Effects of Tofogliflozin on Cardiac Function in Elderly Patients With Diabetes Mellitus

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Abstract

Background: Patients with type 2 diabetes mellitus (T2DM) are at increased risk for impairments in diastolic relaxation and heart failure with preserved ejection fraction (EF). Recent clinical data suggest that several sodium glucose transporter-2 (SGLT2) inhibitors are found to reduce cardiovascular disease (CVD) events in elderly diabetic patients, but the effect of tofogliflozin, one of the SGLT2 inhibitors, on CVD is unknown. We retrospectively investigated the effect of tofogliflozin on cardiac function in elderly patients with T2DM.

Methods: Patients received 20 mg of tofogliflozin daily for 1 month. EF, ratio of early filling to atrial filling (E/A), a change in mitral inflow E and mitral e' annular velocities (E/e'), left atrial dimension (LAD) and maximal diameter of inferior vena cava (IVC_{max}) were measured between baseline and 1 month after the administration of tofogliflozin.

Results: Body weight, systolic and diastolic blood pressures significantly decreased, while renin and aldosterone level significantly increased after 1 month of tofogliflozin treatment. Most of the physiological parameters and the level of serum electrolyte did not change significantly. E/A, E/e' and LAD significantly decreased, while no significant changes were observed in EF and IVC_{max}. The interactions of E/e' between time, gender and age were not significant.

Conclusion: The present study suggested that tofogliflozin improved left ventricular diastolic function irrespective of gender and age, while preserving IVC, renal function and electrolyte balance.

Keywords: Tofogliflozin; SGLT2 inhibitor; Type 2 diabetes mellitus; Elderly; Left ventricular diastolic function

Introduction

Type 2 diabetes mellitus (T2DM) is one of the important causes of heart failure (HF), as well as cardiovascular disease (CVD) [1, 2]. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of antidiabetic drugs that inhibit glucose reabsorption in the renal proximal tubules followed by excretion of glucose into the urine [3]. Six SGTL2 inhibitors (ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin and luseogliflozin) have been currently available in Japan [4]. Recent cardiovascular studies have demonstrated that SGLT2 inhibitors significantly decreased major adverse cardiovascular events, death and hospitalizations for HF during the treatment with canagliflozin, empagliflozin and dapagliflozin in T2DM patients with complication of CVD [5-8]. Furthermore, empagliflozin and canagliflozin have known to reduce cardiovascular risk, including weight loss as well as blood pressure lowering [6, 8-10]. A prospective study has also found that treatment with dapagliflozin improved left ventricular (LV) diastolic functional parameters in T2DM patients with HF [11]. LV diastolic dysfunction has been known to associate strongly with HF [12, 13]. Thus, the use of SGLT2 inhibitors which improve cardiovascular outcomes in patients with T2DM has been attracting attention. However, little is known concerning the effect of tofogliflozin, one of the SGLT2 inhibitors, on the LV diastolic function of T2DM patients with HF. The purpose of this study was to investigate the effect of tofogliflozin on the cardiac functions, including LV diastolic function in patients with T2DM.

Patients and Methods

The present study was a retrospective study to investigate the effect of tofogliflozin, one of the SGLT2 inhibitors, on LV diastolic functional parameters in elderly patients with T2DM. This study included elderly patients with a diagnosis of T2DM who attended clinics at the Kanazawa Medical University Himi Municipal Hospital from April 2017 to March 2018. Elderly was defined as aged ≥ 65 years. All patients received a single 20 mg dose of tofogliflozin daily for 1 month. Patients with significant comorbid conditions were excluded. Demographic and baseline characteristics and data that were collected

throughout the 1-month treatment period were extracted from patients' medical records. The data for patient characteristics were collected, gender (male/female), age (years), NYHA classification, co-administered drugs, serum glycated hemoglobin (HbA1c), levels of hematocrit, brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), serum electrolyte (i.e. sodium, potassium and chloride), serum renin and aldosterone were measured at baseline and 1 month.

