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Impact of sodium-glucose cotransporter-2 inhibitors on kidney outcomes in type 2 diabetes: A tertiary center experience

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Abstract:

BACKGROUND: Diabetic nephropathy (DN) is a complication of chronic hyperglycemia associated with diabetes mellitus (DM). Several studies have demonstrated the positive impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors on kidney outcomes. The objective of the study was to evaluate the effects of dapagliflozin, an SGLT2 inhibitor, on kidney outcomes in Saudi patients with type 2 DM.

MATERIALS AND METHODS: Study included all Saudi patients with type 2 DM who visited our center from August 1, 2021, to July 31, 2022, and had been on dapagliflozin for at least 3 months. Data was abstracted through chart review for all patients included in the study. Paired t-test or Wilcoxon signed-rank test were used to compare the results before and after treatment for continuous variables and the McNemar test was used to compare the results for categorical data.

RESULTS: Study included 184 Saudi patients with type 2 diabetes with a mean age of 61.32 years (SD=9.37). Dapagliflozin 10 mg/day significantly reduced hemoglobin A1C (HbA1C) from a mean (SD) of 9.00 to 8.40 ($P < 0.001$). Among a subgroup of patients with significant proteinuria ($n = 83$), dapagliflozin significantly reduced ACR from a median of 93.1 to 64.9 mg/g ($P = 0.001$). Following treatment, the estimated glomerular filtration rate improved from a mean of 69.83 to 71.68 mL/min and the mean arterial pressure (MAP) fell from 90.03 to 89.06 mmHg, both were not statistically significant. Despite a statistically insignificant increase in the episodes of urinary tract infections (UTIs), the hospitalization rate declined. No episodes of amputations or ketoacidosis occurred during the study period.

CONCLUSION: SGLT2 inhibitors had beneficial effects among Saudi patients with type 2 diabetes by improving diabetic control and lowering proteinuria. Dapagliflozin did not result in significant harm, including UTIs, amputations, and ketoacidosis.

Keywords:

Dapagliflozin, diabetic kidney disease, diabetic nephropathy, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes

Introduction

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus (DM) characterized by albuminuria and a decline in renal function.[1,2] This clinical syndrome is likely to present in 20%–50% of diabetic patients and has emerged as the single largest contributor to end-stage kidney disease (ESKD).[3,4] The prevalence of DN is likely to rise owing to the alarming increase in the diabetic

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population across the globe. At present, over 442 million people suffer from DM globally.[5,6] Saudi Arabia has the highest diabetic population in the Middle East and North African region, with 17.7% of the total population affected by DM.[7] Diabetes is characterized by hyperglycemia, which has been linked to a number of chronic microvascular and macrovascular complications. Microvascular consequences include diabetic neuropathy, retinopathy, and nephropathy, whereas macrovascular consequences include coronary artery disease, peripheral vascular disease, and cerebrovascular disease.[8] Prolonged hyperglycemia in patients can result in both microvascular and macrovascular sequelae.[9] The microvascular complications in DM are manifested as neuropathy, nephropathy, and diabetic retinopathy.[10] Microvasculature complications arise as a result of vascular endothelial dysfunction under hyperglycemic conditions. Hyperglycemia-associated endothelial damage is caused by the activation of multiple biochemical pathways, reactive oxygen species, dysregulation of various growth factors, and epigenetic changes.[11] Inflammation is another feature of hyperglycemic conditions manifested by an increase in interleukin-6, transforming growth factor-beta, and vascular endothelial growth factor which leads to vascular permeability.[12]

The incidence of DN is usually 3% during the first 10–20 years after the onset of diabetes.[13] DN is a complex diabetic complication that has several environmental and genetic predisposing factors; however, robust predictors of DN are still lacking. At present, most cases are diagnosed at much later stages of high albuminuria and reduced glomerular filtration.[14] The standard treatment approach for DM aims at blood glucose and blood pressure control. Unfortunately, such interventions have demonstrated little efficacy in halting the progression of DN.[15] The emergence of new classes of medications such as sodium-glucose cotransporter-2 (SGLT2) inhibitors has provided better prognoses not only by lowering blood glucose but also by directly preventing the progression of some DM complications.[16] SGLT2 inhibitors provide renal and cardiovascular protection by decreasing intraglomerular pressure and hyperfiltration, decreasing blood pressure, increasing EPO production, and decreasing uric acid secretion.[17] Thus, by altering the renal hemodynamics, SGLT2 inhibitors reduce the risk of development and the worsening of albuminuria and decrease markers of renal damage to improve long-term kidney outcomes.[18] In clinical trials, SGLT2 inhibitors have shown efficacy in reducing the risk of ESKD and death on account of cardiovascular and renal complications.[19] In addition, they have demonstrated reno-protective effects such as a reduction in serum creatinine levels, albuminuria, and albumin-to-creatinine ratio (ACR).[20] Interestingly, the cardiorenal protective effects of SGLT2 inhibitors are independent of glucose-control efficacy.[21] FDA-approved SGLT2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin.[22] This study's aim was to assess the magnitude of the benefits of SGLT2 inhibitors on DN in Saudi patients with type 2 DM.

