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RESEARCH ARTICLE
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EFFICACY AND SAFETY OF SODIUM-GLUCOSE CO-TRANSPORTER (SGLT2) INHIBITORS ON CARDIOVASCULAR AND RENAL OUTCOMES IN OBESE DIABETIC PATIENTS, A RETROSPECTIVE COHORT ANALYSIS

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ABSTRACT

Background Individuals with both obesity and type 2 diabetes mellitus (T2DM) face an elevated risk of developing cardiovascular and kidney-related complications. SGLT2 inhibitors, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has been found to have promising effects on cardiovascular health and renal function in this high-risk population. By inhibiting SGLT2, works to reduce glucose reabsorption in the kidneys which in turn can lead to improved glycemic control, weight loss and reduced blood pressure. These effects contribute to its beneficial impact on cardiovascular outcomes and kidney function, making it a valuable treatment option for individuals with obesity and T2DM who are at risk of these complications. **Objective:** This study aimed to assess the impact of SGLT2 inhibitors on cardiovascular and renal outcomes in patients with obesity and type 2 diabetes. **Methodology** The study involved 500 adults with obesity and type 2 diabetes who received SGLT2 inhibitors treatment for a minimum of 6 months. Data collected include demographic data, clinical information and treatment records. The primary focus was on changes in cardiovascular parameters and renal function, assessed at 1 week, 1 month, 3 months and 6 months after starting treatment. Secondary outcomes included hospitalization for heart failure, mortality rates and safety events. **Study place and duration** The study included electronic medical records of patients treated at Jinnah postgraduate medical centre between January 2022 to December 2024. **Results**: The study found that SGLT2 inhibitors therapy for 6 months led to significant reductions in blood pressure and body weight. Renal function improved, with increased eGFR and decreased serum creatinine levels. Glycated hemoglobin levels initially rose but later decreased. Albuminuria decreased modestly over time. **Conclusions** SGLT2 inhibitors shows promise in improving cardiovascular and renal outcomes in patients with obesity and type 2 diabetes, warranting further research to optimize its therapeutic potential and explore long-term benefits

INTRODUCTION

The growing prevalence of type 2 diabetes mellitus (T2DM) is a major global health issue, largely fueled by the increasing rates of obesity[1,2]. Globally, approximately 463 million people had diabetes in 2019, with projections indicating this number will rise to 700 million by 2045[3]. Type 2 diabetes accounts for most cases and, particularly when paired with obesity, significantly increases the risk of cardiovascular and kidney complications, leading to substantial illness and death[4]. Cardiovascular disease is the leading cause of mortality in people with type 2 diabetes, and chronic kidney disease also adds to the overall burden of the disease [5]. Conventional treatments for type 2 diabetes have mainly aimed at controlling blood sugar levels [6]. However, given the significant risks of cardiovascular and kidney complications associated with diabetes, there is a growing need for a more comprehensive approach that addresses these outcomes[7,8]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of medications that not only improve blood sugar control but also lower blood pressure, promote weight loss and reduce the risk of kidney problems and heart failure[9,10]. SGLT2 inhibitors has demonstrated benefits in reducing major cardiovascular events, including cardiovascular death, and slowing the progression of kidney disease in people with type 2 diabetes[11,12]. SGLT2 inhibitors provides substantial cardiovascular and kidney benefits regardless of body mass index (BMI) category. Real-world studies across diverse populations have confirmed the effectiveness and safety of SGLT2 inhibitors, with large-scale observational studies in various regions showing improved cardiovascular and kidney outcomes. These findings indicate that SGLT2 inhibitors may be especially beneficial for patients with obesity and type 2 diabetes who are at higher risk of cardiovascular and kidney complications[13-18]

This study aims to investigate the cardiovascular and renal benefits of SGLT2 inhibitors specifically in patients who have both obesity and type 2 diabetes mellitus (T2DM). By focusing on this patient population, the study seeks to provide valuable insights into the potential therapeutic effects of SGLT2 inhibitors on cardiovascular and kidney outcomes in this particular group. The research will contribute to the existing body of evidence on the efficacy and safety of SGLT2 inhibitors, offering a more nuanced understanding of its benefits in the context of obesity and T2DM .

