Low-GDP fluid (Gambrosol trio®) attenuates decline of residual renal function in PD patients: a prospective randomized study

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Abstract

Background. Residual renal function (RRF) impacts outcome of peritoneal dialysis (PD) patients. Some PD fluids contain glucose degradation products (GDPs) which have been shown to affect cell systems and tissues. They may also act as precursors of advanced glycosylation endproducts and associated factors in the adult population of Telde, Gran Canaria. Diabet Med 2006; 23: 148–155


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RRF was assessed every 4 to 6 weeks along the study period of 18 months. Data from 69 patients revealed a significant difference in monthly RRF change: −1.5% (95% CI = −3.07% to +0.03%) with low GDP (43 patients) vs −4.3% (95% CI = −6.8% to −2.06%) with standard fluids (26 patients) (P = 0.0437), independent of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker medication. Twenty-four-hour urine volume declined more slowly with low-GDP fluid compared to standard fluids (12 vs 38 mL/month, P = 0.0241), and monthly change of phosphate level was smaller (+0.013 vs +0.061 mg/dL, P = 0.0381).

Conclusions. Our prospective study demonstrates for the first time a significant benefit concerning preservation of RRF and urine volume of using a PD fluid with low GDP levels. These findings suggest that GDPs might affect patient outcome related to RRF.

Keywords: carbonyl stress; glucose degradation products; peritoneal dialysis; residual renal function

Introduction

Numerous clinical studies have provided evidence that residual renal function has a major impact on the outcome of patients treated with peritoneal dialysis (PD). Several investigators have demonstrated that residual renal function (RRF) is significantly related to survival whereas peritoneal clearance is not [1,2]. In addition, morbidity, poor nutritional status and fluid overload are associated with declining residual renal function. The paramount importance of RRF for dialysis patients was recently reviewed by Wang [3].

Glucose degradation products (GDPs) are formed during heat sterilization and storage of glucose-containing PD fluids. Since the early 1990s, the conditions of formation, action in biological cell systems and especially impact on peritoneal tissue have all been investigated [4–6]. The GDPs formed in peritoneal dialysis fluids consist of a large number of chemically different substances. The recently identified 3,4-dideoxyglucose-3-ene is so far the most biologically active and accounts for most of the toxicity of PD fluid [7]. GDPs are known to be precursors of advanced glycosylation endproducts (AGEs) [8]. Based on the finding that GDPs in PD fluids can enter the systemic circulation, they might contribute to an increase of systemic carbonyl stress via AGE formation [9]. This can lead to diabetes-like complications in the peritoneal cavity as well as in other target tissues and organs, of which the kidney is especially vulnerable being the major organ for AGE elimination [10]. AGEs may act directly on cells of target organs, as shown in vitro by Justo et al. [11] with induction of apoptosis in renal tubular cells. It is discussed whether AGEs are also involved in diabetic lesions, i.e. nephropathy and impaired antibacterial defence [12]. AGEs have also been found to act locally by binding to and activating mesothelial cells via the receptor for AGE (RAGE) [13], thus contributing systemically to renal pathophysiology in progressive diabetic as well as non-diabetic nephropathies. Based on the findings that GDPs, besides induction of local reactions, also exert detrimental systemic effects, we reasoned that residual renal function in PD patients may be affected by peritoneal administration of GDPs, and we conducted a randomized clinical study to address this hypothesis prospectively.

Materials and methods

Study design

The multicentre, prospective, randomized, controlled, open, parallel study (ISRCTN26252543) compared two types of PD fluid that differ only in the content of GDPs. The study was conducted from 1999 until 2005 in 15 study centres in Germany, 7 in France and 1 in Austria. The study protocol was approved by the ethics committees of all participating centres.

