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Treatment of severe ultrafiltration failure with nonglucose dialysis solutions in patients with and without peritoneal sclerosis

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Abstract

Introduction. Ultrafiltration failure (UFF) in peritoneal dialysis (PD) patients is a reflection of changes in the peritoneal membrane, which can include mesothelial damage, neoangiogenesis, and occasionally, peritoneal fibrosis. These structural changes are probably induced by the use of bioincompatible dialysis solutions. Therefore, we investigated the effects of the treatment with a combination of nonglucose dialysis solutions in patients with severe UFF.

Methods. Ten patients with UFF (net ultrafiltration <400 mL/4 h on 3.86% glucose) were treated with a combination of glycerol and icodextrin with or without amino acid-based dialysis solutions for 3 months. Four of them were diagnosed with encapsulating peritoneal sclerosis (PS), proven by peritoneal biopsies. Standard peritoneal permeability analyses (SPA), using 3.86% glucose, were performed, and dialysate CA125 appearance rate (AR-CA125) was analysed at the start, after 6 weeks and after 12 weeks. PS and non-PS patients were compared.

Results. One patient underwent transplant after 6 weeks, one was withdrawn from PD because of clinical signs of encapsulating PS before the 3-month period ended. PS patients had been treated with PD for a longer duration than the non-PS patients (102 versus 52 months, $P = 0.05$), but no differences in baseline transport parameters or AR-CA125 were present. During the study, no differences were observed for transport characteristics when the results of the whole group at 6 and 12 weeks were compared to baseline. For the non-PS patients, however, a significant increase in the transcapillary ultrafiltration rate (from 2.2 mL/min to 2.6 mL/min, $P < 0.05$) and a decrease in the MTAC creatinine (from 14.3 mL/min to 12.6 mL/min, $P < 0.05$) were found after 6 weeks of glucose-free treatment. Free-water transport, measured as the maximum dip in the dialysate-to-plasma ratio of sodium and as the transport through the ultrasmall pores in the first minute, tended to improve, but this difference did not reach significance. In addition, the AR-CA125 increased significantly (from 2.8 U/min to 16.1 U/min, $P < 0.05$). Continued treatment did not reach statistical difference even after 3 months. No changes were observed in the PS patients.

Conclusions. In the present study, an improvement of UFF in the non-PS patients was obtained by withdrawal of glucose-based dialysis solutions. The abnormalities in PS patients are probably irreversible. Early withdrawal of glucose-based dialysis solutions or at least a marked reduction in glucose exposure should be considered in UFF patients, but the identification of the patients who would benefit most needs further studies.

Keywords: ultrafiltration failure; biocompatibility; nonglucose solutions; therapy

Introduction

Glucose-induced ultrafiltration becomes insufficient in an important part of peritoneal dialysis (PD) patients. This can occur at any stage of PD treatment, but is most important in long-term patients [1–4]. Some patients eventually develop peritoneal sclerosis (PS). Impaired ultrafiltration is often associated with fast small-solute transport, leading to a rapid dissipation of the osmotic gradient [1,5,6]. High fluid absorption rates [7] and a decreased conductance to glucose have also been described [7–9]. Decreased osmotic conductance to glucose implies impairment of free-water transport.

In addition to these functional abnormalities, anatomical changes have been described, such as diabetiform reduplications of the basement membrane of peritoneal capillaries [10], thickening of the submesothelial compact collagenous zone of the parietal peritoneum, sometimes accompanied by loss of surface mesothelium [11,12] and interstitial fibrosis in omental tissue [13]. In addition, an increased number of vessels have been found [13]. The thickness of the submesothelial compact zone was related to the duration of PD, the absence of mesothelium and the prevalence of

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vasculopathy [12]. A correlation has also been described between the number of peritoneal vessels and the fibrotic alterations [13]. In patients with PS, these fibrotic and vascular abnormalities are also present, but it is much more severe.

Cancer antigen 125 (CA125) can be used as a marker of mesothelial cell mass [14,15]. With the use of conventional bioincompatible dialysis solutions, the balance between mesothelial degeneration and regeneration can be disturbed. This leads to a reduction of mesothelial cell mass, which is reflected by a decrease in effluent CA125.