Echocardiographic examination was performed with commercially available ultrasound systems, Hitachi Ultrasonic Diagnostic Apparatus Hivision Perius. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging and the Guideline from Japanese Society of Echocardiography [13-15]. The maximal diameter of the inferior vena cava (IVC$_{max}$) was defined by the following procedure. Below the costal arch in parallel with the trunk and in the recumbent position before the inferior vein transitions to the right atrium at end-expiration. The largest diameter was measured between 0.5 and 3 cm from the inflow to the right atrium in the IVC long-axis cross-section at supine position. Maximum diameter was measured at expiration at the proximal hepatic vein junction. The left atrial dimension (LAD) was also measured. In parallel, ejection fraction (EF) and the ratio of early filling to atrial filling (E/A) were obtained by the early diastolic (E) and atrial wave (A) velocities, and the E-wave deceleration time was measured by means of pulsed wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained by averaging the septal and lateral mitral annulus, and the mitral e' annular velocities (E/e') were calculated.

Statistical analysis

To examine differences in characteristics of the patients between baseline and 1 month after tofogliflozin treatment, paired *t*-test was conducted for each variable, HbA1c, body weight, systolic blood pressure, BNP, eGFR, BUN, serum electrolytes, blood osmotic pressure, renin, aldosterone, EF, E/A, E/e', LAD and diameter of IVC. In addition, to investigate the source of variation, the fixed effect of treatment time period, gender, age and their interactions (time × gender, time × age) as well as the random effect of subjects were assessed using analysis of variance with a mixed effect model. All statistical analyses were two-tailed, and P < 0.05 was regarded as statistically significant. The data were analyzed using the freely available EZR (Easy R) software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16].

Ethical considerations

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was formally approved by the Clinical Research Ethics Committee of Kanaz-

Table 1. Characteristics of the Patients

Variables	Number of patients
Gender (N, male/female)	18/24
Age (years)	83.0 ± 7.6
NYHA I/II (III, IV: none)	33/9
Co-administered drug	
DPP-4	33
BG	12
SU	10
Insulin	2
ARB	10
β-blocker	5
CCB	22
Diuretics	14

DDP-4: dipeptidyl peptidase-4; BG: biguanides; SU: sulphonylureas; ARB: angiotensin receptor blocker; CCB: calcium channel blocker.

awa Medical University Himi Municipal Hospital (receipt no. 107).

Results

The baseline characteristics of 42 elderly patients with T2DM (male: 18, female: 24) are summarized in Table 1. The total number of patients included was 42. Their mean age was 83.0 ± 7.6 (mean ± standard deviation (SD)), with range of 65 - 97 years of age. NYHA I/II was 33/9. Co-administered drugs were dipeptidyl peptidase-4 (DPP-4) (n = 33), calcium channel blocker (CCB) (n = 22), diuretics (n = 14), etc. During the study period, myocardial infarction, stress cardiomyopathy and exacerbation of HF were not observed.

Comparison of patient characteristics at baseline and 1 month after administration of tofogliflozin is summarized in Table 2. HbA1c tended to decrease 1 month after administration of tofogliflozin from 7.33% at baseline to 7.08% (P = 0.056). Body weight significantly decreased from 55.1 to 52.7 kg (P < 0.01). Systolic and diastolic blood pressures also showed significant decreases from 137.4 to 124.1 mm Hg and from 74.5 to 69.3 mm Hg, respectively (P < 0.01). Serum renin and aldosterone showed significant increase from 3.45 to 6.97 ng/mL (P < 0.01) and from 89.3 to 104.4 pg/mL (P < 0.05), respectively. No significant changes were observed on hematocrit, BNP, eGFR, BUN, serum electrolytes (sodium, potassium and chloride) and blood osmotic pressure during the treatment with tofogliflozin.

