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Original Article

Role of Dapagliflozin (DAPA) In Improvement of Ejection Fraction In Non-Insulin-Dependent Diabetic Patients

Syed Fahad UL Hassan, Ishtiaq Munir Janjua, Muhammad Zahid Hussain

Department of Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To determine the role of Dapagliflozin in improving ejection fraction in Non-Insulin Dependent Diabetic patients
Study design: Prospective analytical study
Place and Duration of Study: Department of Medicine, PEMH, Rawalpindi, Pakistan, from Jan to Jun 2022.
Methodology: Patients aged 40 - 70 years diagnosed with type 2 diabetes mellitus and stable HF with preserved or mid-range EF who had been on oral anti-diabetic medication for more than 1 year, other than SGLT2 inhibitors, were included in the study after informed consent and started on Dapagliflozin (DAPA) at a dose of 5 mg per day. Following Dapagliflozin administration, other medications were kept unchanged. Upon the onset of treatment with Dapagliflozin, blood tests and physical examinations were conducted at baseline, as well as at the three-month and six-month marks thereafter. 2-D Beginning at month zero and continuing until month six of Dapagliflozin therapy, echocardiography was performed. Patients with type-I DM and pre-existing heart structural disease were excluded from the study.
Results: After a period of six months following the administration of the final dose of dapagliflozin, significant alterations in a variety of parameters were found. The value of E/e' dropped from 9.3 to 8.5 cm/s, which is a strong indicator of a significant decrease. This was indicated by the p-value of 0.020. To add a little bit of spice to the dish, both LAVI and LVMI exhibited a considerable decline, going from 31.0 to 26.0 mL/m2 (p=0.001) and 75.0 to 67.0 g/m2 (p=0.001), respectively. This was an interesting development. On the other hand, the levels of BNP did not reveal a significant variation after being treated with dapagliflozin for a period of six months (from 27.9 to 28.9 pg/mL; p=0.132).
Conclusion:
Individuals diagnosed with both type 2 diabetes and heart failure experienced improvements in their left ventricular diastolic functional parameters upon receiving SGLT2 inhibitors. Our research may thus provide a fresh perspective on SGLT2 inhibitors in the management of T2DM patients.

Keywords: DAPA-CKD, DAPA-HF, Dapagliflozin, heart failure; Sodium–Glucose Cotransporter 2 inhibitors.

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INTRODUCTION

Heart failure (HF) with reduced ejection fraction (HFrEF) and HFpEF are associated with type 2 diabetes mellitus (T2DM). SGLT2s are anti-hyperglycemic drugs used to treat type 2 diabetes mellitus (T2DM). These medicines selectively reduce renal glucose reabsorption to eliminate glucose through urine.[1,2] They achieve this without insulin, which is great.

Diabetes mellitus type 2 (T2DM), also known as type 2 diabetes, is a risk factor for heart failure (HF) even in those without structural heart disease or Stage-1 heart failure.[3] It is. Heart failure (HF) is caused by uncontrolled type 2 diabetes. A 1% increase in glycosylated haemoglobin (HbA1c) increases HF risk by 8-19%.[4] Age raises HF risk, according to studies. Diabetes-related cardiomyopathy causes left ventricular (LV) diastolic dysfunction, which causes heart failure (HF) in both HFrEF and HFpEF patients.[5] The left ventricle's diastolic filling ability is measured by diastolic dysfunction. Dapagliflozin reduced the risk of cardiovascular death or HF hospitalization in a large clinical trial of type 2 diabetes patients at risk for atherosclerotic cardiovascular disease. The clinical trial included atherosclerotic cardiovascular disease-risk patients.[6]

The latest WHO study estimates that over 23 million people have heart failure (HF). Heart failure with reduced ejection fraction (HFrEF) patients who take sodium-glucose cotransporter 2 (SGLT2) inhibitors to manage their type 2 diabetes have better glycemic control and fewer cardiovascular events and heart failure hospitalizations.[7] US-Canadian scientists did this research. In the early stages of SGLT2 inhibitor research, glycemic management was a secondary goal to reducing cardiovascular events in

