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Original Article

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Role of SGLT2 inhibitors in improving cardiac functions (on Echocardiography) in patients having Diabetes Mellitus and ischemic heart disease

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ABSTRACT

BACKGROUND & OBJECTIVE: Sodium-glucose cotransporter-2 inhibitors (SGLT2i or SGLT2 inhibitors) have a distinctive mechanism of action unrelated to insulin secretion or action. By causing glucosuria, they reduce plasma glucose by inhibiting SGLT2 in the proximal tubules of the kidneys. This mechanism of action corrects several metabolic abnormalities, which are, in fact, CVD risks in addition to normoglycemia. This study was conducted to assess the average change in ejection fraction resulting from the use of SGLT2 inhibitors in enhancing cardiac function in patients with Diabetes Mellitus and ischemic heart disease.

METHODOLOGY: This is a descriptive case series conducted from 10th December 2022 to 9th May 2023 in the Department of Medicine, Faisalabad Medical University; 435 type II diabetes mellitus patients were selected, according to inclusion and exclusion criteria. All received a daily dose of 20 mg of SGLT2 for three months. Echocardiography was done before and after the treatment period left ventricular ejection fraction (EF) was evaluated, and improvement in cardiac function was noted.

RESULTS: In this study, the mean age of participants was 46.54±8.52 years. 314 (72.18%), or the majority, were between 30 and 50. The male-to-female ratio was 1.1:1, with 228 (52.41%) men and 207 (47.59%) women. The mean ejection fraction at baseline was 53.45 ± 4.12. The mean change in ejection fraction of SGLT2 inhibitors in improving cardiac functions among patients having Diabetes Mellitus and ischemic heart disease was 50.79 ± 3.76. (p-value ≤0.001).

CONCLUSION: SGLT2 inhibitors effectively improve cardiac functions among patients with Diabetes Mellitus type II and ischemic heart insult.

KEYWORDS: Type 2 diabetes, SGLT2 inhibitors, Cardiac function.

INTRODUCTION

Diabetes mellitus (DM) can be divided broadly into three types: diabetes Mellitus type I, also known as the on which is insulin-dependent or juvenile diabetes; diabetes Mellitus type 2, also called adult-onset diabetes; and the last third type, also known as pregnancy-induced diabetes mellitus, where expecting women without prior history of diabetes acquire high blood sugar levels during this specific period [1,2]. Worldwide, the prevalence of diabetic mellitus (DM) has risen to epidemic levels [1]. 20% of adults over 60 have type 2 diabetes, and the majority of cases are discovered after the age of 40. Diabetes mellitus type 2 (T2DM) is a chronic metabolic condition that affects people worldwide and has become a grave issue for health, particularly in Asia [1].

Pakistan is ranked second out of 21 nations in the Middle East and North Africa (MENA) region for the occurrence of total patients of diabetes mellitus, with 7.5 million cases (20-79 years old), and 18th out of 21 for the prevalence of diabetes (20-79 years old), at 6.9%. According to the NDSP-II (National Static Development Plan) 2016–17, there are approximately 27.4 million patients with diabetes mellitus in Pakistan (aged 20 or older). On the other hand, Pakistan may have 13.8 million adult cases of diabetes (aged 20 years or older), according to the pooled prevalence of diabetes at

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13.7%. Almost half of the cases were evaluated using the National Strategic Development Plan-II. However, around 17.1 million people aged 20 and above have diabetes, with a prevalence rate of 16.98%, according to the Diabetes Prevalence Survey (DPS-PAK) 2017. These pooled cases are twice as many as those reported by the IDF.

Worldwide, the prevalence of diabetes is springing up at a disconcerting rate. By 2045, it is anticipated that 629 million adults between the ages of 20 and 79 will have diabetes. Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes [3]. For people with type 2 diabetes (T2D), cardiovascular disease (CVD) is the main cause of morbidity and mortality, and diabetes increases the risk of CVD by 2-4-fold. To improve glycaemic management, a glucose-lowering drug (GLM) should also positively affect weight, blood pressure, dyslipidaemia, and cardiovascular and renal outcomes [4].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors act in a distinct manner that does not fosterling on insulin secretion or action.. Via causing glucosuria, they reduce plasma glucose via inhibiting SGLT2 in the proximal tubule of the kidney. This particular action method corrects several irregularities related to metabolism and hemodynamic that are also CVD risks in addition to reducing plasma glucose [5]. The substantial decrease in HF hospitalizations in patients without a history of HF at baseline, which has consistently been demonstrated in all Cardiovascular outcome trials (CVOTs), is the favorable CV benefit of SGLT2i that is most clinically important [6].

