Acta Med. Okayama, 2022
Vol. 76, No. 6, pp. 705–713


Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

*Original Article*

# The Impact of Tofogliflozin on Physiological and Hormonal Function, Serum Electrolytes, and Cardiac Diastolic Function in Elderly Japanese Patients with Type 2 Diabetes Mellitus

**Toshihiro Higashikawa[a,b]*, Tomohiko Ito[a], Takurou Mizuno[a], Keiichiro Ishigami[a], Kengo Kuroki[a], Naoto Maekawa[a], Daisuke Usuda[a], Toshihide Izumida[a], Shinya Yamada[a], Ryusho Sangen[a], Kazu Hamada[a], Jun Kiyosawa[a], Atsushi Saito[a], Masaharu Iguchi[a], Yuji Kasamaki[a], Takeshi Nakahashi[a], Akihiro Fukuda[a], Hitoshi Saito[a], Tsugiyasu Kanda[a], and Masashi Okuro[b]**

[a]*Kanazawa Medical University Himi Municipal Hospital, Himi, Toyama 935-8531, Japan,*
[b]*Department of Geriatric Medicine, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan*

**The sodium glucose transporter 2 (SGLT2) inhibitor tofogliflozin is a glucose-lowering drug that causes the excretion of surplus glucose by inhibiting SGLT2. Because of tofogliflozin's osmotic diuresis mechanism, patients' serum electrolytes, body fluid levels, and cardiac function must be monitored. We retrospectively analyzed the cases of 64 elderly Japanese patients with type 2 diabetes mellitus (T2DM) who received tofogliflozin for 3 months. Their HbA1c, serum electrolytes (sodium, potassium, chloride), hematocrit, brain natriuretic peptide (cardiac volume load marker) and renin and aldosterone (RAA; an index of regulatory hormones involved in body fluid retention) were continuously monitored during the investigation period. Renal function and cardiac function (by echocardiography) were assessed throughout the period. HbA1c significantly decreased ($\beta 1 = -0.341$, $p < 0.0001$, linear regression analysis [LRA]). Most of the hormonal, electrolyte, and physiological parameters were maintained throughout the study period. In these circumstances, E/e' tended to decrease ($\beta 1 = -0.382$, $p = 0.13$, LRA). Compared to the baseline, E/e' was significantly decreased at 1 and 3 months ($p < 0.01$, $p < 0.05$). In the higher E/e' group (E/e' ≥ 10, n = 34), E/e' decreased significantly ($\beta 1 = -0.63$, $p < 0.05$, LRA). ΔE/e' was correlated with body-weight change during treatment ($r = 0.64$, $p < 0.01$). The 3-month tofogliflozin treatment improved glycemic control and diastolic function represented by E/e' in T2DM patients, without affecting serum electrolytes, renal function, or RAA. No negative impacts on the patients were observed. Three-month tofogliflozin treatment lowered glucose and improved cardiac diastolic function.**

**Key words:** tofogliflozin, SGLT2 inhibitor, elderly patient, HbA1c, cardiac diastolic function

Hyperglycemia is a major feature of type 2 diabetes mellitus (T2DM). One of the new classes of T2DM drugs, sodium-glucose co-transporter 2 (SGLT2) inhibitors, induce the body to excrete glucose into the urine, resulting in lowered blood glucose levels [1]. The use of SGLT2 inhibitors for controlling the glucose levels of individuals with T2DM has been endorsed by the American Diabetes Association and the European Association for the Study of Diabetes [2]. As

Received March 18, 2022; accepted July 11, 2022.
*Corresponding author. Phone : +81-766-74-1900; Fax : +81-766-74-1901
E-mail : himikmu@yahoo.co.jp (T, Higashikawa)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

of this writing, six SGLT2 inhibitors are available in Japan: ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin, and these are widely used for patients with T2DM [3]. A considerable number of elderly individuals with T2DM has been reported in Japan [4]. After the launch of SGLT2 inhibitors, several serious adverse reactions have been recognized as a major safety concern, with reports of events such as urinary tract infections, dehydration, and electrolyte imbalance [5].

These concerns led to 'Recommendations on the appropriate usage of SGLT2 inhibitors' issued by a committee of Japanese experts in June 2014 [6], and post-marketing surveillance (PMS) was initiated regarding the use of tofogliflozin in elderly patients in clinical settings. The PMS results indicated that the incidence of adverse events in patients aged > 65 years resembled the incidence observed in preapproved trials [7].

SGTL2 inhibitors, including tofogliflozin, have been known to act on proximal tubules and to act as a mechanism of mild osmotic diuresis [8]. SGLT2 inhibitors also change serum and urinary electrolyte levels and body fluid composition [9]. One of our previous studies demonstrated that during a 1-year investigation, no electrolyte imbalance occurred after the administration of tofogliflozin [10].