PD regimes are mainly based on glucose-based dialysis solutions, but from the aforementioned facts, it is clear that glucose has some disadvantages. It seems likely that the exposure to extremely high glucose concentrations is one of the causative factors in ultrafiltration failure (UFF). The question arises whether this process is reversible. Therefore, in this prospective study, the effect of the withdrawal of glucose in dialysis solutions on transport parameters and CA125 was analysed in patients with severe UFF. A diagnosis of encapsulating PS was made in some of them within 1 year of completion of the study.

Methods

Ten patients with UFF were included in the study. UFF was defined as net ultrafiltration of <400 mL after a 4-h dwell period with a 3.86% glucose solution. After explaining the aim of the study and obtaining patients' written informed consent, treatment began with nonglucose dialysis solutions for at least 3 months. The dialysis regime consisted of two to three exchanges with a 2.5% glycerol-based dialysate (Baxter, Utrecht, the Netherlands), one exchange with a 1.1% amino acid-based dialysate (Nutrineal®, Baxter) and one exchange with 7.5% icodextrin-containing dialysate (Extraneal®, Baxter). The number of glycerol exchanges and the dwell times were adjusted to the patients' needs. Plasma osmolality was monitored throughout the study, because of the risk of hyperosmolality by absorption of glycerol. The study protocol was approved by the Committee of Medical Ethics at the Academic Medical Center of Amsterdam.

A standard peritoneal permeability analysis (SPA) was performed before the start of the study, after 6 weeks and after 3 months. When a patient remained on nonglucose treatment it was repeated every following 6 weeks. The SPA was performed during a 4-h dwell period, as described earlier [16]. The test was done with 3.86% glucose, using the volume the patient was used to. The dwell test was preceded and followed by a rinsing procedure with 1.36% glucose to avoid the possible effects of the residual volume before the test, and to calculate the residual volume after the test. Dialysate samples were taken before instillation and at multiple time points during the test (10, 20, 30, 60, 120, 180 and 240 min). The effect of a dead-space volume was avoided by temporary draining of 100–200 mL before the collection of each sample. Blood samples were taken at the beginning and at the end of the test period. A volume marker, dextran 70, 1 g/L (Hyskon, Medisan Pharmaceuticals AB, Uppsala, Sweden), was used to calculate fluid kinetics. To prevent a possible anaphylactic reaction to dextran 70, dextran 1 (Promiten, NPBI, Emmercompascuum, the Netherlands) was injected intravenously before instillation of the test bag [17].

Measurements

Total dextran was determined by means of high performance liquid chromatography [18]. Creatinine and urate were measured by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). All electrolytes were determined using ion-selective electrodes. Glucose was measured by the glucose oxidase–peroxidase method, using an autoanalyser (SMA-II, Technicon, Terrytown, LA, USA). Dialysate CA125 was determined by a commercial microparticle enzyme immunoassay (MEIA), using a monoclonal antibody against CA125 (Abbott Laboratories IMx, IL, USA), validated for use in dialysate in our laboratory [19]. CA125 is expressed as its dialysate appearance rate, that is, the total amount present in the effluent divided by the duration of the dwell. Plasma osmolality was measured by the depression of freezing point (Advanced Micro Osmometer).

Fluid kinetics

Transcapillary ultrafiltration (TCUF) and effective lymphatic absorption were assessed with the intraperitoneally administered volume marker dextran 70. TCUF was calculated from the dilution of the volume marker, by subtracting the initial intraperitoneal volume (IPV) from the theoretical IPV (when both lymphatic absorption and sampling would not have been present) at any time. The effective lymphatic absorption rate (ELAR) was calculated as the peritoneal dextran clearance [20].

The dialysate-to-plasma ratio of sodium (D/P sodium) was calculated as the dialysate sodium concentration divided by the plasma sodium concentration. The maximum dip in D/P sodium is the difference between the initial D/P sodium and the lowest D/P sodium. A correction for Na^+ diffusion from the circulation to the dialysate, known to cause blunting of the decrease in D/P Na^+, was made as described earlier [21], using the mass transfer area coefficient (MTAC) of urate. The calculated sodium concentration in the dialysate due to diffusion can then be subtracted from the measured concentration at any time point, resulting in the actual Na^+ sieving.

Solute transport

Peritoneal handling of low-molecular-weight solutes was expressed as MTAC. The MTAC represents the maximal theoretical diffusive clearance of a solute at $t = 0$, before transport has actually started. In this study, we used the Waniewski model [22,23]. Glucose absorption was calculated as the difference between the amount of glucose instilled and the amount recovered, relative to instillation. All transport parameters were corrected for body surface area and expressed as per 1.73 m^2 body surface area.