Patients who met the inclusion criteria and gave written informed consent were randomly assigned to the study group or the control group, i.e. treatment with either Gambrosol® trio (Gambro AB, Lund, Sweden), a multicompartment bag with minimal amounts of GDPs, (3,4-DGE < 1 µM) or standard PD fluids from different manufacturers in single-compartment bags, all containing significant amounts of 3,4-DGE (13–20 µM) [5]. Standard fluids were Gambrosol® for 50% of the patients (Gambro AB), Stay-safe® for 31% (Fresenius Medical Care, Bad Homburg, Germany) or Dianeal® for 19% (Baxter GmbH, Unterschleißheim, Germany). Randomization was performed by means of a centrally managed list based on a table of random numbers in blocks of four and stratified for the presence of diabetes. The PD regime was prescribed according to individual needs, i.e. number of bags/day, bag volume, glucose and calcium concentrations and PD mode.

Selection of patients

Inclusion criteria for the study were age between 18 and 80 years, end-stage renal disease (ESRD), glomerular filtration rate (GFR) ≥ 3 mL/min/1.73 m² (arithmetic mean of renal urea and creatinine clearances) or ≥ 6 mL/min/1.73 m² (creatinine clearance) as measured by 24-hour urine collection and being negative for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Patients were excluded from participation in the study if they were pregnant or lactating or had several peritonitis episodes in the past or cancer.

The study protocol was approved by the institutional review board in each study centre, with adherence to the Declaration of Helsinki. Before enrolment, written informed consent was obtained from all patients.

Assessment of residual renal function

Residual renal function was calculated as arithmetic mean of renal creatinine and urea clearances. Clearances were assessed at study entry and every 4 to 6 weeks along the study period of 18 months, according to the patient’s routine frequency of appointments in the dialysis centre. Creatinine and urea concentrations were measured in plasma and 24 h urine. Residual renal function was normalized to the standard body surface area of 1.73 m².

Body surface area was calculated with the Mosteller formula.
Assessment of fluid balance

Blood pressure measurements were performed on a regular basis by the patient and at the study centres. Single measurements of systolic and diastolic blood pressures at 1 week intervals were included in the evaluation. Ultrafiltration was assessed on a daily basis by the patients who documented bag weight of the fresh fluid according to the volume declared on the bags (e.g. 2000 g for a 2-L bag) and weighed the fluid bags after drainage. Single-day assessments at 1-week intervals were included in the evaluation. At the time of study initiation, the differences in overfill in between producers of PD fluid was not well-known, and the protocol therefore did not include instructions to weigh the bags before instillation. It was later established that standard fluid bags are overfilled by approximately 150 mL/bag [14]. The overfill volume for Gambrosol® trio is considerably less (0–44 mL per bag at 1.5% glucose and 41–85 mL per bag at 2.5% glucose). Calculation of ultrafiltration volumes with comparison between patients treated with fluids from different producers, whether in the study group or the control group, could therefore not be made.

Body weight and 24-hour urine volume were measured for assessment of residual renal function at the described intervals.

Blood sampling and measurement of serum parameters

Blood collection and measurement of serum parameters [C-reactive protein (CRP), total protein, albumin, electrolytes and phosphate] was performed according to the routine procedures in the respective study centres.

CA125 as a measure for mesothelial cell mass and viability

CA125 in spent dialysate was measured after 1, 6, 12 and 18 months. Samples from the overnight bag were collected, frozen and stored at −20°C for later analysis of CA125. Analysis was performed using commercially available kits for CA125. Due to the extended duration of the study and changes in the manufacturer’s product range, kits from different suppliers had to be used (CA125 ELISA from Roche Diagnostics GmbH, Mannheim, Germany; CA125 II Radioimmunonassay from Fujirebio diagnostics Inc, Malvern, USA; CA125 125I IRMA Kit from Diasorin, Stillwater, USA) and were applied to samples of patients from both study groups.