SGLT2 inhibitors have recently attracted renewed attention. Cardiological studies demonstrated that the use of the SGLT2 inhibitors canagliflozin, empagliflozin, and dapagliflozin for T2DM patients with cardiovascular disease (CVD) was associated with decreased rates of major adverse cardiac events, including heart failure (HF) [11-13]. Empagliflozin and canagliflozin decreased patients' weight and blood pressure [14]. A prospective study revealed that dapagliflozin improved left ventricular (LV) diastolic functions in T2DM patients with HF [15]. In general, an excess load of body fluids as well as an imbalance of electrolytes exacerbate cardiac and renal function, especially in elderly patients. The present study thus focused on monitoring factors that affect cardiac function, such as electrolytes, brain natriuretic peptide (BNP), the body fluid load, and renin and aldosterone (RAAs) in elderly T2DM patients taking tofogliflozin.

Despite concerns about its potential effect on the electrolyte balance, the effects of tofogliflozin on the serum electrolyte balance, body composition and adrenal cortical hormone remain unknown, especially in elderly individuals with T2DM. Our earlier investigations demonstrated that, regardless of age and gender, one of the indices of cardiac diastolic function, the ratio between the early mitral inflow velocity and the mitral annular early diastolic velocity (E/e') was improved in elderly individuals with T2DM who were treated with tofogliflozin [16,17]. Tofogliflozin's mechanism of action is controversial; multimodal effects on cardiac diastolic function, diuretic promotion, blood-pressure lowering, protection of the RAA system, and a reduction of epicardial fat have been described [18]. The E/e' measured by tissue Doppler imaging revealed a strong association with the mean LV diastolic pressure obtained by micromanometer-tipped catheters [19].

These findings suggested that the E/e' plays an important role as a marker of cardiac diastolic function. In the present study we conducted a linear regression analysis to investigate the trend of these physiological and cardiac diastolic parameters. In addition, to determine the effect of tofogliflozin on the E/e', we applied the linear regression model to a higher E/e' (≥ 10) group and investigated the correlation between the change in the E/e' and other factors in elderly Japanese patients with T2DM under treatment with tofogliflozin.

## Patients and Methods

This study was a retrospective analysis of the cases of patients aged ≥ 65 years diagnosed with T2DM who visited Kanazawa Medical University Himi Municipal Hospital during the period from April 2018 to March 2020. A single daily 20-mg dose of tofogliflozin was administered to each of the patients for 3 months, and the patients did not receive any other agents such as a diuretic, β-blocker, or angiotensin receptor blocker (ARB). Data were collected according to the flow chart shown in Fig. 1.

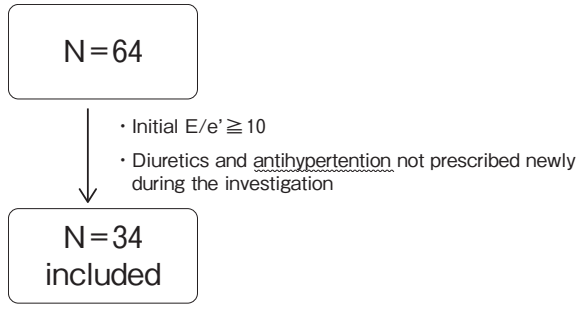


Fig. 1 Outline of the study.

The changes in each patient's HbA1c was measured to assess the efficacy of tofogliflozin during the study period. At baseline, 1, and 3 months after the initiation of tofogliflozin administration, the patients' serum HbA1c, hematocrit, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), creatinine, and serum electrolyte concentration (including sodium [$Na^+$], potassium [$K^+$], and chloride [$Cl^-$]) were measured. The adrenocorticotropic hormones renin and aldosterone were also measured.

Cardiac function was evaluated by echocardiography. The maximal diameter of the inferior vena cava (IVCmax) was measured by the following procedure: lowering the costal arch in parallel with the trunk and setting the patient in the recumbent position before the inferior vein transitions to the right atrium at end-expiration. The largest diameter was determined between 0.5 and 3 cm from the inflow to the right atrium in the IVC long-axis cross-section at expiration at the proximal hepatic vein junction in the supine position. The left atrial dimension (LAD) was also measured.

Concurrently, the ejection fraction (EF) and the ratio of early filling to atrial filling (E/A) were obtained by the early diastolic and atrial wave velocities, and the early diastolic wave deceleration time was measured by pulsed wave Doppler recording from the apical four-chamber view. The spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained by averaging the septal mitral annulus, and the ratio of mitral e annular velocities (E/e') was calculated. The estimated right ventricle systolic pressure (RVSP) was calculated by measuring the continuous wave Doppler values. The pulmonary capillary wedge pressure (PCWP) was calculated by Naguehs' formula [20]: $(PCWP = 1.24 \times (E/e') + 1.9)$.

We assessed the effects of the tofogliflozin treatment on the patients' physiological and cardiac variables by performing a linear regression analysis, using the administration period (months) as an independent variable and Y as a dependent variable. The population regression equation is as follows:

Y (ex. HbA1c) = b0 + b1 × administration period (0, 1, and 3 months) + e (random error)

The slope of the regression curve $b1 = 0$ is the null hypothesis. Electrolyte abnormalities were evaluated by linear regression analyses, using the concentrations of serum electrolytes including sodium, potassium, and chloride. Dehydration was evaluated by using the hematocrit as a dependent variable. Cardiac functions were also evaluated by linear regression analyses. The cardiac variables assessed were the EF, E/e', E/A, LAD, right systolic ventricular pressure (RSVP), PCWP, and IVCmax.