Table 1. Demographic data of 10 patients who participated in the study

Patient	Sex	Dialysis scheme (before start)	Duration of PD (months)	Net UF (mL)	AR-CA125 (U/min)	Peritoneal sclerosis
1	F	CCPD 8 × 3.86%	56	−9	0.64	−
2	F	CAPD 5 × 3.86%	77	167	2.1	−
3	M	CCPD 6 × 3.86%	96	89	6.1	+
4	M	CAPD 4 × 3.86%	48	255	21.5	−
5	F	CAPD 3 × 3.86%	12	390	3.4	−
6	M	CCPD 4 × 3.86%, 1 × 2.27%	30	88	1.1	−
7	F	CAPD 3 × 3.86%, 1 × ICO	70	336	0.52	+
8	F	CAPD 3 × 2.27%, 1 × 1.36%	99	162	1.13	−
9	M	CAPD 2 × 2.27%, 1 × 3.86%	108	81	1.08	+
10	M	CAPD 2 × 2.27%, 1 × 3.86%	115	213	3.67	+

M: male; F: female; CCPD: continuous cyclic peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; ICO: 7.5% icodextrin-based dialysis solution; AR-CA125: appearance rate for CA125 in the dialysate per minute; the reasons for dropout are given in parenthesis; Tx: renal transplant; PS: peritoneal sclerosis; UF: ultrafiltration.

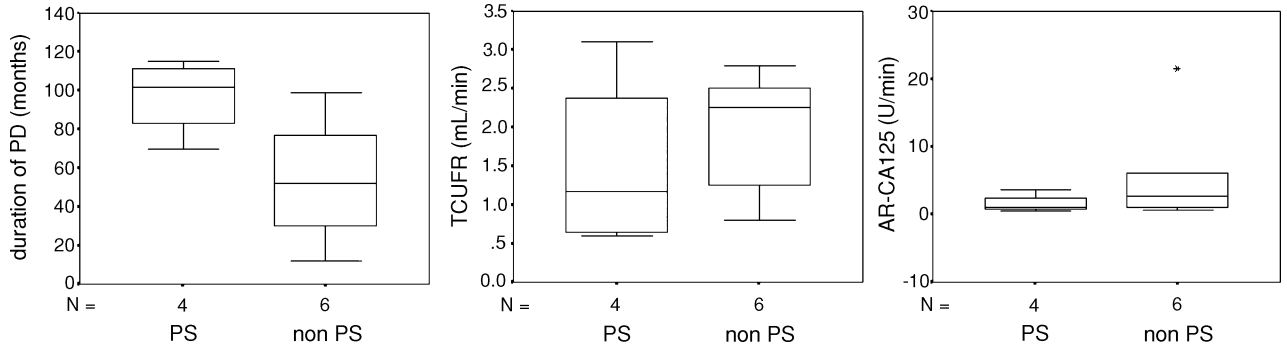

Fig. 1. The basal values for duration of PD, TCUFR and CA125 appearance rates in the dialysate between the patients with peritoneal sclerosis (PS) and without peritoneal sclerosis (non-PS). Medians, quartiles (boxes) and extremes (whiskers) are given.

Statistical analysis

Data were expressed as medians and ranges. Analysis of paired observations was performed by the paired Student *t*-test. The results after 6 weeks and after 3 months were compared with the baseline levels. Comparisons between the patients with and without PS were tested nonparametrically using the Mann–Whitney *U*-test.

Results

Patients

The demographic data of the patients participating in the study as well as the duration of follow-up and the dropout reasons are shown in Table 1. The study was started with the participation of 10 patients. One patient was withdrawn after 6 weeks because of clinical signs of encapsulating PS and another one because of unmanageable overhydration, just before the 3-month period had ended. Three others were diagnosed with encapsulating PS, proven by peritoneal biopsies, within 1 year after the study ended. Two patients underwent transplant after 3 months. Statistical analysis was therefore only possible at the start, after 6 weeks and after 3 months.

PS and nonsclerosis patients differed in duration of PD (102 versus 52 months, $P = 0.05$), but not in the appearance rate of CA125 at the start of the treatment (2.8 U/min versus 1.1 U/min, $P = 0.4$), and transcapillary ultrafiltration rate (TCUFR) (2.2 mL/min versus 1.2 mL/min, $P = 0.5$), as shown in Figure 1.

