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Research Article

Sodium-Glucose cotransporter 2 Inhibition with Dapagliflozin Ameliorates Extracellular Volume Expansion in Diabetic Kidney Disease Patients

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Abstract

Background: Sodium-glucose cotransporter (SGLT) 2 inhibitors, a new class of antidiabetic drugs, have diuretic properties, but their effects on urinary Na excretion and the fluid status have not been fully evaluated.

Methods: Diabetic kidney disease (DKD) patients with fluid retention were enrolled in this study. The SGLT2 inhibitor dapagliflozin was administered in addition to conventional treatment. Blood and 24-h urine samples were collected before dapagliflozin dosing on day 0 and afterwards on days 2 and 7. The fluid volume was measured using a bio impedance analysis device on days 0 and 7. The paired t-test or repeated-measure ANOVA was used to compare variables. Stepwise multivariate regression analysis was used to assess associations between independent variables.

Results: The body weight, diastolic blood pressure and brain natriuretic peptide significantly decreased, and serum albumin and urinary glucose excretion significantly increased over 1 week. The urine volume increased by 18.7% ± 13.4% (p=0.251), urinary Na excretion increased by 43.0%±20.4% (p=0.035) and urinary Cl excretion incread by 39.2% ± 19.7% (p=0.051) on day 2 compared with day 0, but these parameters returned to the baseline level on day 7. Stepwise multivariate regression analysis showed that HbA1c (p=0.031) and urinary glucose excretion (p=0.018) were independent determinants of changes in urinary Na excretion on day 2. Dapagliflozin significantly decreased the intracellular water (ICW) (6.2% ± 1.4%, p=0.001), extracellular water (ECW) (8.5% ± 2.0%, p=0.001) and total body water (TBW) (7.2% ± 1.6%, p=0.001) between days 0 and 7. The ECW/TBW, which reflects the extracellular volume expansion, significantly decreased from 0.424 ± 0.007 to 0.418 ± 0.006 (p=0.020).

Conclusions: SGLT2 inhibition with dapagliflozin increases transient urinary Na excretion, and decreased body fluid volume with the amelioration of extracellular volume expansion in DKD patients. This effect of SGLT2 inhibition may lead to a novel therapeutic strategy for body fluid control, especially in patients with increased extracellular water.

Keywords: Bioimpedance analysis, Diuresis, Extracellular water, Extracellular volume expansion, Fluid retention, Fluid distribution, Intracellular water, Natriuresis, SGLT2 inhibitor

Introduction

The incidence and prevalence of diabetes mellitus has increased globally, mainly due to the increase in type 2 diabetes. This overall increase in the number of people with diabetes has had a major impact on the development of diabetic kidney disease (DKD), one of the most frequent complications of diabetes [1, 2]. DKD is a risk factor for end-stage renal disease, cardiovascular disease, and all-cause death [3-5]. Fluid retention with peripheral edema and nephrotic-range proteinuria is a frequent and important clinical feature of DKD that itself predicts adverse renal and cardiovascular outcome [6].

Sodium-glucose cotransporter (SGLT) 2 inhibitors are a new class of antihyperglycemic drugs that have been used for the treatment of diabetes mellitus with a lower risk of hypoglycemic events than conventional antidiabetic drugs, such as insulin and sulphonylureas [7] and that have cardiovascular and reno protective effects [8-11]. SGLT2 is located in the brush border membrane of the early proximal tubule and mediates the majority of glucose reabsorption of the kidney [12]. SGLT2 is thought to be responsible for 90% of glucose reabsorption in the S1 segment of proximal tubules in the kidney, while SGLT1 is thought to account for <3% glucose reabsorption in the S2/S3 segments [13, 14]. Because SGLT2 mediates the transport of glucose and Na in 1:1 stoichiometry [15], the inhibition of SGLT2 may lead to reduced Na reabsorption in the proximal tubule, thereby accelerating Na excretion [16]. A recent report of type 2 diabetic patients with a normal renal function showed that the SGLT2 inhibitor canagliflozin induced transient Na excretion without increasing water intake [17]. We also reported that the SGLT2 inhibitor dapagliflozin accelerated rapid urinary Na and water excretion in a type 2 diabetic patient with fluid retention [18]. However, the effect of SGLT2 inhibitors on the fluid status and distribution in addition to urinary Na excretion has not yet been fully evaluated in patients with fluid retention. Therefore, we examined whether or not the SGLT2 inhibitor dapagliflozin increases the urinary Na excretion and changes the fluid status and distribution in DKD patients with fluid retention.