Materials and Methods

In a retrospective chart review study at a tertiary care center, all Saudi patients with type 2 DM, aged 18 years or older, who had been taking dapagliflozin (an SGLT2 inhibitor) for at least 3 months, and who visited our center between August 1, 2021, and July 31, 2022, were included. Non-Saudis, patients under the age of 18 years, and those on renal replacement therapy, dialysis, or kidney transplantation were excluded. Demographic data such as age, gender, and nationality were obtained from the electronic health record. Dapagliflozin 10 mg tablet was the SGLT2 inhibitor available at our center. To determine the effectiveness of dapagliflozin in Saudi patients with type 2 DM, we compared the laboratory parameters before and after the initiation of dapagliflozin. Laboratory data included estimated glomerular filtration rate (eGFR), glycosylated hemoglobin (HbA1C), sodium (Na), potassium (K), and low-density lipoprotein (LDL). Proteinuria was assessed by measuring the urinary ACR expressed in mg/g. The baseline data including hypertension, dyslipidemia, coronary artery disease, congestive heart failure, and relevant medications such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), anti-mineralocorticoids, oral hypoglycemic medications, and insulin were included. Clinical events including urinary tract infections (UTIs), hospitalizations, limb amputation, and ketoacidosis were also collected. Ethical approval was obtained from the Institutional Review Board (IRB) vide Letter No. IRB/1598/22 dated 11/08/2022, with a waiver of informed consent since there was no direct relation with human subjects in this study.

We presented numerical data as mean (standard deviation [SD]) and median (interquartile range [IQR]) based on the data distribution, while categorical data were presented as frequency (percentage). We used the paired *t*-test or Wilcoxon signed-rank test to compare the results before and after treatment for continuous variables and the McNemar test to compare the results for categorical data. $P = 0.05$ or less was used to define statistical significance. Version 1.3.1093 of RStudio (RStudio Incorporation, Boston, MA, USA) was used to conduct the statistical analysis.

Results

A total of 184 subjects with a mean (SD) age of 61.32 (9.37) years were included in the analysis, and

over half of whom (54.3%) were male. The most common comorbidities in our participants were dyslipidemia (83.7%), followed by hypertension (78.2%) and cardiac disease (9.7%). The most prescribed medications were oral hypoglycemics (83.7%), insulin (76.6%), ARBs (51.6%), ACEi (31.5%), and mineralocorticoid antagonists (2.17%) [Table 1].

The effect of dapagliflozin on different clinical and laboratory parameters is shown in Table 2. The use of dapagliflozin was associated with a significant improvement in glycemic control, HbA1C reduced from a mean (SD) of 9 (1.7) % to 8.40 (1.5) % ($P < 0.001$). In a subgroup of patients with significant proteinuria, defined as ACR of 30 mg/g or higher ($n = 83$ patients), dapagliflozin significantly reduced ACR from a median (IQR) of 93.1 (51.05–172.15) to 64.9 (33.45–137.65) mg/g ($P = 0.001$). The use of dapagliflozin resulted in a slight, but not statistically significant, decrease in mean arterial pressure (MAP). The MAP values decreased from an initial mean (SD) of 90.03 (10.32) mmHg to 89.06 (10.39) mmHg ($P = 0.31$). There was also an improvement in kidney functions; eGFR improved from a mean (SD) of 69.83 (26.66) to 71.68 (28.91) mL/min after treatment but did not reach statistical significance ($P = 0.14$). The use of dapagliflozin did not result in any significant change in sodium, potassium, or LDL levels.

