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SGLT-2 inhibitors in chronic peritoneal dialysis patients: a follow-up study

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Abstract

Background Sodium-glucose transporter-2 inhibitors (SGLT-2i) are recommended for use in patients with type 2 diabetes comorbid atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. Limited reports are currently available for their use in dialysis patients. In an observational, retrospective follow-up study, we reported the clinical characteristics of chronic peritoneal dialysis (PD) patients on SGLT-2i.

Methods We enrolled 50 diabetic chronic PD patients, and 11 continued SGLT-2i after PD treatment. We reported the patients' ultrafiltration, HbA1c, urinary tract infection episodes, and venous CO2 during follow-up and compared the differences in these factors between patients with and without SGLT-2i.

Results The mean age of the patients was 65 ± 15 years, and 16 (32%) patients were female. The age, gender, heart failure, and primary kidney disease were not different between patients with and without SGLT-2i at enrollment. In an average of 31 months follow-up, patients with SGLT-2i had higher ultrafiltration (1322 ± 200 ml/day vs. 985 ± 415 ml/day, $p = 0.013$), hemoglobin (11.2 ± 1.7 vs. 10.2 ± 1.7 g/dl), white blood cell count (9.2 ± 3.7 vs. 7.4 ± 2.1 10^9/L), and a lower venous CO2 ($p = 0.036$). The urine amount, the overall survival, the technical survival, and the chance of UTI were not different between patients with and without SGLT2i.

Conclusion SGLT-2i may increase ultrafiltration volume and hemoglobin levels in chronic PD patients. SGLT-2i did not increase urinary tract infection but was linked to subclinical metabolic acidosis.

What was known The effect of SGLT-2i in chronic PD patients is not clear?

This study adds SGLT-2i is associated with increased ultrafiltration, hemoglobin, white blood cell counts, and a decreased CO2 in PD patient.

Potential impact SGLT-2i may increase ultrafiltration in PD patients.

Keywords Peritoneal dialysis, Ultrafiltration, SGLT-2

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) work by inhibiting glucose reabsorption in the kidneys, increasing urinary glucose excretion. This mechanism helps lower blood sugar levels in people with diabetes. Additionally, SGLT-2i has cardiovascular benefits [1, 2]. Studies such as the EMPA-REG OUTCOME trial [3] and the DAPA-HF trial [4] have demonstrated that SGLT-2i can reduce the risk of heart failure in individuals with or without diabetes. These findings have led to the incorporation of SGLT-2i into heart failure treatment guidelines. SGLT-2i also showed promising results in slowing the progression of chronic kidney disease. The DAPA-CKD [5] and EMPA-KIDNEY trials [6] have provided evidence that SGLT-2i can reduce the risk of kidney failure and cardiovascular events in individuals with or without diabetes.

In an animal model, SGLT-2i may decrease glucose absorption from PD solution by inhibiting SGLT-2 on the peritoneum [7]. Ultrafiltration may increase because the PD solution's glucose may last longer and provide more extended osmotic water transport. In a case report, we reported increased ultrafiltration in incident PD patients [8]. We reported an observational, retrospective, and follow-up study of patients who continued on SGLT-2i after PD treatment and compared the characteristics of the patients to those without SGLT-2i.

Methods

This study complied with the Declaration of Helsinki and was performed according to ethics committee approval. The study was approved by the institutional review board of China Medical University Hospital (CMUH111-REC1-183). We reviewed all chronic PD patients (on PD for over 3 months) with diabetes from Jan 2019 to Dec 2021. We identified 50 chronic PD patients with diabetes, and all patients were followed until Dec 2022. Eleven patients continued to have SGLT-2i after PD treatment (eight patients had dapagliflozin, and three patients had empagliflozin), and 39 discontinued SGLT-2i. We performed a fast peritoneal equilibration test (PET) on the day of the PD catheter insertion; effluent samples were collected at 1 h, and a blood sample was collected at 1 h [10]. The 1-hour D/P ratios of creatinine were calculated in all patients. Patient characteristics, including age, gender, hypertension, diabetes, congestive heart failure (CHF), primary kidney disease, body mass index (BMI), Kt/V, D/P creatinine, urine, anti-diabetic medications, and PD formula, were collected at the enrollments. CHF was defined as Killip Class II or higher at the time of admission or the development of congestive heart failure after hospitalization [9]. The ultrafiltration, urine, blood pressure, sodium, potassium, white cell count (WBC), hemoglobin, blood urea nitrogen (BUN), calcium, and phosphorus were recorded monthly. HbA1c, CO2, magnesium, and iPTH (intact parathyroid hormone) were recorded every 3 months. The average values were used if the patients had more than two readings. A urinary tract infection was defined as $>10^5$ cfu/mL of a uropathogen in midstream urine culture with the presence of an irritative voiding symptom [10]. Patient-reported genital infections were recorded.

