Effects of Luseogliflozin on Left Ventricular Diastolic Function in Patients with Type 2 Diabetes and Established Cardiovascular Disease.

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Abstract

Background:
This study aimed to evaluate the effect of luseogliozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), on left ventricular (LV) diastolic function in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Methods:
We enrolled 25 patients with T2DM and CVD and performed physical examinations, blood tests, and echocardiography before and 24 weeks after luseogliozin treatment. The primary endpoint was defined as a change in the septal E/e' ratio as a parameter of LV diastolic function.

Results:
Luseogliozin administered for 24 weeks significantly reduced HbA1c levels (8.2 ± 1.2% to 7.4 ± 0.6%, p < 0.01) and systolic blood pressure (125.6 ± 18.1 mmHg to 119.3 ± 16.8 mmHg, p = 0.04) compared to baseline. Luseogliozin significantly reduced left atrial diameter (42.2 ± 5.7 mm to 39.9 ± 6.8 mm, p = 0.01) and LV diameter (diastolic, 49.5 ± 6.9 mm to 47.6 ± 7.6 mm, p = 0.01; systolic, 35.8 ± 9.1 mm to 33.9 ± 9.8 mm, p < 0.01). Early diastolic mitral annular tissue (e') velocity and septal E/e' ratio were significantly improved in the group of e' velocity < 6.0 cm/sec of baseline (e' velocity, 4.8 ± 0.6 cm/sec to 5.8 ± 0.9 cm/sec, p < 0.01; septal E/e' ratio, 13.0 ± 4.9 to 10.9 ± 3.4, p = 0.03, respectively).

Conclusions:
These results suggest the possibility that luseogliozin improves overt LV diastolic function in patients with T2DM and CVD.

Background
Type 2 diabetes mellitus (T2DM) patients have an increased risk of developing heart failure and cardiovascular disease (CVD) [1,2]. Among diabetic patients, the risk of developing chronic heart failure is more than twice as high in men and five times higher in women compared to nondiabetic patients [2]. On the other hand, diabetes is a major complication in patients with heart failure; 25% of patients with chronic heart failure and 42% of patients with acute heart failure have diabetes [3–5]. One of the major complications of heart failure in patients with T2DM is a coronary risk factor, which worsens heart failure with reduced ejection fraction (HFrEF) due to cardiac ischemia. More importantly, diabetes may not only lead to ischemic heart disease but also to left ventricular (LV) diastolic dysfunction and heart failure with
preserved ejection fraction (HFpEF) [6]. LV diastolic dysfunction, which is highly prevalent among patients with diabetes, is an independent and important predictor of adverse outcomes [7,8].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents that enhance urinary glucose excretion by reducing glucose reabsorption in the renal proximal tubules [9,10]. Large-scale, randomized placebo-controlled trials of SGLT2 inhibitors, such as empagliflozin for the EMPA-REG OUTCOME trial [11], canagliflozin for the CANVAS Program [12], and dapagliflozin for the DECLARE-TIMI 58 [13], found that heart failure-associated hospitalizations in patients with T2DM and CVD were significantly reduced. Additionally, the separation of the placebo and active arms in these studies became apparent within months. Also, these clinical trials have indicated that the cardiovascular benefits of SGLT2 inhibitors were not directly associated with their glucose-lowering effects.

However, it has not been still fully clarified why SGLT2 inhibitors could prevent cardiovascular events [14,15]. Moreover, the benefits of SGLT2 inhibitors in patients with HFpEF have been controversial in clinical trials and animal studies [16,17]. To overcome these backgrounds, we focused on the LV diastolic dysfunction in patients with T2DM and CVD as a major clinical indicator. In this study, we examined the beneficial effects of luseogliiflozin, an SGLT2 inhibitor, on LV diastolic dysfunction.

**Methods**

**Patients**

A prospective study was performed to investigate the effect of luseogliiflozin in patients with T2DM and CVD at a single center. Between July 2015 and October 2016, patients with T2DM and CVD from the outpatient center at Saiseikai Fukuoka General Hospital, Japan, were enrolled. Eligibility criteria were as follows: (1) T2DM with glycated hemoglobin (HbA1c) (NGSP) of $\geq 6.5\%, < 10.0\%$; (2) previous history of CVD such as chronic heart failure, ischemic heart disease, arrhythmia, cardiomyopathy, and valvular disease; and (3) experiencing no changes in a treatment regimen for glucose-lowering drugs or any other drugs during the 24 weeks before the start of this study. Exclusion criteria were as follows: (1) already taking an SGLT2 inhibitor, (2) age $< 30$ years or $\geq 75$ years, (3) diagnosis of type 1 diabetes or insulin-dependent diabetes, (4) symptomatic heart failure (NYHA II–IV), (5) severe renal dysfunction (eGFR $< 45$ mL/min/1.73 m$^2$), (6) severe liver dysfunction (over 3 × upper limit of normal), (7) diabetic ketoacidosis or diabetic coma, or (8) the presence of malignancy. The protocol was approved by the ethics committee of the Saiseikai Fukuoka General Hospital (approval number: 2019 7 - 3; date: July 7, 2019). This study was conducted according to the principles of the Helsinki Declaration II. The protocol was reviewed and approved by the Institutional Review Board, and all participants provided informed consent before beginning this study. Analysis of all participants was performed anonymously.