Follow-up

Values for peritoneal transport characteristics and CA125 in the 3 months of glucose-free treatment are given in Table 2. No statistically significant changes were observed for transport characteristics after 6 weeks or 3 months of glucose-free treatment, compared to the baseline levels. A trend towards improvement was observed in free-water transport, measured as an increase in the maximum dip in D/P sodium from 0.020 to 0.048 ($P = 0.15$) and in glucose absorption, which decreased from 75% to 67% ($P = 0.09$) after 12 weeks. In addition, the CA125 appearance rate increased after 6 weeks of glucose-free treatment and remained so after continued treatment with glucose-free solutions.

A separate analysis was performed for the patients with and without encapsulating PS, as shown in Tables 3 and 4.

The individual data for the six non-PS patients are shown in Figure 2. In these patients, net ultrafiltration became higher for four out of six patients (Figure 2A). The TCUFR improved after 6 weeks (Figure 2B), but no further improvement was seen after 3 months. A positive trend towards

Table 2. Transport characteristics for the 10 ultrafiltration-failure patients who participated in the study; medians and ranges are given

	Start ($n = 10$)	6 weeks ($n = 10$)	3 months ($n = 8$)
Net UF (mL)	165 (−9–390)	212 (11–434)	189 (−223–712)
TCUFR (mL/min)	1.9 (0.6–3.1)	2.0 (0.7–3.2)	2.2 (1.0–4.0)
ELAR (mL/min)	0.56 (0–2.14)	0.71 (0.17–2.08)	1.0 (0.45–3.65)
Max dip D/P Na^+	0.020 (0–0.09)	0.038 (0.01–0.09)	0.048 (0.01–0.15)
MTAC creat (mL/min)	14.3 (9.2–17.3)	13.6 (8.3–16.5)	13.0 (7.1–16.4)
Glucose abs (%)	75 (55–89)	72 (54–81)	67 (50–78)
AR-CA125 (U/min)	1.62 (0.52–21.5)	4.22 (0.01–46.7)*	3.80 (0.01–25.9)*

Net UF: net ultrafiltration after 4 h (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m^2); ELAR: effective lymphatic absorption rate (mL/min/1.73 m^2); max dip D/P Na^+: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m^2; glucose abs: absorption of glucose after 4 h (%); AR-CA125: appearance rate of cancer antigen-125 in the dialysate (U/min).
*$P < 0.05$.

Table 3. Peritoneal transport characteristics of six patients with ultrafiltration failure without peritoneal sclerosis; medians and ranges are given

	Start	6 weeks	*P*-value
Net UF (mL)	165 (−9–390)	302 (11–434)	0.2
TCUFR (mL/min)	2.2 (0.8–2.8)	2.6 (1.0–3.2)	<0.05
ELAR (mL/min)	0.6 (0–2.14)	1.6 (0.18–2.04)	0.1
Max dip D/P Na^+	0.020 (0.010–0.090)	0.050 (0.030–0.090)	0.08
MTACcreat (mL/min)	14.3 (9.2–17.3)	12.6 (8.3–14.3)	<0.05
Glucose abs (%)	78 (55–98)	68 (58–81)	0.17
AR-CA125 (U/min)	2.8 (0.64–21.5)	16.1 (0.20–46.7)	<0.05

Net UF: net ultrafiltration after 4 h (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m^2); ELAR: effective lymphatic absorption rate (mL/min/1.73 m^2); max dip D/P Na^+: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m^2; glucose abs: absorption of glucose after 4 h (%); AR-CA125: appearance rate CA125 in the dialysate (U/min).

Table 4. Peritoneal transport characteristics of four patients with peritoneal sclerosis; medians and ranges are given

	Start	6 weeks	*P*-value
Net UF (mL)	151 (81–336)	136 (98–383)	0.8
TCUFR (mL/min)	1.17 (0.60–3.11)	0.96 (0.73–2.48)	0.3
ELAR (mL/min)	0.6 (0.23–1.69)	0.4 (0.17–0.77)	0.3
Max dip D/P Na^+	0.016 (0–0.080)	0.028 (0.010–0.060)	0.9
MTACcreat (mL/min)	14.2 (10.4–15.2)	14.3 (9.1–16.5)	1.0
Glucose abs (%)	72 (66–80)	73 (54–73)	0.6
AR-CA125 (U/min)	1.11 (0.52–3.67)	1.28 (0.01–5.14)	0.5