Correspondence: Dr Syed Fahad UL Hassan, Department of Medicine, Pak Emirates Military Hospital Rawalpindi Pakistan
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diabetes patients. However, subsequent randomized trials on SGLT2 inhibitors, specifically empagliflozin and dapagliflozin, such as the EMPEROR-Reduced and DAPA-HF trials, showed reductions in cardiovascular events, particularly heart failure hospitalizations, in HFrEF patients, regardless of diabetes.[8,9] HFrEF patients showed these outcomes. According to pioneering research studies, HFrEF patients should use SGLT2 inhibitors such as Dapagliflozin, regardless of DM.[9] The 2020 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Type 2 Diabetes recommends this. In the proximal tubule of the nephron, the sodium-glucose cotransporter 2 reabsorbs 90% of urine glucose. Glucosuria inhibits SGLT2 in hyperglycemic patients. High urine filtered glucose levels prevent this. When blood glucose levels normalize, glucosuria may lessen. Dapagliflozin reduces cardiovascular mortality and heart failure worsening in patients with heart failure with reduced ejection fraction (HFrEF), with or without diabetes mellitus (DM). Compared to untreated patients. In addition to its hypoglycemic effects, dapagliflozin increases urine sodium excretion, alters tissue sodium regulation, lowers body weight, and lowers systolic blood pressure.[10] SGLT2 inhibitors were tested for treating type 2 diabetes glucose levels. Cardiovascular disease risk decreases.

METHODOLOGY

It was a Prospective analytical study that was carried out in the Department of Internal Medicine of Pak Emirate Military Hospital, Rawalpindi, Pakistan, from Jan to Jun 2022. The size of the sample was established with the help of the WHO sample size calculator by taking into account a confidence interval of 90% and an error margin of 10%.[11] The total number of samples that were calculated was 58. It was decided to use a sample approach called sequential non-probability sampling for the study, with a total of 58 patients with T2DM who started on dapagliflozin and were followed up for 6 months and studied for Ejection fraction by 2D echocardiography, and compared with 10 control subjects who fulfilled the inclusion criteria but weren't started on dapagliflozin and were followed up similarly with baseline and 2D echo.

Inclusion Criterion: Individuals between the ages of 40 and 70 years old who had a confirmed diagnosis of type 2 diabetes mellitus (T2DM) and stable heart failure (HF), and who had been using at least one oral anti-diabetic medication, excluding SGLT2 inhibitors, for a minimum of one year were enrolled in the study once informed consent was obtained.

Exclusion Criterion: Patients aged more than 70 years, with type 1 Diabetes Mellitus, pre-existing debilitating heart disease or heart failure, chronic kidney disease, chronic lung disease, and malignancy were all excluded from this study.

This study was carried out following approval from the ethical committee of PEMH Rawalpindi (ser # A/28/EC 394/2022). A total of 58 patients were selected in the study. Participants with stable HF who were using at least one anti-diabetic drug other than SGLT2 inhibitors began dapagliflozin at a dose of 5 mg per day after completing baseline investigations and a 2-dimensional echocardiogram. To compare the effect of DAPA on EF, 10 individuals with the same disease and cardiac status were taken as controls after informed consent and follow-up after starting DAPA, keeping the other parameters constant. Following the beginning of Dapagliflozin administration in 58 subjects, other medications were kept unchanged for glycemic control. Blood tests and physical examinations were conducted at the initial stage, as well as after 3 months and 6 months of Dapagliflozin treatment. 2D echo was done at baseline and at 6 months. Patients were followed for 3 months of Dapagliflozin treatment, and glycemic control was assessed. The daily dosage was doubled, from 5mg to 10 mg, if the patient's HbA1c hadn't decreased after 3 months of dapagliflozin treatment. Patients were followed for 6 months, and a 2D echo was done after 6 months of dapagliflozin treatment. Ejection fraction improvement was determined by the ratio of mitral inflow E to mitral e' annulus velocities (E/e'), LV mass index, and left atrial volume index. Pro-BNP and 2-D Echo were also considered. Data was analyzed by using Statistical Package for Social Sciences (SPSS) 23.00. Normality of data was checked by using Kolmogorov-Smirnov test. e' and A (cm/s) were normally distributed and represented by Mean±SD while LV end-diastolic volume, LV end-systolic volume, LVEF, LVMI, LAVI, E/e', E and E/Awere not distributed normally and were represented using median (IQR). Qualitative data was represented by using percentage and frequency. Paired samples t-test (for normally distributed quantitative data) and wilcoxon rank test (for non normally distributed quantitative data) were applied and *p*-value of ≤0.05 was considered as statistically significan.

