

An Observational Study on the Effect of Canagliflozin on Left Ventricular Diastolic Function in Patients with Type 2 Diabetes Mellitus in a Tertiary Care Hospital of West Bengal

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ABSTRACT

Background: The incidence of type 2 diabetes mellitus (T2DM) is increasing in India. Left ventricular diastolic dysfunction (LVDD) is a complication of T2DM, which may develop irrespective of glycemic and hypertension control. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, e.g., empagliflozin and canagliflozin have been shown to reduce all-cause mortality including cardiovascular mortality in T2DM patients.

Aims and objectives: The aims of this study were to evaluate the effect of canagliflozin on cardiac and renal parameters and improvement of LVDD at the end of 6 months in T2DM patients.

Materials and methods: About 100 T2DM patients meeting inclusion and exclusion criteria were put on Canagliflozin (100 mg/day) and followed up for 6 months. Clinicodemographic profiles with blood pressure (BP) and body mass index (BMI) and fasting blood sugar, HbA1c, serum creatinine, eGFR, urine albumin/creatinine ratio (UACR) were assessed at baseline and 6 months. Also, echocardiographic parameters like average E/e', septal and lateral e' velocity, TR velocity and LA volume index (LAVI) were assessed and statistically analysis by SPSS 22.0 software.

Results: Majority of patients were male (56%), aged between 45 and 60 years (57%), and obese (51%). Significant findings were, (1) Canagliflozin for 6 months improved E/A in 60 years and LAVI in <45 years' age-group. (2) It improved LAVI in hypertensives and patients of <10 years of disease duration. (3) It improved serum creatinine and UACR.

Keywords: Canagliflozin, Glomerular filtration rate, Hypertension, Left ventricular diastolic dysfunction, Type 2 diabetes mellitus.

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INTRODUCTION

During the period of rapid industrialization, there has been a significant increase in the incidence and prevalence of type 2 diabetes mellitus (T2DM) and associated diastolic dysfunction of the left ventricle (LV) in early T2DM.¹⁻³ Additionally, T2DM may develop LV dysfunction regardless of glycemic management, hypertension, or even the association with coronary heart disease.^{4,5}

Accelerated developments of advanced glycaemic end-products (AGE), activation of their receptor (RAGE), and activation of NADPH oxidase (Nox), an enzyme that generates reactive oxygen species (ROS), all contribute to a proinflammatory milieu characterized by oxidative stress. The AGE-RAGE axis and Nox derived ROS have an immense role in the genesis and progression of micro and macrovascular diabetic complications.⁶

Compared to conventional anti-diabetic drugs, the sodium glucose cotransporter 2 (SGLT2) inhibitors empagliflozin and canagliflozin have shown promise in lowering cardiovascular mortality and improving left ventricular diastolic dysfunction (LVDD) in individuals with Type 2 diabetes.^{7,8} Sodium glucose cotransporter 2 inhibitors prevent hospitalization in heart failure, as seen in the early stages of EMPAREG and CANVAS studies.⁹⁻¹¹ More research is needed to determine the impact of SGLT2 inhibitors of LVDD.

As a result, we conducted observational prospective research to assess the impact of Canagliflozin on LVDD in T2DM patients.

AIMS AND OBJECTIVES

Data on effect of Canagliflozin on LV function of T2DM patients are low. The aims of this study are:

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- To establish a relation of cardiac and renal parameters of T2DM patients with Canagliflozin (SGLT2 inhibitors).
- To evaluate the improvement of LVDD at the end of 6 months in T2DM patients on Canagliflozin.

MATERIALS AND METHODS

A hospital-based, cross-sectional, and observational study was undertaken in North Bengal Medical College and Hospital (NBMC&H), Sushrutanagar, Darjeeling, West Bengal from April 2020 to March 2021, involving 100 patients with T2DM admitted to the indoor or attending the OPD of the Department of Medicine.

Table 1: Effect of canagliflozin on diastolic function parameters according to age-group (n = 100)

Diastolic function parameter	<45 years (n = 20)		45–60 years (n = 57)		>60 years (n = 23)		p-value
	At baseline	6 months	At baseline	6 months	At baseline	6 months	
E/A	0.96 ± 0.06	1 ± 0.67	0.91 ± 0.1	0.93 ± 1.10	0.82 ± 0.08	0.85 ± 0.08	<0.001
E/e'	11.21 ± 1.39	11.06 ± 1.36	11.18 ± 1.18	10.9 ± 1.21	11.91 ± 1.23	11.79 ± 1.21	0.016
TR velocity	0.14 ± 0.43	0.14 ± 0.45	1.46 ± 1.21	1.37 ± 1.14	2.54 ± 0.73	2.42 ± 0.7	<0.001
LA volume index	29.91 ± 3.35	29.4 ± 2.01	29.98 ± 3.1	30.3 ± 2.63	32.03 ± 3.23	32.82 ± 1.3	0.026