Net UF: net ultrafiltration after 4 h (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m^2); ELAR: effective lymphatic absorption rate (mL/min/1.73 m^2); max dip D/P Na^+: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m^2; glucose abs: absorption of glucose after 4 h (%); AR-CA125: appearance rate of CA125 in the dialysate (U/min).

improvement was observed in free-water transport, as shown by the increase of the maximum dip in D/P sodium (Figure 2C). In addition, the MTAC creatinine decreased in the first week of treatment (Figure 2D) and glucose absorption also tended to decrease (Figure 2E). The appearance rate of CA125 in the dialysate showed an increase with the glucose-free regime, as shown in Figure 2F. PS patients did not show any improvement with the glucose-free treatment. Fluid profiles show a higher transcapillary ultrafiltration after 6 weeks treatment with nonglucose dialysis solutions in the non PS patients, but not in the patients suffering from peritoneal sclerosis, as shown in Figure 3.

Hyperosmolality syndrome was not observed during the study period; a median rise in plasma osmolality of 301 (287–318) to 304 (297–318) mOsmol/kg H_2O was found ($P = 0.16$).

Discussion

The results of the present study indicate that the withdrawal of glucose-containing dialysis solutions can improve peritoneal function in patients with severe UFF, but without PS. In addition, the results of this intervention support the hypothesis that exposure of the peritoneum to glucose or glucose degradation products (GDPs) is important in the pathogenesis of UFF. The failure to reach a statistical significance for the majority of the parameters studied is likely to be due to the small group of patients included and the severity of this UFF. This suggests the presence of very extensive peritoneal morphological alterations that are partly irreversible. It is supported by the lack of an effect in patients who developed clinical signs of encapsulating PS within 1 year after the start of the study. The very low dialysate CA125 appearance rates present at the start of glucose-free treatment are supportive of marked mesothelial damage.

Various toxic effects of glucose on peritoneal tissues have been described. Glucose can damage the mesothelial cell layer by direct toxicity. This can occur either by inhibition of mesothelial cell proliferation, which is concentration dependent and reversible with the withdrawal of glucose [24], or by the cytotoxic effect of GDPs [25]. GDPs are formed during the heat-sterilization process of glucose. These GDPs are also classified as reactive carbonyl compounds and consist mainly of aldehydes. The