Assessment of peritoneal membrane transport characteristics

The Personal Dialysis Capacity (PDC®) software tool, based on the three-pore model of peritoneal transport [15], was applied to assess transport characteristics of the peritoneal membrane. According to a special fluid exchange protocol, urine, blood and dialysate samples were taken during a standardized continuous ambulatory peritoneal dialysis (CAPD) day, as described by van Biesen et al. [16]. Peritoneal exchange is described by the following parameters: surface area representing the diffusion capacity of small solutes, reabsorption rate of fluid into the blood compartment after peak time when the glucose gradient has largely dissipated and large pore fluid flow for quantification of protein loss to the PD fluid.

Medication

Blood pressure medication. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are known to affect renal function beneficially [17]. The number of patients who received ACE inhibitors or ARBs at any time during the study is shown in Table 1. These data were included in the statistical analysis applied to the RRF data. The number of patient months with ACE inhibitor medication was 376 of 583 (64.5%) in the low-GDP group and 107 of 357 (30%) in the standard fluid group (P = 0.0001). The number of patient months with ARB medication was 62 of 583 (10.6%) in the low-GDP group and 77 of 357 (21.6%) in the standard fluid group (P < 0.0001) (Table 1).

Diuretics. Diuretics were administered in 40 of 43 patients in the low-GDP group and in 24 of 26 patients in the standard fluid group (P = 0.912) (Table 1).

Phosphate binders. In the low-GDP and the standard fluid groups, 40 of 43 and 24 of 26 patients, respectively, received phosphate binders during the study period (P = 0.912). Three of 43 and 4 out of 26 patients received phosphate binder medication only part-time during the study period. Groups did not differ in type of phosphate binder administered (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Concomitant medication. Data are given as percentage of patients. If not otherwise stated, data are not significantly different between study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td><strong>Blood pressure medication</strong></td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>Percentage of patient months with medication:</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Phosphate binders</td>
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<tr>
<td>Ca-based</td>
</tr>
<tr>
<td>Al-based</td>
</tr>
<tr>
<td>Sevelamer</td>
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</table>

*P = 0.0244 (chi-square test). **P < 0.0001 (chi-square test).

Statistical analyses

The final sample size was based on the possibility of showing 1 mL/min/1.73 m²/year difference between the groups in the slope of RRF decline, with a power of 0.8 and a significance level of 0.05. An interim regression analysis was performed after inclusion of 31 patients, and the data available at the time was used for calculation of sample size. Considering 11 RRF observations per patient, a ratio of the number of observations of 0.6 (standard group vs low-GDP group) and assuming a SD of RRF 2.5 mL/min/1.73 m² and SD of time 6.5 months, the required sample size was estimated to be 66 patients.

Assuming missing RRF data from 20% patients, 80 patients were randomized. Sample size calculations were done with the PS (Power and Sample Size) software, version 2.1.31 (Vanderbilt Medical Center).

An as-treated analysis was conducted, including all patients with RRF measurements. For evaluation of the RRF data, multivariate analysis was performed applying a regression model for repeated measures with heterogeneous compound symmetry structure, adjusted for the relevant covariates, i.e. age, diabetes, gender, time on PD, blood pressure medication with ACE inhibitors and angiotensin receptor blockers and possible interactions. To test goodness of fit of an exponential as well as a linear decrease model, likelihood ratio test and Akaikes and Schwarz’s criteria were applied [18–20].

Dropout analysis was done by simple chi-square test for patients who dropped out early and by log-rank and Wilcoxon tests for patients providing RRF data, the log-rank test being more significant than the Wilcoxon test due to higher weighing of longer survival times. CA125 data were

<table>
<thead>
<tr>
<th>Table 2. Dropout reasons for patients included in the evaluation (n = 69)</th>
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<tbody>
<tr>
<td><strong>Reason</strong></td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Several peritonitis episodes and/or switch to HD</td>
</tr>
<tr>
<td>Switch to automated PD*</td>
</tr>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td>Handling difficulties</td>
</tr>
<tr>
<td>Others*</td>
</tr>
</tbody>
</table>