RESULTS

A total of 58 patients with type 2 DM with stable HF were selected and included in the study after informed consent. The ratio of the mitral inflow E to the mitral e' annulus velocities (E/e'), the LV mass index, and the left atrial volume index were the parameters used to determine whether or not there was an improvement in ejection fraction. Other factors that were included were Pro-BNP levels and 2-D Echo measures.

A total of 53 patients with type 2 DM aged 30 to 60 years completed the study, with a mean age of 46.96 +/- 9.07 years. Out of 53 individuals, 32(60.4%) were male, and 21(39.6%) were female. The duration of DM was also inquired, which showed that 23(43.4%) patients had DM for more than 5 years, while 22(41.5%) had DM for 3 - 5 years, and only 8(15.1%) of study group individuals had DM for less than 3 years. Comorbid conditions along with the primary disease of DM were noted, which turned out to be Cardiovascular disease in most patients, 20(37.7%), followed by Dyslipidemia in 13(24.5%) patients. Other comorbid conditions were also noted in 8 (15.1%) patients i.e Osteoarthritis, Hepatitis B or C, IBD whereas 12(22.6%) had no other comorbid disease other than DM.

HbA1c was noted at the start of the study before starting patients on dapagliflozin, which showed that 16(30.2%) patients had HbA1c < 8.5 % and 37 (69.8%) had HbA1c between 8.5- 11.0%, which showed improvement after 6 months of treatment with dapagliflozin along with other oral hypoglycemic drugs. After 6 months, 30(56.6%) had HbA1c < 8.5 % and 20(37.7%) had HbA1c between 8.6- 9.5%, and a few, 3(5.7%) still had HbA1c in range of 9.6 - 11.0%. (Table-I)

Baseline 2-D echo before starting dapagliflozin showed that 35(66.0%) had heart failure with preserved ejection fraction (HFpEF) of 50-55%, and the remaining 18(34.0%) had mid-range ejection fraction (HFmrEF), out of which 11(72.2%) had EF 45-49% and 7(27.8%) had EF of 40-45%. Repeat 2-D Echo was done after 6 months treatment of Dapagliflozin which showed improvement in EF as out of total 53 subjects, 23(43.4%) had EF of 60%, 26(49.1%) had EF 50-55%, few patiients didn't show marked improvement in EF as 3(5.7%) had EF in range of 45 - 49 % and 1 () had EF 40-44% and EF of 3 () patients was decreased < 40% which were due to non-complaint with medication and dietary advice as evident by the history and increase in HbA1c levels done at 6 month of study.

Table-I: Clinical Characteristics of Study Participants (n = 53)

	Variable		Result n (%)
1	DM Duration	1 - 3 years	8 (15.1%)
		3 - 5 years	22 (41.5%)
		> 5 years	23 (43.4%)
2	HbA1c	7.0 - 8.5 %	16 (30.2%)
		8.6 - 9.5 %	13 (24.5%)
		9.6 - 11.0 %	8 (15.1%)
3	Comorbid	Cardiovascular Disease	20 (37.7%)
		Dyslipidemia	13 (24.5%)
		Misc	8 (15.1%)
		None	12 (22.6%)
4	HF	HFpEF (EF 50 - 55%)	35 (66.0%)
		HFmrEF (EF 40 - 49%	18 (34.0%)