METHODOLOGY

The study included electronic medical records of patients treated at Jinnah postgraduate medical centre between January 2022 and December 2024. The study collected demographic and medication data, including age, sex, BMI, duration of diabetes and smoking history, as well as information on SGLT2 inhibitors treatment duration with concomitant use of other medications like antihypertensive and lipid-lowering agents. Clinical data was collected at multiple time points, including baseline and follow-up measurements of key physiological parameters such as blood pressure, eGFR, serum creatinine, HbA1c, and proteinuria levels, assessed at 1 week, 1 month, 3 months, and 6 months after treatment commencement. The study's primary outcomes were changes in cardiovascular and renal function after SGLT2 inhibitors treatment. Cardiovascular outcomes included changes in blood pressure, HbA1c levels and major adverse cardiovascular events. Renal outcomes involved monitoring kidney function and the occurrence of end-stage renal disease. Secondary outcomes included weight loss, heart failure hospitalization rates and overall mortality. Safety outcomes involved tracking adverse events such as hypoglycemia and infections.

INCLUSION & EXCLUSION CRITRIA

The study focused on adults with type 2 diabetes (T2DM) and a body mass index (BMI) of 30 kg/m2 or higher who received SGLT2 inhibitors treatment for a minimum of six months. The study excluded certain individuals based on health conditions and circumstances. These included patients with a history of gestational diabetes, active cancer, or malignancy in the past 5 years.

STATISTICAL ANALYSIS

The study used SPSS 22.0 for statistical analysis. Continuous data were summarized based on their distribution, with normally distributed data presented as mean ± standard deviation and non-normally distributed data as median with interquartile range. Categorical data were presented as frequencies and percentages. To evaluate changes over time, repeated measures ANOVA was used, followed by Bonferroni-corrected post-hoc tests to account for multiple comparisons. The impact of various factors on cardiovascular and renal outcomes was assessed using multivariable logistic regression models, which reported odds ratios with 95% confidence intervals. Statistical significance was determined at a p-value of less than 0.05.

RESULTS

The study included 500 patients with obesity after applying several exclusion criteria. The participants' general characteristics are summarized in Table 1. The cohort consisted of 53.0% males and 47.0% females with a mean age of 60.44 ± 11.66 years. Key characteristics included a mean BMI of 37.79 ± 4.34 kg/m2 and a median diabetes duration of 15.00 months (IQR 11.25–21.00). Many participants had a history of smoking and drinking and approximately half were taking antihypertensive or lipid-lowering medications concomitantly. The median duration of SGLT2 inhibitors treatment was 9.00 months (IQR 7.00–11.00).

Table 1 **Demographic characteristics and distribution of participants (*n* = 500)**

Variables	Description
Sex, *n* (%)	
Male	**265 (53.00%)**
Female	**235 (47.00%)**
Age (year)	**60.44 ± 11.66**
Body mass index (BMI)	**37.79 ± 4.34**
Diabetes duration (months)	**15.00 (11.25, 21.00)**
History of smoking	
Yes	**327 (65.40%)**
No	**173 (34.60%)**
Alcohol use	
Yes	**267 (53.40%)**
No	**233 (46.60%)**
Duration of treatment with SGLT2 inhibitors (months)	**9.00 (7.00, 11.00)**
Concomitant use of antihypertensive drugs	
Yes	**253 (50.60%)**
No	**247 (49.40%)**
Concomitant use of lipid-lowering drugs	
Yes	260 (52.00%)
No	240 (48.00%)

SGLT2 inhibitors led to significant improvements in various health metrics. Serum creatinine levels showed a consistent decrease ($p < 0.001$), indicating improved kidney function. Initially, HbA1c levels slightly increased after 1 week of treatment but subsequently decreased ($p < 0.001$). Albuminuria exhibited a modest reduction over time, with significant decreases observed at 3 months ($p < 0.01$). Furthermore, body weight analysis revealed a significant reduction after 6 months of SGLT2 inhibitors treatment ($p < 0.001$). These findings suggest that SGLT2 inhibitors has a positive impact on kidney function, blood sugar control, and body weight.