Table 1: Baseline characteristics of Saudi DM-2 patients on dapagliflozin, 2021-2022 (*n*=184)

Baseline characteristics	*N* (%)
Age (years)	61.32 (9.37)
Male	100 (54.3)
Female	4 (45.6)
Comorbidities	
Dyslipidemia	154 (83.7)
Hypertension	144 (78.2)
Coronary artery disease	11 (5.9)
Heart failure	7 (3.8)
Medications	
Oral hypoglycemics	154 (83.7)
Insulin	141 (76.6)
ARBs	95 (51.6)
ACEi	58 (31.5)
Mineralocorticoid antagonists	4 (2.1)

Continuous variables are expressed as mean (SD), while categorical are expressed as *n* (%). ACEi=Angiotensin-converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, SD=Standard deviation

Figure 1 depicts a comparison of adverse events before and after introducing dapagliflozin. With the dapagliflozin treatment, there were more episodes of UTIs, defined by positive urine culture (12 events vs. 7 events). However, the rate of hospitalizations declined after initiating SGLT2 inhibitors (28 events vs. 36 events). Notably, no episode of ketoacidosis or limb amputation was reported during the study period.

Discussion

The positive effect of SGLT2 inhibitors in lowering proteinuria and preserving kidney function has been replicated by many studies.[23,24] However, data on the impact of this class of medications in the Arab population, especially in Saudi Arabia, are limited.[25] Our present study is the second largest to demonstrate the significant improvement of glycemic control, preserved kidney function, and the lowering of the degree of proteinuria in type 2 DM Saudi patients with the use of SGLT2 inhibitors without a significant increase in adverse events.

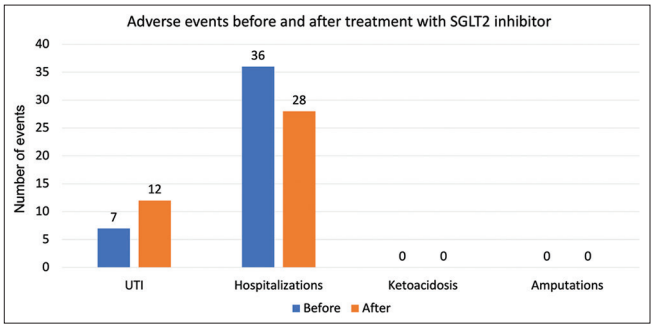

Figure 1: The rate of hospitalization and urinary tract infection before and after sodium-glucose cotransporter-2 inhibitor use. UTI = Urinary tract infection, SGLT2 = Sodium-glucose cotransporter-2

Table 2: Effect of sodium-glucose cotransporter-2 inhibitors on laboratory parameters in Saudi type 2 DM patients on dapagliflozin, 2021-2022 (*n*=184)

Effect of SGLT2 inhibitors	Before Mean±SD	After Mean±SD	*P-value*
HbA1C (%)	9.00±1.7	8.40±1.49	<0.001
ACR (mg/g), median (IQR)*	93.10 (51.05–172.15)	64.90 (33.45–137.65)	0.001
MAP (mmHg)	90.03±10.32	89.06±10.39	0.313
eGFR (mL/min/1.73 m^2)	69.83±26.66	71.68±28.91	0.141
Na (mmol/L)	138.12±3.17	137.84±4.79	0.470
K (mmol/L)	4.55±0.48	4.54±0.47	0.814
LDL (mmol/L)	2.52±0.98	2.50±0.90	0.811

*ACR was compared in the subset of patients with albumin/creatinine ratio >30 mg/g (*n*=83). Data are expressed as mean (SD) or median (IQR) for ACR. SGLT2=Sodium-glucose cotransporter-2, HbA1C=Glycosylated hemoglobin, ACR=Albumin-to-creatinine ratio, MAP=Mean arterial pressure, eGFR=Estimated glomerular filtration rate, Na=Sodium, K=Potassium, LDL=Low-density lipoprotein, SD=Standard deviation, IQR=Interquartile range

Our findings depicted a significant decrease in the ACR levels after initiating SGLT2 inhibitors. This finding is in line with international studies.[26,27] For example, Kobayashi *et al*., demonstrated that SGLT2 inhibitors resulted in a significant improvement of ACR in Japanese patients with type 2 DM.[26] More importantly, several large randomized controlled studies have demonstrated the anti-proteinuric effect of SGLT2 inhibitors.[28,29] For example, Cherney *et al*., in their EMPA-REG OUTCOME trial, reported that ACR was significantly reduced after the empagliflozin treatment in patients with DN.[28] Although the proteinuria-lowering effect of empagliflozin in Saudis with type 2 DM was recently demonstrated by Butt *et al*.,[25] our study further confirms the anti-proteinuric effect of SGLT2 inhibitors and extends the benefit to a different SGLT2 inhibitor, dapagliflozin. The class effect of SGLT2 inhibitors as anti-proteinuria was demonstrated by a study which showed that six different SGLT2 inhibitors resulted in a similar and significant reduction of ACR.[30]