*Two patients switched to APD and had to leave the study due to lack of low-GDP fluid in larger APD bags which became available at a later stage of the study.
*Other dropout reasons were: patient’s wish to switch back to his old system, pain not related to PD, transplant rejection, infusion pain, decision of investigator, sufficient renal function and refusal of further participation.
analysed applying a general linear model. Single comparisons of baseline characteristics were made using Student’s t-test if data were normally distributed and Mann–Whitney–Wilcoxon test otherwise. Differences in categorical variables were evaluated with the chi-square test. Time course of the parameters blood pressure, 24-hour ultrafiltration, body weight, urine volume, serum CRP protein, albumin, electrolytes and phosphate was assessed applying a repeated measures model with autoregressive-moving average (ARMA) covariance structured matrix. A P-value below 0.05 was considered significant for all applied statistical tests. All reported P-values are two-tailed. Data are given as mean ± standard deviation if normally distributed or as median (range) if non-normally distributed. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

Baseline characteristics of patients

Eighty patients were randomized, 43 to the low-GDP group and 37 to the standard fluid group. One patient randomized to standard fluid group was erroneously treated with low-GDP fluid and was evaluated in this group which resulted in 44 patients in the low-GDP group and 36 in the standard fluid group. Eleven randomization patients were excluded from evaluation due to either dropout before the first RRF measurement (n = 1 in the low-GDP group, n = 7 in the standard fluid group; P = 0.0109), exclusive treatment with icodextrin (n = 1 in the standard fluid group) or unusable documentation (n = 2 in the standard fluid group). Reasons for this early dropout, before the first RRF measurement, were in the low-GDP group: transplantation (n = 1) and in the standard fluid group: refusal of treatment with icodextrin (n = 1), switch to HD (n = 1), residual renal function after randomization below inclusion criteria (n = 1) and unknown (n = 3). Of the 69 patients with analysable RRF data, 18 patients in the low-GDP group and 12 patients in the standard fluid group dropped out at different points of time during the study period. Reasons for dropout are given in Table 2. Dropout analysis in patients included in the evaluation revealed no difference between the study groups (log-rank test: P > 0.3 and Wilcoxon test: P > 0.4). The dropout rate among the 69 patients was 2.4%/month.

All patients performed CAPD, except four patients in the low-GDP group and two patients in the standard fluid group, who were temporarily treated with APD during the study period, and one patient in the standard fluid group who exclusively performed APD. The baseline patient characteristics were similar in the two treatment groups (Table 3). Median exposure time was 17.8 months (range 0–18.9) in the low-GDP group and 16.3 months (range 0–18.9) in the standard fluid group.

Residual renal function

A total of 785 measurements of RRF could be evaluated. Median number of observations per patient was 12 (range 1–19) in both groups. RRF at the start was not significantly different in the different groups (Table 3). Goodness of fit of the data was superior with the exponential model when compared to the linear model, i.e. result of the likelihood ratio test was −2 log likelihood 1508.5 vs 2656.0, and Akaike’s and Schwarz’s criteria resulted in Akaike Information Criterion (AIC) 1556.5 vs 2704.0. The exponential approach was therefore applied. When comparing the regression results, monthly change in RRF was significantly different between groups: −1.5% (95% CI = −3.07% to +0.03%) in the low-GDP group vs −4.3% (95% CI = −6.8% to −2.06%) in the standard fluid group (P = 0.0437), as depicted in Figure 1. Based on the statistical analysis, RRF after 18 months was higher by 2.3 mL/min/1.73 m² in the low-GDP group compared to the standard fluid group.

Due to the unstratified randomization, resulting in different use of ACE inhibitors and ARBs in the two groups throughout the study, these variables were added as separate covariates to the statistical analysis in order not to blur any possible effect on the primary endpoint. The statistical analysis demonstrated that the difference in RRF decline between the groups does not depend on ACE inhibitor therapy (P > 0.2) or ARB therapy (P > 0.8).

To test for data robustness, a similar statistical analysis was performed, including the patient exclusively treated with icodextrin in the standard fluid group and assigning the patient who was randomized to the standard fluid group but treated with low-GDP fluid, to the standard fluid group. The result matched the original finding, with a monthly change in RRF of −1.5% (95% CI = −3.09% to +0.05%) in the low-GDP group and −4.5% (95% CI = −6.84% to −2.08%) in the standard fluid group (P = 0.043).