Fig. 1 Effect on systolic, diastolic blood Pressure after SGLT2 inhibitors treatment.

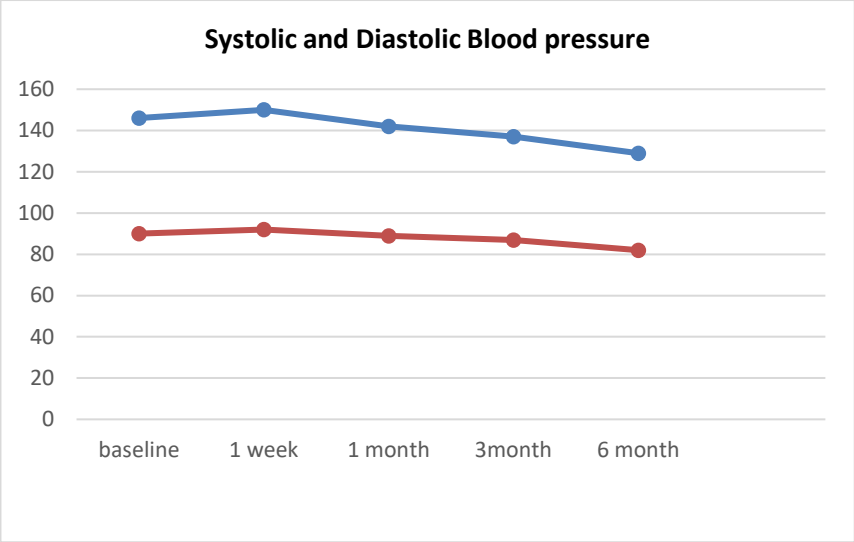


Fig. 2 Effect on creatinin, eGFR and Albuminuria after SGLT2 inhibitors treatment.