Changes in echocardiographic endpoints are summarized in Table 3. After 1 month's administration of tofogliflozin, the E/A showed significant decrease from 0.69 to 0.60 (P < 0.05). The E/e' also showed significant decrease from 12.6 to 9.6 (P < 0.01). The LAD also showed significant decrease from 39.7 to 36.8 (P < 0.01). EF and IVC$_{max}$ were not significantly changed during the treatment with tofogliflozin.

A 3-month interim analysis using a small number of sam-

Table 2. Characteristics of Laboratory Test Results

Variables	Baseline	1 month	P-value*
HbA1c (%)	7.3 ± 1.1	7.1 ± 0.9	0.06
Body weight (kg)	55.1 ± 12.2	52.7 ± 11.6	< 0.01
Systolic blood pressure (mm Hg)	137.4 ± 27.0	124.1 ± 18.8	< 0.01
Diastolic blood pressure (mm Hg)	74.5 ± 13.5	69.3 ± 11.4	< 0.01
Hematocrit	37.9 ± 6.9	38.4 ± 5.9	0.3
BNP (pg/mL)	321.5 ± 805.7	191.0 ± 371.0	0.08
eGFR	63.1 ± 23.2	60.9 ± 30.5	0.4
BUN (mg/dL)	19.1 ± 8.6	18.5 ± 7.7	0.6
Na^+ (mEq/L)	139.1 ± 4.0	139.2 ± 3.5	0.9
K^+ (mEq/L)	4.2 ± 0.7	4.1 ± 0.6	0.4
Cl^- (mEq/L)	103.7 ± 4.1	103.8 ± 5.5	0.9
Blood osmotic pressure (mOsm/L)	293.0 ± 9.3	291.7 ± 7.5	0.3
Renin (ng/mL)	3.5 ± 5.2	7.0 ± 9.2	< 0.01
Aldosterone (pg/mL)	89.3 ± 48.6	104.4 ± 59.7	< 0.05

*Paired *t*-test. HbA1c: glycated hemoglobin; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen.

ples (n = 18) has also found that E/e' (mean ± SD) on baseline, 1 month and 3 months were 12.13 ± 4.70, 9.50 ± 3.23 and 9.71 ± 4.09, respectively (baseline vs. 1 month, P < 0.01, baseline vs. 3 months, P < 0.01, by paired *t*-test).

The results of analysis of variance of E/e' with a mixed effect model were summarized in Table 4, showing that fixed effect (treatment time) and random effect (subjects) were significant (P < 0.05), whereas the interactions (time × gender, time × age) were not significant. Figure 1 shows an interaction plot likely to exist between time and gender, which was not significant (P = 0.09).

Discussion

The present study found that LV diastolic function as measured by E/A, E/e' and LAD for patients with T2DM under stable HF had significantly improved 1 month after administration of tofogliflozin in elderly patients with T2DM. Other cardiac functional parameters such as EF and diameter of IVC did not change 1 month after administration of tofogliflozin. The results also suggested that body weight and blood pressure

Table 3. Characteristics of Cardiac Function

Variables	Baseline	1 month	P-value
EF	63.6 ± 10.9	62.9 ± 11.0	0.1
E/A	0.7 ± 0.3	0.6 ± 0.2	< 0.05
E/e'	12.6 ± 5.0	9.6 ± 3.2	< 0.01
LAD (mm)	39.7 ± 7.4	36.8 ± 7.3	< 0.01
IVC_{max} (mm)	13.7 ± 4.5	13.6 ± 4.2	0.6

*Paired *t*-test. EF: ejection fraction; E/A: early filling/atrial filling; E/e': change in inflow E and mitral e' annular velocities; LAD: left atrial dimension; IVC_{max}: maximal diameter of inferior vena cava.

significantly decreased, consistent with the previous results [17]. The results of analysis of variance of cardiac parameter E/e' with a mixed effect model found that the observed significant decrease of E/e' by tofogliflozin was independent of the underlying source of variation, such as gender and age. Random effect was also significant, indicating that the effect of tofogliflozin varied between subjects. The mechanism still remains unclear, but it is suggested that SGLT2 inhibitor in reducing the risk of adverse cardiovascular outcomes in patients with T2DM including anti-atherosclerotic effect is considered unlikely, given the speed of the observed decrease in cardiovascular mortality. Hemodynamic effects, such as reductions in blood pressure and intravascular volume, involving osmotic diuresis, may provide a more plausible explanation. Metabolic effects, such as cardiac fuel energetics, and hormonal effects, such as increased glucagon release, may also be included in the mechanism [18].

