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Comparison of Longitudinal Membrane Function in Peritoneal Dialysis Patients According to Dialysis Fluid Biocompatibility

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Introduction: Preservation of peritoneal function is essential in long-term peritoneal dialysis. Biocompatible dialysis solutions might prevent or postpone the membrane alteration resulting in ultrafiltration failure and consecutive morbidity and mortality.

Methods: We conducted an observational cohort study in which we made a longitudinal comparison between the course of peritoneal solute and fluid transport during treatment with conventional and biocompatible solutions. Therefore, prospectively collected peritoneal transport data from the yearly standard peritoneal permeability analysis were analyzed in 251 incident patients treated between 1994 and censoring in 2016. Fluid transport included small pore and free water transport. Solute transport was assessed by creatinine mass transfer area coefficient and glucose absorption. Linear mixed models including change point analyses were performed. Interaction with peritonitis was examined.

Results: One hundred thirty-five patients received conventional and 116 biocompatible solutions. Sixty-seven percent (conventional) and 64% (biocompatible) of these underwent minimally three transport measurements. Initially, biocompatible fluids showed higher small solute transport and lower ultrafiltration than conventional fluids up to 3 years. Thereafter, conventional fluids showed an increase in small solute transport (+2.7 ml/min per year; 95% confidence interval [CI]: 0.9 to 4.5) and a decrease of free water transport (−28.0 ml/min per year; 95% CI: −60.4 to 4.4). These were minor or absent in biocompatible treatment. Peritonitis induced a decrease of transcapillary ultrafiltration after 2 years on dialysis with conventional solutions (−291 ml/min per year; 95% CI: −550 to −32) while this was absent in biocompatible treatment.

Conclusion: Despite a higher initial solute transport with biocompatible solutions, these have less influence on functional long-term peritoneal alterations than conventional solutions.

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Problems related to the quality of the peritoneal membrane are likely to develop more frequently than in the past as the duration of peritoneal dialysis increases. They can be provoked by long-term exposure to dialysis solutions, both in adults[1] and in children.[2] The use of conventional (CON) peritoneal dialysis (PD) solutions can cause alterations in peritoneal transport, such as ultrafiltration (UF) failure and an increase in the transport of low molecular weight solutes.[3]

These observations have not been the main reason for the development of the so-called biocompatible (BIO) dialysis solutions. The reasons consisted first of the discovery of glucose degradation products (GDPs) generated during heat sterilization of dialysis solutions, which were very cytotoxic *in vitro*,[4] and second of the toxicity of acid dialysis solutions on polymorphonuclear leucocytes.[5] The relevance of these data for patient care is questionable because the dialysis fluid concentration of GDPs is more than 1000 times lower than that of glucose, and the pH of a dialysis solution in a patient increases immediately to values

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greater than 6 due to dilution by the residual dialysate volume.[6] The reduction of inflow pain reported with biocompatible solutions[7] and the *in vitro* data were reasons for our center to switch from a conventional PD solution to a biocompatible one in 2004.

The aim of the present study was to analyze the time course of prospectively collected observational data on peritoneal function in consecutive incident PD patients treated with BIO and compare them with those in a previously published database consisting of similar patients treated with CON.[3] Furthermore, the interaction with the occurrence of peritonitis was investigated. We hypothesized that peritoneal function would be better preserved with BIO compared to CON. In addition, peritonitis was hypothesized to accelerate peritoneal transport alterations.

METHODS

Study Design

This is a prospective, longitudinal cohort study of incident PD patients included between 1994 and 2014 who were followed-up until censoring in 2016. Longitudinal data collection of the yearly standardized peritoneal permeability analysis (SPA) was conducted.[8,9] These were performed for clinical patient assessment; therefore, the analysis was not subject to approval by a committee of medical ethics. Patients were divided in two groups based on the dialysis prescription, which consisted of a conventional PD solution (Dianeal in the CON group) until 2004, or a more biocompatible one (Physioneal in the BIO group). Participants were at least 18 years old, of any ethnic origin, and received PD in a university hospital. Both automated PD (APD) and continuous ambulatory PD patients were included. The use of one amino acid–based solution or 1 icodextrin exchange next to CON or BIO solutions was allowed. Patients were followed from the start of PD until kidney transplantation, transfer to hemodialysis, death, or the 5th year on dialysis, represented by the fifth consecutive SPA. Data collection included baseline demographics, comorbidity, and primary kidney disease. Comorbidity was scored by Davies' comorbidity index.[10] Patients were excluded from the study if no baseline SPA in the first year of PD was conducted, if their dialysis prescription regimen (e.g., switch from CON to BIO) had been altered during the course of PD, and if they received a previous renal transplant. When the interaction with peritonitis was analyzed, patients were excluded if the baseline SPA was preceded by peritonitis.

SPA Data Collection

Yearly SPAs are incorporated in routine clinical practice in the Academic Medical Center. The methodology and concomitant calculations were previously described in extent.[8,9,11] Briefly, all SPAs consisted of a 4-hour dwell with 3.86% glucose during which intermediate dialysate samples were collected at multiple time points: 0 (before instillation), 10, 30, 60, 120, 180, and 240 minutes. Additional blood samples were drawn at 0 and 240 minutes. A volume marker (dextran 70, 1 g/l; Hykson, Medisan Pharmaceuticals AB, Uppsala, Sweden) allowed for the calculation of fluid kinetics.[12] Solute transport and net UF were measured after 4 hours and included the mass transfer coefficient (MTAC) of creatinine, calculated according to Waniewski *et al*.[13] Also, glucose absorption at 4 hours was calculated as the difference between the amount of glucose instilled and the amount recovered relative to the instilled amount. Net UF is the difference between the drained and the instilled volume. Transcapillary UF was calculated after 60 minutes ($TCUF_{0\text{-}60}$) from the dilution of the volume maker, small pore fluid transport (SPFT) and free water transport (FWT) were determined after 60 minutes from sodium kinetics.[14] Delta dialysate/plasma sodium (D/P sodium) was calculated as the difference between the dialysate sodium concentration divided by the plasma sodium concentration at 60 minutes and the dialysate sodium concentration divided by the plasma sodium concentration at 0 minutes.