Statistical analysis

Data are reported as the means (standard deviations) or frequencies (percentages) where appropriate. The differences between the patients with and without SGLT-2i were compared using *a t*-test in continuous variables and a chi-square test in categorical variables. Overall survival and technical survival were drawn using Kaplan-Meier analysis. All analyses were performed using R Statistical Software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria) and finalfit, survminer packages. A $p<0.05$ was considered statistically significant.

Results

The mean age of the patients was 65±16 years, and 32% were female (Table 1). The BMI was higher in patients with SGLT-2i (28.2±4.1 vs. 25.1±4.5 kg/m^2, $p=0.044$). Eleven patients (22%) patients had CHF. The percentage of patients with CHF was not different between patients with SGLT-2i and those without. Diabetes was the primary kidney disease in 35 (70%) patients, hypertension in 6 (12%) patients, and chronic glomerulonephritis in 9 (18%) patients. Sixteen (41%) of 39 patients without SGLT-2i had insulin, 16 had dipeptidyl peptidase-4 inhibitor (DPP4), and 8 had sulfonylurea as the anti-diabetic treatment. The use of anti-diabetic medications was not different from the patients on SGLT-2i. The Kt/V, D/P creatinine, and urine amounts were not different between the two groups at the enrollment. The rate of patients with IPD was not different between the two groups. The 1.5% and 2.5% dextrose PD solutions were the most prescribed formulas in the two groups of patients.

In an average 31-month follow-up (Table 2), the daily ultrafiltration was higher in patients on SGLT-2i (1322±200 ml/day) than in the patients without SGLT-2i (985±415 ml/day, $p=0.013$). Six patients had urinary tract infections (UTIs), five patients died (cardiovascular death $N=3$, infection $N=1$, traffic accident $N=1$), and 9 patients dropped out of PD. The mortality, dropout rate, the rate of UTIs, and the rate of genital infection were not different between the two groups. The overall survival curve of patients with SGLT-2i was not different from that of the patients without SGLT-2i (Fig. 1, $p=0.54$). No difference in technical survival was found in two groups of patients (Fig. 2, $p=0.96$). The SBP and DBP were not different in the two groups. The average HbA1c

Table 1 Characteristics of all participants

Characteristics	No SGLT-2i *N* = 39		SGLT-2i *N* = 11		*p*
Age (years)	67	± 13	59	± 21	0.104
Female	12	30.8	4	36.4	0.999
Weight (kg)	65.3	13.4	74.3	18.2	0.076
BMI (kg/m^2)	25.1	± 4.5	28.2	± 4.1	0.044
CHF	8	20.5	3	27.3	0.309
Primary kidney disease					
Diabetes	27	69.2	8	72.7	0.944
Hypertension	5	12.8	1	9.1	
CGN	7	17.9	2	18.2	
Kt/V	1.79	± 0.33	1.69	± 0.39	0.414
D/P creatinine	0.73	± 0.16	0.7	± 0.15	0.627
Urine (ml/day)	423	± 243	525	± 338	0.231
Anti-diabetic medications					
Insulin	12	30.7	3	27.3	0.218
DPP4	16	41.0	2	18.2	
Sulfonylurea	8	20.5	1	9.1	
Pioglitazone	5	12.8	1	9.1	
IPD	9	23.1	2	18.2	0.998
Dialysate formula					
1.5	6	15.4	0	0	0.411
2.5	14	35.9	7	63.6	
2.5 + 1.5	12	30.8	3	27.3	
2.5 + 1.5 + icodextrin	2	5.1	0	0	
2.5 + icodextrin	5	12.8	1	9.1	