Methods

Patients

This was a prospective study that enrolled 13 DKD patients with high HbA1c and fluid retention, including generalized edema and pleural effusion, between February 2016 and May 2017. DKD includes diabetic nephropathy and other types of kidney dysfunction in diabetic patients [1]. Patients with prior renal replacement or current dialysis were excluded. At enrollment, 8 patients had been admitted to Jichi Medical University (Shimotsuke, Tochigi, Japan), and 5 had been treated as outpatients at Nasu Minami Hospital (Nasukarasuyama, Tochigi, Japan). Ten patients had received some kind of diuretic treatment (e.g. Furosemide, azosemide, trichlormethiazide, spironolactone, or tolvaptan) (Table-1). The exclusion criteria for participants were as follows: patients without peripheral edema, active malignancy, hemodialysis, peritoneal dialysis, patients taking some SGLT2 inhibitor and failure to cooperate with the study or provide consent to participate. After enrollment, dapagliflozin was administered in addition to conventional treatment. We evaluated the effect of dapagliflozin on the fluid status and electrolytes and fluid excretion for 1 week, as in our previously report [19].The initial dose of dapagliflozin in all patients was 5 mg/day, and the dosage remained constant throughout the study. The study was approved by the ethical committee of Jichi Medical University and Nasu Minami Hospital. Written informed consent was provided by all patients, and this study was conducted in accordance with the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013).

Table 1: Changes of clinical parameters day 0, day 2 and day 7 after dapagliflozin administration

Characteristics	Day 0	Day 2	Day 7	*p* value
BW (kg)	65.7 ± 4.1	65.5 ± 5.1	63.4 ± 4.0	0.014
Systolic blood pressure (mmHg)	143 ± 7	131 ± 9	131 ± 7	0.135
Diastolic blood pressure (mmHg)	81 ± 5	68 ± 5	69 ± 4	0.005
Heart rate (beats/min)	70 ± 2	71 ± 3	69 ± 3	0.718
Hematocrit (%)	33.3 ± 1.5	34.7 ± 2.1	34.3 ± 1.6	0.209
Serum albumin (g/dL)	2.6 ± 0.3	2.5 ± 0.4	2.9 ± 0.3	0.004
Plasma glucose (mg/dL)	178 ± 30	129 ± 11	172 ± 30	0.717
Blood urea nitrogen (mg/dL)	26.9 ± 2.7	25.6 ± 3.7	27.5 ± 3.1	0.837
Serum creatinine (mg/dL)	1.75 ± 0.18	1.59 ± 0.19	1.86 ± 0.18	0.553

eGFR (mL/min/1.73m^2)	36.1 ± 5.6	36.4 ± 4.8	34.8 ± 5.4	0.124
Serum Na (mEq/L)	140 ± 1	140 ± 1	139 ± 1	0.269
Serum Cl (mEq/L)	104 ± 1	103 ± 2	03 ± 2	0.239
Serum K (mEq/L)	4.0 ± 0.2	3.8 ± 0.2	3.8 ± 0.1	0.209
Serum uric acid (mg/dL)	7.1 ± 0.5	7.3 ± 0.4	6.4 ± 0.5	0.155
Serum BNP (pg/mL)	105 ± 35	N/A	77 ± 25	0.041
Serum osmolarity (mOsm/kg)	295 ± 2	N/A	295 ± 2	0.406
Urine osmolarity (mOsm/kg)	324 ± 21	345 ± 23	306 ± 25	0.285
Fractional excretion of Na (%)	1.6 ± 0.4	2.4 ± 0.4	1.9 ± 0.4	0.101
Fractional excretion of urea nitrogen (%)	37.9 ± 3.7	39.4 ± 4.3	38.6 ± 3.3	0.486
Urinary K excretion (mEq/day)	26.8 ± 3.9	28.5 ± 4.1	28.1 ± 6.1	0.825
Urinary glucose excretion (g/day)	2.3 ± 1.1	16.0 ± 3.6	15.6 ± 4.0	<0.001
Urine protein (g/day)	4.6 ± 1.6	4.4 ± 1.8	4.5 ± 1.9	0.305