A stratified analysis was performed for E/e' with a cutoff value of $E/e' = 10$, which is based on an investigation of Doppler echocardiography which demonstrated that an $E/e' < 8$ accurately predicted normal mean (M)-LVDP and $E/e' > 15$ identified increased M-LVDP [19].

Significant differences in variables between the baseline (0 months) and 1 and 3 months of treatment were assessed by paired *t*-test. The correlation between changes in cardiac diastolic parameters and the changes in physiological parameters in the upper E/e' group ($E/e' \geq 10$) was estimated by a Pearson's correlation analysis. All of the data were analyzed with the use of the freely available EZR (Easy R) software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [21].

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Kanazawa Medical University Himi Municipal Hospital. Written informed consent for their data to be used and published was obtained from all patients.

## Results

The baseline patient data are summarized in Table 1. The 64 Japanese patients were 82.0 ± 6.3 years old (range: 67-96 yrs; average ± standard deviation [SD]); there were 28 males (80.57 ± 6.06 yrs old) and 36 females (83.25 ± 6.30 yrs). The baseline value of HbA1c was 7.4 ± 1.49%, and that of hematocrit was 36.9 ± 1.7%. The following combinations of treatments were recorded: antidiabetic agents (in 64% of the patients), dipeptidyl peptidase-4 (DPP-4) inhibitors (12.5%), sulfonylureas (28.1%), biguanides (3.1%), insulin (0%), and thiazolidinediones and glinides (1.6%). Diuretics were administered to 25% of the total patients. Antihypertensive agents were administered to 45.3% of the total patients. Symptomatic hypoglycemic episodes and serious adverse events such as hypoglycemia, pyelonephritis, dehydration, and ketoacidosis were not observed in any of the patients.

The changes in the values of physiological variables following the initiation of treatment with tofogliflozin for 3 months are provided in Table 2. The patients' HbA1c, body weight (BW), systolic blood pressure,

**Table 1** Characteristics of patients involved

| | | |
|---|---|---|
| n | 64 | |
| Age (years) | 82.0 | ± 6.29 |
| Sex (male/female) | 28 | 36 |
| HbA1c (%) | 7.4 | ± 1.49 |
| Hematocrit (%) | 36.9 | ± 1.69 |
| Weight (kg) | 54.2 | ± 2.59 |
| Systolic BP (mmHg) | 137.5 | ± 23.29 |
| Diastolic BP (mmHg) | 72.2 | ± 13.42 |
| Glucose (mg/dL) | 173.8 | ± 15.93 |
| ALB (g/dL) | 3.37 | ± 0.50 |
| LDH (IU/L) | 198.8 | ± 13.6 |
| AST (IU/L) | 22.1 | ± 1.38 |
| ALT (IU/L) | 17.6 | ± 3.72 |
| TG (mg/dL) | 128.2 | ± 47.28 |
| r-GTP (IU/L) | 20.8 | ± 12.27 |
| Creatinine (mg/dL) | 0.89 | ± 0.08 |
| eGFR (mL/min) | 61.4 | ± 5.67 |
| BNP(pg/mL) | 209.03 | ± 357.96 |
| BUN (mg/dL) | 19.5 | ± 2.34 |
| Anti-diabetic treatment | | |
| DPP-4 inhibitor (%) | 41 | (64) |
| Sulfonylurea (%) | 8 | (12.5) |
| Biguanide (%) | 18 | (28.1) |
| Insulin (%) | 2 | (3.1) |
| Thiazolidinedione (%) | 0 | (0) |
| Glinide (%) | 2 | (1.6) |
| Diuretics(%) | 16 | (15) |
| Antihypertention(%) | 29 | (45.3) |

and hematocrit showed decreases throughout the 3-month study period. Renin showed a significant increase between the baseline and at 3 months ($p < 0.01$ by paired *t*-test). The changes in cardiac variables following the initiation of 3-month tofogliflozin treatment are shown in Table 3. The E/e' and PCWP showed significant decreases between baseline and 3 months ($p < 0.05$ by paired *t*-test). No significant changes were observed in other cardiac parameters.

Table 4 summarizes the parameter estimates of physiological variables revealed by the linear regression analyses. The parameter b1, which denotes the slope of the regression curve, was significant (*i.e.*, the null hypothesis of b1 = 0 was rejected) for HbA1c and serum $Na^+$, whereas the b1 slopes for body weight, serum $K^+$, serum $Cl^-$, hematocrit, eGFR, BNP, and renin and aldosterone were not significant during the study period.