Bold values indicate statistically significant; E/A (mean ± SD) increased in all 3 groups but it is statistically significant in the <45 years age-groups. E/e' (mean ± SD) reduced in all 3 groups but it is statistically significant in the 45–60 years group. TR velocity (mean ± SD) reduced in 45–60 years and >60 year groups, statistically significant in >60 year group. Left atrial volume index (LAVI) (mean ± SD) was reduced in the <45 years age-group in a statistically significant manner

Convenient sampling method was used. Patients with glycosylated hemoglobin (HbA1C) level between 7.0 and 15.0% and who had no change in their antidiabetic or other medications 6 months prior to the study were included. Patients below 35 years or above 75 years of age, on sodium-glucose co-transporter inhibitor drugs, cardiac arrhythmias, acute heart failure or myocardial infarction, severe renal dysfunction (serum creatinine \geq 2.5 mg/dL), severe liver dysfunction (enzymes \geq 3* upper limits or normal), acute genitourinary infection, diabetic ketosis, and malignancy were excluded.

The follow-up period for each subject was 6 months. Clinical and diagnostic profiles for each subject including age, gender, occupation, residence, duration of diabetes and temporal profile, and drug history for antihypertensives and antidiabetics were collected. Particular attention was given to measuring blood pressure (BP) (mean of three observations at 1-minute intervals), body mass index (BMI), clinical cardiological examination. Investigations included fasting blood sugar (FBS), HbA1C, serum creatinine, eGFR (estimated GFR using MDRD criteria), urinary albumin/creatinine ratio (UACR), and echocardiography (by a machine of Logic P9 model manufactured by GE Healthcare).

Following echocardiographic parameters were used to assess LVDD:

- Average E/A.
- Septal and lateral e' velocity.
- Average E/e'.
- TR velocity.
- LA volume index.

Left ventricular diastolic dysfunction was diagnosed as per American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) criteria.¹²

Clinical follow-up was done at monthly OPD visits. Blood tests, other investigations, and echocardiography were done at baseline and at 6 months follow-up.

All patients received canagliflozin tablets (100 mg/day) from baseline through the period of 6 months. Informed consent (IC) was obtained from each patient or their caregiver after a proper explanation of the purpose and method of the study. The Institutional Ethics Committee gave its approval for the research to be conducted.

Statistical Analysis

Data were entered into an MS Excel spreadsheet. The calculation was done with the help of MS Excel and statistical software SPSS v 22.0. The normal distribution of the continuous variables was evaluated using Kolmogorov-Smirnoff test. Descriptive statistics were expressed by mean, SD, and proportion of characteristics.

Categorical variables were analyzed with Chi-square and Fisher exact test. Continuous variables with normal distributions were analyzed using an unpaired t-test and those not following normal distribution were analyzed by Mann-Whitney U-test. The p-value \leq 0.05 was considered significant with a 95% confidence interval.

RESULTS

Clinicodemographic profile of subjects: Total number (n) = 100.

- Age distribution: <45 years–20 (20%); 45–60 years–57 (57%); >60 years–23 (23%).
- Sex distribution: Male–56 (56%); female–44 (44%).
- Body Mass Index (BMI): Underweight = 2%; normal = 25%; overweight = 22%; obese = 51%.
- Blood pressure status: Normotensive = 42%; hypertensive = 58%.
- Nephropathy status: Nephropathy present = 50%; No Nephropathy = 50%.

DISCUSSION

The mean age (\pm SD) of our study population was 52.75 \pm 8.66 years with a maximum number of patients belonging to the 45–60-year age-group (57%). Compared to 3 other similar studies, where the mean age was 64.2, 58, and 71.8 years respectively our subjects belonged to the age of at least one decade earlier.^{13–15} This may reflect the increasing incidence of T2DM in younger people in our country.

Marginal male preponderance was observed in our study (M = 56%) which can also be seen in the Emperor Preserve Trial, where female patients were 44.6% in the Empagliflozin receiving group.¹⁴

The mean \pm SD BMI of our study population was 24.95 \pm 3.2 kg/m² with the maximum number of patients in the obese group (51%). A similar study in Japan also showed the mean \pm SD BMI as 27.1 \pm 4.6 kg/m².¹³

Age subgroup analysis of all 4 diastolic function parameters showed statistically significant improvements of E/A (increase) in <45years, E/e' (decrease) in 45–60 years, TR velocity decrease in >60 years and LA volume index (decrease) in <45 years age-groups respectively (Table 1). Improvements in the fundamental echocardiographic parameters may be the reason behind the findings of lower risk of death from cardiovascular or other causes and hospitalization for heart failure in different studies like EMPEROR Preserved Clinical Trial, CANVAS Trial, and EMPAREG Trial.^{14–17}

