Effects of Empagliflozin in Different Phases of Diabetes Mellitus-Related Cardiomyopathy

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Abstract

Background: In diabetes mellitus-related cardiomyopathy (DMCMP), hyperglycemia causes endothelial dysfunction, fibrosis, and myocardial injury, which result in left ventricular (LV) dysfunction. Treatment with sodium–glucose co-transporter 2 inhibitor (SGLT2i) reduces the risk of exacerbation of heart failure (HF). The beneficial effects of SGLT2i on HF depend not only on indirect actions such as osmotic diuresis but also direct actions on the myocardium leading to improvements in LV function. However, it remains unclear whether SGLT2i treatment is equally effective in any phase of DMCMP. The aim of this observational study was to compare the efficacy of SGLT2i treatment on LV dysfunction between early and advanced DMCMP.

Methods: Thirty-five symptomatic non-ischemic HF patients with LV ejection fraction (EF) greater than 40% and type 2 diabetes mellitus (T2DM) treated with administration of empagliflozin (10 mg/day) were enrolled. According to the myocardial extracellular volume fraction (ECV), a reliable marker of cardiac fibrosis quantified by cardiac magnetic resonance, the patients were divided into the early DMCMP group ($n = 16$, $ECV \leq 30\%$) and advanced DMCMP group ($n = 19$, $ECV > 30\%$) and followed-up prospectively. Echocardiography was performed at baseline and after 12 months. LV systolic function assessed as LV global longitudinal strain (GLS) and diastolic function assessed as the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') were compared.

Results: ECV was strongly correlated with T2DM duration ($r^2 = 0.65$, $p < 0.001$). At baseline, both groups had similar backgrounds (LVGLS: $7.9 \pm 2.4\%$ vs. $6.7 \pm 3.0\%$, $p = 0.207$, and E/e' : 13.2 ± 6.1 vs. 12.6 ± 3.8 , $p = 0.694$). After 12 months, the early DMCMP group showed greater improvement in LVGLS (Δ LVGLS: $4.6 \pm 1.5\%$ vs. $1.6 \pm 3.3\%$, $p = 0.003$) and E/e' ($\Delta E/e'$: -3.4 ± 5.5 vs. -0.1 ± 3.5 , $p = 0.043$) than in the advanced DMCMP group.

Conclusions: The positive effects of empagliflozin on LV dysfunction were more remarkable in DMCMP with mild cardiac fibrosis than with advanced fibrosis. Early intervention of SGLT2i for DMCMP is preferable.

Background

Type 2 diabetes mellitus (T2DM) is an important risk factor for the development of cardiovascular disease and heart failure (HF) [1]. Diabetes mellitus-related cardiomyopathy (DMCMP), which manifests as left ventricular (LV) dysfunction that cannot be ascribed to hypertension, coronary artery disease, or significant valvular disease, is well described. Hyperglycemia drives microvascular endothelial dysfunction, LV dysfunction, and LV remodeling through progresses of myocardial hypertrophy, cardiomyocyte stiffening, and interstitial fibrosis, which lead to DMCMP with HF with preserved ejection fraction (HFpEF) phenotype [2]. Decreased LV global longitudinal strain (GLS) and the increased ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') are observed as signs

of LV dysfunction from the early phase of DMCMP [3, 4]. If LV remodeling progresses, DMCMP turns to HF with reduced ejection fraction (HFrEF) phenotype [2].

Several mega-trials have shown that treatment with sodium–glucose co-transporter 2 inhibitor (SGLT2i) reduces the risk of major adverse cardiovascular events, including exacerbation of HF [5–7]. Furthermore, it was recently shown that SGLT2i treatment was associated with lowering the risk of cardiovascular death and hospitalization for HFrEF consistently from the early to late phases after administration, regardless of the presence or absence of T2DM [8, 9]. Thus, the beneficial effects of SGLT2i treatment on HF are not explained only by their indirect actions such as glycemic control or osmotic diuresis, but also by their direct actions on the myocardium, which lead to LV functional improvements [10, 11]. One example of direct actions is inhibition of the sodium-hydrogen exchanger (NHE), which may in turn lead to a reduction in cardiac injury, hypertrophy, fibrosis, remodeling, and LV dysfunction [12].

However, it remains unclear whether SGLT2i treatment is equally effective for all patients with DMCMP. The aim of this cohort study was to compare the efficacy of SGLT2i treatment on LV dysfunction between the early and advanced phases of DMCMP.