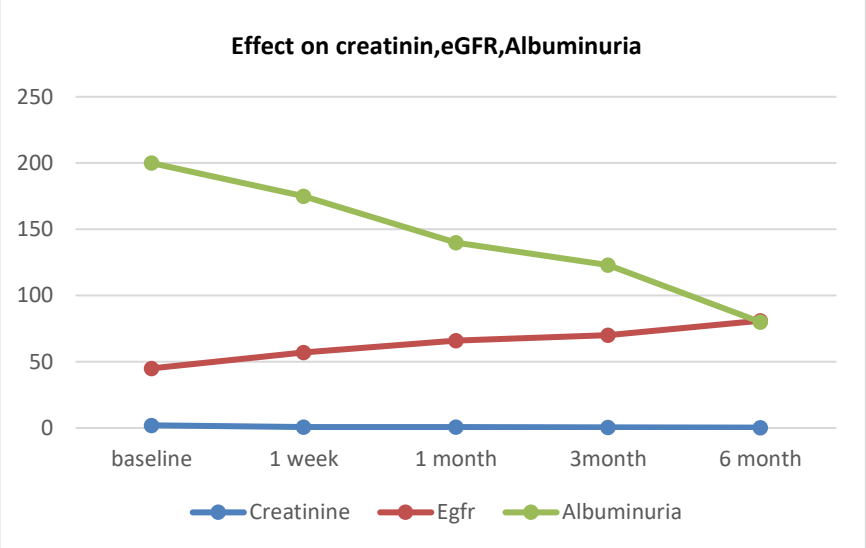


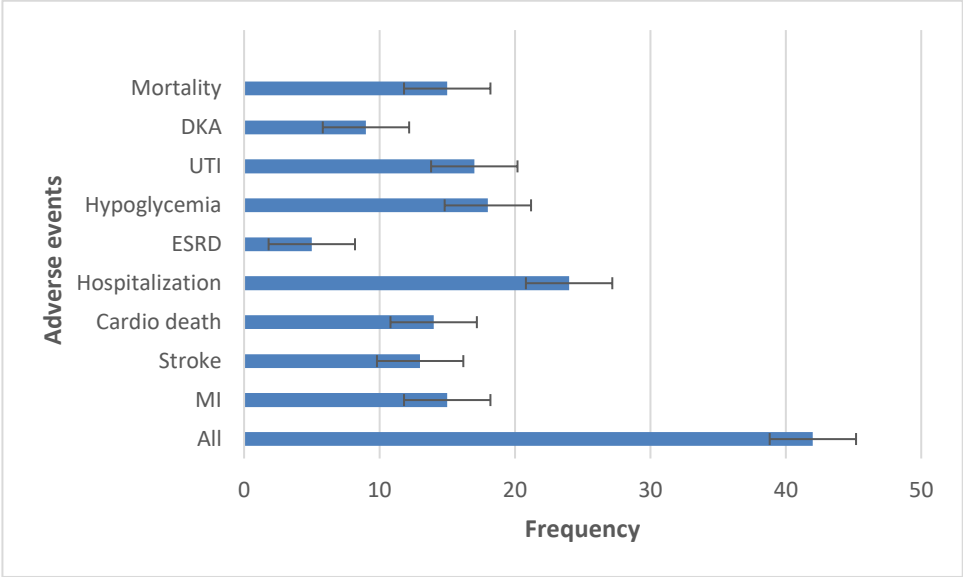
Table 3 Multivariate analysis of factors associated with the occurrence of MACE

Variable	MACE group (*n* = 38)	Non-MACE group (*n* = 462)	*P*	Multivariate logistic OR (95% CI)	*P*
Sex, *n* (%)			0.413		
Male	19 (50.00%)	246 (53.25%)			
Female	19 (50.00%)	216 (46.75%)			
Age (years)	62.00 (51.00, 71.00)	62.00 (51.00, 71.00)	0.840		
BMI	37.89 (34.06, 41.53)	37.95 (34.09, 41.53)	0.706		
Diabetes duration (months)	15.00 (11.00, 20.00)	15.00 (11.75, 21.00)	0.795		
History of smoking			0.118		
Yes	21 (55.26%)	306 (66.23%)			
No	17 (44.74%)	156 (33.77%)			
Duration of treatment with SGLT2 inhibitors (Months)	9.00 (7.00, 11.00)	9.00 (7.00, 11.00)	0.738		
Concomitant use of antihypertensive drugs			0.280		

Yes	17 (44.74%)	236 (51.08%)			
No	21 (55.26%)	226 (48.92%)			
Concomitant use of lipid- lowering drugs			0.536		
Yes	20 (52.63%)	240 (51.95%)			
No	18 (47.37%)	222 (48.05%)			
SBP	134.34±9.85	134.18±9.88	0.185		
DBP	90.96 (85.01, 95.52)	90.61 (85.01, 95.41)	0.013	0.937 (0.888–0.989)	**0.018**
HbA1c	8.02 (7.45, 8.56)	8.03 (7.45, 8.56)	0.019	1.241 (1.016–1.516)	**0.034**
Creatinine	1.04 (0.82, 1.28)	1.04 (0.82, 1.28)	0.534		
eGFR	56.56 (48.97, 68.87)	56.74 (48.99, 69.42)	0.646		
Albuminuria	25.03 (12.78, 106.50)	25.07 (12.40, 107.96)	0.702		
CKD risk			0.142		
Yes	9 (23.68%)	72 (15.58%)			
No	**29 (76.32%)**	**390 (84.42%)**			

The safety outcomes of SGLT2 inhibitors are outlined in Table 2. During the study period, 8.40% of patients experienced major adverse cardiovascular events (MACE), including myocardial infarction (3.00%), stroke (2.60%), and cardiovascular death (2.80%). Additionally, 4.8% of patients were hospitalized due to heart failure, and 1.0% progressed to end-stage renal disease (ESRD). The overall mortality rate was 3.0%. Other notable adverse events included hypoglycemia (3.6%) and urinary issues (3.4%). These findings provide insight into the safety profile of SGLT2 inhibitors in this patient population.