Values expressed mean ± standard error. N/A: not available

BW: body weight, eGFR: estimated glomerular filtration rate

BNP: brain natriuretic peptide

Blood and urine sample collection

Blood and 24-h urine samples plus body weight (BW) data were collected before dapagliflozin dosing on day 0 (Day 0) and afterwards on day 2 (Day 2) and after 1 week (Day 7). Hematocrit, serum albumin, plasma glucose, HbA1c, blood urea nitrogen, serum creatinine, serum Na, serum Cl, serum K, serum uric acid, serum and urine osmolarity, and urine protein were measured. Brain natriuretic peptide (BNP) was measured using a commercial clinical diagnostic testing service (SRL, Inc., Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation coefficients modified for Japanese patients [20].

Measurement of the fluid volume using a bioimpedance analysis

Fluid volume analyses were performed using a bioimpedance analysis (BIA) device with eight tactile electrodes (InBody S10; InBody Japan Inc., Tokyo, Japan) [19, 21] on Days 0 and 7,similar to our previous study [19]. BIA measurements of resistance and reactance were taken with the patient in the recumbent position after 5 minutes of rest using a multifrequency analyzer (1, 5, 50, 250, 500, and 1000 kHz). Intracellular water (ICW), extracellular water (ECW), total body water (TBW: ICW+ECW), and the ratio of ECW to TBW (ECW/TBW) were calculated from the sum of each segment, using the equations in the BIA software program [19, 22].

Statistical analyses

The data are expressed as the mean ± standard error. We used the paired t-test for two groups and repeated-measure ANOVA for three groups with post hoc Turkey HSD tests to examine differences between each two groups. Stepwise multivariate regression analysis was used to assess associations between independent and dependent variables for the changes of urinary Na excretion and body fluid volume. P values of less than 0.05 were considered to be statistically significant. The statistical analyses were performed using JMP 12.2.0 (SAS Institute, Inc., Cary, NC, USA).

Results

The baseline characteristics of the 13 DKD patients were as follows: age 65.5 ± 3.9 years, 8 males and 5 females, duration of diabetes 10.2 ± 2.5 years, BW 67.5 ± 4.1 kg, body mass index

26.0 ± 1.2 kg/m^2, plasma glucose 178 ± 30 mg/dL, HbA1c 7.1% ± 0.3%, blood urea nitrogen 26.9 ± 2.7 mg/dL, serum creatinine 1.75 ± 0.18 mg/dL, and eGFR 36.1 ± 5.6 mL/min/1.73 m2(CKD stage 2, n=2; stage 3, n=5; stage 4, n=5; stage 5, n=1). The usage rate of antidiabetic drugs was 84.6% (DPP-4 inhibitor 46.2% and insulin 30.8%), and the usage rate of diuretic drugs was 76.9% (loop diuretic 76.9%, thiazide diuretic 15.4%, mineralocorticoid receptor antagonist 15.4% and vasopressin V2-receptor antagonist 15.4%). The mean body weight (BW) decreased by 3.7%±1.4% over 7 days (Table-1). The diastolic blood pressure and BNP, a marker of extracellular volume [23], significantly decreased after dapagliflozin treatment (Table-1). Serum albumin and urinary glucose excretion significantly increased after dapagliflozin administration (Table-1). Urine volume increased by 19% ± 13% (p=0.251) (Figure-1a,d), urinary Na excretion increased by 43% ± 20% (p=0.035) (Figure-1b, e) and urinary Cl increased by 39.2% ± 19.7% (p=0.051) (Figure-1c,f) on Day 2 compared with Day 0, but these parameters returned to the baseline level (Day 0) on Day 7 (Figure-1a,f). In contrast, the urinary K excretion was not apparently changed during the week (Table-1). Urinary glucose excretion significantly increased Day 2 (2.3 ± 1.1 vs. 16.0 ± 3.6 g/day, p<0.001), and the level remained high until Day 7 (15.6 ± 4.0 g/day vs. Day 2, p=0.983) (Figure-1f).