**DM = Diabetes Mellitus, HF = Heart failure,*
Heart Failure with mid-ranged ejection fraction = HFmrEF,,
HFpEF = Heart Failure with Preserved Ejection Fraction,
EF = Ejection Fraction,
HbA1c = glycated or glycosylated hemoglobin

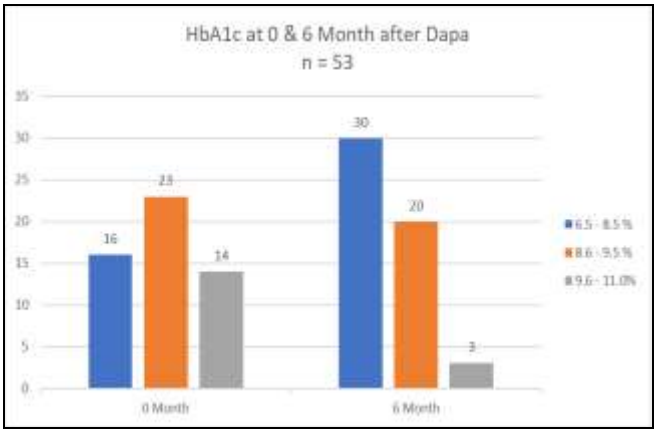


Figure-1: Distribution of HbA1c levels at baseline and six months after dapagliflozin (DAPA) therapy (n = 53)

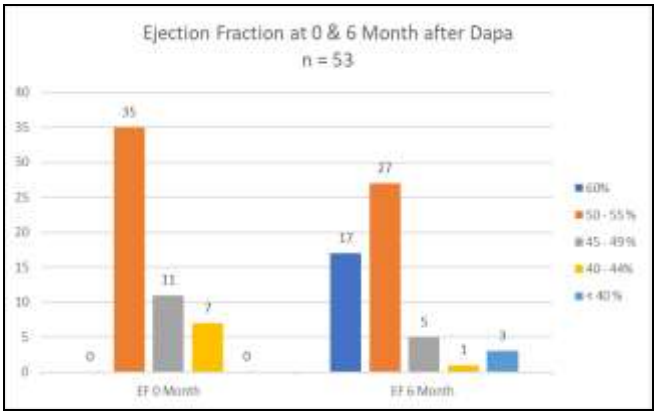


Figure-2: Comparison of Ejection Fraction after DAPA (n=53)

Table-II: Echocardiographic parameters

Variables	Baseline	6month	*p*-value
LV end-diastolic volume (ml)	74.2 (55.1–104.1)	68.5 (54.8–93.8)	0.27
LV end-systolic volume (ml)	24.7 (17.0–54.5)	20.5 (15.2–57.1)	0.105
LVEF (%)	62.3 (49.3–68.3)	63.6 (55.3–71.0)	0.011
LVMI (g/m2)	75.0 (61.7–92.0)	67.0 (55.0–81.9)	< 0.001
LAVI (mL/m2)	31.0 (23.0–45.0)	26.0 (21.0–32.0)	0.001
e' (cm/s)	6.36±1.73	6.82±1.88	0.031
E/e'	9.3 (7.7–11.8)	8.5 (6.6–10.7)	0.02
E (cm/s)	58.1 (46.8–70.9	55.1 (45.3–73.7)	0.682
A (cm/s)	76.1±17.8	75.6±16.8	0.765
E/A	0.71 (0.6–0.80)	0.70 (0.62–0.81)	0.818

**LV = Left Ventricular,*
EF = Ejection Fraction, LVMI stands for Left Ventricular Mass Index,
LAVI = Left Atrial Volume Index, E/A = early to atrial filling velocity ratio;
E/e' = early mitral inflow velocity to early diastolic mitral annulus velocity ratio