In line with previous reports from Saudi Arabia,[25] our study demonstrated that SGLT2 inhibitors resulted in a better control of type 2 DM in Saudi patients. However, the study also confirms the antihyperglycemic effect of a different SGLT2 inhibitor in Saudis with type 2 DM. The underlying mechanism of action of SGLT2 inhibitors may explain the significant changes in HbA1C observable after treatment. The blockage of SGLT2 leads to inhibition of the proximal tubular reabsorption of sodium and glucose resulting in increased renal elimination of glucose.[31,32]

Several studies have shown that SGLT2 inhibitors may cause an initial drop in eGFR, which progressively returns to base values over the next few months.[27,32] This drop is due to the hemodynamic effect of SGLT2 inhibitors rather than structural kidney damage. In the present study, we recorded an improvement in eGFR values after treatment, which did not meet statistical significance. However, we assessed the GFR 3–12 months after initiation of SGLT2 inhibitors, the point at which the GFR starts to improve. This may explain our finding of better eGFR in dapagliflozin users. Chan *et al*., also reported an improvement in eGFR in their 1-year follow-up study.[33]

In keeping with previous reports from Saudi Arabia,[25] the present study showed a slightly reduced MAP after initiating SGLT2 inhibitors. Some international studies have similarly reported a reduction in arterial pressure (AP) after treatment with SGLT2 inhibitors.[34,35] This reduction in AP may contribute to the lowering of cardiovascular complications.[36,37] However, the significant improvement in ACR despite the nonsignificant reduction in MAP may indicate that the reduction in ACR is not dependent on the reduction in blood pressure but is rather related to the reduction in intraglomerular pressure after treatment.

Our study demonstrated that dapagliflozin is safe and did not result in any significant metabolic derangement in terms of electrolyte disturbances. However, there were numerically higher rates of UTIs in dapagliflozin users. In accordance with our findings, previous reports from Saudi Arabia found no significant increase in the rate of UTIs following initiation of SGLT2 inhibitors.[25] It is unclear if this was related to the culture of hygiene and circumcision or just because we included a relatively healthy uncomplicated population, as evidenced by the low burden of comorbidities and relatively well-preserved kidney function.

Despite the numerically higher number of UTIs, the use of SGLT2 inhibitors was associated with a lower hospitalization rate. This may indicate that the adverse events, including UTIs, were mild and manageable without hospitalization.[38-40]

While previous reports raised concerns about the increased rate of amputation following the initiation of SGLT2 inhibitors,[41] such findings were not demonstrated in subsequent reports.[42-45] In line with the more recent reports, our study found no amputation in our Saudi population. Although our study population comprised mainly relatively healthy participants, it is reassuring that no amputations were found. In addition, previous reports had observed an increased rate of ketoacidosis[18,39,46] in SGLT2 inhibitor users, but our study revealed no event of ketoacidosis, which again is reassuring.

Our study has strengths and limitations. We believe the main strength is that our study is one of the first to demonstrate the efficacy and safety of SGLT2 inhibitors in the Saudi population. However, our study is limited because it was retrospective and restricted to a single center, situations that limit generalizability. Furthermore, the small sample size and the short follow-up period limited our ability to assess the long-term efficacy and safety. Besides, our population consisted of patients with relatively preserved kidney function, which limits our ability to estimate the safety and efficacy of this class of medications in Saudi patients with more advanced kidney disease.

Conclusion

The results of the present study show that the use of dapagliflozin 10 mg/day in Saudis with DM was safe and resulted in the improvement of glycemic control, lowering of proteinuria levels, and a reduction in the rate of hospitalization. After using dapagliflozin, there

was a statistically insignificant increase in the episodes of UTI (12 events vs. 7 events). However, there was no episode of ketoacidosis or limb amputation. Further long-term studies with larger sample sizes, preferably randomized controlled studies, are necessary to demonstrate the safety and efficacy of SGLT2 inhibitors in Eastern populations.

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Conflicts of interest
There are no conflicts of interest.

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