Table 3. Baseline patient characteristics. Data are given as mean ± SD or median and range, according to distribution

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low-GDP fluid (n = 43)</th>
<th>Standard fluids (n = 26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>52.0 ± 12.0</td>
<td>53.8 ± 14.6</td>
<td>0.588</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.9 ± 14.6</td>
<td>76.3 ± 12.5</td>
<td>0.389</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>60</td>
<td>54</td>
<td>0.589</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>20.9</td>
<td>19.2</td>
<td>0.865</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
<td>2.6 (0–47.6)</td>
<td>1.3 (0–45.5)</td>
<td>0.386</td>
</tr>
<tr>
<td>Urine volume (mL)</td>
<td>1700 (750–3500)</td>
<td>1650 (950–3800)</td>
<td>0.544</td>
</tr>
<tr>
<td>RRF at study entry (mL/min/1.73 m²)</td>
<td>6.7 ± 3.1</td>
<td>6.2 ± 2.4</td>
<td>0.923</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular vasculopathy/nephrosclerosis</td>
<td>10 (23.3%)</td>
<td>3 (11.5%)</td>
<td>0.228</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>7 (16.3%)</td>
<td>5 (19.2%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>13 (30.2%)</td>
<td>5 (19.2%)</td>
<td>0.313</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3 (7.0%)</td>
<td>4 (15.4%)</td>
<td>0.262</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>5 (11.6%)</td>
<td>4 (19.2%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (11.6%)</td>
<td>5 (15.4%)</td>
<td>0.385</td>
</tr>
</tbody>
</table>
Fluid balance

There were no significant differences in the recorded blood pressures, whether regarded as systolic, diastolic or mean arterial pressure (MAP) during the course of the study (Table 4), although systolic blood pressures tended to decrease more in the standard fluid group. The recorded ultrafiltration increased in both groups during the observation period (Table 4), but no conclusions can be drawn from these data due to the different overfill volumes. Baseline values for body weight were comparable in both patient groups and increased at similar rates (Table 4). Urine volume was not significantly different at the start of the study (Table 3). The decline of 24-hour urine volume was significantly less pronounced in the low-GDP group compared to the standard fluid group as shown in Figure 2 (decrease by 12 vs 38 mL/month, P = 0.0241).

CRP and albumin

Serum CRP levels at baseline were not significantly different between groups [median 0.4 mg/dL (range 0.02–4.4) vs 0.6 mg/dL (0.2–8.8)], and no significant change in CRP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-GDP group</th>
<th>Standard fluid group</th>
<th>P-value</th>
<th>Low-GDP group</th>
<th>Standard fluid group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h ultrafiltration not corrected for overfill (ml)</td>
<td>202 ± 148</td>
<td>446 ± 116</td>
<td>0.10</td>
<td>15 ± 11</td>
<td>28 ± 8</td>
<td>0.23</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>133 ± 4</td>
<td>137 ± 3</td>
<td>0.34</td>
<td>−0.23 ± 0.31</td>
<td>−0.46 ± 0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82 ± 2</td>
<td>80 ± 2</td>
<td>0.54</td>
<td>−0.23 ± 0.14</td>
<td>−0.22 ± 0.18</td>
<td>0.68</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>99 ± 3</td>
<td>99 ± 2</td>
<td>0.96</td>
<td>−0.22 ± 0.18</td>
<td>−0.30 ± 0.14</td>
<td>0.94</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>73.4 ± 3.4</td>
<td>75.7 ± 2.7</td>
<td>0.49</td>
<td>0.07 ± 0.07</td>
<td>0.10 ± 0.05</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Fig. 1. Decline of residual renal function with low-GDP fluid and standard fluid as assessed with multivariate analysis (solid line); dashed lines represent 95% confidence interval for predicted values. Dots show single measurements.