T2DM is one of the most crucial comorbidities associated with CVD that attributes to end organ damage. T2DM also increases the risk for developing HF [19] and its associated complications, including death [20]. SGLT2 inhibitors have been known to improve glycemia and promote weight loss and body fat mass reduction in humans and animals with diabetes, in part, due to caloric loss by high excretion of urinary glucose and an enhancement of oxidative metabolism from carbohydrate to fatty acid [21, 22]. The effect of tofogliflozin on cardiac function has been known to increase EF from 48% to 61%, in parallel with increase of ketone bodies (beta-hydroxybutyrate and acetoacetate) levels in a T2DM case [23]. Although we did not measure ketone bodies, the mechanism of the effect may underlie some metabolic shift. Tofogliflozin has been known to be a most selective SGLT2 inhibitor. Compared to SGLT1, the selectivity of tofogliflozin is highest, approximately 3,000-fold [24]. SGLT2 transporter is located mostly in the kidney, whereas SGLT1 is located in various organs, i.e.

Table 4. Results of Two-Factor Mixed Effect Model to Evaluate Effects and Interaction of E/e'

SOV	df	Sum sq.	Mean sq.	F	Prob > F	Significance
Time	1	76.6	76.6	8.0	0.01	*
Subject	23	574.2	25.0	2.6	0.01	*
Gender	1	43.5	43.5	1.7	0.2	
Time × gender	1	30.3	30.3	3.2	0.09	
Error	23	221.2	9.6			
Total	49	984.1	20.1			
Time	1	81.2	81.2	7.7	0.01	*
Subject	23	539.9	23.5	2.2	0.03	*
Age (< 80 years)	1	77.9	77.9	3.3	0.08	
Time × age	1	7.5	7.5	0.7	0.4	
Error	23	243.9	10.6			
Total	49	984.1	20.1			

Analysis of variance table for the mixed effects model. SOV: source of variance; Sum sq.: sum of squares; df: degree of freedom; Mean sq.: mean squares; F: F statistic; Prob: probability. $*P < 0.05$; $**P < 0.01$.
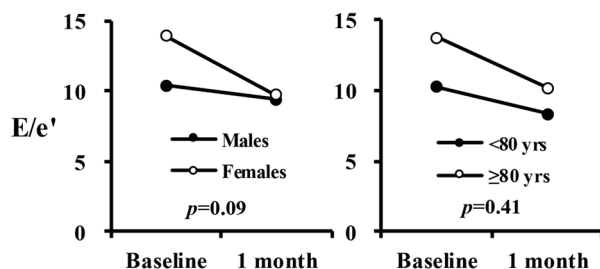
small intestine, kidney, parotid glands, submandibular glands and in the heart [25]. These results suggest that the effect of SGLT2 inhibitors on cardiac functions commonly observed by both tofogliflozin and canagliflozin may not be mediated via SGLT1.