Figure 3 indicates the incidence of adverse events after SGLT2 inhibitors treatment



A logistic regression analysis was conducted to identify factors associated with major adverse cardiovascular events (MACE) and chronic kidney disease (CKD) in patients with obesity and type 2 diabetes mellitus (T2DM) treated with SGLT2 inhibitors. The multivariate analysis revealed that lower diastolic blood pressure (DBP) (OR 0.937, 95% CI 0.888–0.989, p = 0.018) and higher HbA1c levels (OR 1.241, 95% CI 1.016–1.516, p = 0.034) were independently associated with an increased risk of MACE. Furthermore, elevated albuminuria (OR 1.031, 95% CI 1.022–1.041, p < 0.001) and reduced estimated glomerular filtration rate (eGFR) (OR 1.466, 95% CI 1.278–1.681, p < 0.001) were significantly linked to a higher risk of CKD. These findings highlight key factors that may influence cardiovascular and renal outcomes in this patient population.

Table 4 Multivariate analysis of factors associated with CKD risk in patients with type 2 diabetes

Variable	CKD risk group	No CKD risk group	*P*	Multivariate logistic	*P*
	(*n* = 81)	**(*n* = 419)**		**OR (95% CI)**	
Sex, *n* (%)			0.133		
Male	48 (59.26%)	217 (51.79%)			
Female	33 (40.74%)	202 (48.21%)			
Age (years)	62.00 (51.0- 71.0)	62.00 (51.0-71.0)	0.042		**0.86**
BMI	37.95 (34.9- 41.6)	37.95 (34.0- 41.4)	0.655		
Diabetes duration (months)	15.00 (11.0- 21.0)	15.00 (11.5-20.5)	0.226		
History of smoking			**0.351**		
Yes	55 (67.90%)	272 (64.92%)			
No	26 (32.10%)	147 (35.08%)			
Duration of treatment with SGLT2 inhibitors months)	9.00 (7.00, 11.00)	9.00 (7.00, 11.00)	**0.175**		
Concomitant use of anti-hypertensive drugs			0.271		
Yes	44 (54.32%)	209 (49.88%)			
No	37 (45.68%)	210 (50.12%)			
Concomitant use of lipid-lowering drugs			0.440		
Yes	41 (50.62%)	219 (52.27%)			
No	40 (49.38%)	200 (47.73%)			
SBP	134.21 (126.5-141.9)	134.21 (126.5-141.9)	0.308		
DBP	83.90 (79.3- 88.6)	83.90 (79.3-88.6)	0.321		
eGFR	56.64 (48.9-69.11)	56.74 (49.0-69.4)	<0.001	0.682 (0.59–0.78)	**<0.01**
Albuminuria	25.09 (12.78- 108.34)	25.06 (12.37-107.26)	<0.001	1.031 (1.02–1.04)	**<0.01**
Creatinine	0.69 (0.46-0.93)	0.69 (0.46-0.93)	0.862		
HbA1c	**8.90 (7.4-10.42)**	**8.88 (7.41-10.41)**	**0.829**		

DISCUSSION

This cohort study provides novel insights into the therapeutic role of SGLT2 inhibitors in populations with obesity and T2DM, a population at elevated risk for adverse outcomes. Over a 6-month treatment period, they demonstrated significant improvements in both cardiovascular and renal parameters, further supporting its role as a key therapeutic option in this high-risk subgroup. Adverse events were infrequent in this study, with hypoglycemia occurring in 3.6%, urinary tract infections in 3.4%, and diabetic ketoacidosis in 1.8% of patients. These findings are com parable to other studies investigating the safety profile of SGLT2 inhibitors[19]. Besides, our findings demonstrated a significant reduction in SBP and DBP after 6 months of SGLT2 inhibitors treatment, following an initial increase in the first week. The incidence of MACE was 8.4%, with myocardial infarction occurring in 3.0%, stroke in 2.6%, and cardiovascular death in 2.8% of the patients. These rates are comparable to previous real-world studies evaluating SGLT2 inhibitors in patients with T2DM with a high cardiovascular risk profile[20]. Obesity is a well-established risk factor that worsens cardiovascular outcomes in individuals with T2DM, contributing to increased MACE rates in this population [21]. In this study, a significant reduction in body weight was observed during the 6-month treatment period ($p < 0.001$). This finding aligns with other studies showing the weight-reducing effects of SGLT2 inhibitors, which are particularly beneficial for patients with obesity. Weight loss, although relatively modest in percentage, contributes to improved metabolic and renal outcomes, which are crucial in this population [22].