BMI: body mass index, CHF: congestive heart failure, CGN: chronic glomerulonephritis, DPP4: Dipeptidyl peptidase-4 inhibitor, IPD: intermittent peritoneal dialysis

Table 2 Characteristics of 50 chronic peritoneal dialysis patients in follow-up

Characteristics	No SGLT2i *N* = 39		SGLT2i *N* = 11		*p*
Follow-up (month)	33	± 16	28	± 17	0.371
Ultrafiltration (ml/day)	985	± 415	1322	± 200	0.013
Mortality	4	10.3	1	9.1	1.000
Dropout	8	20.5	1	9.1	0.670
Urine (ml/day)	452	± 253	532	± 312	0.383
UTIs	5	12.8	1	9.1	0.999
Genital infection	1	2.6	1	9.1	0.328
SBP (mmHg)	142	± 15	138	± 14	0.432
DBP (mmHg)	87	± 6	85	± 5	0.318
HbA1c %	7.2	± 1.4	6.7	± 1.2	0.263
CO2 (mmHg)	26.0	± 3.3	23.6	± 3.2	0.036
Sodium (meq/L)	136	± 4	135	± 3	0.969
Potassium (meq/L)	4.2	± 0.8	4.2	± 0.6	0.779
WBC (10^9/L)	7.4	± 2.1	9.2	± 3.7	0.037
Hemoglobin (g/dl)	10.2	± 1.7	11.2	± 1.7	0.045
Hematocrit (%)	30.5	± 3.9	33.5	± 4.2	0.031
BUN (mg/dl)	71	± 18	66	± 19	0.411
Creatinine (mg/dl)	10.7	± 3.0	10.6	± 2.8	0.955
Calcium (mg/dl)	8.9	± 0.9	8.9	± 1.1	0.932
Phosphorus (mg/dl)	5.7	± 1.4	6.9	± 2.7	0.063
Magnesium (mg/dl)	2.5	± 0.6	2.6	± 0.5	0.647
iPTH (ng/dl)	268.7	± 231.9	306.8	± 221.8	0.631

SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white cell count, BUN: blood urea nitrogen, iPTH: intact parathyroid hormone

