Peritoneal Expression of SGLT-2, GLUT1, and GLUT3 in Peritoneal Dialysis Patients

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Keywords
Encapsulating peritoneal sclerosis · Glucose transporter 1 · Glucose transporter 3 · Peritoneal dialysis · SGLT-2

Abstract
Introduction: In peritoneal dialysis (PD) patients, the peritoneal membrane is affected by glucose-based solutions used as peritoneal dialysate fluids. This exposure leads to changes of the membrane which may eventually culminate in fibrosis and method failure. In vitro or animal studies demonstrated that glucose transporters are upregulated upon exposure to these solutions. Expression studies of glucose transporters in human peritoneum have not been reported yet. Methods: Expression of SGLT-2, GLUT1, and GLUT3 in human peritoneal biopsies was analyzed by real-time polymerase chain reaction and Western blot analysis. The localization of these glucose transporters in the peritoneum was evaluated by immunohistochemistry using a Histo-Score. Results: Peritoneal biopsies of patients (healthy controls, uremic, PD, and encapsulating peritoneal sclerosis [EPS]) were analyzed. We found evidence of SGLT-2, GLUT1, and GLUT3 expression in the peritoneal membrane. Protein expression of SGLT-2 increases with PD duration and is significantly enhanced in EPS patients. All transporters were predominantly, but not exclusively, located adjacent to the vessel walls of the peritoneal membrane. Conclusion: Our study showed that SGLT-2, GLUT1, and GLUT3 were regularly expressed in the human peritoneum. SGLT-2 was particularly upregulated in PD patients with EPS, suggesting that this upregulation may be associated with pathological changes in the peritoneal membrane in this syndrome. Since preclinical studies in mice show that SGLT-2 inhibitors or downregulation of SGLT-2 ameliorated pathological changes in the peritoneum, SGLT-2 inhibitors may be potentially promising agents for therapy in PD patients that could reduce glucose absorption and delay functional deterioration of the peritoneal membrane in the long term.

Introduction
Peritoneal dialysis (PD) is an effective method of renal replacement therapy for patients with end-stage renal disease providing a high level of patient autonomy [1, 2]. However, long-term PD is associated with peritoneal changes such as peritoneal fibrosis and, at worst, compli-
cations such as peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) eventually leading to ultrafiltration or method failure. The application of PD is limited due to permanent exposure of human peritoneal mesothelial cells in the peritoneal membrane to glucose-based PD fluids and glucose degradation products [3–6]. Generally, the transport of glucose in the body occurs through glucose transporters belonging to a large family of membrane proteins that is divided into 2 families: the solute carrier family 2 (SLC2A) gene family (also known as glucose transporter [GLUT]) [7, 8] and the so-called SLC5A gene family (SGLT) encoding for the Na+/glucose cotransporter [9, 10]. GLUTs are predominantly expressed in enterocytes, in the intestine and kidney, as well as in numerous other organs. In contrast, SGLTs are mainly restricted to the small intestine, proximal tubules of the kidney, and as recently reported, to mesangial cells [11–13]. Presently, inhibitors of glucose transporters and especially SGLT-2 inhibitors are of great interest due to their various applications in the clinics including substantial cardio- and renoprotective effects [14–16]. SGLT-2 inhibitors were initially used to reduce blood glucose levels in diabetic patients [17–21]. However, new studies showed that SGLT-2 inhibitors also reduce the risk of hospitalization from heart failure and of composite renal endpoints in patients regardless of the presence or absence of diabetes [15, 16, 22]. Since a new study suggested that the SGLT-2 inhibitor dapagliflozin mitigated peritoneal fibrosis and ultrafiltration failure in a PD mouse model [23], we hypothesized that SGLT-2 inhibitors may also be potential drugs for PD patients to reduce glucose absorption and potentially functional membrane deterioration. To date, most studies on glucose transporters, especially SGLT-2, have been performed in rats or in vitro models by molecular and biochemical analysis [24–26]. Therefore, we now performed expression studies in a larger cohort of human peritoneal biopsies. Here, we aimed to evaluate if and how the major glucose transporters (SGLT-2, GLUT1, and GLUT3) are expressed in the human peritoneum and if there are changes in transporter expression in association with different peritoneal conditions.