DISCUSSION

The study highlighted the role Of Dapagliflozin (DAPA) In Improvement Of Ejection Fraction In Non-Insulin-Dependent Diabetic Patients. After six months of Dapagliflozin medication, Type 2 Diabetes Mellitus patients with stable Heart Failure showed a significant improvement in Left Ventricular Diastolic Function, as evaluated by E/e' measured improvement. After six months of dapagliflozin treatment, LAVI and LVMI improved significantly. BNP levels dropped significantly in Type 2 Diabetes Mellitus (T2DM) individuals with BNP levels below 100 pg/mL. The study recruited type 2 diabetics and stable heart failure patients from five Japanese medical facilities. This study examined how the SGLT2 inhibitor dapagliflozin affected left ventricular diastolic function. The study examined type 2 diabetes and heart failure (HF) patients' longitudinal myocardial function after SGLT2 inhibitor treatment. Echocardiography was done before and six months after dapagliflozin medication.

LV diastolic function was assessed using the E/e′ ratio, which is the ratio of mitral inflow E to mitral e′ annular velocities. Mitral inflow E divided by mitral e′ annular velocities yielded this ratio. Global longitudinal strain (GLS),[12] which requires the estimation of the mean peak longitudinal strain from standard LV apical images, assessed LV longitudinal myocardial function as shown by Martens *et al.*[13]

Heart failure (HF) is a complicated disease that affects ventricular filling and blood ejection. It is a leading US killer. Hypertension, obesity, and type 2 diabetes are more likely to co-occur in older adults as reported by Mc Murray *et al.*[14] Nassif *et al*., reported that Type 2 Diabetes Mellitus (T2DM) is associated with increased interstitial fibrosis, left ventricular (LV) wall thickness, and LV mass.[15] These factors affect heart function. 75% of normal blood pressure patients have left ventricular diastolic dysfunction. Left ventricular hypertrophy and LV diastolic dysfunction are common in the early stages of myocardial dysfunction in type 2 diabetes mellitus, even when LVEF is preserved as reported by Packer *et al*.[16] Type 2 diabetes enlarges the left ventricle. Symptomatic heart failure is characterized by microvascular compliance alterations, left ventricular hypertrophy, and cardiac performance decline. Sano *et al.,* reported that comorbidities like hypertension, coronary artery disease, microvascular changes, and overweight or obesity can indicate the likelihood of developing advanced type 2 diabetes mellitus (T2DM) over time. These factors indicate progression.[17]

Left ventricular diastolic dysfunction causes heart failure with preserved ejection fraction (HFpEF) and heart failure with decreased ejection fraction (HFrEF), making its assessment crucial to diagnosing either of these disorders.8 Left ventricular diastolic dysfunction has been linked to poor outcomes in patients with heart failure with reduced, preserved, or mid-range ejection fraction (HFrEF, HFpEF, or HFmrEF). SGLT2 inhibitors have been proven to lower blood pressure, weight, and HbA1c.[4] Thus, these drugs can significantly affect left ventricular function. Thus, SGLT2 inhibitors may improve left ventricular diastolic performance in type 2 diabetics.18 Zinman *et al*., suggested that SGLT2 inhibitors improve heart performance. Endothelial dysfunction, aortic stiffness, epicardial fat storage, and visceral adipocyte hypertrophy are ameliorated. The above changes increase LV diastolic chamber performance.[19] According to Lowie *et al*., short-term empagliflozin or canagliflozin treatment enhanced left ventricular diastolic function by lowering left ventricular mass index and improving E/e′.[11]

LIMITATION OF STUDY

The study had several limitations, including a limited sample size and no placebo control group to evaluate findings. These constraints suggest longer prospective studies with larger participant pools and placebo control groups to confirm results. Prospective investigations are best.

CONCLUSION

The SGLT2 inhibitor dapagliflozin improves left ventricular diastolic performance in type 2 diabetics with stable heart failure. The findings offer a new approach to treating Type 2 Diabetes Mellitus patients with heart failure.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SFUH & IMJ: Data acquisition, data analysis, critical review, approval of the final version to be published.

MZH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

5 & 6: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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