*p*-value
MTAC creatinine (mL/min)	-1.11 (-2.94–0.72)	0.23	1.14 (-1.19–3.46)	0.33	2.24 (0.29–4.19)	0.03
Glucose absorption (%)	-4 (-9–1)	0.16	-4 (-11–2)	0.20	6 (1–12)	0.03
Restriction coefficient	-0.06 (-0.22–0.11)	0.50	-0.29 (-0.50–0.09)	0.09	0.01 (-0.17–0.18)	0.95
ELAR (mL/min)	0.17 (-0.34–0.68)	0.51	-0.76 (-1.40– -0.11)	0.02	0.59 (0.06–1.12)	0.03
TCUFR (mL/min)	-0.09 (-0.70–0.51)	0.76	-0.65 (-1.43–0.13)	0.10	-0.08 (-0.73–0.57)	0.81
Free water transport (%)	5.4 (-3.2–14.0)	0.22	-6.2 (-16.8–4.4)	0.25	-6.0 (-15.1–3.1)	0.19

SPA = standard peritoneal permeability analysis; CI = confidence interval; MTAC creatinine = mass transfer area coefficient of creatinine; ELAR = effective lymphatic absorption rate; TCUFR = transcapillary ultrafiltration rate; PD = peritoneal dialysis; CNS = coagulase-negative staphylococci.
[a] Adjusted linear mixed models were performed.
[b] Early peritonitis (*n*=48) was defined as <1 year after the start of PD and compared to a reference group of late peritonitis defined as ≥1 year after start of PD.
[c] Severe peritonitis (*n*=16) was defined as a leukocyte count >1,090 cells/mm^3 on day 3 or >100 cells/mm^3 on day 5 of the peritonitis episode compared to a reference group of less severe peritonitis.
[d] Gram-positive microorganisms (not CNS) compared to a reference group of all other causative microorganisms.
[e] Adjusted for age, sex and diabetes.

remain at a relatively faster peritoneal transport state compared to patients who were peritonitis-free. This was represented by faster transport rates of low molecular weight solutes and less efficient fluid transport in the peritonitis group compared to the natural course.

Previously, Del Peso *et al.* (26) have shown a decreasing MTAC creatinine and increasing ultrafiltration within the first year after the start of dialysis. Similar to our findings, this was not present in patients suffering from peritonitis. Furthermore, Struijk *et al.* (27) have found that after the start of PD, patients present with fast transport of low molecular weight solutes and inefficient ultrafiltration. This indicates an initial effect of the start of PD itself on peritoneal transport. However, after a period of 5 months, stabilization of peritoneal function towards a slower peritoneal transport state was observed. In our study, patients who experienced a first peritonitis episode remained "so-called" faster transporters of small solutes and fluids compared to patients without peritonitis. The latter showed a significant decline in small solute transport and an increase in the efficiency of fluid transport. The relatively faster transport state after the first peritonitis episode might be explained by low-grade inflammatory damage to the peritoneum. Peritoneal inflammation induces neo-angiogenesis, which increases the effective peritoneal surface area and reduces the osmotic conductance to glucose. An alternative explanation might be the slight,

but not significant, difference between the time from the start of dialysis to the pre- and post-measurements that were compared. Although unlikely, an influence on the difference in the observed transport state cannot be excluded with certainty.

We hypothesized that the timing of peritonitis after the start of PD, the severity of the peritonitis episode and the microorganism causing the peritonitis might be potential modifiers of the effect of the first peritonitis on peritoneal transport characteristics. Previously, a study in 16 patients by Selgas *et al.* (28) showed that peritoneal transport characteristics were influenced by peritonitis only after more than 3 years on PD. In addition, Fusshöller *et al.* (16), found that peritoneal transport characteristics are correlated with the time on PD. However, in the present study, time on PD did not alter the effect of the first peritonitis. An explanation might be that the majority of the peritonitis episodes occurred in the first year after the start of PD. Previously, Davies *et al.* (11), showed that the severity of recurrent peritonitis, in terms of leukocyte count, and the identification of their causative microorganisms was associated with a larger change in small solute transport and ultrafiltration. However, this was not found in single, but not the first, isolated episodes of peritonitis. In contrast, Hung and Chung (29) studied the first peritonitis episode and found an association between the identification of the causative microorganism and an increase in small

solute transport. In addition, culture-negative peritonitis showed less impact on peritoneal transport compared to culture-positive peritonitis. In the present study, the severity of the peritonitis episode altered the association with lymphatic absorption, but not with other parameters of fluid transport. Furthermore, gram-positive microorganisms, when compared to all other microorganisms, enhanced the association with increased low molecular weight solute transport and concomitant increased lymphatic absorption, but not with other parameters of fluid transport.

Although the increasing time course of the restriction coefficient could not be distinguished from the natural course, to the best of our knowledge, the present study is the first to identify an increase in peritoneal size-selectivity to macromolecules after a first peritonitis episode. An earlier study among prevalent PD patients, by Zemel *et al.* (18), showed no difference in the restriction coefficient directly prior to the development of peritonitis compared with the value after recovery. A decreased value was only present during the first two days of acute peritonitis (17). These findings suggest that an increase of the restriction coefficient after the first peritonitis episode takes some time to develop.