Fig. 2. Decline of 24-h urine volume with low-GDP fluid and standard fluid as assessed with ARMA model (solid line); dashed lines represent 95% confidence interval for predicted values. Dots show single measurements.
values throughout the study period was found (Table 5). There were no differences in serum albumin (Table 5).

**Phosphate and calcium**

Serum calcium was similar in both groups (Table 5). The baseline level for serum phosphate was 5.16 mg/dL in the low-GDP group and 4.73 mg/dL in the standard fluid group ($P = 0.1471$) (Table 5). During the observation period, serum phosphate levels remained almost constant in the low-GDP group (change by 0.0135 mg/dL/month), whereas an increase by 0.0607 mg/dL/month was observed in the standard fluid group ($P = 0.04$).

Measured serum phosphate levels at the end of the study period were 5.5 ± 1.7 mg/dL in the low-GDP group and 6.2 ± 1.4 mg/dL in the standard fluid group. Time to dropout was not related to phosphate levels ($P > 0.2$ using different non-parametric tests). Phosphate binder medication of all types was similar in both groups (Table 1). The dietary protein or phosphate intake was not controlled.

**CA125**

A substantial difference in CA125 levels was found between the groups that persisted throughout the study period, with median levels of 61.2 U/mL (range 0–293.7) in the low-GDP group and 18.7 U/mL (range 0–111.0) in the standard fluid group ($P < 0.001$).

**Peritoneal membrane transport characteristics**

The area parameter at the start was 21 699 ± 5485 and 20028 ± 6685 cm$^2$/1.73 m$^2$ in the low-GDP and standard groups, respectively (NS). No differences in start values were detected for the other PDC parameters. During the study period, no important changes were observed in any of the two study groups (data not shown).

**Peritonitis episodes**

A total of 16 peritonitis episodes were experienced in the low-GDP group in 11 of 43 patients (25.6%). In the standard fluid group, nine peritonitis episodes in 6 of 26 patients (23.1%) were documented ($P = 0.815$). Four patients in the low-GDP group (9%) and two patients in the standard fluid group (8%) experienced relapsing or recurrent peritonitis episodes ($P = 0.818$). Peritonitis rates were 1 of 36.4 patient months in the low-GDP group and 1 per 39.7 patient months in the standard fluid group (NS).

**Discussion**

This is the first randomized, controlled study on the impact of GDPs in PD fluids on residual renal function (RRF) in incident as well as prevalent patients treated with peritoneal dialysis (PD). It shows a significant and clinically relevant beneficial effect of low-GDP fluid. In the patients using low-GDP fluid, the decline of RRF was significantly slower compared to patients treated with standard PD fluids, an effect that was shown to be independent of ACE inhibitor and ARB medication. This finding is consistent with an earlier, short-term study indicating higher renal creatinine and urea clearances and higher urine volume associated with use of low-GDP fluid [21].

However, in a recent prospective study, Fan and coworkers failed to detect a similar difference in RRF between patients treated for 12 months with standard PD fluids and fluids referred to as biocompatible [22]. In this context, it is worth noting that considerable differences in GDP concentrations can be found even among so-called low-GDP fluids, especially with respect to the content of 3-DG and the most cytotoxic component, 3,4-DGE [7]. A closer look at the study by Fan et al. reveals that more than 85% of the patients in the biocompatible fluid group were treated with a fluid that contains considerable amounts of 3,4-DGE (11 μM) and 3-DG (178 μM), which is well within the range of standard PD fluids [5]. A clearer definition of the term ‘low-GDP’ should be considered in this context. Another drawback of their study might be that RRF was assessed only twice, after 3 and 12 months. It is our experience that RRF determinations are subject to large intra-patient fluctuations with inaccuracy of 24-hour urine collection performed by the patients being a major cause. Thus, frequent measurements are mandatory for a reliable assessment of RRF changes over time. In an editorial comment to the Fan study, Locatelli and La Milia wisely remarked that any beneficial effect of a biocompatible PD fluid on RRF is rather to be expected if the fluid is introduced at an earlier stage of chronic kidney disease, i.e. in patients with relatively well-preserved RRF, than at a later stage when the RRF is poor [23]. They cite several studies showing no effect of so-called biocompatible PD fluids on RRF, but a closer look at those studies shows that the RRF