Statistical Analyses

Baseline characteristics are expressed as mean and standard deviation or percentage. Differences in baseline (transport) characteristics between the CON and BIO group were tested with an unpaired Student *t* test, Mann-Whitney U test (continuous data), or χ^2 test (categorical data).

Linear mixed models with an unstructured covariance matrix were used to compare the course of SPA measurements[15] between subjects in the CON and BIO groups. Favorable characteristics of these models are their ability to account for the dependency of observations within patients and the possibility to deal with missing data (missing at random) in an appropriate fashion.

To identify the model which best represented the time course of peritoneal transport parameters, so-called "change point analyses" were performed stratified by treatment group. First, the analyses per transport parameter were performed for CON and BIO separately. Second, the time courses were compared directly to assess the differences between the treatment groups. In these change point analyses, an alteration in the slope before and after a certain change point in the course of follow-up was allowed.[16] For example, a transport parameter could be relatively stable over the first 2 years of PD and start to increase or decline (to

change) afterwards. A model without a change point might overestimate the change in the first 2 years and/or underestimate the change afterwards. Over the 5-year follow-up period, three potential change points were considered at 2, 3, or 4 years on PD. To establish if a model that includes a change point had a better data fit compared to a model without a change point, the Akaike information criterion (AIC) was calculated. The AIC is based on the value of the maximum likelihood and on the number of parameters in the model and can be used to compare the fit between models.[17] The change point model with the best fit (lowest AIC) was then fitted by restricted maximum likelihood to estimate the yearly change in the peritoneal transport parameter.

The transport parameters were modeled as a linear function of time with a random intercept and a random time effect per patient. The fixed regression coefficient for time ($\beta 1$) estimated the rate of change of the transport parameter per dwell per year. To allow for a change in the slope before and after a certain change point, an additional covariate $\beta 2$ was added. This covariate was zero for measurements taken before the change point and, based on the measurements taken after the change point, measured the difference in the slope before and after the change point. A fabricated example is as follows: the time course of transport parameter net UF was studied. A change point was chosen based on the AIC at 2 years on PD. The regression coefficient $\beta 1$ showed a slight increase of +50 ml/dwell per year during the first 2 years on PD. For these 2 years, the regression coefficient $\beta 2$ was set to 0. Therefore, $y = \beta 1 + \beta 2 = +50 + 0 = +50$ ml/dwell per year. However, after 2 years, the regression coefficient $\beta 2$ showed a decrease of -100 ml/dwell per year. Therefore, the overall course of this transport parameter was best described by $y = \beta 1 + \beta 2 = +50 + -100 = -50$ ml/dwell per year. This overall slope would have been an underestimation for the first 2 years on PD and an overestimation for the period thereafter. Therefore, the introduction of a change point resulted in a better model fit and consecutive understanding of the transport parameter.

The time course of peritoneal transport is presented as graphs of the mean, which include a graphic symbol representing a significant change point. Adjustment was made for comorbidity, as this is a potential confounding factor associated with the evolvement of peritoneal transport parameters over time. These results are presented in Supplementary Tables S1 and S2. The best fitting models were compared between the CON and BIO groups. When a change point had been identified, an interaction term "change point × dialysis solution" was added to the model. Furthermore, a stratified analysis, including the previous interaction term if applicable, was performed for patients who remained peritonitis-free and patients with one or more episodes of peritonitis during follow-up. Results are expressed as slopes with a 95% confidence interval. Data analyses were performed using SPSS 24.0.

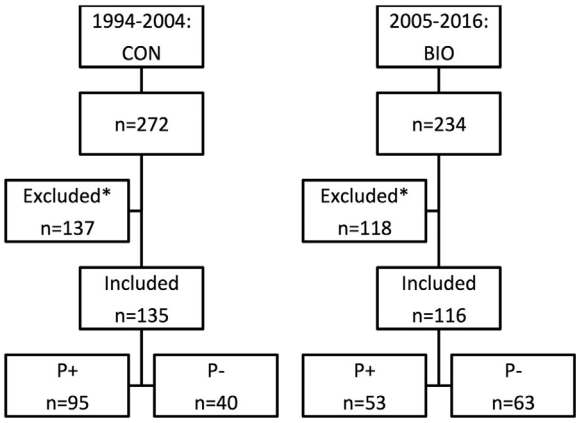

Figure 1. Flowchart representing patient selection. *Reasons for exclusion include missing baseline standardized potential permeability analysis (SPA), follow-up SPA, or data on peritonitis. CON, treated with conventional solutions; BIO, treated with more biocompatible solutions; P+, with peritonitis during follow-up; P−, without peritonitis during follow-up.

RESULTS

Population Characteristics

The study population consisted of 251 incident PD patients (Figure 1). Of these, 135 were included between 1994 and 2004 and treated with CON. From 2004, 116 incident patients were included and treated with BIO. Table 1 summarizes their demographic and baseline characteristics. Only the contribution of APD was higher in BIO, which is in accordance with a general trend. Median follow-up time was 2.3 years in CON and 2.2 years in BIO. The main reasons for censoring in both groups were death or an available renal transplant.

