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Reno Protective Effect of Sodium Glucose Cotransporter-2 Inhibitor (Dapagliflozin) in Type 2 Diabetic Patients

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ABSTRACT
Background: Many studies reported a renal protection by sodium glucose cotransporter-2 inhibitor (SGLT2i) using in Type 2 diabetes mellitus (T2DM). **Objective:** Our study was designed to evaluate the renal benefit offered by SGLT2 inhibitor (dapagliflozin) in type 2 diabetic patients. **Patients and Methods**: 100 diabetic patients, 50 treated by dapagliflozin 10 mg once daily for 12 months and 50 treated by placebo for the same period. Patients were recruited from those attending Endocrinology Unit in Benha University Hospital. Clinical and laboratory data were performed to patients who were followed up every 3 months for 1 year. **Results:** No significant difference among the two groups regarding age, sex, residence, and the common adverse effects. Urinary albumin/creatinine ratio was statistically lower in SGLT2i group compared to placebo group at the end of the study but was non-significant at base line. Estimated glomerular filtration rate (eGFR) was statistically higher in SGLT2i group compared to placebo group at the end of the study although there was non-significant difference at base line. No significant difference between the two groups regarding HbA1c at base line, 3 and 6 months later but was statistically lower in SGLT2i group after 9 months and 1 year. BMI, SBP and DBP were statistically lower in SGLT2i group at the end of the study but there was non-significant difference at base line. **Conclusion**: We found reno protective properties by using sodium glucose cotransporter-2 inhibitor (dapagliflozin) in type 2 diabetic patients, a great impact on glycemic control and other pleiotropic effects without significant differences regarding common adverse effects.
Keywords: Renal protection, SGLT2i, T2DM.

INTRODUCTION

Diabetic kidney disease is the leading cause of kidney failure worldwide. In the USA, it accounts for over 50% of individuals entering dialysis or transplant programmes. Unlike other complications of diabetes, the prevalence of diabetic kidney disease has failed to decline over the past 30 years. Hyperglycemia is the primary etiological factor responsible for the development of diabetic kidney disease. Once hyperglycemia becomes established, multiple pathophysiological disturbances, including hypertension, altered tubuloglomerular feedback, renal hypoxia, lipotoxicity, podocyte injury, inflammation, mitochondrial dysfunction, impaired autophagy and increased activity of the sodium–hydrogen exchange, which contribute to progressive glomerular sclerosis and the decline in glomerular filtration rate. The quantitative contribution of each of these abnormalities to the progression of diabetic kidney disease, as well as their role in type 1 and type 2 diabetes mellitus, remains to be determined [(1)].SGLT2 protein is a symporter involved in the cotransport of glucose and sodium in the proximal convoluted tubule (PCT) of a nephron. The SGLT2 protein mediates the active transport of glucose through the luminal membrane against a concentration gradient along with sodium [(2)]. Therefore, pharmacological inhibition of SGLT2 promotes renal glucose excretion, thereby lowering plasma glucose levels without affecting hypoglycemia, because the inhibition of SGLT2 could trigger alpha cell to secrete glucagon to circulation, thereby increasing the hepatic glucose production, which in turn maintain the blood glucose level [(3)].

The inhibition of glucose accumulation in tubular cells by SGLT2i significantly decreased high-induced reactive oxygen species (ROS) generation and RAGE-AGEs induction in tubular cells. In addition, SGLT2 inhibitor has been shown to reduce high glucose-induced inflammatory and fibrotic markers in HK2 cells as shown by the decreased expressions of toll-like receptor-4 (TLR4), type IV collagen, interleukin-6 secretion and nuclear factor kappa B (NF-kB) [(4)]. Correspondingly, the inhibition of high glucose-induced ROS generation in proximal tubular epithelial cells by SGLT2 inhibitor led to decreases of MCP-1 mRNA, and DNA fragments [(5)]. These findings indicated that SGLT2 inhibitor might prevent proximal tubular damage associated with glucotoxicity. SGLT2 inhibitor could also ameliorate high glucose-induced oxidative stress and inflammation in kidney [(6)].