The parameter estimates of cardiac variables shown by the linear regression analyses are provided in Table 5. No significance in parameter b1 was observed in any cardiac parameters throughout the study period. Table 6 summarizes the E/e' parameter estimates obtained by the linear regression analyses, with the cutoff value set at 10. In the high E/e' group (E/e' ≥ 10), significance in parameter b1 of the E/e' was observed ($p < 0.05$). No

**Table 2** Characteristics of laboratory test results

| Variable | Baseline | | 1 month | | 3 months | | ※ *P*-value |
|---|---|---|---|---|---|---|---|
| HbA1c (%) | 7.40 | ± 1.49 | 7.03 | ± 1.01 | 6.70 | ± 0.80 | < 0.01 |
| Body Weight (kg) | 54.21 | ± 10.38 | 52.14 | ± 10.02 | 51.51 | ± 9.77 | < 0.01 |
| Systolic Blood Pressure (mmHg) | 137.51 | ± 23.39 | 124.18 | ± 16.42 | 127.46 | ± 19.21 | < 0.01 |
| Diastolic Blood Pressure (mmHg) | 72.21 | ± 13.42 | 69.73 | ± 16.42 | 72.09 | ± 12.19 | 0.94 |
| Hematocrit (%) | 39.96 | ± 6.76 | 37.95 | ± 5.44 | 38.18 | ± 5.29 | 0.02 |
| BNP (pg/mL) | 209.03 | ± 357.96 | 140.34 | ± 228.15 | 177.75 | ± 269.83 | 0.11 |
| eGFR | 61.45 | ± 22.69 | 58.4 | ± 23.02 | 59.42 | ± 26.92 | 0.25 |
| BUN (mg/dL) | 19.52 | ± 9.36 | 19.95 | ± 7.02 | 19.74 | ± 7.51 | 0.90 |
| $Na^+$ (mEq/L) | 138.71 | ± 3.33 | 139.56 | ± 2.89 | 140.17 | ± 3.27 | < 0.01 |
| $K^+$ (mEq/L) | 4.19 | ± 0.54 | 4.19 | ± 0.51 | 4.23 | ± 0.52 | 0.59 |
| $Cl^-$ (mEq/L) | 102.62 | ± 11.48 | 104.40 | ± 4.95 | 105.0 | ± 3.26 | < 0.05 |
| Blood Osmotic Pressure (mOsm/L) | 292.42 | ± 7.09 | 292.85 | ± 7.26 | 295.18 | ± 7.36 | < 0.05 |
| Renin (ng/ml) | 3.90 | ± 6.37 | 6.88 | ± 8.51 | 6.86 | ± 11.87 | < 0.05 |
| Aldosterone (pg/ml) | 90.88 | ± 47.78 | 105.31 | ± 64.29 | 88.04 | ± 38.68 | 0.771 |

**Table 3** Characteristics of cardiac function results

| Variable | Baseline | | 1 month | | 3 months | | ※ *P*-value |
|---|---|---|---|---|---|---|---|
| EF (%) | 64.52 | ± 9.02 | 62.73 | ± 10.48 | 63.62 | ± 8.98 | 0.35 |
| E/e' | 11.88 | ± 4.09 | 9.95 | ± 3.09 | 10.46 | ± 4.02 | 0.02 |
| E/A | 0.69 | ± 0.30 | 0.60 | ± 0.18 | 0.71 | ± 0.51 | 0.78 |
| LAD (mm) | 37.98 | ± 7.04 | 36.76 | ± 6.95 | 37.08 | ± 6.40 | 0.30 |
| PCWP (mmHg) | 16.63 | ± 6.97 | 14.23 | ± 5.73 | 14.87 | ± 6.88 | 0.02 |
| RSVP (mmHg) | 26.84 | ± 9.57 | 28.02 | ± 10.53 | 27.35 | ± 7.43 | 0.78 |
| SWT (mm) | 10.47 | ± 1.86 | 10.68 | ± 1.82 | 10.41 | ± 1.95 | 0.16 |
| PWT (mm) | 10.30 | ± 1.81 | 10.53 | ± 1.79 | 10.30 | ± 1.90 | 0.73 |
| IVC max (mm) | 13.96 | ± 3.61 | 13.68 | ± 3.54 | 13.60 | ± 3.78 | 0.16 |

EF, ejection fraction; E/e', mitral e annular velocities; E/A, ratio of early filling to atrial filling; LAD, left atrial dimension; PCWP, Pulmonary Capillary Wedge Pressure; RSVP, right systolic ventricular pressure; SWT, shuttle walking test; PWT, posterior LV wall thickness; IVC max: maximal diameter of the inferior vena cava
※Paired *t*-test compared to baseline with 3 months after administration

**Table 4** Parameter estimates of linear regression analyses

| Parameter | Coefficient | Estimates | S.E. | *P*-value |
|---|---|---|---|---|
| HbA1c | $\beta 0$ | 7.39 | 0.25 | <0.0001* |
| | $\beta 1$ | −0.34 | 0.20 | <0.0001* |
| Body Weight | $\beta 0$ | 53.97 | 2.26 | <0.0001* |
| | $\beta 1$ | −1.35 | 1.85 | 0.12 |
| serum-$Na^+$ | $\beta 0$ | 138.75 | 0.71 | <0.0001* |
| | $\beta 1$ | 0.72 | 0.55 | 0.01 |
| serum-$K^+$ | $\beta 0$ | 4.18 | 0.11 | <0.0001* |
| | $\beta 1$ | 0.01 | 0.82 | 0.67 |
| serum-$Cl^-$ | $\beta 0$ | 102.71 | 1.62 | <0.0001* |
| | $\beta 1$ | 1.53 | 1.29 | 0.22 |
| Hematocrit | $\beta 0$ | 37.08 | 1.78 | <0.0001* |
| | $\beta 1$ | 0.61 | 1.62 | 0.24 |
| eGFR | $\beta 0$ | 60.77 | 5.45 | <0.0001* |
| | $\beta 1$ | −1.00 | 4.21 | 0.63 |
| BNP | $\beta 0$ | 191.35 | 64.45 | <0.0001* |
| | $\beta 1$ | −15.63 | 50.69 | 0.54 |
| Renin | $\beta 0$ | 4.40 | 2.08 | <0.0001* |
| | $\beta 1$ | 1.48 | 1.61 | 0.07 |
| Aldosterone | $\beta 0$ | 95.72 | 11.94 | <0.0001* |
| | $\beta 1$ | −0.08 | 8.97 | 0.98 |