Peritoneal Function at the Initial SPA

Table 2 summarizes the results at baseline. At PD initiation, BIO patients had a significantly faster transport of small solutes and a lower level of net UF at 4 hours compared to CON patients.

Modeling the Course of Peritoneal Transport

The courses of the peritoneal transport parameters over time are shown in Figure 2. The best fitting models to describe these courses of peritoneal function were selected per parameter. If required, the model allowed a change point for a better model fit. These change points are marked in Figure 2. The models best fitting the slope of the peritoneal transport parameters were

Table 1. Baseline characteristics

Characteristics	CON	BIO
N of patients	135	116
N of SPA's, median (IQR)	3 (1–4)	3 (1–6)
3 or more SPA's, %	67	64
Male, %	56	53
Age, yr, mean (SD)	55 (16)	53 (15)
Davies comorbidity score, %		
Low	21	29
Intermediate	61	59
High	18	12
Primary kidney disease, %		
Renovascular	26	27
Diabetic nephropathy	28	26
Glomerulonephritis	16	12
Other	30	35
PD modality, % CAPD	85	45
Peritonitis incidence, episodes/yr	1.1	0.9
Follow-up duration, yr, median (IQR)	2.3 (1.3–3.4)	2.2 (0.4–5.7)
Patients with SPA data at 2 yrs, n (%)	124 (90)	101 (87)
Patients with SPA data at 3 yrs, n (%)	90 (67)	74 (64)
Patients with SPA data at 4 yrs, n (%)	60 (44)	44 (38)
Patients with SPA data at 5 yrs, n (%)	25 (19)	25 (22)

BIO, treated with more biocompatible solutions; CAPD, continuous ambulatory peritoneal dialysis; CON, treated with conventional solutions; IQR, interquartile range; PD, peritoneal dialysis; SPA, standardized peritoneal permeability analysis.

compared between the CON and BIO group (Table 3). The best model fit, with or without a change point, did not change when the course of peritoneal transport was adjusted for comorbidity (data are shown in Supplementary Table S1).

The BIO Group: A Relatively Stable Course of Peritoneal Transport

For almost all parameters in the BIO group, the model with the best fit was the one without a change point**.** Only glucose absorption (GA) showed a better model fit with a change point at 4 years. During the first 3 years on PD, a subtle decrease of GA was observed, whereas an increase was present from the change point onwards.

The CON Group: Significant Alterations in the Course of Peritoneal Transport

Almost all parameters in CON required a change point to obtain an adequate fit. The models including a change point were significantly better than the models that fitted a constant linear time course. The best fitting model for MTAC creatinine, GA, net UF, FWT, and delta D/P sodium was the one with a change point at 3 years. MTAC creatinine and GA showed a slight decrease in the first 2 years on PD, whereas an increasing course was observed from 3 years onwards. The opposite was present for net UF and FWT. The model that fitted best for $TCUF_{0\text{-}60}$ was one with a change point. $TCUF_{0\text{-}60}$ showed a decrease in the first 3 years, which accelerated to a steeper decline at the change point. The best fitting model for SPFT required no change point due to its constant and linear downward time course.

Comparison of the Course of Peritoneal Transport between the CON and BIO Groups

The time courses of the peritoneal transport parameters in CON and BIO groups were compared using the best-fitted models. Table 3 shows the results. In the CON group compared to BIO group, MTAC creatinine increased significantly after the 3-year change point. GA showed a similar but nonsignificant trend. Of the fluid transport parameters at 1 hour, only the time course of FWT showed a difference. An increase was identified before the 3-year change point in the CON group compared to the BIO group, whereas a nonsignificant decrease was observed thereafter. As expected, delta D/P sodium followed a course similar to that of FWT (Figures 2 and 3; and Tables 3 and 4). In addition, SPFT showed a borderline steeper decrease in the CON group compared to the BIO group. For all other parameters, no differences in the time course of peritoneal transport were identified.

The Interaction With Peritonitis

Patients were further stratified in two subgroups: patients with one or more peritonitis episodes during follow-up (P+) and patients who remained peritonitis-free (P−). As a consequence, the best-fitting model changed for some but not for all parameters. Six patients, equally distributed over the CON and BIO groups were excluded due to a peritonitis-episode preceding the baseline SPA. Figure 3 and Supplementary Table S2 show the results. These stratified analyses resulted in a more linear time course in the CON/P- group, whereas in the CON/P+ group no parameter needed a change point. In the CON/P− group, a decrease in net UF was found after 3 years on PD, similar to the model without stratification. Some best-fitting models induced new change points in

Table 2. Baseline transport characteristics

Characteristics	CON	BIO	*P*
Time from start of PD to baseline SPA, months	4 (3-6)	4 (3-7)	
MTAC creatinine, ml/min	10.1 (3.6)	11.8 (4.1)	0.001
Glucose absorption, %	63 (11)	67 (11)	0.006
Net UF, ml	620 (416-773)	490 (270-699)	0.005
Transcapillary UF, ml	460 (358-578)	466 (364-658)	0.274
SPFT, ml	310 (239-392)	320 (247-493)	0.204
FWT, ml	146 (61)	141 (79)	0.643
Delta D/P sodium	0.07 (0.03)	0.07 (0.04)	0.512

Results are expressed as a mean with SD or median with interquartile range. BIO, treated with more biocompatible solutions; CON, treated with conventional solutions; D/P, dialysate/plasma; FWT, free water transport at 60 minutes; MTAC, mass transfer area coefficient; Net UF, net ultrafiltration at 4 hours; PD, peritoneal dialysis; SPA, standardized peritoneal permeability analysis; SPFT, small pore fluid transport; TCUF, transcapillary ultrafiltration at 60 minutes.