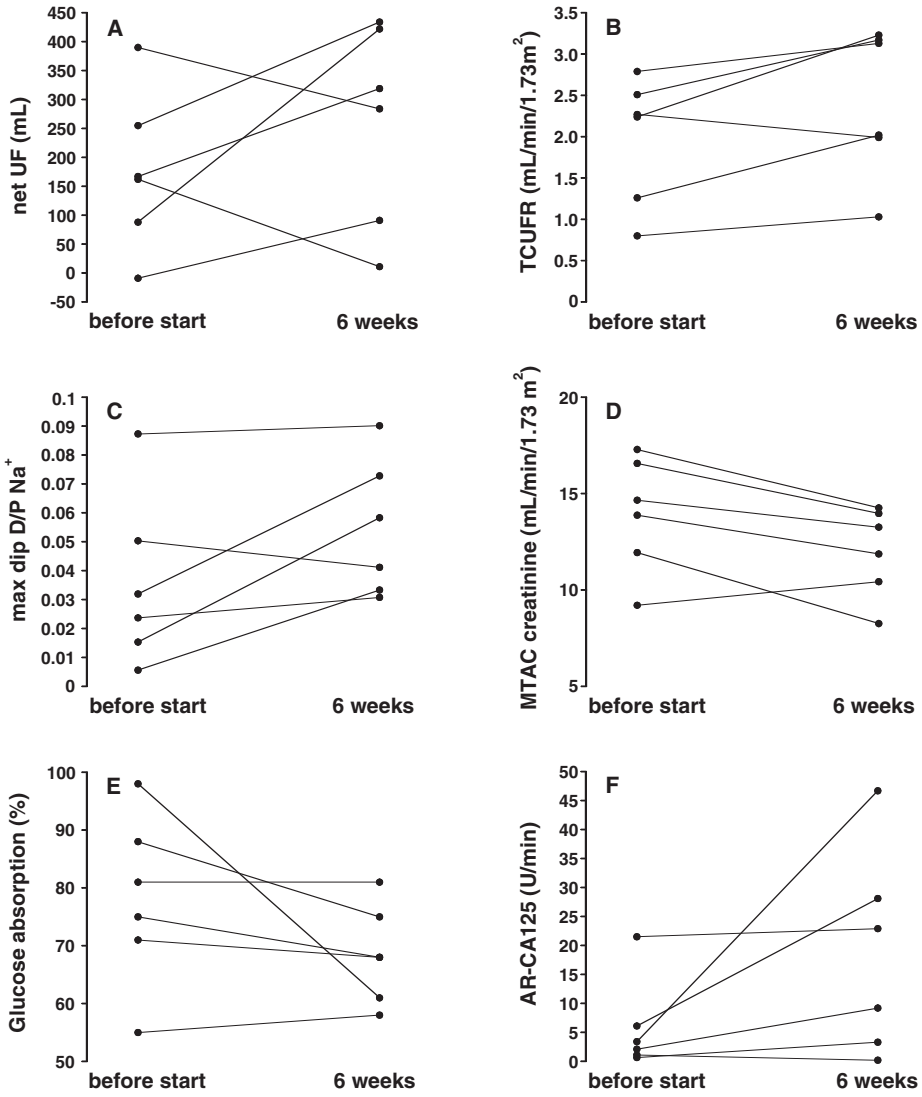

Fig. 2. Differences in values for the six patients without peritoneal sclerosis in net ultrafiltration (**A**), transcapillary ultrafiltration (**B**), maximum dip in D/P sodium (**C**), MTAC creatinine (**D**), glucose absorption (**E**) and appearance rate of CA125 (**F**) between the start of glucose-free treatment and after 6 weeks.

acute effects of GDPs on the cell function of human peritoneal mesothelial cells include dose-dependent inhibition of cell growth, viability and cytokine release [26]. The most biologically active of all GDPs is 3,4-dideoxyglucosone-3-ene (3,4-DGE) [27]. Diminishing the concentration of GDPs by sterilizing the glucose in a very acidic environment, and being separated from the electrolytes resulted in less cytotoxicity *in vitro* [28]. A second disadvantage of GDPs is the ability to trigger a chain of spontaneous nonenzymatic reactions with the amino group in peptides and proteins, referred to as the Maillard reaction. Schiff's bases are formed when a carbonyl group reacts with an amino group. These can rearrange to intermediate Amadori products, and this may eventually result in the formation of stable carbohydrate cross-links between proteins, the so-called advanced glycated end-products (AGEs) [29]. The AGE modification preferentially occurs in long-lived structural proteins, such as collagen and eye lens. The AGE formation is accelerated in diabetes mellitus and is believed to contribute to diabetic complications, among them nephropathy. High plasma levels of AGE precursors and AGE-modified proteins are also found in nondiabetic renal failure patients [30]. This state of high reactivity in uraemia is referred to as 'carbonyl stress' and it may be a causative as well as consequential factor in the progression of renal disease. Accumulation of AGEs was described in peritoneal biopsies of nondiabetic patients on PD [31,32], which increased with time on PD [32]. The AGE formation leads to progressive cross-linking of collagenous tissues, increasing the rigidity of vessels and leading to fibrosis [33,34]. The AGEs are also considered to have vasoactive effects on endothelial cells. They are probably responsible for the neoangiogenesis in patients with diabetic complications [35]. Most likely, they are also able to cause neoangiogenesis in peritoneal tissues. Finally, the exposure to the high glucose concentrations can lead to a state of 'pseudohypoxia' in the

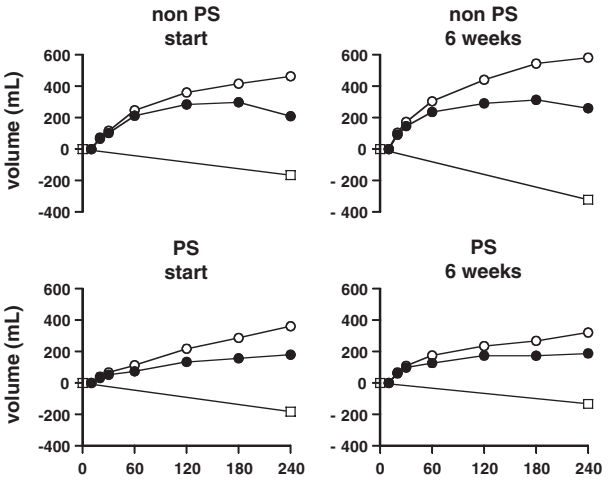

Fig. 3 Fluid profiles for the non-PS patients and the PS patients, at start (left panel) and after 6 weeks (right panel). Transcapillary ultrafiltration (open circles), net ultrafiltration (closed circles) and fluid absorption (closed squares) are given. A significant increase in transcapillary ultrafiltration was observed in the non-PS group ($P = 0.03$), but not in the PS patients.