Dapagliflozin is reversible, extremely particular and active when taken orally and a competitive human SGLT2 inhibitor approved by the European Union. In the structure, an aglycone group enables it to compete for the glucose binding site and blocks the reabsorption of glucose. This increases the elimination of glucose, enhanced glycemic regulation and loss of weight. The activity of drug is determined by blood glucose control and hepatic function of the patient. The advantages of this drug include reduced risk of hypoglycemia and a drop in blood pressure. Dapagliflozin can be taken alone or along with other drugs including metformin, sulfonylurea, DPP-4 inhibitors, or insulin [(7)].

The aim of the present study was to evaluate the renal benefit offered by SGLT2 inhibitor (dapagliflozin) in type 2 diabetic patients.

PATIENTS AND METHODS

This is prospective study of 100 diabetic patients, 50 treated by dapagliflozin in a dose of 10 mg once daily

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for 12 months ± other antidiabetic agents and 50 treated by other antidiabetic agents for the same period. Patients were recruited from those attending Endocrinology Unit in Benha University Hospital.

The following were exclusion criteria:

1. Type 1 DM.
2. Other causes of CKD in diabetic patients as: Polycystic kidney, obstructive uropathy, pyelonephritis, and analgesic nephropathy.
3. Systemic diseases, which might affect kidney functions: e.g., autoimmune diseases, malignancy or other endocrinal disorders.

Laboratory investigations were examined in Clinical Pathology Department in Benha University Hospital according to routine methods in the laboratory in the form of KFTs (Serum creatinine, blood urea, urinary albumin/creatinine ratio, eGFR) and HbA1c every 3 months for 1 year.

None of our patients were lost or discontinued the drug during the follow up periods.

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for the social sciences) version 20 to obtain: Descriptive statistics were calculated for the data in the form of mean and standard deviation (±SD) for quantitative data and frequency and percentage for qualitative data. In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests. Student's t-test: - Used to compare mean of two groups of quantitative data, for continuous non-parametric data, Mann-Whitney U- test was used for inter-group analysis. Friedman test: - Used to compare mean of variables in more than two different time periods of quantitative data. Inter-group comparison of categorical data was performed by using chi square test (X^2-value), A P value <0.05 was considered statistically significant.

RESULTS

Our study included two groups; SGLT2i group was 50 patients each. There was non-significant difference among the two groups regarding age, sex, residence and common adverse effects. BMI, SBP and DBP were statistically lower in SGLT2i group compared to placebo group at the end of the study but there was non-significant difference between the two groups at base line regarding these parameters (**Table 1).**

Table (1): C**omparison of different sociodemographic characteristics and adverse effects among the studied groups (base line and after 1 year)**

	SGLT2i (50)		Placebo (50)		Statistical test X^2	P value
	No	%	No	%		
Sex						
Male	36	72.0	33	66.0	0.421	0.517
Female	14	28.0	17	34.0		
Residence						
Urban	30	60.0	23	46.0	1.97	0.161
Rural	20	40.0	27	54.0		
Smoking						
Yes	7	14.0	13	26.0	2.25	0.134
No	43	86.0	37	74.0		
Documented hypoglycemia	0	0	1	2	1.01	0.31
UTI	7	14	5	10	0.4	0.53
Genital tract infection	8	16	7	14	0.1	0.78
Ketoacidosis	0	0	0	0	1	1
Hypovolemia	5	10	3	6	0.54	0.46
Hypotension	2	4	3	6	0.21	0.65
Others (GIT troubles, allergy -----)	4	8	5	10	0.1	0.73
	Mean	**±SD**	**Mean**	**±SD**	**St t test**	**P value**
Age (yrs)	50.5	7.02	50.36	7.91	0.094	0.93
BMI (kg/m2)	29.64	6.09	30.12	6.07	0.395	0.694
BMI 12	24.66	4.05	30.54	5.38	6.18	<0.001**
SBP(mmHg)	127.58	18.02	129.9	15.79	0.685	0.495
SBP 12	115.1	6.74	127.8	11.48	6.75	<0.001**
DBP(mmHg)	85.82	11.87	88.33	10.78	1.09	0.278
DBP 12	78.9	6.8	88.6	9.04	6.07	<0.001**