<table>
<thead>
<tr>
<th>Serum parameter</th>
<th>Low-GDP group</th>
<th>Standard fluid group</th>
<th>P-value</th>
<th>Low-GDP group</th>
<th>Standard fluid group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dL)</td>
<td>0.78 ± 0.61</td>
<td>1.28 ± 0.59</td>
<td>0.42</td>
<td>−0.0027 ± 0.0624</td>
<td>−0.0099 ± 0.0610</td>
<td>0.84</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.74 ± 0.15</td>
<td>3.72 ± 0.13</td>
<td>0.90</td>
<td>−0.0038 ± 0.0126</td>
<td>0.0058 ± 0.0111</td>
<td>0.44</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>6.9 ± 0.6</td>
<td>6.9 ± 0.5</td>
<td>0.96</td>
<td>0.078 ± 0.034</td>
<td>0.087 ± 0.030</td>
<td>0.78</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.16 ± 0.29</td>
<td>4.73 ± 0.21</td>
<td>0.15</td>
<td>0.0135 ± 0.0227</td>
<td>0.0607 ± 0.0178</td>
<td>0.04</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.35 ± 0.04</td>
<td>2.36 ± 0.03</td>
<td>0.95</td>
<td>0.0035 ± 0.0036</td>
<td>0.0028 ± 0.0027</td>
<td>0.83</td>
</tr>
</tbody>
</table>
was well below 4 mL/min at the study start. In our study, the initial RRF was at least 50% higher. Low RRF at study start and infrequent measurements of RRF could be contributing reasons to the lacking difference in RRF reported from a previous clinical study using the same quality low-GDP fluid as in our present study [24].

But how can GDPs damage the kidneys? The effect of peritoneal dialysis on renal morphology and function was investigated by Breborowicz and co-workers in rats treated with standard PD fluid. They found albuminuria and accumulation of extramesangial matrix in the glomeruli and collagen in the peritubular space, similar to diabetic nephropathy [25]. In analogy to the mode of action of diet-derived AGEs on the kidney, as reviewed by Uribarri and Tuttle [26], peritoneally administered reactive carbonyls (GDPs) entering the circulation can contribute to the systemic AGE load [9]. AGEs are classified as uraemic toxins, and, via RAGE interaction or independent events, they exert direct pro-inflammatory and pro-oxidative nephrotoxicity and may also alter the haemodynamics and structure of the kidney [11].

We also investigated the time course of parameters that describe the hydration status, i.e. blood pressure, body weight, 24-hour ultrafiltration and urine volume and additionally such inflammatory parameters that might be related to hydration and nutrition status, CRP and albumin. The statistical analysis revealed that the study groups differed in none of these parameters, showing that better preservation of residual renal function was not at the expense of fluid overload. This is in line with the findings of Cheng and co-workers who showed that extracellular fluid was not significantly different in patients with different urine outputs [27] but in contrast to a study by Konings et al., who found an inverse correlation of renal creatinine clearance and extracellular fluid volume [28]. Based on our results, maintenance of fluid balance does not seem to be the major component affected by preservation of residual renal function, but this conclusion is limited by the lack of information on ultrafiltration volume in our study.

Renal function is also a prerequisite for adequate handling and regulation of inorganic phosphate, and hyperphosphataemia develops with progression of renal failure. Hyperphosphataemia is one of the major risk factors for mortality in ESRD patients [29]. Control of phosphate levels would thus be beneficial with respect to patient survival. Our data show that phosphate levels are better controlled in the low-GDP group, indicating that even low absolute levels of RRF in ESRD might have an impact on phosphate regulation. This is in line with the findings of Wang and co-workers [30]. Shortcomings of the study with respect to this aspect might be that protein intake was not controlled. Nevertheless, comparable albumin levels indicate similar protein intake in both groups, as no differences in inflammatory or hydration status were detected. Groups did not differ in calcium-based phosphate binder medication and serum calcium levels indicating similar amounts of administered phosphate binders.