Methods

Patients

This was a prospective observational study conducted at a single center. Consecutive symptomatic HF patients with T2DM who were hospitalized in Fujieda Municipal General Hospital (Japan) and treated with administration of empagliflozin (at a dose of 10 mg daily) were screened for eligibility. The diagnosis of T2DM was based on the World Health Organization criteria [13]. After the cardiac assessment, patients diagnosed as DMCMP with LV ejection fraction (EF) greater than 40% were enrolled. Cardiac magnetic resonance (CMR) was performed in all participants, and their myocardial extracellular volume fraction (ECV), a reliable marker of cardiac fibrosis, was evaluated. According to previous reports [14, 15], global ECV > 30% was considered elevated with advanced replacement myocardial fibrosis. Therefore, the patients were divided into the early DMCMP group (global ECV ≤ 30%) and advanced DMCMP group (global ECV > 30%) and followed-up prospectively.

Exclusion criteria were as follows: (1) age less than 20 or greater than 80 years, (2) in-hospital death, (3) New York Heart Association (NYHA) class I or brain natriuretic peptide (BNP) < 100 pg/mL, (4) LVEF ≤ 40%, (5) other cardiomyopathies, (6) valvular or congenital heart disease, (7) normal LV systolic function: LVGLS (absolute value) ≥ 18% [3], (8) type 1 diabetes mellitus or insulin-dependent T2DM: C-peptide immunoreactivity index < 0.8 [16] or insulin user, (9) newly diagnosed T2DM (less than 1 year) or no antidiabetic medications before administration of empagliflozin, (10) current or previous use of SGLT2i, (11) persistent arrhythmia, (12) pacemaker implantation, (13) contraindication for CMR (implanted metallic objects, allergy to contrast media, and bronchial asthma), (14) estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m², (15) malignant tumor or inflammatory disease, (16) pregnancy, (17)

refusal to informed consent, and (18) prior history of myocardial infarction, cerebral infarction, pancreatitis, and hospitalization for HF. For the exclusion of ischemic cardiomyopathy, coronary angiography was performed in all participants. Patients with $\geq 90\%$ coronary artery stenosis were excluded. Patients with 75% stenosis were also excluded if functional ischemia was proven by over 10% ischemic area matched with angiography in myocardial perfusion scintigraphy. For the exclusion of hypertensive heart disease, patients with diastolic blood pressure ≥ 90 mmHg were excluded [2]. For the exclusion of other cardiomyopathies, patients with regional LV wall motion abnormalities, late gadolinium enhancement (LGE), excessive LV dilatation (LV end-diastolic volume index: > 97 mL/m² [2]), and excessive LV hypertrophy (LV myocardial mass index: > 69 g/m² for women or 91 g/m² for men [17]) as evaluated by CMR were not included.

Outcomes

The primary outcome was the improvement in LV function, defined as changes in LV systolic function assessed as LVGLS, and diastolic function assessed as E/e' between baseline and 12 months after the administration of empagliflozin.

The secondary outcomes were the NYHA class after 12 months and the changes in glycated hemoglobin (HbA1c) and BNP levels between baseline and after 12 months.

Anthropometrics and blood examination

At the time of enrollment, age, gender, height, body weight, blood pressure, and heart rate of all participants were recorded. NYHA class and blood samples including hemoglobin, HbA1c, sodium, eGFR, and BNP at admission were used as baseline data. Fasting C-peptide and plasma glucose was checked with hematocrit at the time of CMR, and the C-peptide immunoreactivity index was calculated using the following formula: fasting C-peptide/fasting plasma glucose $\times 100$. Serum HbA1c and BNP levels were measured routinely at baseline and at 12 months.

Ultrasonic echocardiography

Ultrasonic echocardiography was performed at baseline and after 12 months using an Aplio 400® (Canon Medical Systems Corporation, Tochigi, Japan) by two cardiac ultrasonographers who were blinded to the patients' backgrounds. Two-dimensional gray-scale cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from standard parasternal and apical views. According to the guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [18], standard echocardiographic measurements were performed. LVEF was measured using the modified Simpson method. The E-wave velocity was measured using pulsed-wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived e' was obtained by averaging the septal and lateral mitral annulus, and the E/e' was calculated to obtain an estimate of LV filling pressure. LVGLS was measured using two-dimensional speckle-tracking echocardiography. Speckle-tracking strain was analyzed with the 2D Wall Motion Tracking Application® software (Canon Medical Systems Corporation, Tochigi, Japan). While maximizing the frame rate, the LV endocardial border was

traced manually at the end-diastolic frame. The software automatically tracked the myocardium throughout the cardiac cycle. The peak values of six segmental longitudinal strains were obtained from the apical four-, three-, and two-chamber views, and LVGLS was calculated by averaging the values (Fig. 1).