Comparison between the hypertensive and normotensive subgroups showed statistically significant improvement in LA volume index (decrease) in hypertensives compared to normotensives (Table 2). Sodium-glucose cotransporter 2 inhibitors

Table 2: Effect of canagliflozin on diastolic function parameters according to blood pressure status (n = 100)

Diastolic function parameters	Hypertensive (n = 58)		Normotensive (n = 42)		p-value
	At baseline	6 months	At baseline	6 months	
E/A	0.90 ± 0.11	0.93 ± 0.11	0.90 ± 0.09	0.92 ± 0.09	0.651
E/é	11.47 ± 1.31	11.33 ± 1.3	11.18 ± 1.19	10.87 ± 1.23	0.059
TR velocity	1.49 ± 1.26	1.40 ± 1.19	1.38 ± 1.29	1.31 ± 1.23	0.421
LA volume index	31.02 ± 3.18	30.91 ± 2.43	29.66 ± 3.26	30.41 ± 2.74	0.004

Bold values indicate statistically significant; In both groups, mean ± SD E/A were increased and mean ± SD E/é reduced but they were not statistically significant. But LAVI was reduced in hypertensives (unlike normotensives) which was statistically significant (p = 0.004)

Table 3: Effect of canagliflozin on diastolic function parameters according to duration of diabetes (of study population) (n = 100)

Diastolic function parameters	<10 years (n = 55)		10–15 years (n = 20)		>15 years (n = 25)		p-value
	At baseline	6 months	At baseline	6 months	At baseline	6 months	
E/A	0.97 ± 0.06	1 ± 0.06	0.85 ± 0.1	0.88 ± 0.1	0.78 ± 0.02	0.81 ± 0.01	0.476
E/é	11.14 ± 1.23	10.91 ± 1.24	10.96 ± 1.01	10.68 ± 1.02	12.13 ± 1.2	12 ± 1.21	0.754
TR velocity	0.58 ± 0.76	0.55 ± 0.73	2.04 ± 1.26	1.9 ± 1.18	2.86 ± 0.04	2.72 ± 0.07	0.002
LA volume index	29.36 ± 2.85	29.3 ± 2.16	30.43 ± 3.49	31.92 ± 2.48	32.84 ± 2.75	32.79 ± 1.19	0.041

Bold values indicate statistically significant; E/A (mean ± SD) increased in all groups but was statistically not significant. E/é (mean ± SD) reduced in all groups but statistically not significant. TR velocity (mean ± SD) reduced in all groups, but statistically not significant. LA volume index (mean ± SD) reduced in <10 years and >15 years group. In <10 years group it was statistically significant

Table 4: Effect of canagliflozin on diastolic function status of study population with renal function (n = 100)

Renal function	Total population (n=100)		p-value*
	At baseline	6 months	
S.Cr	1.12 ± 0.17	1.10 ± 0.15	0.066
MDRDGFR	61.97 ± 10.06	62.78 ± 8.86	0.205
Urine ACR	32.48 ± 7.10	30.86 ± 5.38	<0.001

Association between decreasing urinary ACR and use of Canagliflozin for 6 months was statistically significant (p < 0.001); Bold values indicate statistically significant; Serum creatinine and urine albumin/creatinine (ACR) decreased from their baseline values to 6 months

have been shown to reduce BP even ambulatory BP, presumably due to their diuretic effect.¹³ The above-mentioned finding may be explained in the light of antihypertensive potential of SGLT2 inhibitors. Other lesser-known mechanisms should also be explored.

Subgroup analysis according to the duration of diabetes (<10 years, 10–15 years, and >15 years) showed significant improvement in the LA volume index in <10 years group in SGLT2 users (Table 3). Other studies have shown the impact of duration of diabetes on LV diastolic function which deterioration with increasing duration of diabetes.¹⁸

The use of Canagliflozin showed a significant reduction in serum creatinine and urine ACR from baseline to 6 months in our subjects (Table 4). Similar studies with SGLT2 inhibitors showed a statistically significant reduction in the decline of eGFR in the serum creatinine and other outcomes^{13,14} These drugs reduce sodium and glucose reabsorption in the proximal tubule and sodium transport to macula densa thereby triggering tubuloglomerular feedback. Thus, they may ease long-term glomerular pressure, minimize albuminuria, and slow down renal function deterioration.¹⁹

CONCLUSION

- Canagliflozin improves diastolic function parameters of T2DM patients irrespective of their age, BP status, and duration of diabetes.
- Canagliflozin improves the renal function of T2DM patients by reducing the urinary albumin/creatinine ratio.

Limitations

Population size of the study was small and time-period was short. Long-term prospective studies with large study population are necessary in this regard.

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AUTHORS CONTRIBUTIONS

KKD: Data curation, formal analysis and writing original draft; DC: Visualization, writing review and editing; SB: Conceptualization, methodology and supervision.

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