Stepwise multivariate linear regression analysis including age, body mass index, systolic blood pressure, diastolic blood pressure, serum albumin, plasma glucose, eGFR, urinary glucose excretion and urine protein showed that HbA1c (p=0.031) and urinary glucose excretion (p =0.018) were independent determinants of changes in urinary Na excretion on Day 2.

The BIA showed that ICW decreased by 6.2% ± 1.4%, ECW decreased by 8.5% ± 2.0%, and TBW decreased by 7.2% ± 1.6% between Days 0 and 7 (Table-2, Figure-2a,b). In addition, TBW in all parts of the body (arms, trunk and legs) significantly decreased after the administration of dapagliflozin (Day 7), and all parts of the body (arms, trunk, and legs) showed a similar reduction pattern (Table-2, Figure-2c). The ECW/TBW significantly decreased after dapagliflozin administration (0.424 ± 0.007 vs. 0.418 ± 0.006, p=0.020) (Table-2, Figure-2d).

In a stepwise multivariate regression model that included age, body mass index, systolic blood pressure, serum albumin,

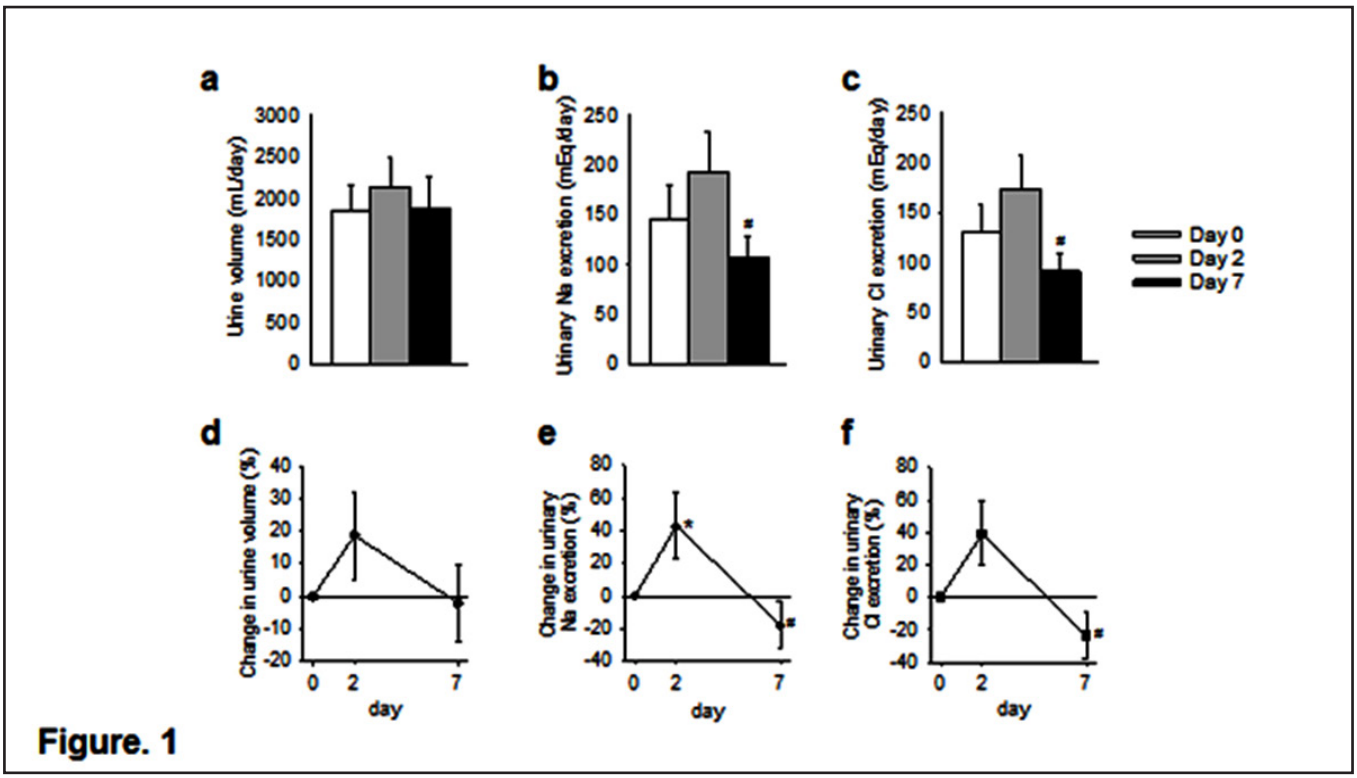

Figure: 1 Absolute levels of and changes in urine volume **(a) (d),** urinary Na excretion **(b) (e),**and urinary Cl excretion **(c) (f)** on days 0, 2, and 7 after dapagliflozin treatment. n=8, * p<0.05 vs. Day 0. # p<0.05 vs. Day 2.

Table 2: Changes in fluid status on day 0 and day 7 after dapagliflozin administration

Characteristics	Day 0	Day 7	*p* value
ICW (L)	22.2 ± 2.0	20.9 ± 2.0	0.001

ECW (L)	16.6 ± 1.9	15.2 ± 1.6	0.003
TBW (L)	38.8 ± 3.9	36.1 ± 3.6	0.001
Arms TBW (L)	3.6 ± 0.4	3.2 ± 0.4	0.013
Trunk TBW (L)	14.7 ± 1.3	14.0 ± 1.2	0.002
Legs TBW (L)	15.5 ± 2.1	14.3 ± 2.0	0.007
ECW/TBW	0.424 ± 0.007	0.418 ± 0.006	0.020
Arms ECW/TBW	0.399 ± 0.004	0.395 ± 0.004	0.004
Trunk ECW/TBW	0.420 ± 0.006	0.415 ± 0.006	0.011
Legs ECW/TBW	0.431 ± 0.008	0.426 ± 0.007	0.041

Values expressed mean ± standard error.