LV diastolic dysfunction is the most frequently observed early LV functional abnormality in patients with T2DM [26]. The LV diastolic dysfunction is thought to be due to the underlying pathophysiological abnormality of cardiac function, and thus its assessment plays an important role for diagnosis of patients with HF. The LV diastolic dysfunction is known to be independently relevant to outcomes in patients with HF [12, 13]. SGLT2 inhibitors have a multimodal effect on cardiac function including improvement in endothelial dysfunction and aortic stiffness [27]. Short-term treatment with empagliflozin is known to reduce LV diastolic function as assessed in terms of e' [28]. The effects of canagliflozin on LV diastolic function as assessed by E/e' and left ventricular mass index (LVMI) had significantly improved by 3 months treatment of canagliflozin while maintaining EF [29]. Soga et al also showed that 6-month treatment with dapagliflozin improved LV diastolic functional parameters including E/e', left atrial volume index (LAVI) and LVMI [11]. Although the precise mechanism of the effect of SGLT2 inhibitors on LV diastolic function remains uncertain, significant correlation was reported between E/e' and pulmonary capillary wedge pressure [30, 31], indicating that decrease of E/e' would be beneficial in T2DM patients with HF.

The present study also showed significant increase in renin and aldosterone. The renin-angiotensin-aldosterone system is a hormonal system known to regulate blood pressure and fluid and electrolyte balance, as well as systemic vascular resistance [32]. We have already revealed that the electrolyte level was stable between before and after tofogliflozin treatment [33]. A previous study demonstrated that canagliflozin increased plasma renin activity while decreased plasma atrial natriuretic peptide and N-terminal pro-b-type natriuretic peptide levels, presumably via compensatory mechanism for sodium retention, leading to subsequent urine output recovery [34]. SGLT2 inhibitor is also known to reduce urinary angiotensinogen/creatinine ratio [35]. Renin-angiotensin blocker also showed improvement in LV function [36]. These results suggest that LV diastolic function is relevant to the function of renin-angiotensin system.

The present study also showed significant decrease in systolic blood pressure during 1-month treatment with tofogliflozin, consistent with the Japanese post-marketing study [17]. Reductions in blood pressure are known to correlate with the amelioration of albuminuria in patients with T2DM [37]. Several clinical trials have also shown that SGLT2 inhibitors exert blood pressure-lowering effects through their diuretic actions, which may partially contribute to the amelioration of albuminuria in diabetic patients [38]. On the other hand, in a rodent study high-dose ipragliflozin reduced the LV chamber size while maintaining stably in blood pressure [39]. The effect of SGLT2 inhibitor on blood pressure still remains controversial, which may be partially caused by the time at which blood pressure was measured. Tofogliflozin has also been known to improve insulin resistance in both animals and humans [40-42].

Figure 1. Interaction plot in E/e′ between time, gender and age.

Study limitations

The results of our study should be considered in the context of several potential limitations. First, due to the observational nature of the study, and despite robust statistical techniques, a possibility of residual, unmeasured confounding cannot be excluded. Specifically, certain patient and physician factors may not be adequately captured. Second, the present study evaluated only 1 month of drug treatment period, which could be insufficient to detect change in physiological parameters. However, the 3-month interim analysis using a small number of samples has found that E/e' significantly decreased both 1 month and 3 months period, suggesting that the effect on E/e' could exhibit in relatively short term and 1 month could be enough to become stable. Longer-term follow-up will be needed to clarify the effects of tofogliflozin on various physiological parameters.

Conclusions

The present study found that tofogliflozin improved LV diastolic function regardless of gender and age, under preserving IVC, renal function and electrolyte balance. Tofogliflozin could improve LV diastolic function in elderly patients with T2DM. SGLT2 inhibition may emerge as an effective and safe adjunctive therapy for HF that promotes hemodynamic stability and helps correct volume overload, while avoiding the risks of volume depletion, independent of effects on hyperglycemia. Nevertheless, the mechanisms responsible for the acute cardioprotective effects of SGLT2 inhibition, such as sodium and water homeostasis and plasma volume regulation remain unknown in patients with T2DM and in those with HF. Further studies will be expected to elucidate these mechanisms.

Acknowledgments

None to declare.

Financial Disclosure

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Patients were not required to give informed consent to the study because the retrospective analysis used anonymous clinical data that were obtained after each patient agreed to the treatment schedule by written consent.

Author Contributions

Toshihiro Higashikawa wrote the manuscript; Daisuke Usuda and Susumu Takagi collected data for review; all authors read and approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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