**Table 5** Parameter estimates of linear regression analyses

| Parameter | Coefficient | Estimates | S.E. | *P*-value |
|---|---|---|---|---|
| EF | $\beta 0$ | 63.88 | 2.00 | <0.0001* |
| | $\beta 1$ | −0.19 | 0.94 | 0.72 |
| E/e' | $\beta 0$ | 11.29 | 0.91 | <0.0001* |
| | $\beta 1$ | −0.38 | 0.50 | 0.13 |
| E/A | $\beta 0$ | 0.94 | 0.28 | <0.0001* |
| | $\beta 1$ | 0.03 | 0.38 | 0.84 |
| LAD | $\beta 0$ | 37.58 | 1.52 | <0.0001* |
| | $\beta 1$ | −0.23 | 0.88 | 0.59 |
| Estimated RVSP | $\beta 0$ | 27.06 | 2.20 | <0.0001* |
| | $\beta 1$ | 0.11 | 1.22 | 0.84 |
| Estimated PCWP | $\beta 0$ | 15.90 | 1.23 | <0.0001* |
| | $\beta 1$ | −0.47 | 0.62 | 0.13 |
| IVCmax | $\beta 0$ | 13.93 | 0.79 | <0.0001* |
| | $\beta 1$ | 0.12 | 0.45 | 0.56 |

significance in parameter b1 of the E/e' was observed in the lower E/e' group (E/e' < 10) throughout the study period.

The results of the correlation analysis between changes in cardiac parameters and changes in physiological functions in the high E/e' group (E/e' ≥ 10) are shown in Table 7. Most of the combinations of variable changes showed a low correlation ($r < 0.5$), but the ΔE/e' showed positive correlations with the ΔBW ($r = 0.65$), ΔBMI (body mass index) ($r = 0.60$), and ΔFat mass ($r = 0.58$).

## Discussion

This is the first study to identify positive correlations of the change in cardiac function represented by the E/e' ratio with the body weight, BMI, and fat mass of elderly patients with T2DM during 3-month treatment with tofogliflozin. Our analyses also revealed a significant decrease in HbA1c and significant increases in the serum sodium and chloride concentrations, while the patients' serum and urinary potassium concentrations, hematocrit, eGFR, and BNP remained constant, as suggested by the regression coefficient b1.

Stability of the serum electrolyte concentration and body fluid composition was reported in 20 patients with T2DM during tofogliflozin treatment, although the study time was relatively short at 8 weeks [22]. The PMS of tofogliflozin showed that the HbA1c of Japanese patients with T2DM decreased significantly whereas their hematocrit increased significantly, which is consistent with the present results [7]. Regarding the effect of tofogliflozin on the hematocrit, Hirose *et al.* observed a slight increase in the hematocrit from 40.3% (treatment start) to 42.6% (after 8-week treatment). The above-cited PMS study comprehensively measured laboratory test results but not serum electrolytes [7].

The administration of tofogliflozin in Japanese patients with T2DM is known to result in adverse events such as hyperketonemia, ketonuria, and pollakiuria [23]. Although SGLT2 inhibitors improve glucose metabolism in patients with T2DM, these drugs also decrease body weight, blood pressure, liver function, serum lipids, and uric acid [24]. Our previous research demonstrated a significant increase in the serum chloride concentration, mainly in elderly individuals with T2DM who were taking tofogliflozin [25]. Güder *et al.* reported that a higher serum aldosterone level predicted an adverse prognosis in patients with chronic HF. It is therefore important to monitor patients' serum aldsterone level after the start of treatment with an SGLT2 inhibitor [26].

Kataoka *et al.* reported that (*i*) SGLT2 inhibitors enhance chloride reabsorption in renal tubules and (*ii*) serum chloride has tonicity associated with extracelluar fluid. Serum chloride plays a significant role in maintainig intravascular fluid [27]. Schork *et al.* observed that a loss of extracelluar fluid is accompanied by an upregulation of RAAs and an elevation of the serum aldosterone level that later returned to the initial level over a 3-month period [28]. Our present analyses revealed that the patients' aldosterone values did not increase between baseline and 3 months of treatment. In light of the above-described mechanism, it appears that a permanent loss of extracelluar water does not