ICW: intracellular water, ECW: extracellular water, TBW: total body water

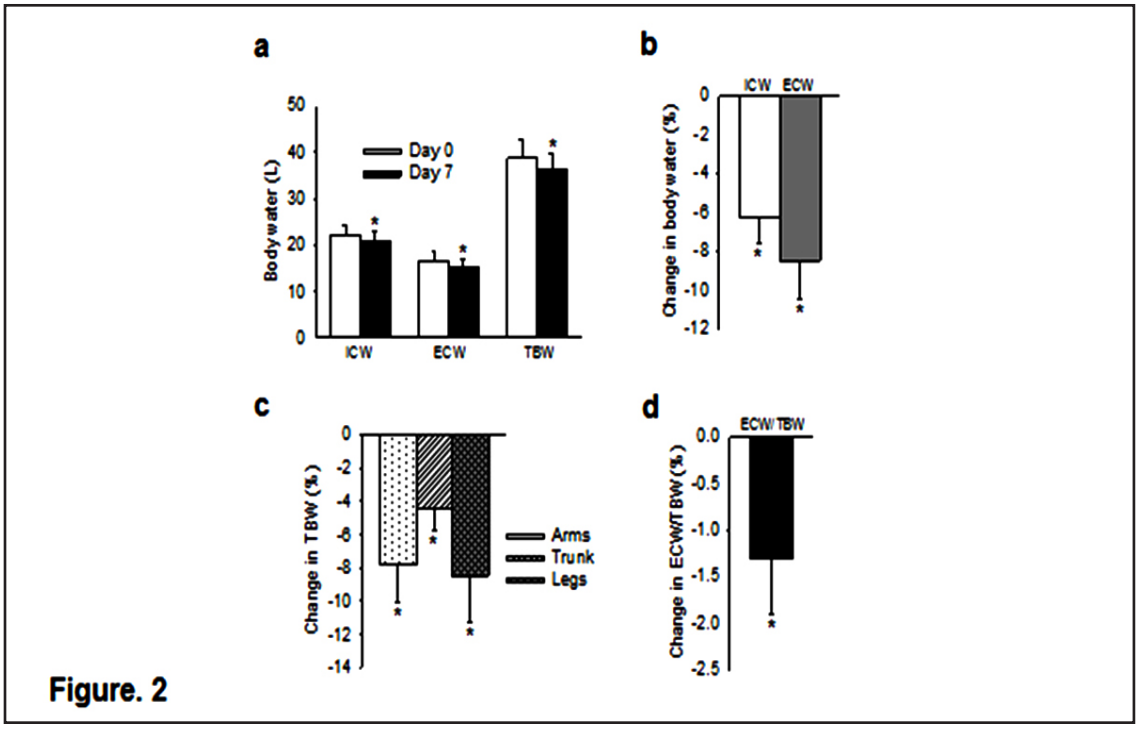

Figure: 2 Changes in the ICW, ECW, and TBW before (Day 0) and after (Day 7) dapagliflozin treatment **(a)**. The reduction rate of ICW and ECW between Days 0 and 7 **(b).** The reduction rate of TBW in each part of the body (arms, trunk and legs) **(c)** and the change in ECW/TBW **(d)**. n=11, * p<0.05 vs. Day 0. ICW: intracellular water, ECW: extracellular water, TBW: total body water.

plasma glucose, eGFR, urinary glucose excretion and urine protein, there were not independent determinants of changes in urinary TBW and ECW/TBW.

Discussions

This study showed that the SGLT2 inhibitor dapagliflozin induced a transient increase in urinary Na excretion, and dapagliflozin decreased body fluid volume along with a reduction of ECW/TBW, a marker of extracellular volume expansion in DKD patients. To our knowledge, this is the first study in which a BIA device was used to evaluate the amelioration of fluid retention and body fluid distribution in DKD patients treated with SGLT2 inhibitors.

Recent animal and human studies have reported that SGLT2 inhibitors transiently increase the urine volume and Na excretion [17, 24-27]. The SGLT2 inhibitor empagliflozin significantly increased the urine volume and urinary Na excretion in obese type 2 diabetic db/db mice on day 1, and the levels decreased to the baseline level thereafter[25]. In prediabetic SHR/NDmcr-cp (+/+) rats with metabolic syndrome, empagliflozin increased the urine volume and reduced the urinary Na and water balance within 1 week, but thereafter, there was no significant difference in the 24-h urinary Na excretion, Na balance, or water balance between the empagliflozin and control group [26]. Similarly, empagliflozin significantly increased the 0- to 12- and 12- to 24-h urinary Na excretion rates and decreased subsequent 12-h urinary Na excretion in salt-treated obese Otsuka Long Evans Tokushima rats [27]. A recent notable