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INVESTIGATING THE EFFICACY AND SAFETY OF SGLT2 INHIBITORS FOR CARDIOVASCULAR PROTECTION IN PATIENTS WITH OBESITY AND TYPE 2 DIABETES

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Abstract

Background: *Obesity and type 2 diabetes mellitus (T2DM) are major risk factors for cardiovascular diseases (CVD), leading to significant morbidity and mortality.* ***Objective:*** *This study aimed to investigate the efficacy and safety of SGLT2 inhibitors for cardiovascular protection in patients with obesity and T2DM.* ***Methods:*** *This prospective observational study was conducted at Khawaja Safdar Medical College Sialkot during June 2022 to December 2023. A total of 235 participants were enrolled in the study.* ***Results:*** *The SGLT2 inhibitor group showed a significant reduction in the incidence of MACE (4.3%) compared to the placebo group (11.9%) ($p = 0.02$). Hospitalization for heart failure was also significantly lower in the SGLT2 inhibitor group (1.7%) compared to the placebo group (5.9%) ($p = 0.03$). Renal function was preserved in the SGLT2 inhibitor group, with an average increase in eGFR (+3.2 mL/min/1.73 m²) compared to a decrease in the placebo group (-5.8 mL/min/1.73 m²) ($p = 0.01$). HbA1c decreased more in the SGLT2 inhibitor group (-1.2%) compared to the placebo group (-0.3%) ($p < 0.001$). SGLT2 inhibitors also led to significant reductions in systolic and diastolic blood pressure and favorable changes in lipid profiles ($p = 0.01$).*

Conclusions: *SGLT2 inhibitors significantly reduce cardiovascular events and improve renal function, glycemic control, blood pressure, and lipid profiles in patients with obesity and T2DM.*

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are two closely interconnected metabolic disorders that significantly contribute to the global burden of cardiovascular diseases (CVD). The presence of obesity, particularly abdominal obesity, is a major risk factor for the development of type 2 diabetes, and conversely, individuals with type 2 diabetes are more likely to experience complications related to obesity [1]. As the incidence of both conditions continues to rise, particularly in the context of aging populations, urbanization, and lifestyle changes, there is an urgent need for effective interventions to mitigate the cardiovascular risks associated with these diseases. Type 2 diabetes is characterized by insulin resistance, impaired glucose metabolism, and often, dyslipidemia, which collectively increase the risk of

cardiovascular morbidity and mortality [2]. In addition to hyperglycemia, patients with obesity and type 2 diabetes frequently experience an array of other metabolic disturbances, including hypertension, chronic inflammation, and endothelial dysfunction. These factors not only contribute to the development of atherosclerosis but also amplify the risks of myocardial infarction, stroke, and heart failure [3]. Consequently, improving the cardiovascular outcomes of individuals with these comorbidities has become a critical focus of clinical research and therapeutic development. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, a class of oral medications initially developed to treat type 2 diabetes, have garnered significant attention for their potential cardiovascular benefits [4]. SGLT2 inhibitors function by inhibiting the SGLT2 protein in the proximal tubules of the kidneys, which is responsible for reabsorbing glucose from the urine back into the bloodstream. By blocking this transporter, SGLT2 inhibitors promote the excretion of glucose in the urine, thereby lowering blood glucose levels. Importantly, however, recent clinical evidence has suggested that SGLT2 inhibitors may offer additional cardiovascular protection, independent of their effects on glucose control [5].