CMR scanning protocol

All CMR exams were performed using a 3.0-Tesla scanner (Ingenia®, Philips, Eindhoven, Netherlands) with a 32-element cardiac receiver coil. Vector-electrocardiogram-gated standard steady-state free precession cine sequences were acquired in short axes covering the whole LV and long-axis (four-, three-, two-chamber) views. LGE images were acquired 10 min post-contrast (Gadovist® 0.1 mmol/kg) injection. T1 maps were generated before and 15 min after gadolinium contrast injection using a modified Look-Locker inversion recovery sequence [19] during breath-holding in end-expiration to produce 11 raw images with increasing inversion times (TI, 100–5000 ms) in a LV short-axis view (TR/TE, 2.20/1.02 ms; flip angle, 20°). Blood samples were taken for hematocrit determination within 24 h before the scan. All maps were analyzed using Ziostation2® ver. 2.9 2–2 (Ziosoft, Tokyo, Japan). Myocardial T1 values and ECV were determined by drawing regions of interest in each segment of the LV slice according to the American Heart Association 16-segment model (Fig. 1). ECV values were calculated according to the following formula: $ECV = (1 - HCT) \times (1/T1 \text{ value}_{\text{myocardium post}} - 1/T1 \text{ value}_{\text{myocardium pre}}) / (1/T1 \text{ value}_{\text{blood post}} - 1/T1 \text{ value}_{\text{blood pre}})$. The global ECV was calculated by averaging the values of the 16 segments.

Statistical analysis

We included data from all patients in the analysis of baseline characteristics and outcomes according to the intention-to-treat principle. Normally distributed continuous variables are expressed as the mean and standard deviation. Levene's test showed that T2DM duration, eGFR, BNP, left atrial dimension, and LV end-diastolic dimension were not distributed normally. These variables are expressed as the median and interquartile range. Student's *t*-test or Mann–Whitney U test was used to compare differences between the two groups, where appropriate. A simple linear regression analysis was performed to evaluate the correlations. All statistical tests were two-tailed, and values of $p < 0.05$ were considered to indicate statistical significance. IBM SPSS Statistics® version 19.0 (SPSS, Chicago, IL, USA) was used for statistical analyses.

Results

Baseline characteristics

A total of 984 HF patients were hospitalized between April 1, 2017 and June 1, 2019, and 75 of them treated with administration of empagliflozin were screened for eligibility. Therefore, 35 DMCMP patients were enrolled and divided into the early DMCMP ($n = 16$, global ECV: $27.5 \pm 1.9\%$) and advanced DMCMP ($n = 19$, global ECV: $38.7 \pm 5.3\%$) groups. The baseline characteristics of the two groups are summarized

in Table 1. At baseline, both groups had similar backgrounds. There were no significant differences in age, gender, NYHA class, HbA1c, BNP, LVGLS, and E/e'. However, LVEF was significantly lower in the advanced DMCMP group than in the early DMCMP group ($55.9 \pm 10.0\%$ vs. $48.4 \pm 9.8\%$, $p = 0.032$). The T2DM duration of the advanced DMCMP group was significantly longer than that of the early DMCMP group (22 [19–28] vs. 99 [72–118] months, $p < 0.001$). Interestingly, the global ECV value was strongly correlated with T2DM duration ($r^2 = 0.65$, $p < 0.001$, Fig. 2). Finally, 32 patients had 12 months of complete follow-up. Two patients in the early DMCMP group and one patient in the advanced DMCMP group had an incomplete follow-up because of dropout and onset of cerebral infarction, respectively.

Primary outcomes

After 12 months, positive effects of empagliflozin on LV function were observed in both groups. However, the early DMCMP group showed more remarkable improvements in both LVGLS (Δ LVGLS: $4.6 \pm 1.5\%$ vs. $1.6 \pm 3.3\%$, $p = 0.003$) and E/e' (Δ E/e': -3.4 ± 5.5 vs. -0.1 ± 3.5 , $p = 0.043$) than in the advanced DMCMP group (Fig. 3).