**Study protocol**

Stable heart failure patients who had been taking at least one antidiabetic agent other than an SGLT2 inhibitor were treated with luseogliiflozin (2.5 mg/day). After the start of luseogliiflozin treatment, the patients had not changed antidiabetic drugs. All participants underwent physical examinations and blood
tests to measure the following: HbA1c, serum creatinine, eGFR, liver function, lipid profile, and N-terminal pro-brain natriuretic peptide (NT-proBNP). In addition, the following clinical data were obtained at baseline and 24 weeks: body weight (BW), body mass index (BMI), and blood pressure.

Echocardiography examination

All patients underwent transthoracic echocardiographic examination using commercially available instruments before and after 24 weeks of luseogliozin treatment. The left atrial diameter (LAD), left ventricular end-diastolic diameter (LVDd), and end-systolic diameter (LVDs) were measured using two-dimensional guided M-mode. Left ventricular ejection fraction (EF) was assessed using the biplane Simpson's method. Trans-mitral LV inflow velocity was recorded in the apical four-chamber view using pulse-wave Doppler sonography. Peak velocities of the early E-wave (E), atrial-wave (A), E/A deceleration time (DcT) were measured. The e' velocity was obtained, and the E/e' ratio was calculated.

Study outcomes

The primary clinical endpoint was defined as a change in the septal E/e' ratio as a parameter of LV diastolic function between baseline and 24 weeks after the start of luseogliozin treatment. The secondary endpoints included changes in the following variables at 24 weeks after treatment relative to the baseline: (1) echocardiographic parameters: LAD, LVDs, LVDs, EF, E, A, E/A, DcT, and e' velocity; (2) glycemic control parameters: HbA1c level; (3) lipid parameters: TG, LDL cholesterol, and HDL cholesterol; (4) BW, BMI; and (5) NT-proBNP. Twenty-five patients were enrolled in the present study according to the present inclusion and exclusion criteria.

Statistical analysis

All analyses were performed with commercially available software (Microsoft Excel for Mac version 16.32, USA). Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages. Paired t-tests were used to compare variables at baseline and 24 weeks after beginning luseogliozin treatment.

Multiple regression analyses were performed by increasing and decreasing variables and using the response variables as the change of e' velocity and the change of E/e' ratio (after 24 weeks minus before administration). The explanatory variables were set as almost all parameters (diastolic blood pressure was excluded because some values yielded a deficit). The correlation coefficients between the response variables and the explanatory variables were calculated (all correlation coefficients). The explanatory variables in which the absolute value of the correlation coefficient with the change of e' velocity and the change of E/e' ratio change amount is less than 0.25 were excluded. A p-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of study patients
Table 1 shows the baseline characteristics of the 25 patients. The mean age of patients was 61.4 ± 9.1 years (mean ± SD), the mean BW was 72.2 ± 11.1 kg, and the mean HbA1c level was 8.2 ± 1.2%. Of the 25 participants, 23 had chronic heart failure, and 19 had ischemic heart disease. Of the patients, 17 were receiving treatment with statins, and 21 patients were undergoing treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

At 24 weeks after the treatment with luseogliozin, there was a significant reduction in mean BW, BMI, systolic blood pressure, HbA1c, and liver enzyme levels (AST, ALT, γ-GT) compared to baseline levels. On the other hand, there were no significant differences in serum creatinine, HDL cholesterol, LDL cholesterol, TG, and NT-proBNP levels compared to baseline (Table 2).

Study outcome

There was no significant difference in the septal E/e’ ratio at 24 weeks after the treatment with luseogliozin compared to baseline levels. LAD, diastolic LV dimensions, and systolic LV dimensions were significantly reduced compared with baseline levels (Table 2). In the patients with overt LV diastolic dysfunction, which was determined by an e’ velocity of less than 6 cm/sec at baseline (N = 13), the e’ velocity and septal E/e’ ratio significantly improved from 4.8 to 5.8 cm/sec (p < 0.01) and from 13.0 to 10.9 (p = 0.03), respectively (Table 3). On the other hand, there was no significant change in e’ velocity or E/e’ ratio in patients with a baseline e’ velocity of 6 cm/sec or more at baseline (N = 12).