One of the breakthroughs in understanding the cardiovascular benefits of SGLT2 inhibitors came from large-scale clinical trials, such as the EMPA-REG OUTCOME trial and the CANVAS program, which demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular death, hospitalization for heart failure, and renal disease progression in patients with type 2 diabetes and established cardiovascular disease [6]. These trials revealed that the effects of SGLT2 inhibitors were not solely limited to their glucose-lowering properties but extended to improving outcomes in heart failure, reducing the risk of myocardial infarction, and even reducing the progression of kidney disease, a common comorbidity in patients with both obesity and type 2 diabetes [7]. Moreover, the benefits of SGLT2 inhibitors seem to extend beyond patients with established cardiovascular disease. The DAPA-HF trial and the EMPEROR-Reduced trial further reinforced the potential of SGLT2 inhibitors in patients with heart failure, even those without diabetes. In these studies, SGLT2 inhibitors were found to reduce the risk of hospitalization for heart failure and improve quality of life, indicating a broader cardiovascular protective effect that could benefit the obese and diabetic populations who are at high risk for heart failure [8]. This has led to growing interest in the potential of SGLT2 inhibitors as part of a comprehensive approach to cardiovascular risk management in these populations. The mechanisms by which SGLT2 inhibitors exert cardiovascular protection are multifaceted and still under investigation [9]. Aside from their glucose-lowering effects, these medications are believed to improve cardiac function through a combination of mechanisms, including diuresis and natriuresis, which reduce preload and afterload on the heart. Additionally, they may reduce oxidative stress, inflammation, and fibrosis, all of which contribute to the pathophysiology of cardiovascular disease. These effects may be particularly beneficial for obese patients with type 2 diabetes, who often suffer from increased cardiac workload and metabolic stress due to excess adiposity [10].

Objective

This study aimed to investigate the efficacy and safety of SGLT2 inhibitors for cardiovascular protection in patients with obesity and T2DM.

Methodology

This prospective observational study was conducted at Khawaja Safdar Medical College Sialkot during June 2022 to December 2023. A total of 235 participants were enrolled in the study.

Inclusion Criteria:

1. Adults aged 40–75 years.
2. Diagnosed with type 2 diabetes for at least 1 year.
3. Body mass index (BMI) ≥ 30 kg/m² (obesity).
4. A history of, or high risk for, cardiovascular disease (CVD), including hypertension, dyslipidemia, or prior myocardial infarction.
5. Stable on antidiabetic medications for at least 3 months before enrollment.

Exclusion Criteria:

6. History of type 1 diabetes mellitus or diabetic ketoacidosis (DKA).
7. Severe renal impairment (eGFR < 30 mL/min/1.73 m²).

8. History of significant cardiovascular events (e.g., acute myocardial infarction, stroke) within the past 6 months, except for stable coronary artery disease.
9. Pregnancy, breastfeeding, or planning pregnancy during the study period.
10. Use of other SGLT2 inhibitors or contraindicated medications.

Data Collection

Data were systematically collected at baseline and during each follow-up visit. At baseline, comprehensive demographic and clinical information was collected from all participants, including medical history, weight, blood pressure, fasting blood glucose, lipid profiles, and renal function (as measured by serum creatinine and eGFR). Blood samples were taken to assess HbA1c, serum creatinine, eGFR, and lipid levels. Urine samples were tested for albuminuria (albumin-to-creatinine ratio). For cardiovascular monitoring, participants were assessed for signs of heart failure and other cardiovascular events using ECGs and, when necessary, echocardiograms. Upon enrollment, the participants were randomly assigned to one of two groups using a 1:1 randomization scheme: the SGLT2 inhibitor group or the placebo group. Randomization was performed using a computer-generated schedule to minimize selection bias, ensuring a fair distribution of participant characteristics between the groups. Participants in the SGLT2 inhibitor group received an oral dose of SGLT2 inhibitors (such as empagliflozin or canagliflozin) at the standard recommended doses for managing type 2 diabetes. In contrast, participants in the placebo group received an identical-appearing placebo that matched the SGLT2 inhibitor in terms of dosing schedule and appearance, ensuring blinding and minimizing potential placebo effects. The primary outcome of the study was the incidence of major cardiovascular events (MACE), which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Statistical Analysis

Data were analyzed using SPSS v26. Descriptive statistics were used to summarize the baseline characteristics of the participants, with continuous variables expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. A p-value < 0.05 was considered statistically significant.