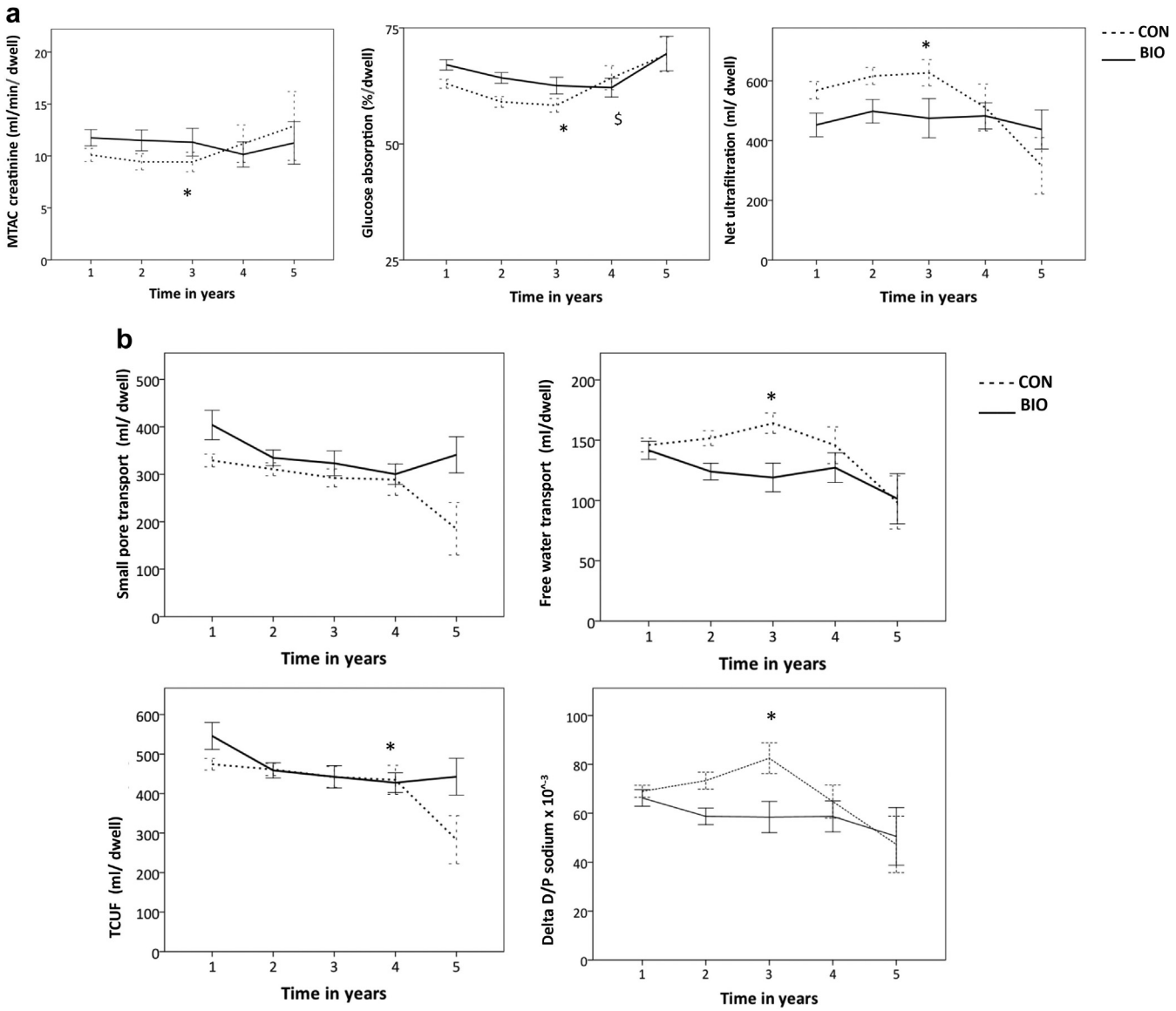

Figure 2. (a,b) Peritoneal transport parameters over time (mean ± SEM) in patients treated with conventional (CON) or more biocompatible (BIO) dialysis solutions. Based on the model best describing the course of the peritoneal transport parameter presented in this figure, a change point is marked (if applicable). An asterisk (*) indicates that a change point in the model describing the course of CON is required; a dollar sign ($) indicates that a change point in model describing the course of BIO is required. The comparison of the best fitting models per parameter and treatment group is presented in Table 3. MTAC, mass transfer coefficient; SPA, standardized peritoneal permeability analysis.

the stratified BIO group. In the BIO/P+ group, the model that best fitted GA, FWT, and $TCUF_{0\text{-}60}$, showed a change point at 2 years. Thereafter FWT and $TCUF_{0\text{-}60}$ slightly increased and GA gradually decreased. In contrast, an increasing course of GA was seen after 3 years in the BIO/P- group. For all other transport parameters, no change point was required.

The Interaction between the Dialysis Solution, Peritonitis, and Peritoneal Transport

The time course of the CON/P- and BIO/P- groups as well as the time course of the CON/P+ and the BIO/P+ groups were compared using the best-fitted models. The results are shown in Table 4. $TCUF_{0\text{-}60}$ in the CON/P+ group showed an initial increase and a significant decrease after 2 years on PD. A similar but not significant trend was observed in the CON/P- group. Interestingly, FWT was initially higher in the CON/P+ group compared to the BIO/P+ group ($P = 0.06$), whereas this was no longer the case after 2 years on PD. No other significant slope differences were identified. Also, no significant differences in the time courses of peritoneal transport between the CON and BIO groups were observed in parameters without a change point when these parameters were stratified for the occurrence of peritonitis.

