Various aspects of peritoneal water transport

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Chapter 10

Treatment of ultrafiltration failure with non-glucose dialysis solutions in patients with and without peritoneal sclerosis

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Abstract

Introduction: Ultrafiltration failure (UFF) in peritoneal dialysis patients is a reflection of changes in the peritoneal membrane, which can include mesothelial damage, neoangiogenesis and sometime 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 non-glucose dialysis solutions in patients with severe UFF.

Methods: Ten patients with UFF (net UF < 400ml/4hr on 3.86% glucose) were treated with a combination of glycerol, icodextrin with or without aminoacid 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 analyzed at start, after 6 weeks and after 12 weeks. PS and non-PS patients were compared.

Results: One patient was transplanted after 6 weeks, one was withdrawn from peritoneal dialysis because of clinical signs of encapsulating PS before the 3 months ended. PS patients were treated for a longer duration than the non-PS patients (102 vs. 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 at 12 weeks were compared to baseline. For the non-PS patients, however, a significant increase of transcapillary ultrafiltration rate (from 2.2 mL/min to 2.6 mL/min, p<0.05) and a decrease of the MTAC creatinine (from 14.3 mL/min to 12.6 mL/min, p<0.05) was found after 6 weeks of glucose-free treatment. Free water transport, measured as the maximum dip in dialysate-to-plasma ratio of sodium and as the transport through the ultra small 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 after 3 months. No changes were observed in the PS patients.

Conclusions: In the present study, an improvement of UFF in 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 identification of the patients who would benefit most, needs further studies.
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. Impaired ultrafiltration is often associated with high small solute transport rates, leading to a rapid dissipation of the osmotic gradient [1,5,6]. Also high fluid absorption rates [7] and a decreased conductance to glucose have 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 has 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 vasculopathy [12]. A correlation has also been described between the number of peritoneal vessels and the fibrotic alterations [13]. In patients with peritoneal sclerosis these fibrotic and vascular abnormalities are also present, but much more severe.

Cancer antigen 125 (CA-125) can be used as a marker of mesothelial cell mass [14,15]. With the use of 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 CA-125.

Peritoneal dialysis regimes are mainly based on glucose-based dialysis solutions, but from the above 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. 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 CA-125 was analyzed in patients with severe ultrafiltration failure. A diagnosis of encapsulating peritoneal sclerosis was made in some of them within one year after completion of the study.
Methods

Ten patients with ultrafiltration failure were included in the study. Ultrafiltration failure was defined as net ultrafiltration of less than 400 mL after a 4 hours dwell with a 3.86% glucose solution. After explanation of the aim of the study and written informed consent the patients started treatment with non-glucose dialysis solutions for at least 3 months. The dialysis regime consisted of 2 to 3 exchanges with a 2.5% glycerol-based dialysate (Baxter, Utrecht, the Netherlands), one exchange with a 1.1% amino acid-based dialysate (Nutrineal®, Baxter B.V.) and one exchange with 7.5% icodextrin containing dialysate (Extraneal®, Baxter B.V.; ML Laboratories, St Albans, UK). 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 after 6 weeks, 3 months, and every 6 weeks that the patient was treated thereafter. The SPA was performed during a four hours dwell period, as described previously [16]. The test was done with 3.86% glucose, using the volume the patient was used to. The test dwell 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 minutes). The effect of a dead space volume was avoided by temporarily 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, Medison 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 autoanalyzer (SMA-II, Technicon, Tarrytown, USA). Dialysate CA125, was determined by a commercial microparticle enzyme immunoassay (MEIA), using a monoclonal antibody against CA125 (Abbott Laboratories IMx, 162
IL, USA), validated for use in dialysate in our laboratory [19]. CA-125 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 depression of freezing point (Advanced Micro Osmometer).

**Fluid kinetics**

Transcapillary ultrafiltration and effective lymphatic absorption were assessed with the intraperitoneally administered volume marker dextran 70. Transcapillary ultrafiltration (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 point. The effective lymphatic absorption rate (ELAR) was calculated as the peritoneal dextran clearance [20].