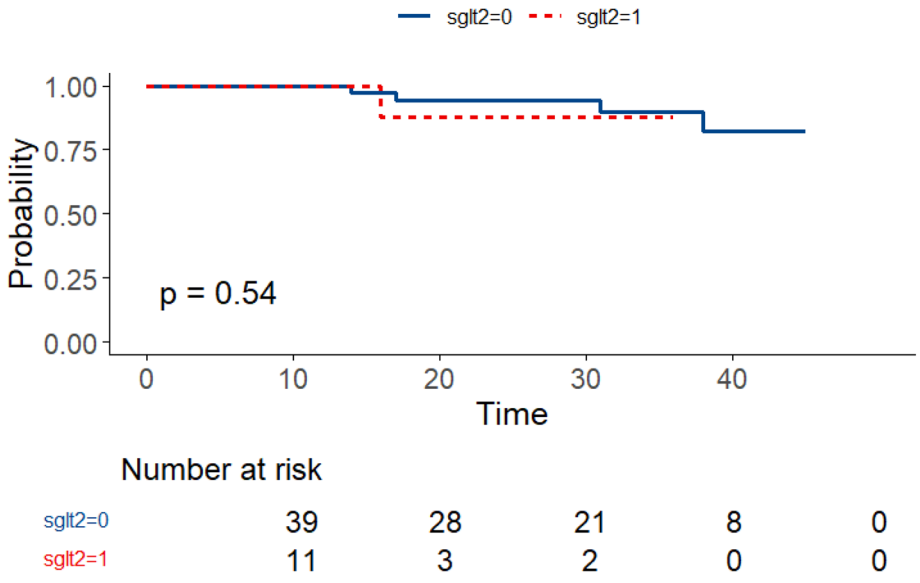

Fig. 1 Overall Survival curve

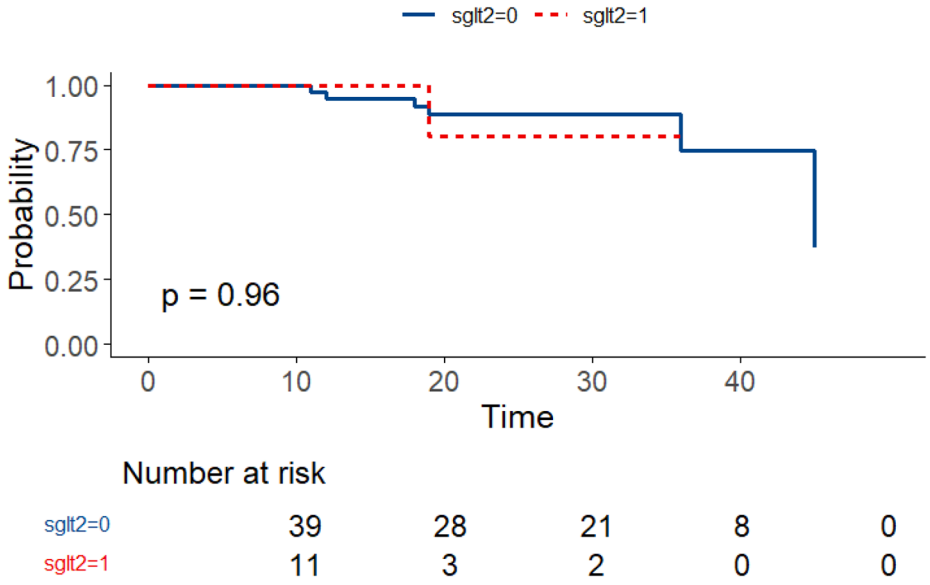

Fig. 2 Technical survival curve

was 7.2±1.4 in patients without SGLT-2i and 6.7±1.2 in patients with SGLT-2i. The venous CO2 was significantly lower in patients on SGLT-2i (p=0.036). The white cell counts (WBC), hemoglobin, and, hematocrit were significantly higher in patients with SGLT-2i (p=0.037, 0.045, and 0.031). The sodium, potassium, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, and intact parathyroid hormone (iPTH) were not different between the two groups.

Discussion

This 31-month follow-up study showed an increased ultrafiltration volume and higher hemoglobin levels in chronic PD patients with SGLT-2i. We previously reported an increased ultrafiltration volume in four incident PD patients [8]. This follow-up study further confirmed the increased ultrafiltration in chronic PD, because SGLT-2i. decrease glucose absorption from the PD solution, thereby increasing the ultrafiltration volume [11]. A randomized, double-blind, placebo-controlled crossover trial is currently undergoing to prove the increased ultrafiltration in PD [12]. The increased

hemoglobin in diabetic patients on SGLT-2i has been reported in previous studies, [13] because SGLT-2i may increase erythropoietin and expand red blood cell mass [14] through the downregulation of hypoxia-inducible factor 1α [15]. The higher hemoglobin may be related to the decreased volume status because the WBC was significantly higher in patients with SGLT-2i. In our clinical observations, patients with SGLT-2i were less likely to have pitting edema.

The decrease of venous CO2 in patients on SGLT-2i may suggest a subclinical metabolic acidosis. The subclinical metabolic acidosis may be explained by euglycemic ketoacidosis, which is a potential complication of SGLT-2i [16]. Because the ketone body was not measured in this study, we cannot confirm the presence of ketoacidosis. Small increases in serum magnesium, potassium, and phosphate levels have been reported in the previous studies [17–19]. In this study, we did not observe a significant difference in serum magnesium, potassium, and phosphate levels in patients on SGLT-2i.

The study has some limitations. First, the overall survival and technical survival were not different in patients with and without SGLT-2i because of the limited study size. Second, the average ultrafiltration volume under different PD prescriptions because of the study's observational nature. Third, all patients had SGLT-2i before PD started. We did not know if SGLT-2i is linked to increased urine amount.

Conclusions

SGLT-2i is linked to increased ultrafiltration volume and hemoglobin levels in chronic PD patients. The chance of UTI was not increased, and a subclinical metabolic acidosis may be present in patients on SGLT-2i. The overall survival and technical survival were not different in patients with and without SGLT-2i.

Author contributions

CY: Draft article, JW: collect the data and the patient recruitment, Charles C.N.: conceptualization, and formal analysis. All authors read and approved the final manuscript.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics approval

The study was approved by the institutional review board of China Medical University Hospital (CMUH111-REC1-183).

Consent to participate

Written informed consent was obtained from all participants.

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