DISCUSSION

This large cohort study of incident PD patients is the first longitudinal comparison of strictly standardized

Table 3. Comparison of the time course of peritoneal transport in patients treated with CON or BIO solutions according to the best-fitting models

CON vs. BIO	Peritoneal transport parameter	Slope difference before the change point or for parameters without a change point (95% CI)	*P*	Slope difference after the change point (95% CI)	*P*
No change point	SPFT, ml/dwell/yr	−32.6 (−65.3 to 0.2)	0.06	N/A	
	MTAC creatinine, ml/min/dwell/yr	0.4 (−0.6 to 1.4)	0.43	N/A	
	Net UF, ml/dwell/yr	12.5 (−48.1 to 73.1)	0.69	N/A	
	FWT, ml/dwell/yr	8.3 (−2.9 to 19.6)	0.15	N/A	
	TCUF, ml/dwell/yr	23.3 (−11.7 to 58.2)	0.19	N/A	
	Delta D/P sodium	0.01 (0.00 to 0.02)	0.04		
Change point at 3 yrs	MTAC creatinine, ml/min/dwell/yr	−0.2 (−1.0 to 0.6)	0.57	2.7 (0.9 to 4.5)	0.01
	Glucose absorption, %/dwell/yr	−0.2 (−2.3 to 2.0)	0.98	4.6 (−0.7 to 9.8)	0.09
	Net UF, ml/dwell/yr	12.2 (−64.1 to 88.6)	0.74	−111.8 (−285.8 to 62.2)	0.85
	FWT, ml/dwell/yr	19.1 (4.1 to 34.0)	0.01	−28.0 (−60.4 to 4.4)	0.08
	Delta D/P sodium	0.02 (0.00 to 0.03)	0.01	−0.03 (−0.07 to 0.01)	0.11
Change point at 4 yrs	Glucose absorption, %/dwell/yr	0.6 (−1.6 to 2.7)	0.92	2.2 (−6.6 to 11.1)	0.82
	TCUF, ml/dwell/yr	17.8 (−28 to 63.6)	0.13	−126.3 (−308.7 to 56.0)	0.61

BIO, treated with more biocompatible solutions; CI, confidence interval; CON, treated with conventional solutions; D/P, dialysate/plasma; FWT, free water transport at 60 minutes; MTAC, mass transfer area coefficient at 4 hours; N/A, not applicable; Net UF, net ultrafiltration at 4 hours; SPFT, small pore fluid transport; TCUF, transcapillary ultrafiltration at 60 minutes.

measurements of both peritoneal small solute transport and various parameters of fluid kinetics between patients treated with CON and BIO dialysis solutions. Only two studies on a longitudinal comparison between the CON and BIO groups' fluids in incident PD patients have been published.[18,19] The global fluid study was restricted to the time course of small solute transport and included various dialysis solutions without distinction in the analyses,[18] whereas the Balance in Australian and New Zealand peritoneal dialysis patients (balANZ) trial was a randomized controlled trial that also included net UF, but the duration of follow-up was restricted to 2 years.[19] Besides, some studies on peritoneal histology have been published, two of which contained a cross-sectional comparison between adult patients treated with CON or with BIO dialysis.[20,21] One study in children focused on effects of PD with BIO solutions on morphology and partly on peritoneal solute transport.[22]

The present observational study showed that treatment with CON compared to BIO is associated with increased small solute transport after 3 years on PD. These findings are in line with the above-mentioned reports.[18,19] Similarly, we identified a plateau phenomenon of solute transport in BIO patients, which was significantly higher than the values in CON. After 3 years, an ongoing increase was found in the CON group. Whereas the investigators of balANZ found a plateau for solute transport in the Balance group from the start of PD, an increase of solute transport in BIO was found in the GLOBAL fluid study. In our study, the initially higher values of solute transport on BIO remained stable during the entire follow-up. The discrepancy between the results during the initial period on PD underlines the difference between early and long-term PD with CON as described or reviewed previously by our group and others.[23–28]

The early alterations are probably dependent on vasoactive factors with a reversible effect on membrane characteristics,[29–32] potentially influenced by the initiation of PD itself, the exposure to glucose,[1,2] the presence of mesothelial-to-mesenchymal transition (MMT),[30] and the occurrence of early peritonitis.[31] Some differences may be due to a better preservation of the mesothelium on BIO. Mesothelial damage during CON has been suggested in experimental studies.[32–34] These might be caused by GDPs and lead to impaired secretion of vascular endothelial growth factor, an important early determinant of small solute transport[27,33,35] that is increased in MMT. However, MMT was also present in children treated with BIO only[21] and was not different between BIO and CON groups,[20] which casts doubt on its role in the early changes. Yet, higher values of small solute transport and lower net ultrafiltration on BIO compared to CON during the first years of PD were reported in some studies.[28,36]

The difference between conventional and biocompatible fluids in long-term PD is fairly consistent and characterized by crossing of the trend lines of small solute transport between 3 and 4 years, associated with lower values in BIO compared to CON. The opposite is present for $SPFT_{0\text{-}60}$, and FWT. Both show a decrease after 3 to 4 years. The developments in small solute transport are likely caused by neoangiogenesis,[21,37] leading to an enlarged peritoneal vascular surface area.[38] Besides the cytotoxic effects of GDPs on the mesothelial cell layer,[32,39–42] a more likely explanation is their promotion of the formation of advanced glycosylation end products that accumulate in the peritoneal vascular wall and induce neoangiogenesis.[33,34]