**Table 6** E/e' parameter estimates of linear regression analyses stratified with cutoff = 10

| Parameter | Coefficient | Estimates | S.E. | *P*-value |
|---|---|---|---|---|
| Upper E/e' (≥10) | β0 | 13.02 | 0.56 | <0.0001 |
| | β1 | −0.64 | 0.32 | <0.05 |
| Lower E/e' (<10) | β0 | 7.94 | 0.46 | <0.0001 |
| | β1 | 0.24 | 0.24 | 0.34 |

E/e', mitral e annular velocities

**Table 7** Correlation analysis between changes in cardiac parameters and changes in physiological functions in upper E/e' (E/e' ≥ 10) group

| | Δ EF | | Δ E/A | | Δ E/e' | |
|---|---|---|---|---|---|---|
| | r | *P*-value | r | *P*-value | r | *P*-value |
| Δ BW | 0.12 | 0.51 | 0.21 | 0.23 | 0.65 | <0.01 |
| Δ sBP | 0.09 | 0.60 | 0.41 | 0.02 | 0.25 | 0.19 |
| Δ dBP | 0.12 | 0.51 | 0.43 | <0.05 | 0.49 | <0.01 |
| Δ HbA1c | 0.16 | 0.38 | −0.15 | 0.40 | 0.26 | 0.19 |
| Δ Ht | −0.27 | 0.12 | 0.34 | 0.04 | 0.28 | 0.14 |
| Δ BMI | 0.07 | 0.66 | 0.21 | 0.21 | 0.60 | <0.01 |
| Δ Fat Mass | 0.26 | 0.20 | −0.08 | 0.69 | 0.58 | <0.01 |

EF, ejection fraction; E/e', mitral e annular velocities; E/A, ratio of early filling to atrial filling; BW, body weight; sBP, systolic blood pressure; dBP, diastolic blood pressure; Ht, hematocrit; BMI, body mass index

tend to occur under treatment with an SGLT2 inhibitor.

In the present study, each body composition parameter was decreased at 1 month of treatment and recovered to the initial level at 3 months. These results bolster the hypothesis that the body weight loss after SGLT2 inhibitor treatment is caused mainly by a reduction of adipose tissue. In addition, the maintenance of body fluid and the RAA homeostasis suggest that the administration of an SGLT2 inhibitor contributes to intrinsic cardiac function with a load-independent mechanism [29]. Regarding the patients' activities of daily living (ADLs), the present study's normal ADL group was comprised of 30 patients (47%), indicating that our study population was not severely biased in terms of physical function.

Our present findings are consistent with the above-described reported results, as we observed that the E/e', a cardiodiastolic parameter, tended to decrease while no change in hemodynamic parameters such as the RVSP, LAD, and IVCmax were observed. These results are similar to previous findings [30]. In our study, the higher E/e' group showed a significant decrease in E/e' during the 3-month observation and a strong relationship between ΔBW and ΔE/e', which sheds light on the differentiation of an SGLT2 inhibitor responder group.

The effects of SGTL2 inhibitors other than tofogliflozin on electrolyte levels have been reported: 24-week treatment with 10-mg dapagliflozin in patients with T2DM resulted in no clinically relevant changes in the serum $K^+$ concentration [31]. SGLT2 inhibitors also increased the serum concentrations of magnesium, $K^+$, and phosphate [9]. Canagliflozin increased serum magnesium in a dose-dependent fashion [32]. Canagliflozin (300 mg) increased $K^+$, although this increase was more frequent in patients with a low eGFR [33]. Hypercalcemia and hypernatremia have also been reported during the administration of canagliflozin to patients with T2DM [34]. The alteration in serum electrolytes' concentrations could be relevant to the mechanism of cardiovascular protection that has been demonstrated for empagliflozin and canagliflozin [9].

Luseogliflozin treatment was reported to lead to favorable changes in body composition and metabolism in Japanese T2DM patients with moderate obesity: a body fat reduction and low reductions of muscle and bone mineral content [35]. Our present analyses demonstrated that the 3-month administration of tofogliflozin significantly decreased the patients' BMI (baseline: $22.9 \pm 3.5$, 3 months: $21.7 \pm 3.2$, $p < 0.01$). This finding is relevant to the above-cited study [25].

We also analyzed the cases of patients who used other anti-T2DM drugs in combination with tofogliflozin. In healthy male volunteers, those drugs exhibited no interactive effect with tofogliflozin [36]. It has been suggested that the combination of an SGLT2 inhibitor with a DPP-4 inhibitor could be an effective therapeutic strategy [37].

Ohara recently reported the effects of SGLT2 inhibitors on body fluid distribution in a comparison with conventional diuretics [38]. However, the combined effects of an SGLT2 inhibitor and a diuretic on cardiac function remain unknown.

As suggested by the results obtained with other SGLT2 inhibitors described above, changes in patients' electrolyte concentration, renal function, and sarcopenia should be monitored during treatment with tofogliflozin. Further investigation is required to elucidate any causal relationship between this drug's effects and cardiac function. Our present investigation was a retrospective observational analysis without interventions or control for the uses of combination drugs and the patients' food and fluid intake, which could be confounding factors that interfere with the interpretation of tofogliflozin's efficacy and safety profiles.