Secondary outcomes

There were no significant differences between the two groups in NYHA class after 12 months (1.2 ± 0.4 vs. 1.3 ± 0.5 , $p = 0.755$) and the changes in HbA1c and BNP between baseline and after 12 months (Δ HbA1c: $-1.6 \pm 1.5\%$ vs. $-1.0 \pm 1.4\%$, $p = 0.249$, Δ BNP: -305 [201–400] pg/mL vs. -398 [143–537] pg/mL, $p = 0.594$, Table 2).

Discussion

The present study showed positive effects of empagliflozin on LV functional parameters observed in both early and advanced DMCMP patients. However, the improvements were more remarkable in early DMCMP patients than in advanced DMCMP patients. HF parameters, such as NYHA class and BNP, were equally improved in both groups.

Characteristics of DMCMP

Hyperglycemia causes microvascular endothelial dysfunction, cardiac interstitial fibrosis, and structural cardiac changes such as LV hypertrophy, which leads to the development of DMCMP [2]. LV diastolic dysfunction is a classical LV functional abnormality observed in the preclinical phase of DMCMP [4]. LV longitudinal myocardial dysfunction has also been reported as one of the earliest markers of LV dysfunction in DMCMP [3]. If LV remodeling progresses, DMCMP develops into symptomatic HF showing restrictive HFpEF or dilated HFrEF phenotypes. Phenotype-specific pathophysiological mechanisms have recently been proposed for LV remodeling and dysfunction consisting of coronary microvascular endothelial dysfunction, interstitial fibrosis, and myocardial hypertrophy in HFpEF, and cardiomyocyte cell death and extensive replacement fibrosis in HFrEF [2].

In this study, symptomatic HF patients with T2DM were enrolled. Thus, although we named the group of patients with $ECV \leq 30\%$ as the early DMCMP group, they were not strictly in the early phase of DMCMP. Their ECV values were as high as those reported in a previous report of T2DM patients with normal LV function [20], but their LVGLS and E/e' were relatively worse than those reported in other DMCMP research targeting stable HF [10, 11]. Baseline LVEF was lower in the advanced DMCMP group than in the early DMCMP group; thus, the advanced DMCMP group patients might be having the nearly dilated HFrEF phenotype. Their ECV values were very high and suggested extensive replacement fibrosis.

Impact of SGLT2i on LV functional parameters

In line with previous reports using dapagliflozin [10, 11], the administration of empagliflozin also improved LV functional parameters such as LVGLS and E/e'. Tanaka et al. showed that dapagliflozin was more effective in improving LVGLS in DMCMP with HFpEF phenotype than the HFrEF phenotype [11]. Furthermore, regarding DMCMP with non-HFrEF phenotype, our research revealed that patients with mild myocardial fibrosis showed greater improvements in LV systolic and diastolic function than patients with advanced myocardial fibrosis after the administration of empagliflozin. We also found that the progression of myocardial fibrosis correlated with T2DM duration. Combined with a previous report and our research results, SGLT2i treatment is more effective for LV dysfunction in an earlier phase than the later phase of DMCMP. Thus, it is recommended that SGLT2i treatment should be used for DMCMP from the early phase.

Mechanisms of direct cardiac effects

It is hypothesized that the direct cardiac effects of SGLT2i depend on a reduction in intracellular sodium by inhibiting NHE-1 which is expressed in the heart and vasculature [12]. In patients with T2DM and HF, the activity of NHE-1 is markedly enhanced. This increase facilitates the accumulation of intracellular sodium, which stimulates the reverse activity of the sodium-calcium exchanger, leading to an increase in intracellular calcium and myocardial injury [21]. The inhibition of NHE-1 reduces intracellular sodium and calcium concentrations, increases mitochondrial calcium, which restores mitochondrial function and redox state, activates ATP production in the failing heart, and improves LV function [12]. In animal models, SGLT2i treatment, via the inhibition of NHE-1, reduces cardiac hypertrophy and fibrosis, slows the progression of DMCMP, and improves systolic and diastolic function [22–24]. These findings suggest that empagliflozin promotes reverse LV remodeling; thus, the lesser the degree of myocardial fibrosis and injury, the greater is the extent to which LV function could be restored by SGLT2i treatment.