UTI: urinary tract infection, GIT: gastrointestinal tract, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, 12: after 12 months

Urinary albumin/creatinine ratio was statistically lower in SGLT2i group compared to placebo group at the end of the study but was non-significant between the two groups at base line. A significant reduction in urinary albumin/creatinine ratio appeared after 3 months from the start of treatment and continued till the end of the study in patients received dapagliflozin **(Tables 2, 3).**

eGFR was statistically higher in SGLT2i group compared to placebo group at the end of the study although there was non-significant difference between the two groups at base line. A significant increase in eGFR appeared after 3 months from the start of treatment and continued till the end of the study in patients received dapagliflozin **(Tables 2, 3).**

Table (2): Comparison between the studied groups regarding eGFR and urinary A/C ratio

	SGLT2i (50)		placebo (50)		Statistical test	P value
	Mean	±SD	Mean	±SD		
eGFR (ml / min / m^2)						
Base line	85.86	20.93	88.24	26.4	0.50	0.619
After 3m	88.54	22.79	84.6	25.53	0.814	0.418
After 6m	91.62	24.18	81.64	25.42	2.01	0.047*
After 9m	97.22	28.77	77.8	23.48	3.70	<0.001**
After 12m	112.88	42.66	75.54	23.44	5.41	<0.001**
U.A/C ratio (mg\g)						
Base line	166.28	261.17	113.02	270.37	1.0	0.319
After 3m	137.06	243.56	151.38	337.69	0.243	0.808
After 6m	111.86	217.9	218.22	458.56	1.48	0.142
After 9m	84.32	191.04	327.96	777.84	2.15	0.034*
After 12m	71.99	178.82	421.52	932.84	2.60	0.011*

eGFR:estimated glomerular filteration rate, m: months, U.A/C ratio:urinary albumin creatinine ratio

Table (3): Differences of eGFRand urinary A/C ratio during follow up periods among SGLT2i group

	SGLT2i (50)		P1 (baseline)	P2 (after 3m)	P3 (after 6m)	P4 (after 9m)
	Mean	±SD				
eGFR (ml / min / m2)						
Base line	85.86	20.93				
After 3m	88.54	22.79	<0.001**			
After 6m	91.62	24.18	<0.001**	<0.001**		
After 9m	97.22	28.77	<0.001**	<0.001**	0.023*	
After 12m	112.88	42.66	<0.001**	<0.001**	<0.001**	0.001**
Urinary A/C ratio (mg\g)						
Base line	166.28	261.17				
After 3m	137.06	243.56	<0.001**			
After 6m	111.86	217.9	<0.001**	<0.001**		
After 9m	84.32	191.04	<0.001**	<0.001**	<0.001**	
After 12m	71.99	178.82	<0.001**	<0.001**	<0.001**	<0.001**

Tables (4, 5) also shows that no significant difference between the two groups regarding HbA1c at base line, 3 months and 6 months later but was statistically lower in SGLT2i group compared to placebo group after 9 months and 1 year. A significant reduction in HbA1C level appeared after 6 months from the start of treatment and continued till the end of the study in patients treated with dapagliflozin. .