This cohort study reports the first long-term clinical comparison of fluid kinetics between CON and BIO,

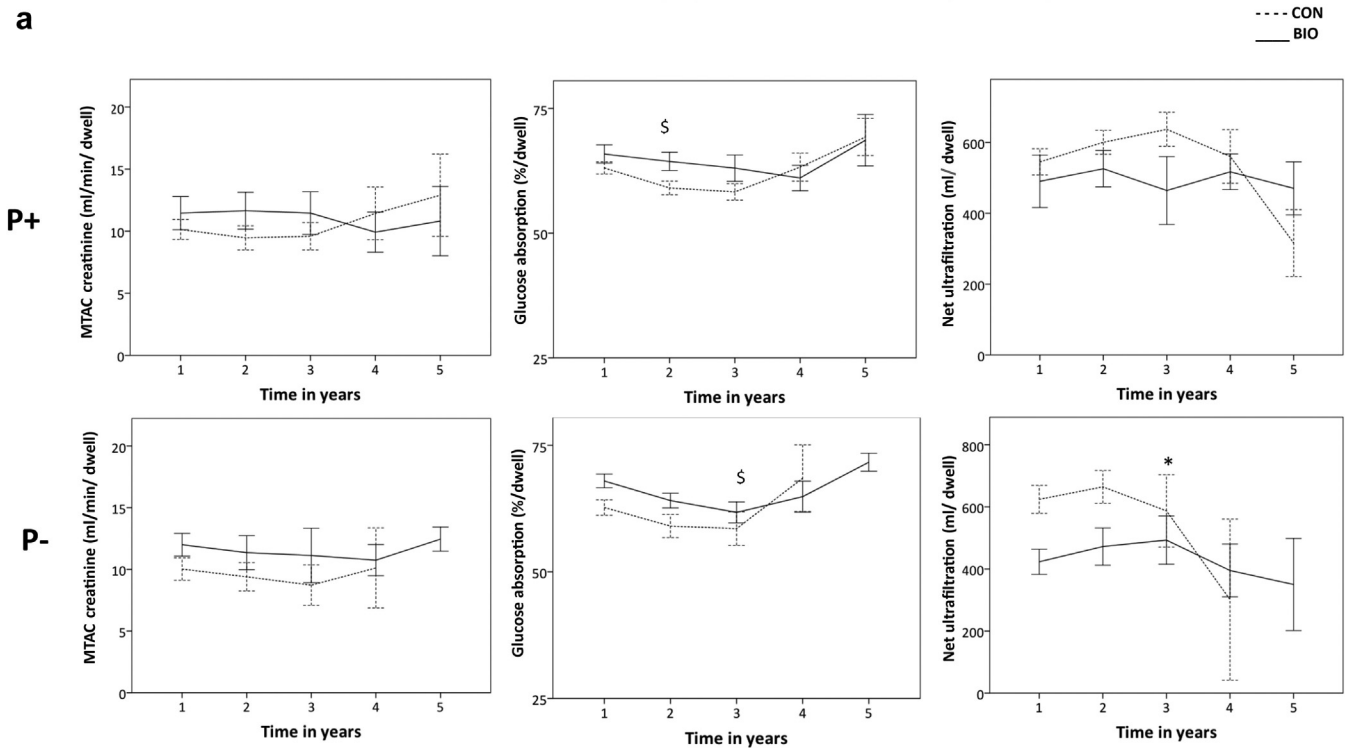

Figure 3. (a,b) The interaction of peritonitis with the course of peritoneal transport over time in patients treated with conventional (CON) or more biocompatible (BIO) dialysis solutions (mean ± SEM). Based on the model best describing the course of the peritoneal transport parameter presented, a change point is marked (if applicable). An asterisk (*) indicates a that change point in the model describing the course of CON is required; a dollar sign ($) indicates that a change point in model describing the course of BIO is required. The comparison of the best-fitting models per parameter and treatment group stratified by the occurrence of peritonitis is presented in Table 4. P+, with peritonitis during follow-up; P−, without peritonitis during follow-up; MTAC, mass transfer coefficient; SPA, standardized peritoneal permeability analysis; TCUF, transcapillary ultrafiltration. (Continued)

including SPFT and FWT. We observed that the sodium dip and FWT, of which it is a representation, significantly increased during the first 3 years on PD in CON compared to BIO, whereas the opposite was true in long-term PD. The increase in FWT in early PD suggests an upregulation of the number and/or function of peritoneal water channels, which results in a higher level of the reflection coefficient. No previous data about this increase has been presented yet. Experimental studies[43,44] hypothesized that exposure of the peritoneal mesothelial layer to a hypertonic dialysis solution might be the key in upregulation of aquaporin-1, which is possibly time- and dose-dependent. Obviously, these *in vitro* studies cannot directly be translated to the clinical setting, especially because endothelial exposure is likely more important in PD patients.

Our observational results in long-term PD confirm a negative association between conventional dialysis solutions and ultrafiltration on the long run. This UF decrease was found for both SPFT and FWT. Previous reports by our group focused especially on loss of osmotic conductance leading to impaired FWT.[45,46] This study shows that SPFT is also affected. In analogy with the severe impairment of FWT in encapsulating peritoneal sclerosis,[47,48] we assume that peritoneal fibrosis is the main cause of this decrease.[48–51] The decline in SPFT with PD duration has not been found previously. A reduced microvascular filtration pressure, caused by narrowing of vascular lumina is most likely,[52,53] probably induced by vasculopathy.[54,55] This may be due to accumulation of advanced glycosylation end products,[14,56–58] the formation of which is enhanced by GDPs.[59] All discussed alterations in fluid transport during CON were mitigated or absent in BIO. Our data suggest that exposure to higher levels of GDPs is associated with interstitial changes leading to impaired FWT for unknown reasons and decreased SPFT due to vasculopathy.