In T2DM patients with the complication of CVD, SGLT2 inhibitors significantly reduced adverse cardiovascular events, death, and hospitalizations for HF (Heart Failure) during treatment with canagliflozin, empagliflozin, and dapagliflozin [7], according to several cardiovascular studies, including the DAPA-HF trial [8] and the EMPEROR-Reduced trial [9].

According to prospective research, Dapagliflozin medication enhanced Characteristics of left ventricular (LV) diastolic function in patients with diabetes Mellitus type II and HF. Higashikawa et al. shepherd a study to appraise the effect of the impact of SGLT2 inhibitors on patients' CVD symptoms who have diabetes mellitus type II and heart disease. The results showed a decrease in mean Ejection Fraction from 64.5 ± 8.9 at the baseline to 62.3 ± 10.6 after one month. Mean E/A decreases from 0.69 ± 0.32 baseline to 0.60 ± 0.18 after one month. The maximal Caliber of the inferior vena cava decreased from 13.7 ± 3.5 at the baseline to 13.5 ± 3.7 after one month [10].

Attention has been focused on SGLT2 inhibitors, which benefit cardiovascular outcomes in T2DM patients. However, little is known about how SGLT2 inhibitors affect heart failure patients with T2DM who have left ventricular diastolic dysfunction, particularly in the Asian Population in their habitat. To decrease morbidity in individuals with T2DM and ischemic heart disease, evaluating how the SGLT2 inhibitors affect cardiac function is essential. The study's goal was: "To access the average change in the ejection fraction due to SGLT2i in improving cardiac function among patients with Diabetes Mellitus and ischemic heart disease".

OPERATIONAL DEFINITIONS:

Type II diabetes mellitus: According to American Diabetes Association (ADA) guidelines, it was labeled by fasting blood glucose more than 126 mg/dL and blood glucose level at 2 hours post prandial more than 200 mg/dL.

Heart Failure: Patients having a history of preserved LV ejection fraction <50% on Echocardiography along with the symptoms of lung congestion like breathlessness, coughing, tachypnea, and dyspnea.

Improved Cardiac: Functions improved cardiac function in mean change in Ejection fraction from baseline to 3 months after treatment with SGLT2 inhibitors.

METHODOLOGY

This is a description case-study series conducted in the Medical Department, Faisalabad Medical University, and affiliated Allied Hospital, Faisalabad, from Dec 10, 2022, to May 9, 2023. The size of the sample is 435 cases, figured out utilizing the calculating sample size for WHO at 95% Confidence level, absolute=1% precision, and taking mean EF 64.5 ± 8.9 at baseline and 62.3 ± 10.6 after one month of SGLT-2 [3] in patients having diabetes and IHD. The sampling technique used was Consecutive, non-probability sampling.

Inclusion Requirements of the studies were age 30-75 years of both Ganders with T2DM and a previous history of CVD, with a documented ejection fraction, echocardiographic evidence, less than 50%. Exclusion Criteria were patients already taking an SGLT2 inhibitor or a history of any type 1 diabetes, renal or serious liver disease, diabetic ketoacidosis, or the existence of malignancy.

Patients who met the inclusion criteria were selected with the approval of the ethical review committee, as indicated by the letter number F.24ERC/FMU/2021-22. Each patient provided informed consent after being informed about the study's procedures, the measures taken to ensure their anonymity, and the assurance that participation would pose no risk to them. A thorough medical history was gathered. Blood pressure, body weight (BW), and body mass index (BMI) were acquired as clinical data at baseline and three months of an echocardiography test. For three months, a single 20 mg dose of SGLT2 was given to each patient. Before and after therapy, all patients received transthoracic echocardiographic examinations using the tools at hand. Three months after treatment, the patient's Left Ventricular Ejection Fraction (EF) was evaluated to see whether cardiac function had improved. All the data was captured on a proforma that was specially created.

SPSS version 25 was used to enter and analyze all of the data. Age, BMI, SBP, DBP, and EF are quantitative variables for determining the means and standard deviations. For qualitative factors, including gender, glycaemic control, and cardiac output, frequency and percentage were determined.

Effect modifiers such as age, gender, BMI (weight in kg/ height in meters), and glycaemic control were controlled by stratification of data. Post-stratification Independent sample and paired t-test were used. A p-value <0.05 is regarded as statistically significant.

RESULTS

The study's participants ranged in age from 30 to 75, with a mean age of 46.54 ± 8.52 years. The majority of the patients, i.e., 314 (72.18%), were between 30 to 50 years of age, 228 (52.41%) were male, and 207 (47.59%) were females, with male to female ratio of 1.1:1. Mean HbA1c levels were 7.31 ± 3.27 (%).