peritoneum. This leads to an effect on intracellular redox status, which stimulates the release of growth factors, such as vascular endothelial growth factor (VEGF). The VEGF induces neoangiogenesis [36,37]. With the formation of new vessels, enlargement of the effective vascular surface area occurs.

Several solutions have been tested to replace glucose as an osmotic agent in PD. Glycerol is the only osmotic agent that can totally replace glucose. It has a low molecular weight for sugar alcohol of 92 daltons that is a normal physiological component of plasma. It was found to be less inhibiting on mesothelial cell proliferation *in vitro* than for other osmotic agents [24,38]. However, an *ex vivo* study suggested that glycerol-based dialysate inhibited the phagocytosis of peritoneal macrophages more than glucose [39]. Long-term use of glycerol-based dialysate as a dialysis solution showed good results in diabetic patients [40,41]. Although it is well tolerated, its use is limited because it induces less ultrafiltration per mOsmol than glucose [42] owing to its greater absorption and lower reflection coefficient [43]. Another disadvantage is the risk of developing a hyperosmolar syndrome in patients with high absorption rates [41]. A second alternative for glucose is the glucose polymer icodextrin. The results of peritoneal tissue exposure to icodextrin-containing dialysis fluids in patients were equivocal. Some studies showed similar values for mesothelial cell mass markers [44,45], whereas another study showed a decrease of CA125 appearance with the use of icodextrin compared to glucose [46]. Nonetheless, icodextrin contains less GDPs than a 1.36% glucose solution [47]. Icodextrin is iso-osmolar to uraemic plasma. It exerts a colloid osmotic pressure over the peritoneal membrane, and is only absorbed to a limited extent. Therefore, its osmotic effect is sustained for a long period [48,49]. Consequently, icodextrin is particularly useful for the longer dwells, especially in patients with a large vascular surface area. The use of icodextrin is limited, however, to once a day because of the maltose accumulation in the circulation that results from the absorption of icodextrin. The third alternative for glucose as a dialysis solution is an amino acid-based solution. This consists of a combination of different amino acids, buffered with lactate. The effect of the amino acid-based solution on mesothelial cell cultures has been found to be similar to glucose [50]. Ultrafiltration with the amino acid-based solution was slightly higher than with a 1.36% glucose solution [51], and peritoneal small-solute transport was significantly higher. This limits the use of the solution: high absorption can give rise to a high nitrogen load. Because none of the solutions discussed earlier could be used to replace glucose solely, we used all three of them combined. In the present study, patients without PS showed improvement in some parameters of transport after the change to the glucose-free regime. The decrease in the small-solute transport rates can be attributed to a smaller effective peritoneal surface area, probably caused by a reduction in vasoactive effects and neoangiogenesis after glucose was abandoned. This could have been caused by a decrease in occupancy of AGE receptors on peritoneal endothelial cells, or by a direct effect on VEGF levels. The improvement in free-water transport could have been the result of a newly formed aquaporin-1 or by reversal of glycation or nitrosylation of aquaporin-1, although this is less likely as the process of advanced glycation is irreversible. The fact that the increase in the maximum dip of the D/P sodium was the only factor that showed a persistent improvement after 12 weeks of treatment supports this hypothesis. The increase in the TCUFR is the consequence of both the decrease in solute transport and the improved free-water transport. The CA125 appearance rates after glucose-free treatment is in accordance with the earlier results. It implies a better preservation of the mesothelial cell layer. The patients who were diagnosed with PS did not show any improvement after switching to a glucose-free regimen. This suggests that a ‘point of no return’ had been passed for this group, and no advantage of abandoning glucose can be expected.

In conclusion, improvement in peritoneal function is possible in patients with severe UFF by switching to glucose-free dialysis solutions. When encapsulating PS is present, no favourable effects are expected to occur. The limited effects in patients without this condition may be caused by the severity of peritoneal damage. Repeating the study in patients who are less severely affected is warranted.

Conflict of interest statement. WS is a part-time employee of Baxter Healthcare.

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