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 previously [21], using the mass transfer area coefficient 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 MTACs. 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 Waniekewski model [22,23]. Glucose absorption was calculated as the difference between the amount of glucose instilled and the amount recovered, relative to instilled. All transport parameters were corrected for body surface area and expressed per 1.73 m² body surface area.

**Statistical analysis**

Data are 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 base-line levels. Comparisons between the patients with and without peritoneal sclerosis were tested non-parametrically, using the Mann-Whitney-U test.

163
Results

Patients
The demographic data of the patients participating in the study, as well as the duration of follow up and the drop-out reason are shown in Table 1. Ten patients started the study. One patient was withdrawn after 6 weeks because of clinical signs of encapsulating peritoneal sclerosis and another one because of unmanageable overhydration, just before the 3 months had ended. Three others were diagnosed with encapsulating peritoneal sclerosis, proven by peritoneal biopsies, within one year after the study ended. Two patients were transplanted after 3 months. Statistical analysis was therefore only possible at start, after 6 weeks and after 3 months.

Peritoneal sclerosis and non-sclerosis patients differed in duration of PD (102 vs. 52 months, \( p=0.05 \)), but not in appearance rate of CA-125 at the start of the treatment (2.8 U/min vs. 1.1 U/min, \( p=0.4 \)), and transcapillary ultrafiltration rate (2.2 mL/min vs. 1.2 mL/min, \( p=0.5 \)), as shown in Figure 1.

\[ \text{Figure 1.} \]
The basal values for duration of PD, TCUFR and CA-125 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.

Follow up
Values for peritoneal transport characteristics and CA-125 in the 3 months of glucose free treatment are given in Table 2. No statistically significant changes after 6 weeks or 3 months of glucose-free treatment were observed for transport characteristics, compared to 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 CA-125 appearance rate
increased after 6 weeks of glucose-free treatment and remained increased after continued treatment with glucose free solutions.

Table 1. Demographic data of 10 patients entering the study.

<table>
<thead>
<tr>
<th>patient</th>
<th>sex</th>
<th>dialysis scheme before start</th>
<th>duration of PD (months)</th>
<th>net UF (mL)</th>
<th>AR-CA125 (U/min)</th>
<th>peritoneal sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>CCPD 8x3.86%</td>
<td>56</td>
<td>.9</td>
<td>0.64</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>CAPD 5x3.86%</td>
<td>77</td>
<td>167</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>CCPD 6x3.86%</td>
<td>96</td>
<td>89</td>
<td>6.1</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>CAPD 4x3.86%</td>
<td>48</td>
<td>255</td>
<td>21.5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>CAPD 3x3.86%</td>
<td>12</td>
<td>390</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>CCPD 4x3.86%Χ1x2.27%</td>
<td>30</td>
<td>88</td>
<td>1.1</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>CAPD 3X3.6%Χ1xICO</td>
<td>70</td>
<td>336</td>
<td>0.52</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>CAPD 3X2.6%Χ1x1.36%</td>
<td>99</td>
<td>162</td>
<td>1.13</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>CAPD 2X2.6%Χ1x3.86%</td>
<td>108</td>
<td>81</td>
<td>1.08</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>CAPD 2X2.6%Χ1x3.86%</td>
<td>115</td>
<td>213</td>
<td>3.67</td>
<td>+</td>
</tr>
</tbody>
</table>

M: male, F: female, CCPD: continuous cyclic peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, ICO: 7.5% icodextrin based dialysys solution, AR-CA125: appearance rate for CA-125 in the dialysate per minute; the reasons for dropout are given in parenthesis; Tx: renal transplant, PS: peritoneal sclerosis

Table 2. Transport characteristics for the 10 ultrafiltration failure patients entering the study. Medians and ranges are given.

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

* p<0.05

Net UF: net ultrafiltration after 4 hours (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m²); ELAR: effective lymphatic absorption rate (mL/min/1.73 m²); Max dip D/P Na+: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m²; Glucose abs: absorption of glucose after 4 hours (%); AR-CA125: appearance rate of cancer antigen-125 in the dialysate (U/min)
A separate analysis was performed for the patients with and without encapsulating peritoneal sclerosis, as shown in Tables 3 and 4.