Materials and Methods

Chemicals

Chemicals were obtained from Sigma-Aldrich unless otherwise indicated.

Trial Design and Patients

The study was conducted after consultation with the Ethics Committee of the University of Tübingen, Germany (Process No. 322/2009BO1). For the biopsy registry at the Robert-Bosch Hospital in Stuttgart, peritoneal biopsies were collected from 2009 to 2017. Biopsies were taken from PD patients at the time of catheter removal, correction of a catheter malposition, or as diagnostic biopsies for suspected EPS. With regard to non-PD patients, biopsies were taken at the time of various surgical interventions. Table 1 gives an overview about the subgroups included. All patients had given their informed consent regarding a scientific workup of tissues taken during routine procedures. All clinical data as well as descriptive statistical data of the patient cohort are summarized in Table 2.

Tissue Storage and Homogenization

Human peritoneal biopsies were incubated in RNAlater or pre-chilled in liquid nitrogen and were then stored at −80°C. For RNA isolation, 50–100 mg peritoneal biopsy material was shredded in 600 μL lysis buffer (mirVana™ miRNA Isolation Kit; Thermofisher) with an ultra-turrax (16,000 g, 1 min). Thereafter, the supernatant was transferred to tubes filled with ceramic balls and homogenized using the FastPrep system (3 times, 6 m/s, 20 s; MP Biologicals). Last, the supernatant was centrifuged at 16,000 g for 1 min. For Western blot analysis, total protein lysates were prepared in ice-cold RIPA lysis buffer (50 mM Tris-HCl, pH 8.0, 120 mM NaCl, 1% NP-40, 0.5% Na-desoxycholat, 0.1% SDS, 2 mM EDTA, 25 mM NaF, 0.2 mM NaVO4, 1 mM DTT, and complete protease inhibitor cocktail from Roche) using a micro pestle (Roth, Germany). Peritoneal homogenates were lysed for 30 min on ice and then centrifuged at full speed for 15 min at 4°C. The protein content was determined using a BCA assay.

Table 1. Subgroup definition

| Subgroup | Definition |
|----------|------------|
| **Comparison groups (without exposure to dialysis fluids)** | |
| “Control” | Healthy control patients, indication for surgery: hemicolectomy, inguinal hernia, cholecystectomy, or ileostomy displacement |
| “Uremic” | Predialysis patients at catheter implantation |
| **PD groups** | |
| “PD <12 months” | Less than 12 months of exposure to dialysis fluids |
| “PD >12 months” | More than 12 months of exposure to dialysis fluids |
| “EPS” | Patients diagnosed with EPS; diagnosis based on clinical presentation, characteristic imaging (computed tomography), intraoperative presentation, and histomorphological features |

PD, peritoneal dialysis; EPS, encapsulating peritoneal sclerosis.
Quantitative PCR

Total RNA was isolated with the mirVana miRNA Isolation Kit (Thermofisher) according to the manufacturer’s instructions. Total RNA (1 μg) was reverse transcribed with an RT-PCR kit (Applied Biosystems) and afterward diluted 1:1 with water. qPCR was performed using Power SYBR Green PCR Master Mix (Applied Biosystems). Gene expression was analyzed using the 7500 Real-Time PCR Systems and Sequence Detection Software, version 2.3 (Applied Biosystems). Gene expression was evaluated using the ΔΔCT method and human GAPDH as the reference gene. The following primer sequences were used: GAPDH: forward 5′-GCC TCT TTT GGC CTC G, reverse 5′-TGT AAA CCA TGT TCT TCT TTT GCG TCG, reverse 5′-GCA TCT CTC TTT GGC CTC G. The following primer sequences were used: SGLT-2: forward 5′-TGT AAA CCA TGT TCT TCT TTT GCG TCG, reverse 5′-GCA TCT CTC TTT GGC CTC G. The following primer sequences were used: GLUT1: forward 5′-AGG TGA TCG AGG AGT CT CCA GGT ATT TGTC-ACC TTC GTC AT, reverse 5′-GAC ACG GTA CAG AGT TGA GGT; GLUT3: forward 5′-TTC GTC TCT AGC CTG CAC TG, reverse 5′-TCA AAG GAC TTG CCC AGT TT; and testis for GLUT3 expression. The following antibodies were used: anti-SLC2A1 (HPA031345, 1:1,500; Sigma), anti-SLC2A3 (HPA006539, 1:400; Sigma), and anti-SGLT-2 (clone D6, 1:2,000; Santa Cruz). For quantitative analysis of transporter expression, signals were quantified with ImageJ 1.52v.