GDPs are known to cause damage to the peritoneal membrane possibly mediated by RAGE [31]. To assess local effects of GDPs, we measured CA125 in overnight dialysis fluid as a marker for mesothelial cell mass and integrity [32] and found significantly higher levels in the low-GDP group compared to the standard fluid group indicating better preservation of the peritoneal mesothelial cell layer, thus confirming results of numerous preceding studies.

Evaluation of the peritoneal membrane characteristics revealed no differences between the groups for start values and no trends within the study period. This is in line with the findings of a previous long-term study over 12 months [24]. The EuroBalance trial, however, showed an increase of D/P creatinine values after 12 weeks using low-GDP lactate PD fluid. Other short studies (14 days) revealed no difference in D/P creatinine values and MTAC between low-GDP bicarbonate and high-GDP standard solutions [33]. Up to now, there are contrasting results considering the effect of biocompatible solutions on membrane function and ultrafiltration. In our study, the PDC test was performed every 6 months, and the database cannot confirm any difference between groups, possibly due to patient dropout and missing data.

Peritonitis incidence was comparable in both study groups, and we observed no beneficial effect of the low-GDP fluid regarding this particular complication. This is in contrast to a recent non-randomized study showing 50% reduction of peritonitis rate with biocompatible PD solutions [34] but in line with the findings in other prospective studies [24,36]. One reason for the lack of difference in our study could be that the peritonitis rates were very low in both groups (36.4 patient months in the low-GDP group and 39.7 in the standard fluid group). The peritonitis rate in our study was comparable to the group using biocompatible solution in the study of Ahmad et al. [34].

Residual renal function is an important risk factor for mortality in PD patients [1,2]. Thus, we conclude that the presented data provide evidence that GDPs in PD fluids may have a major impact on the survival of PD patients. Two recent publications from Korea show an association between the use of a low-GDP PD fluid and improved survival. In a retrospective study involving more than 1100 incident patients observed up to 30 months, Lee et al. found that the relative risk (RR) of death was lowered by 25% in the patient group treated with low-GDP fluid compared to standard PD fluids [35]. In a prospective, observational study over a period of 3.5 years using a database overlapping with the data reported earlier, the same author found a reduction of the RR of death of 39% in patients treated with low-GDP fluid [36]. After correction for age, the use of biocompatible fluid still resulted in mortality risk reduction by 21%. Assuming a mortality risk reduction of 12% each 1 mL/min/1.73 m² of RRF preservation [2], our findings would indicate a risk reduction of death by 28% in patients after 18 months treatment with low-GDP fluid rather than standard fluid.

Our study has several limitations which need to be weighed against our findings. As in most other long-term PD studies, we experienced a large dropout of patients. The loss of patients in the early phase was significantly larger in the group randomized to standard fluid, and we cannot rule out that a selection bias among patients or physicians could have influenced this process. The dropout continued to be large during the study period (2.4%/month), but at that
Hechingen, Germany.

**Conflict of interest statement**

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**Appendix**

The following investigators participated in the DIUREST Study:

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**References**

Impact of peritoneal transport characteristics on cardiac function in Paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report

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Abstract

Background. The peritoneal equilibration test (PET) is recommended in paediatric peritoneal dialysis (PD) patients to assist prescription management. Despite contradictory reports, high transporter status is associated with reduced survival rate in adults. Since cardiac disease is one of the main causes of mortality in paediatric PD patients, we aimed to evaluate whether transport features have any effect on biochemical data and cardiac function in this group.

Methods. One hundred and ten PD patients (13 ± 5 years, PD vintage: 31 ± 27 months) were enrolled into the study.

References

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