report of 13 type 2 diabetic patients with a normal renal function (eGFR ≥60 mL/min/1.73 m2) showed that the SGLT2 inhibitor canagliflozin induced transient urine volume and urinary Na excretion without increasing the water intake [17]. In that study, the administration of canagliflozin tended to increase the urine volume and urinary Na excretion on day 1, and these values returned to the baseline level thereafter [17]. The overall trend in that study was similar to the one in our study, in which the SGLT2 inhibitor dapagliflozin increased the urine volume and Na excretion, with a peak on day 2. However, the study of canagliflozin [17] did not show a significant increase in Na excretion, although our study showed the significant increases in the absolute and fractional excretion of Na on day 2. This discrepancy may be due to the differences in body fluid status between the two studies in addition to the pharmacological differences between canagliflozin and dapagliflozin. Indeed, the SGLT2 inhibitor ipragliflozin significantly increased the daily urine volume on days 1 to 3 in type 2 diabetes patients with heart failure requiring diuretics [28]. Taken together, these findings suggest that SGLT2 inhibitors may exert strong incremental effects on the urine volume in patients with fluid retention compared with those with euvolemia. In addition, interestingly, the increase in urine volume and urinary Na excretion on day 2 returned to baseline level on day 7. This mechanism may be due to the compensation of SGLT1, which is expressed in proximal tubule S2/S3 segment and increases glucose reabsorption during SGLT2 inhibition [14]. Because SGLT1 mediates the transport of glucose and Na in 1:2 stoichiometry [15], Na reabsorption may increase on day 7 to protect excess fluid loss. Further human and animal studies are needed to evaluate whether or not SGLT2 inhibitors show different diuretic activities depending on the body fluid status, and how SGLT1 is involved in the fluid control during SGLT2 inhibition.