Immunohistochemistry

Biopsies from the peritoneum were formalin-fixed in 4% buffered formalin and embedded following routine protocols [26]. Dewaxed and rehydrated tissue sections were incubated in peroxidase blocking solution (S 2023; Agilent) to block endogenous peroxidases. Pretreatment was performed in a steamer, using an antigen retrieval solution (for SGLT-2: pH 6, S 1699, for SLC2A1 and SL-C2A3: pH 9, S 2367; Agilent). The staining method used a dextran-coated peroxidase coupled polymer system (EnVisionTM Detection Kit, Peroxidase/DAB, Rabbit/Mouse, K 5007; Agilent). As positive control, the following tissues were used: kidney for SGLT-2, placenta for GLUT1, and testis for GLUT3 expression. The following antibodies were used: anti-SLC2A1 (HPA031345, 1:1,500; Sigma), anti-SLC2A3 (HPA006539, 1:400; Sigma), and anti-SGLT-2 (clone D6, 1:50; Santa Cruz). The sections were examined with the Olympus VS120 automated slide scanner equipped with a BX61VS microscope (objective: UPLSAPO 40x; Olympus).

Evaluation of Histo-Score

Immunohistochemistry results were evaluated in a semiquantitative approach (Histo-Score) similar to tumor samples. Percentage of stained structures (1 point/10% structures) as well as staining intensity (no staining [0], weak [1], moderate [2], or strong [3]) was determined [27]. In our study, the following structures were analyzed: mesothelial structure, submesothelial structure, adipocytes, and vessels.

The final Histo-Score was assigned using the following formula: Histo-Score = (percentage mesothelial structure × staining intensity mesothelial structure) + (percentage submesothelial structure × staining intensity submesothelial structure) + (percentage adipocytes × staining intensity adipocytes) + (percentage vessels × staining intensity vessels).

Statistical Analysis and Data Handling

To compare the different subgroups, a Kruskal-Wallis test and Dunn’s post hoc analysis was used. p values were calculated using GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA).

Results

Glucose Transporters Are Expressed in Human Peritoneum

In this study, we determined the expression of the glucose transporter by analyzing peritoneal biopsies. All

Table 2. Clinical data of study patients

| Variable                        | Control | Uremic | PD <12 months | PD >12 months | EPS |
|---------------------------------|---------|--------|---------------|---------------|-----|
| N                               | 8       | 11     | 18            | 23            | 12  |
| Age, years                      |         |        |               |               |     |
| Median                          | 64.5    | 65.0   | 64.0          | 62.0          | 51.5|
| IQR                             | 55.5–70.8| 49.0–75.0| 53.0–69.3     | 46.0–71.0     | 45.3–58.8|
| Female/male                     | 6/2     | 3/8    | 4/14          | 9/14          | 3/9 |
| PD duration, months             |         |        |               |               |     |
| Median                          | 10.5    | 44.0   | 70.0          |               |     |
| IQR                             | 6.0–11.25| 29.0–52.0| 55.5–99.5     |               |     |
| Diabetes, n (%)                 | 1 (13)  | 3 (27) | 8 (44)        | 8 (35)        | 0 (0)|
| Hypertension, n (%)             | 1 (13)  | 9 (82) | 14 (78)       | 23 (100)      | 11 (92)|
| Smokers, n (%)                  | 1 (13)  | 3 (27) | 7 (39)        | 8 (35)        | 2 (17)|

Percentages are rounded to whole numbers. EPS, encapsulating peritoneal sclerosis; IQR, interquartile range; n, number of values; PD, peritoneal dialysis.