Multiple regression analyses were performed with the dependent variables set as the change in e’ velocity, referred to as Δe’, and the change in the E/e’ ratio, which is referred to as ΔE/e’. There was a negative correlation between baseline e’ velocity and Δe’. However, this difference was not significant (p = 0.053). A significant negative correlation was similarly observed for the E/e’ ratio (p = 0.016), indicating that patients with a higher E/e’ ratio at baseline showed significant improvement with luseogliozin treatment (Fig. 1).

We found correlations between Δe’ and dyslipidemia (r = −0.315, p = 0.055) and the use of biguanides (r = 0.470, p = 0.021) and calcium channel blockers (r = −0.428, p = 0.060) at baseline. Similarly, we identified correlations between the E/e’ ratio and EF (r = −0.290, p < 0.001), the use of sulfonylureas (r = 0.410, p < 0.001), and the use of β-blockers (r = −0.273, p = 0.017) at baseline (Table 4).

Discussions

This study investigated the effect of luseogliozin on diastolic function in patients with T2DM and CVD. The results showed that the septal E/e’ ratios were not significantly changed among all patients after 24 weeks of luseogliozin treatment. However, patients with an e’ velocity of less than 6 cm/sec at baseline had improved e’ velocity and septal E/e’ ratios. These results suggest that luseogliozin may improve LV diastolic function in patients with T2DM and overt LV diastolic dysfunction at baseline. Also, luseogliozin improved weight loss, glycemic control, and liver function.
Weight loss, lower systolic blood pressure, and decreased HbA1c are common effects of treatment with SGLT2 inhibitors, including luseogliozin. Previous studies suggested the decrease in BW occurs during the initiation of treatment. This weight loss may be attributed to osmotic diuresis due to increased urinary glucose excretion [18]. The decrease in blood pressure is thought to be caused by a decrease in body fluid volume, and the increased excretion of glucose lowers HbA1c levels. Furthermore, the loss of extra energy likely improved the body’s metabolic function which helped improve liver function.

Echocardiographic findings that are used to evaluate LV diastolic function include structural changes, such as an increase in left atrial volume index or LV mass index; functional changes, such as an increased E/e' ratio or reduced e' velocity; and indirect measurements, such as increased tricuspid regurgitant velocity [19]. Among these metrics, e' velocity obtained by tissue Doppler imaging is useful for estimating LV myocardial relaxation activity. Furthermore, decreased e' velocity may indicate the progression of LV diastolic dysfunction [20]. Previous studies have shown that the average E/e' ratio of diabetic patients increases consistently compared to nondiabetic patients [7]. The present study provides us the meaningful clinical implications because this is the first prospective study examining the effects of luseogliozin on LV diastolic function in patients with T2DM and CVD. While there was no significant change in the septal E/e' ratio after 24 weeks of luseogliozin treatment, luseogliozin improved LV diastolic function assessed by e' velocity and E/e' ratio in patients with overt LV diastolic dysfunction at baseline. Recently, several studies have demonstrated the effects of SGLT2 inhibitors on LV diastolic function in patients with diabetes using echocardiography. Verma et al. reported that using empagliozin for 3 months improved the LV diastolic function based on changes in e' velocity among 10 diabetic patients with CVD [21]. Dapagliozin [22] and canagliozin [23,24] significantly reduced the E/e' ratio in T2DM patients, and dapagliozin was associated with improvement of LV longitudinal myocardial function [25]. This study further confirms the cardioprotective effects of SGLT2 inhibitors.

Cardiovascular prognosis in patients with diabetes is poor because diabetes has been linked to HFrEF and HFpEF [26]. The prevalence of HFpEF has been increasing since 2000 and accounts for more than 50% of hospital admissions for heart failure [27]. ACE inhibitors, ARBs [28], and β-blockers [29] are useful for treating HFrEF, and SGLT2 inhibitors have improved cardiovascular outcomes, including HFrEF, in three large clinical trials: EMPA-REG OUTCOME [11], CANVAS Program [12], and DECLARE-TIMI 58 [13]. On the other hand, few studies are focusing on effective therapeutic agents for treating patients with HFpEF. Considering these clinical studies and our present study, we propose that luseogliozin may be particularly effective in treating patients with HFpEF.