In the present study, a BIA revealed that dapagliflozin decreased the body fluid volume in DKD patients with fluid retention. As mentioned above, decreases in the BW and transient increases in the urine volume and urinary Na excretion by SGLT2 inhibitors have been reported in recent studies, including our own [17, 18, 24-27] . In addition, in some studies, changes in fluid biomarkers, such as plasma BNP, atrial natriuretic peptide, and renin activity, suggest the amelioration of fluid retention during treatment with SGLT2 inhibitors [17, 28]. However, the body fluid status in the course of SGLT2 inhibitor treatment has not been accurately and quantitatively measured [17, 18, 25-27]. Therefore, we measured the change in the body water after the administration of dapagliflozin using a BIA device. A BIA is useful for measuring the body composition, including body water, fat mass, and muscle mass [29,30]. Recently, BIAs have been widely used in various clinical and animal research settings to assess the body composition [30-32]. We previously reported that the BIA device In Body was useful for the assessment of the body water in CKD patients with fluid retention [19, 33]. We used the same device in this study and revealed that dapagliflozin significantly decreased both the ECW and ICW as well as the TBW in all parts of the body (arms, trunk, and legs).

Furthermore, interestingly, dapagliflozin administration significantly decreased the ECW/TBW, a marker of hydration status [21]. Recent studies have shown that volume overload is independently associated with the progression of renal disease, cardiovascular disease and high mortality in CKD patients [6, 31, 34]. Similarly, a higher ECW/TBW (> 0.40) value measured by BIA predicts high mortality outcomes in advanced CKD patients [35]. In a study of heart failure patients, an ECW/TBW > 0.390 predicts a higher incidence of heart failure-related re-hospitalization after 6 months, and reducing the value resulted in fewer re-hospitalizations [36]. In our study, dapagliflozin significantly decreased the ECW/TBW value from 0.424 ± 0.007 to 0.418 ± 0.006 over 7 days. Although the degree of the reduction in the ECW/TBW value may be insufficient in the short-term period, dapagliflozin may lead to favorable cardiovascular and renal outcomes on long-term follow-up. In contrast, our recent report of the vasopressin V2-receptor antagonist tolvaptan did not change ECW/TBW [19], while loop diuretics predominantly decrease the ECW [23, 37, 38], similar to the current study. These differences may be due to the presence or absence of natriuretic action. Further studies are required to evaluate the detailed mechanism of SGLT2 inhibitors for fluid reduction and distribution in comparison with tolvaptan and loop diuretics.

This study shows HbA1c and urinary glucose excretion are independent determinants of changes in urinary Na excretion on day 2. These data suggest that the status of glycemic control may be involved in the short-term urinary Na excretion after SGLT2 inhibitor treatment. Our previous study shows the positive relationship between filtered glucose and absolute urinary glucose excretion during SGLT2 inhibition [14]. Filtered glucose in the kidney depends on the glycemic control, and SGLT2 mediates the transport of glucose and Na in 1:1 stoichiometry [15]. Therefore, urinary Na excretion in patients with higher HbA1c may be increased immediately after the administration of SGLT2 inhibitor.

Several limitations associated with the present study warrant mention. First, this study had a small sample size, and therefore further studies with larger sample sizes are needed to confirm our results. Second, the study duration is short. Additional studies including long-term follow-up in our study participants are necessary in order to evaluate the link between the amelioration of fluid reduction by SGLT2 inhibitors and clinical outcomes.

In conclusion, the SGLT2 inhibitor dapagliflozin increases the transient urinary Na excretion and decreased body fluid volume with the amelioration of extracellular volume expansion in DKD patients. In addition, HbA1c and urinary glucose excretion are independent determinants of short-term increase in urinary Na excretion. These effects of SGLT2 inhibition may lead to a novel therapeutic strategy for body fluid control, especially in patients with increased extracellular volume.

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Conflict of interests

The authors declare no conflict of interest.

Ethical approval

The study was approved by the ethical committee of Jichi Medical University and Nasu Minami Hospital. Written informed consent was provided by all patients, and this study was conducted in accordance with the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013).

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