There are several potential study limitations to address. First, because of the observational nature of the study, despite the use of robust statistical techniques we cannot exclude the possibility of unmeasured confounding factors. A relatively short treatment period (3 months) with a small number of patients ($n = 64$) was examined, which could be insensitive to changes in physiological variables. Longer-term follow-up will be required to clarify the effects of tofogliflozin on various physiological variables. This study also lacked control groups, and thus underlying confounding factors (*e.g.*, exercise, diet, restricting smoking, alcohol, types of diuretics) could have affected the results.

In conclusion, the present analyses revealed positive correlations between the changes in a parameter of cardiac function, the E/e', with body weight, BMI, and fat mass in elderly Japanese patients with T2DM during their 3-month treatment with tofogliflozin, while improvements in hyperglycemia and cardiac diastolic function were observed along with the stable maintenance of the serum electrolyte concentration and body

fluid composition. Tofogliflozin treatment also showed less effect on the hemoconcentration, without the adverse event of dehydration due to the decrease in the circulating plasma volume. Tofogliflozin improved left ventricle functions and relieved the cardiac pre-overload without affecting intravascular indices such as the IVCmax and RVSP. Our findings also suggest the improvement of cardiac diastolic function and the stability of electrolytes, RAAs, and body fluid distribution during the course of the patients' treatment with tofogliflozin.

Acknowledgments. We thank Medinfo KK (https://statg.com) for editing a draft of this manuscript.

## References


1. Nair S and Wilding JP: Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab (2010) 95: 34–42.
2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R and Matthews DR: Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care (2015) 38: 140–149.
3. Tahara A, Takasu T, Yokono M, Imamura M and Kurosaki E: Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J Pharmacol Sci (2016) 130: 159–169.
4. Ito H, Shinozaki M, Nishio S and Abe M: SGLT2 inhibitors in the pipeline for the treatment of diabetes mellitus in Japan. Expert opinion on pharmacotherapy (2016) 17: 2073–2084.
5. Terauchi Y, Yokote K, Nakamura I and Sugamori H: Safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): Interim results of a post-marketing surveillance study. Expert opinion on pharmacotherapy (2016) 17: 463–471.
6. Yabe D, Nishikino R, Kaneko M, Iwasaki M and Seino Y: Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. Expert opinion on drug safety (2015) 14: 795–800.
7. Utsunomiya K, Shimmoto N, Senda M, Kurihara Y, Gunji R, Kameda H, Tamura M, Mihara H and Kaku K: Japanese study of tofogliflozin with type 2 diabetes mellitus patients in an observational study of the elderly (J-STEP/EL): A 12-week interim analysis. Journal of diabetes investigation (2016) 7: 755–763.
8. Ferrannini E and Solini A: SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nature reviews Endocrinology (2012) 8: 495–502.
9. Filippatos TD, Tsimihodimos V, Liamis G and Elisaf MS: SGLT2 inhibitors-induced electrolyte abnormalities: An analysis of the associated mechanisms. Diabetes & metabolic syndrome (2018) 12: 59–63.
10. Higashikawa T, Ito T, Mizuno T, Ishigami K, Kohori M, Mae K, Sangen R, Usuda D, Saito A, Iguchi M, Kasamaki Y, Fukuda A, Saito H, Kanda T and Okuro M: The effects of 12-month administration of tofogliflozin on electrolytes and dehydration in mainly elderly Japanese patients with type 2 diabetes mellitus. Journal of international medicine research (2018) 46: 5117–5126.
11. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews DR and CANVAS Program Collaborative Group: Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation (2018) 137: 323–334.
12. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M and Matthews DR: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med (2017) 377: 644–657.
13. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL and Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS and DECLARE–TIMI 58 Investigators: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med (2019) 380: 347–357.
14. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and EMPA-REG OUTCOME Investigators: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med (2015) 373: 2117–2128.
15. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T and Hirata K: Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. Cardiovascular diabetology (2018) 17: 132.
16. Higashikawa T, Ito T, Mizuno T, Ishigami K, Kohori M, Mae K, Usuda D, Takagi S, Sangen R, Saito A, Iguchi M, Kasamaki Y, Fukuda A, Kanda T and Okuro M: Effects of Tofogliflozin on Cardiac Function in Elderly Patients With Diabetes Mellitus. Journal of clinical medicine research (2020) 12: 165–171.
17. Higashikawa T, Ito T, Mizuno T, Ishigami K, Kohori M, Mae K, Usuda D, Takeshima K, Takagi S, Izumida T, Yamada S, Kuroki K, Sangen R, Saito A, Iguchi M, Kamasaki Y, Nakahashi T, Fukuda A, Kanda T and Okuro M: Gender Differences in Cardiac Function Following Three-Month Administration of Tofogliflozin in Patients With Diabetes Mellitus. Journal of clinical medicine research (2020) 12: 530–538.
18. Braha A, Timar B, Diaconu L, Lupusoru R, Vasiluta L, Sima A, Vlad A, Munteanu M, Albai A, Cipu D and Timar : Dynamics of Epicardiac Fat and Heart Function in Type 2 Diabetic Patients Initiated with SGLT-2 Inhibitors. Diabetes, metabolic syndrome and obesity : targets and therapy. (2019) 12: 2559–2566.
19. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM and Tajik AJ: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation (2000) 102: 1788–1794.
20. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA and Quiñones MA: Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. Journal of the American College of Cardiology (1997) 30: 1527–1533.
21. Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant (2013) 48: 452–458.