Table (4): Comparison between the studied groups regarding HbA1c

	SGLT2i (50)		Placebo (50)		Statistical test	P value
	Mean	±SD	Mean	±SD		
HbA1c (%)						
Base line	7.91	1.17	7.9	1.2	0.042	0.968
After 3m	7.89	1.23	7.74	1.4	0.586	0.559
After 6m	7.77	1.18	7.9	1.28	0.512	0.61
After 9m	7.46	1.09	8.24	1.59	2.87	0.005**
After 12m	6.91	0.87	8.68	1.72	6.47	<0.001**

m: months

Table (5): Differences of HbA1c during follow up periods among SGLT2i group

	SGLT2i (50)		P1 (baseline)	P2 (after 3m)	P3 (after 6m)	P4 (after 9m)
	Mean	±SD				
HbA1c %						
Base line	7.91	1.17				
After 3m	7.89	1.23	0.659			
After 6m	7.77	1.18	0.018*	0.032*		
After 9m	7.46	1.09	0.001**	0.001**	0.01*	
After 12m	6.91	0.87	<0.001**	<0.001**	<0.001**	<0.001**

DISCUSSION

This is a prospective study performed to shed light on whether sodium glucose cotransporter-2 inhibitor (dapagliflozin) can be considered as a renoprotective drug for T2DM patients. The renal outcome in our study was assessed by urinary albumin/creatinine ratio and estimated GFR. We intended not to include patients who entered to end stage renal disease or died from renal complications.

Our study showed that SGLT2 inhibitor (dapagliflozin) has a significant favourable impact on kidney function in diabetic patients. This could be inferred from the following: (1) A significant increase in eGFR was found in patients received SGLT2i when compared to placebo group after 6, 9, and 12 months. (2) A significant reduction of urinary albumin/creatinine ratio was found in patients received SGLT2i when compared to placebo group after 9 months and 12 months. (3) In patients treated with dapagliflozin, a significant reduction in urinary albumin/creatinine ratio appeared after 3 months from the start of treatment and continued till the end of the study. (4) In patients treated with dapagliflozin, a significant improvement in eGFR appeared after 3 months from the start of treatment and continued till the end of the study.

This results could be explained by:

These beneficial activities of SGLT2i on renal outcomes may be due to their glucose lowering mechanisms while other renoprotective effects could be independent of them, so SGLT2i protect kidneys by anti-inflammatory effects via reducing serum levels of leptin and IL-6, increasing adiponectin concentrations, mitigating systemic inflammation through decreasing CRP (C-reactive protein) level, and inhibition the IL-1β secretion by macrophages via the ROS-NLRP3-caspase-1 pathway [(8)]**.** As well as some other mechanisms such as lowering serum uric acid levels, blood pressure, and glomerular hyperfiltration are independent of their glucose-lowering properties. The reduction in glycemic variations may contribute to the reduction of decrease in CVD risk, as acute glucose variations during postprandial periods had a potential role in oxidative stress in patients with T2D [(9)]**.**

This results are in agreement with **Kobayashi *et al.*** [(10)] who revealed in their retrospective study including Japanese T2DM patients, the incidence of the renal composite outcome was lower in SGLT2i-treated patients than in GLP1Ra-treated patients, and the influence on the change in eGFR by SGLT2i treatment was superior to that by GLP1Ra treatment. And also **Korakas *et al.*** [(11)] revealed the combination of dulaglutide and dapagliflozin improves arterial stiffness, endothelial glycocalyx and albuminuria compared to DPP-4is in patients with T2DM. **Wiviott *et al.*** [(12)] reported that SGLT2is are associated with superior renal outcomes. **Heerspink *et al.*** [(13)] revealed in their study evaluating the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (Dapa-CKD), demonstrated its superiority in terms of renal outcomes in patients with or without diabetes mellitus (DM).

Moreover **Persson *et al.*** [(14)] revealed that dapagliflozin prevented the progression of CKD in individuals with normoglycemia, prediabetes, and type 2 diabetes, with similar safety across these

subgroups. These data support the favorable benefit-to-risk ratio of dapagliflozin in patients with CKD independent of glycemic status. Also demonstrated that the effects of dapagliflozin on kidney failure, heart failure, and mortality outcomes were consistent regardless of the glycated hemoglobin subgroups. Major hypoglycemia or ketoacidosis events did not occur in participants with normoglycemia or prediabetes, providing reassurance that dapagliflozin can be safely used in these individuals. And explained that albuminuria, hemoglobin, and hematocrit were identified as important mediators, pointing to a potential reduction in fluid overload. The recognized effect of SGLT2 inhibitors on hemoglobin and hematocrit may reflect improvement in renal hypoxia and restoration in the hypoxia-inducible factor 1a/2a balance, stimulating erythropoiesis and reducing inflammation [(15)].