The individual data for the 6 non-peritoneal sclerosis patients are shown in Figure 2. In these patients net UF became higher for 4 out of 6 patients (Figure 2A). TCUFR improved after 6 weeks (Figure 2B), but no further improvement was seen after 3 months. A positive trend towards improvement was observed in free water transport, as shown by the increase of the maximum dip in D/P sodium (Figure 2C). In addition, MTAC creatinine decreased in the first weeks of treatment (Figure 2D) and glucose absorption tended to decrease (Figure 2E). The appearance rate of CA-125 in the dialysate showed an increase with the glucose-free regime, as shown in Figure 2F. Peritoneal sclerosis patients did not show any improvement with the glucose-free treatment.

### Table 3. Peritoneal transport characteristics for 6 patients with ultrafiltration failure without peritoneal sclerosis. Medians and ranges are given

<table>
<thead>
<tr>
<th></th>
<th>start</th>
<th>6 weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net UF (mL)</td>
<td>165 (9 - 390)</td>
<td>302 (11 - 434)</td>
<td>0.2</td>
</tr>
<tr>
<td>TCUFR (mL/min)</td>
<td>2.2 (0.8 - 2.8)</td>
<td>2.6 (1.0 - 3.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ELAR (mL/min)</td>
<td>0.6 (0 - 2.14)</td>
<td>1.6 (0.18 - 2.04)</td>
<td>0.1</td>
</tr>
<tr>
<td>Max dip D/P Na⁺</td>
<td>0.020 (0.010 - 0.090)</td>
<td>0.050 (0.030 - 0.090)</td>
<td>0.08</td>
</tr>
<tr>
<td>MTACcreatinine (mL/min)</td>
<td>14.3 (9.2 - 17.3)</td>
<td>12.6 (8.3 - 14.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glucose abs %</td>
<td>78 (55 - 98)</td>
<td>68 (58 - 81)</td>
<td>0.17</td>
</tr>
<tr>
<td>AR-CA125 (U/min)</td>
<td>2.8 (0.64 - 21.5)</td>
<td>16.1 (0.20 - 46.7)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Net UF: net ultrafiltration after 4 hours (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m²); ELAR: effective lymphatic absorption rate (mL/min/1.73 m²); Max dip D/P Na⁺: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m²; Glucose abs: absorption of glucose after 4 hours (%); AR-CA125: appearance rate CA-125 in the dialysate (U/min)

### Table 4. Peritoneal transport characteristics for 4 patients with peritoneal sclerosis. Medians and ranges are given

<table>
<thead>
<tr>
<th></th>
<th>start</th>
<th>6 weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net UF (mL)</td>
<td>151 (81 - 336)</td>
<td>136 (98 - 383)</td>
<td>0.8</td>
</tr>
<tr>
<td>TCUFR (mL/min)</td>
<td>1.17 (0.60 - 3.11)</td>
<td>0.96 (0.73 - 2.48)</td>
<td>0.3</td>
</tr>
<tr>
<td>ELAR (mL/min)</td>
<td>0.6 (0.23 - 1.69)</td>
<td>0.4 (0.17 - 0.77)</td>
<td>0.3</td>
</tr>
<tr>
<td>Max dip D/P Na⁺</td>
<td>0.016 (0 - 0.080)</td>
<td>0.028 (0.010 - 0.060)</td>
<td>0.9</td>
</tr>
<tr>
<td>MTACcreatinine (mL/min)</td>
<td>14.2 (10.4 - 15.2)</td>
<td>14.3 (9.1 - 16.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Glucose abs %</td>
<td>~2 (66 - 80)</td>
<td>~3 (54 - 63)</td>
<td>0.6</td>
</tr>
<tr>
<td>AR-CA125 (U/min)</td>
<td>1.11 (0.52 - 3.67)</td>
<td>1.28 (0.61 - 5.14)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Net UF: net ultrafiltration after 4 hours (mL); TCUFR: transcapillary ultrafiltration rate (mL/min/1.73 m²); ELAR: effective lymphatic absorption rate (mL/min/1.73 m²); Max dip D/P Na⁺: maximum decrease in D/P sodium; MTAC creat: mass transfer area coefficient of creatinine in mL/min/1.73 m²; Glucose abs: absorption of glucose after 4 hours (%); AR-CA125: appearance rate CA-125 in the dialysate (U/min)
No hyperosmolality syndrome was observed during the study-period; a median rise in plasma osmolality of 301 (287-318) mOsmol/kg H₂O to 304 (297-318) mOsmol/kg H₂O was found (p=0.16).