Considering that there was no significant difference between the two groups in $\Delta HbA1c$, the reverse remodeling through the inhibition of NHE-1 is independent of the main effect: glycemic control by blocking glucose reabsorption thorough SGLT2. Side effects, such as osmotic diuresis and inhibition of NHE-1, may be the reason why SGLT2i treatment is associated with lowering of the risk of HF exacerbation regardless of the presence or absence of T2DM. The composite of direct and indirect cardiac actions of SGLT2i could improve HF parameters even in advanced DMCMP patients.

Clinical implications

LV longitudinal myocardial dysfunction and diastolic dysfunction are the earliest markers observed in the preclinical phase of DMCMP [3, 4], leading to HF. In the present study, symptomatic HF patients with T2DM were enrolled. Because of the study population, LV systolic function assessed as LVGLS and diastolic function assessed as E/e' were relatively lower than those reported in similar studies targeting stable HF patients [10, 11]. However, empagliflozin improved LV functional parameters. Moreover, the improvements in LVGLS and E/e' after empagliflozin administration were more remarkable in DMCMP patients with milder cardiac fibrosis whose progression was correlated with T2DM duration. These are clinically important findings that lead to early intervention of SGLT2i for HF patients with T2DM.

Study limitations

This study has some limitations. First, this was a small observational study conducted at a single center. Therefore, several biases were possible. Second, a myocardial biopsy was not performed. Although we performed coronary angiography and CMR to increase the diagnostic accuracy of DMCMP, the possibility that patients with another cardiomyopathy were still included cannot be denied. Third, we performed only a short-term assessment of LV function. If the follow-up period was longer, LV functional parameters might have improved further in the advanced DMCMP group.

Conclusions

Empagliflozin had positive effects on LV function, which were more remarkable in DMCMP patients with lower ECV values than in those with higher ECV values. The ECV increase was strongly correlated with T2DM duration. Thus, early SGLT2i administration for HF patients with T2DM is preferable.

Abbreviations

BNP: brain natriuretic peptide, CMR: cardiac magnetic resonance, DMCMP: diabetes mellitus-related cardiomyopathy, ECV: extracellular volume fraction, EF: ejection fraction, eGFR: estimated glomerular filtration rate, E/e': ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity, GLS: global longitudinal strain, HbA1c: glycated hemoglobin, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LGE: late gadolinium enhancement, LV: left ventricular, NHE: sodium-hydrogen exchanger, NYHA: New York Heart Association, SGLT2i: sodium-glucose co-transporter 2 inhibitor, T2DM: type 2 diabetes mellitus.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Fujieda Municipal General Hospital. All participants provided written informed consent before enrollment.

Consent for publication

The consent to publish was obtained from all participants.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

SO designed the study, carried out participant recruitment, performed coronary angiography, analyzed the data, and wrote the manuscript. TK, KH, KW, JN, MA, and AW assisted recruitment and coronary angiography. JN and AW assisted in the manuscript revision. All authors have read and approved the final manuscript.

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Tables

Due to technical limitations, table 1 & 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Example of assessment of left ventricular global longitudinal strain (LVGLS) and extracellular volume fraction (ECV) Apical four- (A), three- (B), and two-chamber (C) views of two-dimensional speckle-tracking echocardiography imaging are shown. LVGLS was calculated by averaging the values from these results. Maps of the LV basal short-axis segment with a modified Look-Locker inversion recovery sequence; native T1 mapping (D), post-contrast T1 mapping (E), and calculated ECV mapping (F) of the same segment are shown. Global ECV value was calculated by averaging the values of the American Heart Association 16-segment model (G).

Figure 2

Scatter plot of extracellular volume fraction (ECV) value and type 2 diabetes mellitus (T2DM) duration. The basic linear regression line shows a strong correlation between global ECV value (y-axis) and T2DM duration (x-axis).

Figure 3

Results of primary outcomes Left ventricular global longitudinal strain (LVGLS; absolute value) and ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') at baseline and 12 months after administration of empagliflozin are shown in (A) and (C). Primary outcomes, changes in LVGLS and E/e' between 12 months (Δ LVGLS and $\Delta E/e'$) are shown in (B) and (D). Improvements in LVGLS and E/e' are more remarkable in the early diabetes mellitus-related cardiomyopathy (DMCMP) group than in the advanced DMCMP group.

Supplementary Files

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