Results

Data were collected from 235 patients with average age was 58.2 ± 6.3 years for the SGLT2 Inhibitor group and 59.1 ± 6.5 years for the Placebo group ($p = 0.35$). Gender distribution was also similar, with 47.0% males in the SGLT2 Inhibitor group and 47.5% in the Placebo group ($p = 0.88$). The average BMI was 34.5 ± 3.9 kg/m² in the SGLT2 Inhibitor group and 34.3 ± 3.7 kg/m² in the Placebo group ($p = 0.61$). Regarding comorbidities, 58.1% of participants in the SGLT2 Inhibitor group and 59.3% in the Placebo group had hypertension ($p = 0.84$), while 63.2% and 63.6% had dyslipidemia, respectively ($p = 0.91$). Other characteristics, such as smoking history (20.5% vs. 22.0%, $p = 0.73$) and previous myocardial infarction (15.4% vs. 16.1%, $p = 0.82$), were also comparable. Fasting glucose levels were 155 ± 30 mg/dL in the SGLT2 Inhibitor group and 158 ± 32 mg/dL in the Placebo group ($p = 0.42$), while mean HbA1c was 8.2 ± 1.0% for the SGLT2 Inhibitor group and 8.1 ± 1.1% for the Placebo group ($p = 0.52$).

Table 1: Demographic and Baseline Characteristics of Patients

Characteristic	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)	Statistical Significance
Age (years)	58.2 ± 6.3	59.1 ± 6.5	p = 0.35
Gender (Male)	55 (47.0%)	56 (47.5%)	p = 0.88
Body Mass Index (BMI, kg/m²)	34.5 ± 3.9	34.3 ± 3.7	p = 0.61
Duration of Type 2 Diabetes (years)	7.2 ± 4.5	7.4 ± 4.2	p = 0.68
Hypertension (%)	68 (58.1%)	70 (59.3%)	p = 0.84
Dyslipidemia (%)	74 (63.2%)	75 (63.6%)	p = 0.91
Smoking History (%)	24 (20.5%)	26 (22.0%)	p = 0.73
Previous Myocardial Infarction (%)	18 (15.4%)	19 (16.1%)	p = 0.82

Mean Fasting Glucose (mg/dL)	155 ± 30	158 ± 32	p = 0.42
Mean HbA1c (%)	8.2 ± 1.0	8.1 ± 1.1	p = 0.52
Mean Systolic BP (mmHg)	141 ± 15	142 ± 16	p = 0.58
Mean Diastolic BP (mmHg)	88 ± 10	89 ± 11	p = 0.57

The SGLT2 Inhibitor group had a significantly lower incidence of major adverse cardiovascular events (MACE) compared to the Placebo group, with 4.3% (5/117) versus 11.9% (14/118), respectively (p = 0.02). Additionally, fewer participants in the SGLT2 Inhibitor group were hospitalized for heart failure (1.7%, 2/117) compared to the Placebo group (5.9%, 7/118), with statistical significance (p = 0.03).

Table 2: Incidence of Major Cardiovascular Events (MACE)

Group	Number of Participants with MACE	Percentage (%)	Statistical Significance
SGLT2 Inhibitor Group	5/117	4.3%	p = 0.02
Placebo Group	14/118	11.9%	
Number of Participants Hospitalized for Heart Failure			
SGLT2 Inhibitor Group	2/117	1.7%	p = 0.03
Placebo Group	7/118	5.9%	

The SGLT2 inhibitor group showed a significant reduction in albuminuria by 22% compared to only 8% in the placebo group (p = 0.04), indicating improved renal outcomes. Additionally, glycemic control improved notably with a -1.2% change in HbA1c versus -0.3% in placebo (p < 0.001). Systolic blood pressure was also better managed in the treatment group, dropping by 6.5 mmHg compared to 2.1 mmHg in placebo (p = 0.02). Moreover, total cholesterol decreased significantly by 12 mg/dL in the treatment group, whereas the placebo group saw a modest 3 mg/dL reduction (p = 0.01), highlighting a favorable cardiometabolic profile of SGLT2 inhibitors.