Importantly, the multivariate analysis identified that higher HbA1c levels and elevated DBP were independently linked to an increased risk of MACE. These results indicate that, although SGLT2 inhibitors provides cardiovascular benefits, optimizing glycemic control and blood pressure

management remains critical in reducing cardiovascular risk in this high-risk population. Our findings are consistent with previous research underscoring the need for multifactorial interventions to mitigate cardiovascular risk in individuals with T2DM. For instance, elevated HbA1c levels have been proven to markedly raise the likelihood of MACE in patients with T2DM, particularly those undergoing coronary artery bypass grafting, where higher HbA1c levels correlated with increased risks of both MACE and mortality [23]. Similarly, elevated DBP has also been recognized as an independent risk factor for MACE in patients with T2DM and coronary artery disease [24].

In addition to its cardiovascular benefits, SGLT2 inhibitors demonstrated significant renal protection in our cohort, as evidenced by improved eGFR and reduced serum creatinine levels. Notably, only 1% of patients with obesity and T2DM progressed to ESRD during the study period, which highlights SGLT2 inhibitors's potential to slow the progression of renal disease in this high-risk population [25]. This finding is consistent with earlier studies supporting the nephroprotective properties of SGLT2 inhibitors. Similarly, real-world evidence from a study in Singapore demonstrated a 33% reduction in the risk of developing ESRD in patients treated with SGLT2 inhibitors, showing a sustained risk reduction across various stages of CKD [26]. The reduction in albuminuria observed in our study further supports the renal benefits of SGLT2 inhibitors, consistent with findings from previous research. However, it is important to approach the renal effects of SGLT2 inhibitors with caution, as some studies have reported no significant improvement in albuminuria, highlighting variability in the drug's impact on proteinuria in different populations[27].

Our multivariate analysis identified that elevated albuminuria and lower eGFR were independently linked to an elevated risk of CKD progression, highlighting the importance of early identification and intervention for renal risk factors in individuals with obesity and T2DM. These findings are consistent with prior studies,which have demonstrated that elevated albuminuria is a significant predictor of renal function decline and CKD progression. For instance, a systematic review emphasized that albuminuria, alongside serum creatinine and eGFR, is a critical indicator of cardiorenal outcomes and kidney disease progression in patients with T2DM [28-29]. Additionally, albuminuria has been closely linked to accelerated CKD progression, particularly among those with reduced eGFR. In a real-world cohort of patients with T2DM, those presenting with severely increased albuminuria (UACR > 300 mg/dL) and eGFR between 30 and 59 mL/min/1.73 m2 exhibited a 65.1% greater likelihood of progressing to a more advanced CKD stage compared to those with normal albuminuria [30]. Many studies have already explored the cardiovascular and renal effects of SGLT2 inhibitors in patients with T2DM. Subgroup analyses based on this trial further demonstrated that SGLT2 inhibitors consistently decreased cardiorenal events and mortality across different BMI categories, including Asians [31]. However, these analyses were derived from controlled clinical trial settings, which may not fully reflect real-world treatment patterns and patient characteristics. In addition, our research narrows its focus exclusively on the obese population, delivering more targeted findings that can inform clinical management in this high-risk group [32].

This study offers new insights into the benefits of SGLT2 inhibitors for with obesity and type 2 diabetes, a group at high risk for complications. After six months of treatment, SGLT2 inhibitors showed notable improvements in cardiovascular and kidney function, reinforcing its value as a crucial treatment option for this vulnerable population.

CONFLICT OF INTEREST Nil

CONCLUSIONS

In conclusion, SGLT2 inhibitors demonstrated significant benefits in reducing blood pressure, improving renal function, and decreasing body weight in patients with obesity and type 2 diabetes.

The therapy also showed promise in reducing major adverse cardiovascular events and slowing chronic kidney disease progression.

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