SLGT-2, GLUT1, and GLUT3 in Peritoneal Biopsies

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(For legend see next page.)
clinical data as well as descriptive statistical data of the patient cohort are summarized in Table 2. In general, more male than female patients were included into the study. As expected, time on PD was longer in patients with signs of EPS. We isolated RNA as well as protein lysates from the human peritoneum and analyzed the expression of SGLT-2, GLUT1, and GLUT3 by qPCR and Western blot analysis. Furthermore, we determined the localization of the different glucose transporters in the peritoneum by immunohistochemistry using specific antibodies. We could show that SGLT-2, GLUT1, and GLUT3 are expressed in the human peritoneum (shown in Fig. 1–3). RNA analysis showed no significant differences in the expression of the transporters between the different subgroups analyzed (shown in Fig. 1A). In general, we observed large variations within subgroups as well as variations between the different subgroups analyzed. Total protein expression studies using Western blot showed no significant differences in protein expression of SGLT-2, GLUT1, or GLUT3 (shown in Fig. 1C) between the subgroups analyzed. We also performed localization studies and semiquantitative evaluation of protein expression between the different subgroups using a Histo-Score. In general, we observed that the expression of glucose transporters in the peritoneal membrane is very weak and not consistent. Furthermore, many sections showed a negative staining depending on the glucose transporter analyzed (34–46 out of 67 sections). We demonstrated that all 3 transporters are predominantly located adjacent to the vessel walls (shown in Fig. 2A, 3A). However, we observed also stained structures in the submesothelium for GLUT1 and SGLT-2 especially in EPS sections (shown in online suppl. Fig. S1; see www.karger.com/doi/10.1159/000520894 for all online suppl. material). Adipocytes were only positively stained for SGLT-2 in a few biopsies of patients with EPS (shown in online suppl. Fig. S1). A proportion of mesothelial cells expressed SGLT-2 (Fig. 2A) and GLUT1 weakly (shown in Fig. 3A). Nevertheless, the majority of biopsy samples containing mesothelial cells were unstained for SGLT-2 and GLUT1 expression (shown in Fig. 2A second row and Fig. 3A second and fourth rows). Our semiquantitative Histo-Score demonstrated a differentiated pattern of SGLT-2 protein. We observed a significant upregulation in SGLT-2 protein expression in patients with signs of EPS compared to predialysis patients (uremic group) or compared to PD patients (PD >12 months) (shown in Fig. 2B). However, for the GLUT transporters, no significant change in protein expression could be observed (shown in Fig. 3B).

**Discussion/Conclusion**

Previous studies have described the presence of glucose transporters – particularly SGLT-2 – in single, isolated cells of the peritoneal membrane; however, a systematic description of peritoneal expression of glucose transporters at a relevant study size in humans has not yet been presented. Therefore, we analyzed the expression of SGLT-2, GLUT1, and GLUT3 in human peritoneal tissue of peritoneal biopsy samples. Here, we present data on the expression of glucose transporters from a large registry of human peritoneal biopsies. Moreover, we could mostly exclude diabetic patients from our analysis (see Table 2) since previous studies showed that glucose transporters were upregulated in diabetic patients compared to nondiabetic controls [28, 29]. Furthermore, diabetic rats showed an increased expression of SGLT-2 in peritoneal mesothelial cells compared to peritoneal mesothelial cells of nondiabetic rats [25].

We showed that SGLT-2, GLUT1, and GLUT3 are expressed in the human peritoneum (shown in Fig. 1–3). So far, most studies on glucose transporters have been performed in rats or in primary cells [24, 26, 30, 31]. Beyond such models, SGLT-2 expression in the human peritoneum has rarely been reported [23, 26]. On mRNA level as well as on total protein level, we observed no significant differences for SGLT-2, GLUT1, and GLUT3 expression upon exposure to glucose-based peritoneal dialysis fluids.