Our study showed that SGLT2 inhibitor (dapagliflozin) has a significant impact on glycemic control: (1) A significant reduction of HbA1C was found in patients treated by dapagliflozin when compared with placebo group after 9 months and 12 months. (2) In patients treated with dapagliflozin, a significant reduction in HbA1C level appeared after 6 months from the start of treatment and continued till the end of the study.

This result could be explained by:

SGLT2 inhibitors are the novel addition to oral anti-diabetic drugs (OADs) inhibit glucose reabsorption in the kidney mediated by SGLT2 and results in elimination of glucose via urine, also known as urinary glucose excretion (UGE), which leads to decreased levels of glucose in the blood [(16)]**.** Selective inhibition of SGLT2 inhibitors can reduce glucose renal threshold to as low as 40 to 120 mg/dL[(17)]**.** SGLT-2 inhibitors act independently on insulin, these agents should not confer a risk of hypoglycemia and could be employed as monotherapy or in combination with other agents. Given their mechanism of action, these agents should be effective in patients with any degree of insulin resistance or β-cell function. [(18)]**.** T2D individuals treated with SGLT2i demonstrate improved glycemic control due to increased glucose- and incretin-stimulated insulin secretion and enhanced insulin sensitivity [(19)].

This result is in agreement with **Calapkulu *et al.*** [(20)] who revealed that dapagliflozin decreases the fasting plasma glucose, postprandial plasma glucose and HbA1c levels by increasing glucose excretion in the urine. **Hassoun *et al.*** [(21)] revealed dapagliflozin in combination with other antidiabetic medications exhibited significant improvement in glycemic control. **Jiang *et al.*** [(22)] revealed that dapagliflozin adjunct to insulin is a safe and effective therapy for improving glycemic variations, insulin sensitivity, and weight loss in newly diagnosed T2D patients. They observed that dapagliflozin, as an adjunct to insulin, significantly reduced basal and bolus insulin doses in T2D after 5-week treatment, with no weight changes and hypoglycemia. Also analyzed β-cell function and insulin sensitivity in patients between groups, subjects receiving dapagliflozin as an add on therapy had statistically improved in insulin sensitivity and beta cell function, and explained that SGLT2 inhibitors have the potential ability to preserve beta cell mass in diabetic mouse model [(23)].

Shyr *et al.* [(24)] revealed that treatment with the SGLT2 inhibitor dapagliflozin restored insulin content, decreased proinsulin : insulin ratio and reduced oxidative and endoplasmic reticulum stress. Their data from mouse models demonstrate that: i) hyperglycemia per se, and not insulin hypersecretion, drives β-cell failure in diabetes, ii) recovery of β-cell function by SGLT2 inhibitors is potentially through reduction of oxidative and ER stress, iii) SGLT2 inhibitors revert/prevent β-cell failure when used in early stages of diabetes, but not when loss of β-cell mass/identity already occurred, iv) common execution pathways may underlie loss and recovery of β-cell function in different forms of diabetes.

Our study showed that SGLT2 inhibitor (dapagliflozin) has a pleiotropic effects on body mass index and blood pressure: (1) A significant reduction of BMI in dapagliflozin group patients compared to placebo group at the end of the study (after 12 months). (2) A significant reduction of SBP and DBP was reported after 1 year in dapagliflozin group patients compared to placebo group.