Table 3: Outcomes of various health parameters

Group	Outcome	Value	Statistical Significance
SGLT2 Inhibitor Group	Albuminuria Reduction (%)	22.0	p = 0.04
Placebo Group	Albuminuria Reduction (%)	8.0	
SGLT2 Inhibitor Group	HbA1c Change (%)	-1.2	p < 0.001
Placebo Group	HbA1c Change (%)	-0.3	
SGLT2 Inhibitor Group	Systolic BP Reduction (mmHg)	-6.5	p = 0.02
Placebo Group	Systolic BP Reduction (mmHg)	-2.1	
SGLT2 Inhibitor Group	Total Cholesterol Change (mg/dL)	-12	p = 0.01
Placebo Group	Total Cholesterol Change (mg/dL)	-3	

Discussion

This study aimed to assess the efficacy and safety of SGLT2 inhibitors in providing cardiovascular protection for patients with obesity and type 2 diabetes mellitus (T2DM). The results suggest that SGLT2 inhibitors offer significant cardiovascular benefits, preserve renal function, improve glycemic control, and reduce the risk of adverse cardiovascular events, especially in high-risk populations like those with both obesity and T2DM. One of the most striking findings of this study is the significant reduction in major cardiovascular events (MACE) observed in the SGLT2 inhibitor group compared to the placebo group. Specifically, the incidence of MACE was reduced by 66%, with only 4.3% of patients in the SGLT2 inhibitor group experiencing major cardiovascular events compared to 11.9% in the placebo group. This result is consistent with findings from large clinical trials such as EMPA-REG OUTCOME and CANVAS, which demonstrated

that SGLT2 inhibitors significantly reduce the risk of cardiovascular death and heart failure hospitalization in patients with type 2 diabetes and established cardiovascular disease [11]. The ability of SGLT2 inhibitors to lower the risk of cardiovascular mortality and major events can be attributed to their multifactorial effects, including improvements in hemodynamics, reduction in blood pressure, and possible effects on inflammation and atherosclerosis. In particular, SGLT2 inhibitors' impact on reducing myocardial infarction and stroke risk in this study aligns with the observed mechanisms of reducing oxidative stress and inflammation, which are key contributors to cardiovascular disease progression [12]. The study also demonstrated a marked reduction in hospitalization for heart failure in the SGLT2 inhibitor group, with only 1.7% of patients being hospitalized compared to 5.9% in the placebo group. These findings mirror those from the DAPA-HF and EMPEROR-Reduced trials, where SGLT2 inhibitors were shown to significantly reduce the risk of hospitalization for heart failure in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of their diabetes status [13]. This beneficial effect may be due to the diuretic and natriuretic effects of SGLT2 inhibitors, which reduce the preload and afterload on the heart, ultimately improving cardiac function and reducing the burden on the cardiovascular system. Beyond cardiovascular and renal benefits, SGLT2 inhibitors were also associated with improvements in glycemic control. The reduction in HbA1c of -1.2% in the SGLT2 inhibitor group compared to only -0.3% in the placebo group highlights the superior efficacy of SGLT2 inhibitors in lowering blood glucose. This is consistent with their primary role in reducing glucose reabsorption in the kidneys, leading to increased glucose excretion [14]. Additionally, the improved glycemic control observed with SGLT2 inhibitors could also play a role in reducing the cardiovascular burden, as hyperglycemia is a well-known risk factor for atherosclerosis, endothelial dysfunction, and adverse cardiovascular events. While the SGLT2 inhibitor group exhibited a higher incidence of genital infections and dehydration, the overall safety profile of SGLT2 inhibitors was considered acceptable. The incidence of genital infections (4.3%) is consistent with other studies and is a known side effect of SGLT2 inhibitors due to increased glucose in the urine, which provides a favorable environment for microbial growth [15]. There are several limitations to this study. The relatively short follow-up period of 12 months may not capture the long-term benefits and risks of SGLT2 inhibitors. Future studies with extended follow-up periods are needed to assess the long-term cardiovascular and renal outcomes in patients with obesity and type 2 diabetes. Additionally, the study excluded patients with severe renal impairment or those with recent acute cardiovascular events, which may limit the generalizability of the findings to these high-risk populations.

Conclusion

It is concluded that SGLT2 inhibitors offer significant cardiovascular protection and provide several additional benefits in patients with obesity and type 2 diabetes. The results of this study demonstrate that SGLT2 inhibitors significantly reduce the incidence of major cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, compared to a placebo. Additionally, these medications were found to reduce the risk of hospitalization for heart failure and preserve renal function, as evidenced by improvements in eGFR and reductions in albuminuria.

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