Peritonitis has been studied as a potential course-interacting factor. In a previous longitudinal study, peritonitis was associated with an earlier and more pronounced rise in solute transport and a reduced rise in $TCUF_{0\text{-}60}$.[60] In addition, a study by Zanzhe *et al.*[61] found a suggestion that, in the group of patients with peritonitis, changes in small solute transport and UF were overall more severe, especially in long-term PD. However, the investigators emphasize that cause and effect cannot be interfered from their analysis. Our

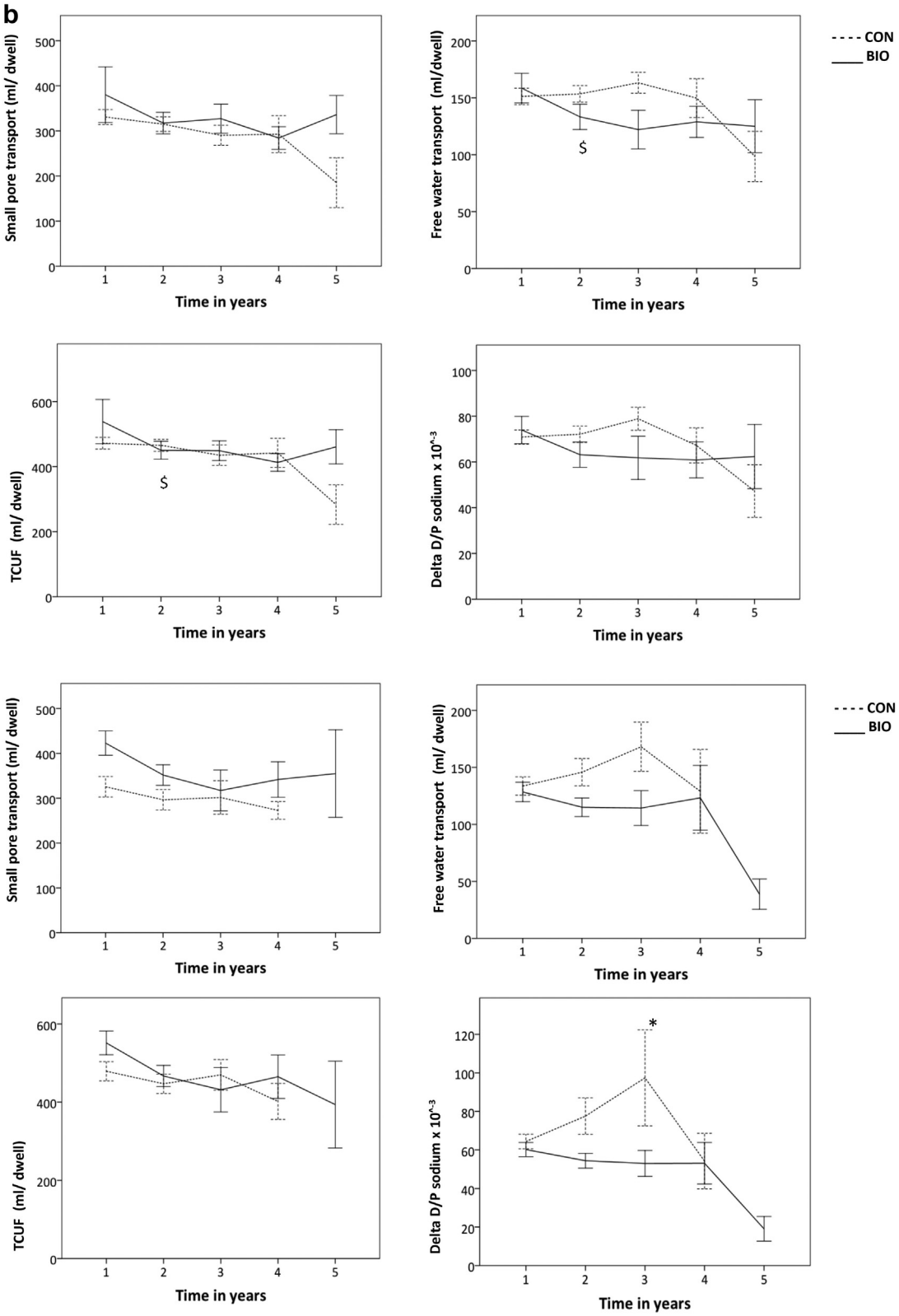

Figure 3. (Continued)

analysis showed that the association of peritonitis with $TCUF_{0\text{-}60}$ was restricted to CON. Peritonitis had no association with solute transport, not in CON, nor in BIO. The GLOBAL fluid study reported an acceleration of solute transport in CON patients with peritonitis.[18] We could not confirm this. An epidemiological and a pathophysiological explanation exist. First, our study suffered from long-term selection of PD and peritonitis

Table 4. The interaction of peritonitis with the time course of peritoneal transport in patients treated with CON or BIO dialysis solutions