![Graphs showing changes in various parameters before and after 6 weeks.](image)

**Figure 2.** Differences in values for 6 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 CA-125 (F), between the start of glucose-free treatment and after 6 weeks.

**Discussion**

The results of the present study indicate that withdrawal of glucose-containing dialysis solutions can improve peritoneal function in patients with severe ultrafiltration failure, but without
peritoneal sclerosis. In addition, the results of this intervention support the hypothesis that exposure of the peritoneum to glucose or glucose degradation products, is important in the pathogenesis of ultrafiltration failure. The failure to reach 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 ultrafiltration failure. 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 peritoneal sclerosis within one year after the start of the study. Also, the very low dialysate CA-125 appearance rates present at the start of glucose free treatment is 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 glucose degradation products [25]. Glucose degradation products (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 acute effects of GDPs on 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, 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 non-enzymatic reactions with the amino group in peptides and proteins, referred as the Maillard reaction. The reaction between a carbonyl group and an amino group goes via reversibly formed Schiff's bases, which rearrange to intermediate Amadori products and may in the end result in the formation of stable carbohydrate cross-links between protein, so called advanced glycated end-products (AGEs) [29]. AGE modification preferentially occurs in long-lived structural proteins, such as collagen and eye-lens. 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 found also in non-diabetic renal failure patients [30]. This state of high reactivity in uremia is referred as "carbonyl stress" and it may be causative as well as a consequential factor in the progression of renal disease. Accumulation of AGEs was described in peritoneal biopsies of non-diabetic patients on PD [31,32], which increased with time on PD [32]. AGE formation leads to progressive cross-linking of collagenous tissues, increasing rigidity of vessels and leading to fibrosis [33,34]. 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 peritoneum. This leads to an effect on intracellular redox-status, which stimulates the release of growth factors, such as VEGF. VEGF induces neo-angiogenesis [36,37]. With the formation of new vessels, enlargement of the effective vascular surface area occurs.

![Figure 3.](image)

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.

Several solutions have been tested to replace glucose as osmotic agent in peritoneal dialysis. Glycerol is the only osmotic agent that can totally replace glucose. It is a low molecular weight 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 phagocytosis of peritoneal macrophages more than glucose [39]. Long-term use 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 CA-125 appearance with the use of icodextrin compared to glucose [46]. Nonetheless, icodextrin contains less glucose degradation products than a 1.36% glucose solution [47]. Icodextrin is iso-osmolar to uremic plasma. It exerts a colloid osmotic pressure over the peritoneal membrane and is only absorbed to a limited extent. Therefore, its osmotic effect sustains 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 daily, because of the maltose accumulation in the circulation that results from the absorption of icodextrin. The third alternative for glucose as dialysis solution is an amino-acid based solution. This consists of a combination of different amino acids, buffered with lactate. The effect on mesothelial cell cultures has been found similar to glucose [50]. Ultrafiltration 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 above could be used to replace glucose solely, we used all three of them combined. In the present study patients without peritoneal sclerosis showed improvement of some parameters of transport after the change to the glucose-free regime. The decrease in 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 can have been caused by a decrease in occupancy of AGF 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 newly formed aquaporin-1 or by reversal of glycation or nitrosylation of aquaporin-1, although this is less likely because 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 of the transcapillary ultrafiltration rate is the consequence of both the decrease in solute transport and the improved free water transport. The CA-125 appearance rates after glucose free treatment, is in accordance with previous results is. It implies a better preservation of the mesothelial cell layer. The patients who were diagnosed with peritoneal
sclerosis did not show any improvement after the switch 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 of peritoneal function is possible in patients with severe ultrafiltration failure by switching to glucose-free dialysis solutions. When encapsulating peritoneal sclerosis is present, no favorable 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 affected less severely is warranted.

References