The mean BMI was 29.03 ± 3.81 kg/m2, as shown in Table I. The mean ejection fraction at baseline was 53.45 ± 4.12. The mean change in ejection fraction of SGLT2 inhibitors in improving cardiac functions among patients having Diabetes Mellitus and ischemic heart disease was 50.79 ± 3.76 (Table II). Stratification of gender, HbAIc, and BMI is shown in Table -III.

Table-I:Distribution of patients according to Age, (n=435).

Variable	Categories	No. of the Patients n(%)	Mean ± SD
Age	30-50	314(72.18)	46.54 ± 8.52
	51-75	121(27.82)	
Gender	Male	228(52.41)	-
	Female	207(47.59)	
HbA1C	≤6.5	314(72.18)	7.31 ± 3.27
	>6.5	121(27.28)	
BMI	≤ 27	183(42.07)	29.03 ± 3.81
	> 27	252(57.93)	

Table-II:Average change in ejection fraction with SGLT2 inhibitors in enhancing cardiac function in patients with Diabetes Mellitus and ischemic heart disease. (n=435).

Ejection fraction	Mean±SD	p-value
Baseline	53.45±4.12	<0.0001
After 3 months of treatment	50.79±3.76	

* **p-value calculated using Paired t-test**

Table-III:Stratification of change in ejection fraction concerning gender, HbA1c & BMI (n=435).

Variable	Categories	Change in Ejection Fraction Mean + SD	P-value
Gender	Male	51.43 + 3.56	<0.001
	Female	50.09 + 3.85	
HbA1C	≤6.5	50.74+3.78	0.638
	>6.5	50.93+3.73	
BMI	≤ 27	50.68+3.82	0.603
	> 27	50.87± 3.72	

DISCUSSION

Recent large randomized controlled studies have shown that SGLT2 inhibitors enhance cardiometabolic effects Despite having diabetes, there are risks associated with overall mortality, cardiovascular death, and hospitalization for heart failure (HHF) [11,12]. Initially, in people with diabetes mellitus type II, SGLT2 inhibitors showed a considerable reduction in poor cardiovascular events and admission to the hospital for worsening of heart failure. With a few theories explaining the precise mechanisms of their activities, it has since been demonstrated that the extent of their impact may be theoretically independent—or, at least, separated—from their glucose-lowering value [4].

Further studies are being conducted to examine their potential effects on cardiovascular events and mortality in larger cohorts, not just diabetic individuals, due to the quick accumulation of such good evidence. There was a sizable randomized controlled study that included individuals with and without diabetes that examined the effects of SGLT2 inhibitors on heart failure patients in response to this [13].

This research was done to ascertain the mean change in ejection fraction of SGLT2 inhibitors in improving cardiac functions among patients having Diabetes Mellitus type II and ischemic cardiovascular disease. Ages in this study ranged from 30 to 75 years, with a mean age of 46.54 ± 8.52 years. Nearly all of the patients, i.e., 314 (72.18%), were between 30 to 50 years of age. Of these 435 patients, 228 (52.41%) were male, and 207 (47.59%) were females, with a male-to-female ratio of 1.1:1.

Mean ejection fraction at baseline was 53.45 ± 4.12%. The mean change in ejection fraction of SGLT2 inhibitors in improving cardiac functions among patients having Diabetes Mellitus and ischemic heart disease was 50.79 ± 3.76%. Higashikawa et al. conducted a study to evaluate the effect of SGLT2 inhibitors on CVD function in diabetic mellitus type 2 patients and HD. The results showed a lessen in mean Ejection Fraction from 64.5 ± 8.9 at the baseline to 62.3 ± 10.6 after one month. Mean E/A decreases from 0.69 ± 0.32 baseline to 0.60 ± 0.18 after one month. The

maximal caliber of the inferior vena cava fell from 13.7 ±3.5 at baseline to 13.5 ± 3.7 after one month [10].

Clinical trials that have recently been published have confirmed the glucose-independent advantages of SGLT2i. For example, the DAPA-HF trial found that dapagliflozin use decreased the composition of worsening heart failure (HF) or death due to cardiovascular reasons to 27% in Heart Failure and Reduced Ejection Fraction (HFrEF) patients, with no difference in outcomes between those with and without diabetes [13]. In addition, regardless matter whether diabetes is present, Clinically significant improvements in HF-related health status or natriuretic peptides in HF patients were noted in the DEFINE-HF study, which examined the effects of dapagliflozin on biomarkers, symptoms, and functional status in patients with heart failure and reduced ejection fraction [14].