Several reasons may explain why previous studies (8–19,29) were unable to identify changes in macromolecular transport after a single peritonitis episode. First of all, individual proteins were not determined and the concomitant restriction coefficient was not calculated (9–16,19,29). Furthermore, studies were mainly carried out in prevalent dialysis patients in which time on PD might have a major influence on peritoneal transport characteristics before and after peritonitis (8–18). In addition, studies compared peritoneal transport characteristics after peritonitis with unstable transport characteristics during peritonitis (8) or did not exclude transport measurements during the inflammatory phase after peritonitis (8,9,19,29). Moreover, some studies (15,16) did not compare two transport measurements conducted from the same patient at all. Lastly, the earliest studies have been performed during a period with higher incidences of peritonitis. We hypothesize that the large number of peritonitis episodes during the earlier days of PD may have masked local changes due to a single peritonitis.

A possible biological explanation for the discreet difference in peritoneal size-selectivity to macromolecules might be that changes are caused in the radius of the large pores as described in the "three-pore model" by Rippe and Stelin (30). Lai *et al.* showed (6) that the number of macrophages, released cytokines and attracted leukocytes are elevated in the peritoneal cavity at least 6 weeks

regardless of clinical remission of peritonitis. However, in general, studies (18,31) found that these numbers return to baseline shortly after the recovery from peritonitis. Also in the present study, when the peritonitis group was compared to the control group, the changes in macromolecular transport and the restriction coefficient could not be distinguished from the natural course. Therefore, increased peritoneal vascular surface area (defined as the MTAC creatinine) rather than the intrinsic permeability of the membrane (restriction coefficient) may cause changes in macromolecular transport.

Interestingly, after the very first peritonitis episode, we identified a significantly lower appearance rate of CA-125 compared to the control group. A previous in-vitro study by Breborowicz *et al.* (32), emphasized that the amount of CA-125 released from mesothelial cells is not a good index of the number or properties of mesothelial cells. However, other patient-based studies (33–37), have shown that levels of CA-125 in peritoneal effluent are highly elevated during peritonitis. This can be explained by the induction of necrosis of mesothelial cells during peritonitis which enhances CA-125 appearance rate. Moreover, it has been suggested both in-vitro (34) and in-vivo (35), that peritonitis might induce irreversible loss of mesothelial cells and therefore CA-125 levels might be permanently lower after recovery from peritonitis. None of the above cited studies was able to confirm this hypothesis. In addition, time on PD was found to be an important determinant of CA-125 effluent levels (36). When compared to the natural course, the enhanced loss of mesothelial cell mass could not be attributed to the first peritonitis episode with certainty.

There are some limitations of the present study that need to be addressed. First, the inclusion of the patients in the peritonitis group was highly dependent on whether SPA measurements were performed before and after the peritonitis episode. When a patient suffered from a severe peritonitis episode causing termination of PD treatment or death, no SPA measurement after the infection was available and the patient was not included in the analysis. The percentage of patients missing SPA data due to switch to hemodialysis or death was consistent with previous literature (38). The majority of the missing SPA data could be attributed to logistic reasons, which may result from unmeasured patient-related or facility-related factors where no SPA was planned or the SPA was cancelled for unknown reasons. Therefore, although the majority of the missing SPA data could be attributed to logistic reasons, there may have been selection bias towards the inclusion of probably healthier patients surviving a potentially less severe peritonitis episode. Patients in the control group needed to survive the first 2 years

of PD as well, including their first 2 SPA measurements, to be eligible for inclusion. This resulted in a relatively healthy control group representing the stable long-term PD patient as well. Therefore, we underline that the same selection process was used in the peritonitis group and in the control group and no differences between both groups were found at baseline in terms of peritoneal transport characteristics or baseline demographics. In addition, the percentage of patients excluded from the study because of insufficient SPA data was similar in both groups. Therefore, we emphasize that, if of any importance, this selection is more likely to have led to an underestimation of the effect of peritonitis on peritoneal transport characteristics and that the influence of a severe first peritonitis episode might be even larger.

Great improvements in PD solutions have been made over the last decades. In our dialysis unit, patients were treated with Dianeal between 1990 and 1997, with Dianeal (Baxter Healthcare Corporation, Deerfield, IL, USA) or Physioneal (Baxter Healthcare Corporation, Deerfield, IL, USA) between 1998 and 2004, and with Physioneal between 2005 and 2010. The use of icodextrin started in 1997. Exposure to glucose and glucose degradation products may have influenced peritoneal host defense or the effect of the peritonitis episode on the peritoneal membrane. Unfortunately, our study is underpowered to perform a stratified analysis and data for exact calculations of exposure to glucose and glucose degradation products during dialysis treatment are unavailable.

One of the strengths of this study is the large number of patients with repeated SPAs that have been prospectively collected as a part of routine clinical care. The large amount of data collected enabled us to form a peritonitis and control group. Moreover, we could analyze peritoneal transport characteristics before and after the acute proinflammatory phase of peritonitis and observe long-lasting effects. Furthermore, all patients in the study were incident to dialysis. Peritonitis episodes were thoroughly documented in an extensive peritonitis database. Lastly, SPAs were used to determine peritoneal transport characteristics, which is advantageous to the Peritoneal Equilibration Test. A SPA provides additional information on pathways of fluid transport and includes the peritoneal clearances of several serum proteins from which the RC can be calculated (24).

In conclusion, the present study has confirmed that the very first peritonitis episode influences the natural course of peritoneal transport characteristics. We have shown that patients who experienced a cured first peritonitis episode later remain at a faster transport state compared to patients without peritonitis. The most likely explanation for these findings might be that cured peritoneal infection may lead to a latent state that later causes long-lasting alterations. These results do not have direct implications for clinical practice. However, the present study provides new insights into the effect of peritonitis on peritoneal transport characteristics. In addition, this study helps to gain better understanding of the peritoneal membrane and peritoneal transport in general, which may contribute to future improvements of PD therapy.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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