Some studies showed that SGLT2 inhibitors reduced all-cause mortality [30], and other meta-analyses and systematic reviews suggested that SGLT2 inhibitors protect against CVD and death in diverse subsets of the patients with T2DM regardless of CVD history [31]. Several mechanisms through which SGLT2 inhibitors have improved cardiovascular events have been studied; however, it is unclear which mechanism is most crucial [15]. The potential effects of SGLT2 inhibitors on LV structure and function are multifaceted, and these effects may be due to effects on systemic hemodynamics and metabolism [32]. SGLT2 inhibitors reduce circulating blood volume through osmosis and natriuresis. The diuretic
effect of SGLT2 inhibitors reduces plasma volume, which is a potential factor in reducing hospitalizations due to heart failure [33]. The most commonly used loop diuretics and thiazides also reduce the intravascular volume and pure sodium balance as well as or better than SGLT2 inhibitors. However, in contrast to empagliflozin, these diuretics have not been proven to reduce cardiovascular mortality. This is probably because SGLT2 inhibitors, unlike loop and thiazide diuretics, do not cause reflex activation of the sympathetic nervous system. Such hemodynamic changes in intravascular volume and blood pressure observed during SGLT2 treatment are not accompanied by an increase in heart rate. Therefore, SGLT2 inhibitors may reduce the activation of the reflex sympathetic nervous system or implicate other neurohormonal pathways that affect the heart [34,35]. The significant effects of SGLT2 inhibitors on cardiovascular outcomes may also be attributed to the anti-oxidative, anti-inflammatory, or anti-apoptotic properties of SGLT2 inhibitors as shown in experimental models [15,36,37]. However, whether such effects seen in such preclinical studies affect humans remains to be determined. In the present study, we could not assess the mechanism through which luseogliozin improved LV diastolic function in patients with T2DM and overt LV diastolic dysfunction at baseline. Further basic experiments are necessary for the future.

In this study, we selected luseogliozin because it is highly selective for SGLT2 and was previously launched in Japan to treat the patients with T2DM. The structural feature of luseogliozin is a 5-thioglucose analog that has a sulfur atom in place of oxygen in the glucose ring [38]. Clinical studies have shown that once-daily administration of luseogliozin, unlike other SGLT2 inhibitors, leads to significant improvement of HbA1c levels at a very low dose of 2.5 mg. Luseogliozin has the lowest effective dose among all SGLT2 inhibitors prescribed in Japan [18]. Recent inhibition kinetics and binding studies of luseogliozin have shown that the dissociation of luseogliozin from SGLT2 appears to be much slower than those of other SGLT2 inhibitors. For instance, the dissociation halftime of luseogliozin–SGLT2 was approximately 7 h [39]. These characteristics of luseogliozin might contribute to its long duration of action; however, the exact mechanism of binding is not revealed. Luseogliozin lowers plasma glucose concentration and BW and has beneficial effects on other clinically relevant parameters, including blood pressure and uric acid, among patients with T2DM [38]. The decreases in HbA1c and BW from baseline to the end of treatment were − 0.63% and − 2.70 kg after 24 weeks of treatment; these results were similar to those produced by other SGLT2 inhibitors [39].

This study contained several limitations that need to be addressed. For instance, it was a single-center study and included a small number of patients without a placebo-controlled group. Further prospective studies with larger populations are needed to confirm our study results. In general, long-term observation is required to investigate the suppression of CV events; since this study was short term, a relationship between CV events could not be confirmed. Furthermore, detail hemodynamic evaluations were not performed using a cardiac catheter examination. Finally, we could not verify whether these effects were specific to luseogliozin or shared by other SGLT2 inhibitors.

Conclusions
Luseogliflozin improved hemodynamics associated with LV diastolic function in patients with T2DM and CVD. These results demonstrate the potential cardioprotective effects of SGLT2 inhibitors in patients with T2DM with CVD.

**Abbreviations**

T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; HFrEF: heart failure with reduced ejection fraction; HfPEF: heart failure with preserved ejection fraction; LV: left ventricular; SGLT2: sodium-glucose cotransporter 2; HbA1c: glycated hemoglobin; NT-proBNP: N-terminal pro-brain natriuretic peptide; BW: body weight; BMI: body mass index; LAD: left atrial diameter; LVDd: left ventricular end-diastolic diameter; LVDs: end-systolic diameter; EF: ejection fraction; e': early diastolic mitral annular tissue; E: peak velocities of the early E-wave; A: peak velocities of the atrial-wave; DcT: E/A deceleration time; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

**Declarations**

Ethics approval and consent to participate.

This study was approved by the local ethics committee of Saiseikai Fukuoka General Hospital.

Consent for publication

The consent to publish was obtained from all participants in this study.

Availability of data and materials

The data analyzed during this study are available from the corresponding author of this article upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

YI wrote the manuscript and research data. TK and NS reviewed/edited the manuscript.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures
Figure 1

Univariate correlates of changes in the e' velocity and E/e' ratio

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xls
- Table2.xls
- Table3.xls
- Table4.xls