		Peritonitis-free				With peritonitis			
CON vs. BIO	Peritoneal transport parameter	Slope difference before the change point or for parameters without a change point (95% CI)	*P*	Slope difference after the change point (95% CI)	*P*	Slope difference before the change point or for parameters without a change point (95% CI)	*P*	Slope difference after the change point (95% CI)	*P*
No change point	MTAC creatinine (ml/min/dwell/yr)	0.4 (−6.1 to 6.9)	0.57	N/A		0.2 (−0.7 to 1.2)	0.63	N/A	
	SPFT (ml/dwell/yr)	43.9 (−5.0 to 92.8)	0.08	N/A		2.3 (−61.8 to 66.5)	0.94	N/A	
	FWT (ml/dwell/yr)	16.5 (−214.6 to 247.6)	0.99	N/A					
	TCUF (ml/dwell/yr)	47 (−10 to 104)	0.10	N/A					
	Net UF (ml/dwell/yr)					33.7 (−36.0 to 103.4)	0.34	N/A	
	Delta D/P sodium					0.01 (0.00 to 0.03)	0.06	N/A	
Change point at 2 yrs	Glucose absorption (%/dwell/yr)					−5.5 (−15.6 to 4.6)	0.29	6.3 (−6.6 to 19.1)	*0.33*
	FWT (ml/dwell/yr)					50 (−2 to 101)	0.06	−50 (−117 to 17)	*0.14*
	TCUF (ml/dwell/yr)					255 (45 to 465)	0.02	−291 (−550 to −32)	*0.02*
Change point at 3 yrs	Glucose absorption (%/dwell/yr)	1.6 (−4.8 to 7.9)	0.62	0.3 (−23.7 to 24.3)	0.98				
	Net UF (ml/dwell/yr)	32 (−169 to 231)	0.75	−278 (−1058 to 501)	0.48				
	Delta D/P sodium	0.02 (0.00 to 0.04)	0.04	−0.03 (−0.07 to 0.01)	*0.14*				

BIO, treated with more biocompatible solutions; CI, confidence interval; CON, treated with conventional solutions; D/P, dialysate/plasma; FWT, free water transport at 60 minutes; MTAC, mass transfer area coefficient at 4 hours; N/A, not applicable; Net UF, net ultrafiltration at 4 hours; SPFT, small pore fluid transport; TCUF, transcapillary ultrafiltration at 60 minutes.

survivors with relatively favorable membrane function and a concomitant decreased number of patients per comparison group; therefore, there was a decreased power to examine the association. Second, our study avoided the bias of peritoneal membrane measurements during the inflammatory phase 1 month after a peritonitis episode. It may be that true baseline values have not been reached at that time. Our study is in accordance with results of an analysis in children showing that peritonitis episodes have no effect on peritoneal morphology.[2]

The strength of our study is the large amount of prospectively, systematically and standardized collected peritoneal transport data in patients treated with CON or BIO with long-term follow-up, which is similar or longer than currently published multicenter cohort studies and trials.[62] No previous comparison in long-term PD including fluid kinetics has been published. The lack of randomized trials with long-term follow-up was emphasized by a meta-analysis by Yohanna *et al.*[62] who showed that follow-up in trials comparing BIO and CON is rather short and the quality of the trials generally poor. Although our data have been collected in a single-center observational fashion, this university center has a large body of PD patients and both extensive clinical and scientific experience in PD. The peritoneal transport measurements were performed according to a protocol for research purposes in the early 1990s and incorporated in standard clinical practice afterwards. They have been robust and reproducible for decades. Furthermore, due to the incorporation of a yearly transport measurement in standard clinical practice, the generalizability is fairly good. A single manufacturer for peritoneal fluids (Baxter Healthcare S.A., Castlebar, Ireland) provided dialysis solutions. This may be considered a strength but also a weak point because the results with other biocompatible solutions might be different. The limitations of our study include the lack of specific glucose regimens per patient, by whichever glucose exposure in BIO cannot be excluded. Icodextrin has been used since 1996; therefore, a small portion of patients included in the first 2 study years received an icodextrin-free dialysis regimen, which might have influenced the initial course of peritoneal transport in patients with a relatively large peritoneal surface area.[63] Unfortunately, no data on residual renal function (RRF) or the residual urinary output volume was available. This factor could have influenced the intensity of a patients' dialysis regimen and consequently altered the course of peritoneal transport. Also, vice versa, the type of dialysis solution could preserve RRF over the course of PD.[64,65] Although, RRF is likely to be equally distributed over both solution groups it is a potential source of confounding that cannot be excluded. The greater use of APD in BIO is unlikely to have influenced the results.[66] No other characteristics of general practice have changed significantly over the course of the study period. Dry dwells and days without PD have never been used in our center. Obviously, informative censoring cannot be excluded and might have altered the results in both directions. Although our modelling strategy aimed to describe the best model fit for peritoneal function over time, a

general limitation remains that statistics will never truly reflect underlying biological processes.

This study emphasizes the detrimental association between conventional dialysis solutions, their potential synergistic interaction with peritonitis, and the acceleration of the changes in peritoneal membrane function during PD. Based on the results of the present study, and in concordance with the results of the multicenter global fluid study and morphological studies, we strongly advocate that the use of conventional solutions should be avoided for long-term PD, which is especially important for patients not eligible for a kidney transplant. Because the more biocompatible solution still contains glucose, future research should be aimed at reducing glucose exposure, for instance, by combinations of (new) osmotic agents.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Peritoneal transport parameters before and after a potential change point in patients treated with conventional or more biocompatible dialysis solutions adjusted for comorbidity.

Table S2. Peritoneal transport parameters before and after a potential "change point" in patients treated with conventional and more biocompatible dialysis solutions with or without peritonitis during follow up.

STROBE Statement.

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