22. Hirose S, Nakajima S, Iwahashi Y, Seo A, Takahashi T and Tamori Y: Impact of the 8-week Administration of Tofogliflozin for Glycemic Control and Body Composition in Japanese Patients with Type 2 Diabetes Mellitus. Internal medicine (Tokyo, Japan) (2016) 55: 3239–3245.
23. Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, Tanizawa Y, Araki E, Ueda M, Suganami H, Watanabe D and Tofogliflozin 003 Study Group: Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovascular diabetology (2014) 13: 65.
24. Yanai H, Hakoshima M, Adachi H, Kawaguchi A, Waragai Y, Harigae T, Masui Y, Kakuta K, Hamasaki H, Katsuyama H, Kaga T and Sako A: Effects of Six Kinds of Sodium-Glucose Cotransporter 2 Inhibitors on Metabolic Parameters, and Summarized Effect and Its Correlations With Baseline Data. Journal of clinical medicine research (2017) 9: 605–612.
25. Higashikawa T, Ito T, Mizuno T, Ishigami K, Kuroki K, Maekawa N, Usuda D, Morita T, Hamada K, Takagi S, Takeshima K, Yamada S, Sangen R, Izumida T, Mori H, Kiyosawa J, Saito A, Iguchi M, Nakahashi T, Kasamaki Y, Fukuda A, Kanda T and Okuro M: Effects of tofogliflozin on adrenocorticotropic hormone, renin and aldosterone, and cortisol levels in elderly patients with diabetes mellitus: A retrospective study of a patient cohort. Medicine (2021) 100: e27638.
26. Güder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE and Störk S: Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation (2007) 115: 1754–1761.
27. Kataoka H and Yoshida Y: Enhancement of the serum chloride concentration by administration of sodium-glucose cotransporter-2 inhibitor and its mechanisms and clinical significance in type 2 diabetic patients: a pilot study. Diabetol Metab Syndr (2020) 12: 5.
28. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, Häring HU, Stefan N, Fritsche A and Artunc F: Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. Cardiovascular diabetology (2019) 18: 46.
29. Connelly KA, Zhang Y, Desjardins JF, Nghiem L, Visram A, Batchu SN, Yerra VG, Kabir G, Thai K, Advani A and Gilbert RE: Load-independent effects of empagliflozin contribute to improved cardiac function in experimental heart failure with reduced ejection fraction. Cardiovascular diabetology (2020) 19: 13.
30. Rau M, Thiele K, Hartmann NK, Schuh A, Altiok E, Möllmann J, Keszei AP, Böhm M, Marx N and Lehrke M: Empagliflozin does not change cardiac index nor systemic vascular resistance but rapidly improves left ventricular filling pressure in patients with type 2 diabetes: a randomized controlled study. Cardiovascular diabetology (2021) 20: 6.
31. Yavin Y, Mansfield TA, Ptaszynska A, Johnsson K, Parikh S and Johnsson E: Effect of the SGLT2 Inhibitor Dapagliflozin on Potassium Levels in Patients with Type 2 Diabetes Mellitus: A Pooled Analysis. Diabetes therapy : research, treatment and education of diabetes and related disorders (2016) 7: 125–137.
32. Tang H, Zhang X, Zhang J, Li Y, Del Gobbo LC, Zhai S and Song Y: Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia (2016) 59: 2546–2551.
33. Weir MR, Kline I, Xie J, Edwards R and Usiskin K: Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). Current medical research and opinion (2014) 30: 1759–1768.
34. Kaur A and Winters SJ: Severe hypercalcemia and hypernatremia in a patient treated with canagliflozin. Endocrinology, diabetes & metabolism case reports 2015, (2015): 150042.
35. Sasaki T, Sugawara M and Fukuda M: Sodium-glucose cotransporter 2 inhibitor-induced changes in body composition and simultaneous changes in metabolic profile: 52-week prospective LIGHT (Luseogliflozin: the Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) Study. Journal of diabetes investigation (2019) 10: 108–117.
36. Kasahara N, Fukase H, Ohba Y, Saito T, Miyata K, Iida S, Takano Y, Ikeda S, Harigai M and Terao K: A Pharmacokinetic/Pharmacodynamic Drug-Drug Interaction Study of Tofogliflozin (a New SGLT2 Inhibitor) and Selected Anti-Type 2 Diabetes Mellitus Drugs. Drug research (2016) 66: 74–81.
37. Scheen AJ: Pharmacokinetic Characteristics and Clinical Efficacy of an SGLT2 Inhibitor Plus DPP-4 Inhibitor Combination Therapy in Type 2 Diabetes. Clinical pharmacokinetics (2017) 56: 703–718.
38. Ohara K, Masuda T, Murakami T, Imai T, Yoshizawa H, Nakagawa S, Okada M, Miki A, Myoga A and Sugase T, Sekiguchi C, Miyazawa Y, Maeshima A, Akimoto T, Saito O, Muto S and Nagata D: Effects of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on fluid distribution: A comparison study with furosemide and tolvaptan. Nephrology (2019) 24: 904–911.