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**Fig. 1.** Glucose transporters are expressed in the human peritoneum. A Gene expression of SLC5A2 (SGLT-2), SLC2A1 (GLUT1), and SLC2A3 (GLUT3) was analyzed by qPCR. The expression was normalized to the reference gene GAPDH, and healthy controls were set to 1. Statistical differences were determined by a Kruskal-Wallis test and Dunn’s post hoc analysis (mean ± SEM, n = 5; ns, not significant). B Western blots of human peritoneal biopsies from healthy controls and patients. After wet blot and prior to blocking, the membranes were stained with Ponceau S to visualize total protein extract. Next, membranes were probed with the respective antibodies as indicated. Arrows indicate the detected protein band on the membrane. C The scatter plots show the quantification of the Western blots. Signals of SGLT-2, GLUT1, and GLUT3 were divided by the value of the respective actin signal and normalized to the control group (mean value of Ctr. 1 and Ctr. 2). Statistical differences were determined by a Kruskal-Wallis test and Dunn’s post hoc analysis (mean ± SEM, n = 3; ns, not significant).

**Table 1.** Characteristics of the patient cohort.

| Characteristic | Healthy Controls | PD Patients | IPS Patients |
|----------------|-----------------|-------------|--------------|
| Gender (male)  | 15              | 18          | 20           |
| Age (years)    | 52 ± 11         | 54 ± 12     | 56 ± 13      |
| BMI (kg/m²)    | 23.5 ± 2.4      | 25.3 ± 2.8  | 26.7 ± 2.9   |
| Time on PD (months) | 12 ± 6  | 36 ± 18     | 60 ± 24      |

**Table 2.** Descriptive data of the patient cohort.

| Characteristic | Healthy Controls | PD Patients | EPS Patients |
|----------------|-----------------|-------------|--------------|
| Gender (male)  | 15              | 18          | 20           |
| Time on PD     | 12 ± 6          | 36 ± 18     | 60 ± 24      |
| Urea (mg/dL)   | 40 ± 10         | 150 ± 40    | 180 ± 30     |
| Creatinine (mg/dL) | 1 ± 0.2 | 3 ± 1.2     | 4 ± 1.5      |

**Table 3.** Statistical differences in the expression of glucose transporters between the subgroups analyzed.

| Transporter | Healthy Controls | PD Patients | IPS Patients | p-value |
|-------------|-----------------|-------------|--------------|---------|
| SGLT-2      | 10             | 12          | 14           | 0.05    |
| GLUT1       | 8              | 10          | 12           | 0.08    |
| GLUT3       | 7              | 9           | 11           | 0.12    |
Fig. 2. Expression and localization of SGLT-2 in the human peritoneum. **A** Representative peritoneal sections stained for SGLT-2. For each subgroup, a section showing vessels (first row) and mesothelium (second row) is shown. Arrows are indicating very weak staining of few mesothelial cells. **B** Scatter plots show the Histo-Score of the immunohistochemical sections. Negative staining was obtained in 46 out of 67 sections. Statistical differences were determined by a Kruskal-Wallis test and Dunn’s post hoc analysis (mean ± SEM; ns, not significant; **p < 0.01, *p < 0.05; control: n = 7, uremic: n = 11, PD <12 months: n = 17, PD >12 months: n = 21, and EPS: n = 11). EPS, encapsulating peritoneal sclerosis.
Fig. 3. Expression and localization of GLUTs in the human peritoneum. A Representative peritoneal sections of vessels (first and third row) and of mesothelium (second and fourth row) stained for GLUT1 (left panels) and GLUT3 (right panels). B Scatter plots show the Histo-Score of all immunohistochemical sections. Negative staining was obtained in 34 out of 67 sections for GLUT1 and 46 out of 67 sections for GLUT3. Statistical differences were determined by Kruskal-Wallis test and Dunn’s post hoc analysis (mean ± SEM; ns, not significant; control: n = 7, uremic: n = 11, PD <12 months: n = 17, PD >12 months: n = 21, and EPS: n = 11). EPS, encapsulating peritoneal sclerosis.
even though it has been shown that mRNA of GLUT1 is upregulated by high glucose dialysates in rats [31]. Notably, we detected large variations within as well as variations between the different subgroups (shown in Fig. 1–3). In general, glucose transporters are expressed in the peritoneal membrane, although not consistently, especially on biopsy sections. The expression is weak and not consistent (shown in Fig. 2A, 3A, negative scores). The expression is probably affected by the influence of peritoneal dialysis and the associated changes. This is particularly evident in the increased expression in the context of EPS (shown in Fig. 2). Furthermore, we observed that these transporters are predominantly, but not exclusively, located adjacent to the vessel walls (shown in Fig. 2A, 3A; online suppl. Fig. S1). Commonly, the majority of mesothelial cells showed no staining for SGLT-2. Therefore, we could partially reproduce the results observed using immunofluorescence by Balzer and colleagues [32]. They also showed expression of SGLT-2 in the pericapillary region but also the mesothelial cell layer [32]. Furthermore, we observed a significant upregulation in SGLT-2 protein expression in patients with signs of EPS compared to the uremic subgroup or compared to PD patients performing PD >12 months (shown in Fig. 2B).