As shown in different nondiabetic animal models, it is logical to infer that the CV advantages of SGLT2i would be self-sustaining of its action to reduce blood sugar. Nondiabetic mice subjected to pressure overload were studied by Byrne et al. The LV systolic function was maintained after the 2-week empagliflozin treatment and was sustained ex vivo without ketones or hemodynamic abnormalities[15]. Empagliflozin reduced the size of the LV cavity, slowed cardiac fibrosis, and enhanced LV systolic performance in a rat model of heart failure due to hypertension[16]. Recently, Zhang et al. treated a pig model of HFpEF with dapagliflozin and found that it decreased blood pressure, inhibited left ventricular concentric remodeling, and reduced macrovascularinflammatory response from hypertensio [17].

The only study examining SGLT2's impact solely in non-diabetic patients is EMPA-TROPISM [18]. Its 84 participants demonstrated that, as compared to a placebo, empagliflozin significantly improved LV function, remodeling, and quality of life. In contrast, the study named EMPIRE-HF, which involved 190 patients with or without diabetes, found no significant variations between empagliflozin and placebo three months after the start of the treatment in any of the endpoints examined (NT-Pro BNP, activity level, and quality of life and symptom relief) [19].

Even though this RCT did not use any imaging to examine LV function or volume, it is noteworthy because the follow-up time was proportionally brief (3 months), setting it apart from the other trials. Except for the very short follow-up period, the participants in this experiment were patients with a milder heart failure phenotype, had higher baseline status and functional capacity, and had lower baseline NT-pro BNP levels [19].

In some investigations, LV function was evaluated by Echocardiography, and in others, CMR. It was found from the echocardiographic tests that SGLT2 inhibitors did improve diastolic function. Twelve patients with advanced/drug-resistant heart failure were included in the third research, although most patients in the other two studies [20] had HF with intact ejection fraction. The ratio of early mitral inflow velocity to early diastolic velocity in the mitral annulus (E/e) ratio improved even in this small group of patients with progressing illnesses. However, this improvement fell short of statistical significance (p-value: 0.06).

One may claim that SGLT2 promotes myocardial remodeling and increased LV sizes based on research that used CMR; however, the findings are mixed. More precisely, in three RCTs called SUGAR-DM-HF, EMPA-TROPISM, and REFORM [21], the LV end-diastolic volume (LVEDV) was evaluated by CMR. The studies SUGAR-DM-HF and EMPA-TROPISM involved 189 patients and showed that the LVEDV significantly improved in the SGLT2 arm was set side by side with the placebo [16]. Surprisingly, this beneficial effect was observed in the nondiabetic cohort that was also part of the EMPA-TROPISM research. After a 12-month follow-up, the researchers of the REFORM study, which involved 56 patients overall, found no appreciable variations in LV volumes between the SGLT2 and placebo groups [21]. It should be highlighted that the patient cohort was made up of people with diabetes who were taking low dosages of loop diuretics and had minor HF symptoms. However, the SGLT2 group in the same trial showed a considerable decrease in the need for diuretics.

The data for BNP/NT-PRO BNP is mixed, with some trials finding improvement[20] and others showing no appreciable differences between the two groups [6]. This could be explained by the variations in the participant's baseline characteristics and the various follow-up times and study methodologies. Large RCTs from the past have demonstrated SGLT2's impressive advantages, particularly in cardiovascular outcomes in the diabetic population[22].These findings highlighted one or more potential previously unknown cardioprotective mechanisms of SGLT2 inhibitors, which set them apart from other oral diabetes drugs. Interestingly, SGLT2 inhibitors' influence on cardiovascular outcomes does not appear to directly result from how well they lower blood sugar. The emphasis has switched to using these medicines for patients regardless of their baseline diabetes status.

There is mounting evidence that the cardioprotective mechanisms are unrelated to glycemic management. Previous research examining the impact of SGLT2 inhibitors in nondiabetic groups has produced promising findings [8]. The most recent recommendations for treating patients with heart failure now include these medicines due to the rapidly mounting evidence of their significant positive impact on risk reduction for cardiovascular death and heart failure hospitalization . Notably, Now recommended in symptomatic individuals with HF and decreased EF on optimal treatment are dapagliflozin and empagliflozin, independent of the presence of diabetes, in light of the)findings of the DAPA-HF and EMPEROR-Reduced studies[13].

CONCLUSION

This study concluded that the SGLT2 inhibitors when used in people with ischemic heart disease and diabetes mellitus, improved cardiac functioning. Therefore, we advise using SGLT2 inhibitors in people with ischemic heart disease and diabetes mellitus to improve cardiac functions and reduce the morbidity and mortality of this particular set of patients.

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Muhammad Owais Fazal: Substantial contributions to the conception and design of the work.
Ghulam Abbas Tahir: The acquisition of data for the work.
Yasir Yaqoob: Analysis and interpretation of data for the work.
Usman Musharaf: Drafting the work .
Abdul Wahid: Reviewing it critically for important intellectual content.
Ayesha Izat: Final approval of the version to be published.