This results could be explained by:

Using of SGLT2 inhibitor associated with weight loss resulting from the loss of glucose (calories) in urine and glucose-induced osmotic diuresis. Their mild osmotic diuretic effect could potentially also reduce blood pressure [(18)]**.**

These results are in agreement with **Cosentino *et al.*** [(25)] who reported that in addition to the glucose-lowering effect of SGLT2i, pleiotropic effects, such as the improvement of blood pressure (BP), body weight (BW), triglyceride, and HDL-cholesterol, are thought to be related to the improvement of cardiovascular and/or renal outcomes. Also **Calapkulu *et al.*** [(20)] revealed a positive effect of dapagliflozin on weight, so dapagliflozin may be a useful treatment option in the overweight/obese and dyslipidemic diabetic patients. **Hassoun *et al.*** [(21)] revealed that dapagliflozin in combination with other antidiabetic medications exhibited significant improvement in weight, BMI, and systolic BP. Additionally, it demonstrated a well-tolerated safety profile. **Horibe *et al.*** [(26)] revealed that the addition of dapagliflozin significantly reduced BM and fat mass in patients with type 2 diabetes receiving oral anti-diabetic agents and skeletal muscle mass showed no significant reduction after treatment with

dapagliflozin for 24 weeks, except for an acute reduction in the legs at 2 weeks, but IHTG content is reduced by dapagliflozin treatment and changes in the plasma amino acid profile were subtle for most of the amino acids after treatment with dapagliflozin for 24 weeks. **Fuchigami *et al.* [27]** revealed in their randomized study conducted on Japanese patients to compare the efficacy of dapagliflozin versus sitagliptin that a body weight reduction of ≥3.0% was significantly achieved with dapagliflozin. Moreover, dapagliflozin was superior to sitagliptin regarding cardiometabolic risks, specifically in suppressing the increase in serum creatinine and the decrease in the eGFR. This suggested that the SGLT2i could be more suitable in preventing cardiovascular events in early stages. **Gameil *et al.* [28]** revealed a metabolic benefits with the administration of SGLT-2 inhibitors mainly through the improvement of the hepatic steatosis, dyslipidemia, glycemic control, and weight loss in patients with concomitant T2D and NAFLD.

Our study showed no significant differences between the two groups regarding common adverse effects. This results could be explained by:

As the mechanism of action of SGLT2i is independent of insulin secretion and insulin action, they reduce plasma glucose concentration with low risk of hypoglycemia, making their use suitable for older individuals **[29].**

These results are in agreement **Dave *et al.* [30]** who analyzed two large U.S.-based databases and found that there was no increase in UTI prevalence with SGLT2i use as compared with that in the use of other anti-diabetic drugs.

Clar *et al.*[31] analyzed the GUTI rate in SGLT2i users, and the results are controversial, ranging from 0 to 12.3% and **Wiviott *et al.* [12]** showed that there was no evidence to suggest that SGLT2 inhibitors were associated with higher risk for AKI versus placebo in clinical trials, in those trials AKI was not well defined and was documented as an adverse event rather than a primary or secondary outcome.

This is disagree with **Halimia and Vergès[32]** who showed SGLT2is were mostly found to induce a significant increase in genital mycotic infections. **Lamos *et al.* [33]** also revealed that SGLT2i has adverse effects including GUTI, polyuria, osmotic diuresis, acute kidney injury (AKI), ketoacidosis, bone fracture, leg and foot amputation, and bladder cancer.

McMurray *et al.* [34] documented adverse events of special interest (AESI) associated with SGLT2i use include diabetic ketoacidosis, amputation, fracture, major hypoglycemia, volume depletion and renal related adverse events.

Limitation of the study: A longer follow up period will be necessary to assess renal protection accurately, additionally the relative small number of studied patients.

CONCLUSION

We found that SGLT2 inhibitor (dapagliflozin) can be considered a reno protective drug in type 2 diabetic patients. The study also confirmed that SGLT2 inhibitor (dapagliflozin) have a pleiotropic effects on body mass index and blood pressure and has a great impact on glycemic control without significant differences between the two groups regarding common adverse effects (UTI, genital tract infection, ketoacidosis, documented hypoglycemia hypovolemia, hypotension, etc.).

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