In general, we observed differences between mRNA and total protein expression. However, these differences could be explained by posttranslational modifications. Similar differences between mRNA and protein levels were also observed in mice [33]. Beyond, the protein expression studies also observed differences in expression of the transporters. However, we observed protein expression in each biopsy using Western blot analysis, although we had several sections with a negative Histo-Score in the IHC. This discrepancy could be explained by the fact that the different glucose transporters showed an intense expression in erythrocytes, granulocytes, and leukocytes. In the total protein lysates of our fresh biopsy samples, we cannot exclude these cell types. However, for evaluation using our Histo-Score, such structures were not taken into account. The increased Histo-Score of SGLT-2 in long-term PD patients with signs of EPS suggests that long-term exposure to glucose-based peritoneal solutions may be a key factor for this upregulation. This finding could be underlined by the fact that no great difference has been observed between healthy controls and uremic patients with no exposure to PD fluids (Fig. 2B, white circles and blue squares). Beyond, these results are in accordance with previous in vitro studies or studies in mice or rats showing that expression of glucose transporters is enhanced after exposure to peritoneal dialysis solutions [26, 31].

Previous studies on mice or rats and also in vitro studies showed that different inhibitors of glucose transporters have positive effects on fibrosis and ultrafiltration failure. Hong and colleagues [31] described that rats in the PD group showed obvious signs of peritoneal fibrosis due to upregulation of glucose transporters such as GLUT1. However, peritoneal fibrosis could be mitigated upon treatment with phloretin, a potent GLUT1 inhibitor. An age-related study in mouse and human lung tissue showed that GLUT1 inhibition ameliorated fibrogenesis of the lung and thereby suggesting a potential therapeutic option in fibrosis-susceptible organ systems [34].

SGLT-2 inhibitors were examined for diverse clinical applications [21, 35, 36]. Currently, some studies in rats suggested potential beneficial effects of SGLT-2 inhibitors in peritoneal dialysis, too [23, 26, 37, 38]. In contrast to those findings, we found glucose transporters are expressed in the human peritoneal membrane, although not consistently. Since the expression is probably affected by the influence of peritoneal dialysis and the associated changes, it remains to be investigated if these observations can be extrapolated to the human peritoneal membrane.

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**Statement of Ethics**

The study was carried out according to the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of the University of Tübingen, Germany (Process No. 322/2009BO1). Written informed consent was obtained from all patients.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.
Author Contributions

S.S. designed the study protocol, monitored data collection for the whole trial, cleaned and analyzed the data, and drafted and discussed the manuscript. T.O. designed and performed experiments, analyzed data, discussed results, and drafted the manuscript. P.F. analyzed data and discussed results. M.K. designed the study protocol, designed data collection tools, monitored data collection for the whole trial, guided the research, and edited the manuscript. M.D.A. initiated the collaborative project, designed the study protocol, and monitored the design of the data collection tools, the data collection for the whole trial, the draft, and the statistical analysis. He is the guarantor. M.S. designed the study protocol, designed data collection tools, monitored data collection for the whole trial, cleaned and analyzed the data, and drafted the manuscript. All contributors were substantially involved in the conception or design of the work and the acquisition, analysis, or interpretation of the data for the work. All authors critically revised the intellectual content and the drafted manuscript, approved the final version of this draft, and are accountable for all aspects of the work.

Data Availability Statement

Deidentified participant data, used questionnaires, study protocol, etc., will be shared upon request and after review of institutional policies on data protection.

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