ORIGINAL ARTICLE

EFFECT OF DAPAGLIFLOZIN AND EMPAGLIFLOZIN ON BODY WEIGHT, LIPID PROFILE AND BLOOD PRESSURE IN TYPE 2 DIABETICS

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Background: Cardiovascular disease (CVD) is a leading cause of death in type 2 diabetes mellitus (T2DM) patients with risk factors including weight, lipid profile, and blood pressure. Evidence suggests sodium-glucose co-transporter 2 (SGLT-2) inhibitors benefit T2DM patients. This study investigated the effects of SGLT-2 inhibitors on these risk factors in T2DM patients. **Methods:** This quasi-experimental study at Sheikh Zayed Medical College/Hospital, Rahim Yar Khan randomized T2DM patients with inadequate glycaemic control. First group received dapagliflozin 5–10 mg and second group received empagliflozin 10–25 mg as add-on therapy to conventional antidiabetic drugs for 12 weeks. The dose was adjusted based on serum blood sugar, with primary endpoints assessing changes in glycaemic control (blood sugar and HbA1c) from baseline. Secondary endpoints included recording additional glycaemic effects (body weight, BMI, lipid profile, and blood pressure) from baseline to endpoint. **Results:** Both drugs showed excellent tolerability and safety profiles with no major adverse effects. Significant reductions in body weight (empagliflozin 86.7±18 to 78±16.5 Kg, p=0.001; dapagliflozin 89.8±12 to 83±10 Kg, p=0.005), and BMI (empagliflozin 28±5.5 to 26.5±4.2 Kg/m², p=0.003; dapagliflozin 29.6±4.2 to 25.7±5.8 Kg/m², p=0.002) were observed. Both drugs significantly improved glycaemic control, fasting blood sugar (empagliflozin 180±32 to 140±44 mg/dL, p=0.003; dapagliflozin 190±48 to 150±33 mg/dL, p=0.005) and HbA1c (empagliflozin 9.7±2.6 to 7.5±1.8%, p=0.004; dapagliflozin 9.0±1.82 to 7.0±2.2%, p=0.001). Neither drug showed significant improvements in blood pressure or serum lipid profile. **Conclusion:** Empagliflozin and dapagliflozin have a modest effect on CVD risk factors in T2DM patients.

Keywords: Dapagliflozin, Empagliflozin, BMI, HbA1c, Lipid Profile, Blood Pressure

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), one of the most prevalent forms of diabetes, is increasing drastically across the globe. The current data depicts that the number of diabetic patients has reached 240 million during the last 20 years. The epidemic of diabetes affects developing countries more as compared to developed nations. This ranks Pakistan at 4th position in world for diabetes with 19.4% prevalence in 2019. The number of diabetic patients in Pakistan is expected to reach 6.8 million over a period of 11 years from 2019 to 2030. There is a strong need to control diabetes to reduce burden on public health system.[1]

Cardiovascular disease (CVD) is one of the leading causes of death in T2DM patients. The risk of CVD is almost double in diabetics as compared to non-diabetic patients. Obesity, hypertension, dyslipidemia, insulin resistance, and subclinical inflammations are important determinants of CVD in T2DM patients.[2]

T2DM and risk factors of cardiovascular diseases like insulin resistance, especially in obese people, physical inactivity, unhealthy diet, increased BMI, and high lipid profile with or without hypertension are associated with family history. T2DM produces macro and microvasculature complications like retinopathy, neuropathy, and nephropathy and macrovascular include angina pectoris, myocardial infarction, stroke, and peripheral vascular disorders.[3] Sodium-glucose co-transporter 2 (SGLT-2) inhibitors have possible beneficial effects on CVD risk factors such as best glycaemic control and body weight. Moreover, SGLT-2 inhibitors also surrogate markers of inflammation and improve cardiovascular health and ejection fraction. Recently SGLT-2 inhibitors have been more suitable drugs for T2DM patients because of these potentially beneficial effects.[4]

The risk factors of CVD and T2DM are the same. Researchers are emphasizing those anti-diabetic drugs that have a potential benefit on traditional and nontraditional risk factors of CVD in T2DM patients. Currently, there are seven classes of antidiabetic drugs and various others are under study. Antidiabetic drugs like metformin, GLP-1 analog DPP-4 inhibitors, and SGLT-2 inhibitors have proven cardiovascular beneficial effects in T2DM.[5]

Empagliflozin and Dapagliflozin have unique mechanisms of action than other conventional anti-diabetic drugs. They control blood sugar by inhibiting the sodium and glucose reabsorption from proximal convoluted tubule of the kidney.[6] Moreover they have additional benefits on body weight, blood pressure, insulin resistance, dyslipidemia, uric acid level, fatty liver, subclinical inflammation and oxidative stress.[7] Researchers are more concerned about SGLT-2 inhibitors regarding their cardiovascular safety profile in various clinical studies. Four major clinical trials by SGLT-2 inhibitors (Empareg-outcome, Canvas, Declare and Credence) showed a significant reduction in risk of heart failure hospitalizations and diabetes related kidney disease.[8] Empagliflozin has proven cardiovascular benefits in T2DM. Recently FDA approved dapagliflozin and empagliflozin use in patients with heart failure irrespective of glycaemic status.[9]

The present study aimed to investigate the effects of empagliflozin and dapagliflozin on CVD risk factors in T2DM patients.

METHODOLOGY

This quasi-experimental study was conducted at Cardiology and Diabetic Clinic of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, Pakistan. A total of 460 patients were scrutinized from these clinical settings, out of which 220 were enrolled in the study. All individuals diagnosed with T2DM, between the ages of 35 and 65 years, currently being treated with oral antidiabetic drugs with a serum HbA1c level 7.5–11% were included in the study.[10,11] The study excluded individuals with a medical history of liver disease, renal insufficiency, neurological disorders, and malignancy. The patients were allocated into two groups using randomization. The patients in group A were administered Tab. Dapagliflozin in doses of 5–10 mg, while the patients in group B were administered Tab. Empagliflozin in doses of 10–25 mg.[12] This additional medication was provided to both groups over 12 weeks.[13]

Patients were reached out weekly to enquire about their medication intake.[14] The dosage of each medication was modified by the individual's blood glucose levels. The study's perspectives were clearly explained to all patients before taking informed consent. The study was approved by the Institutional Review Board (IRB) of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan.

The primary endpoint of our study was to assess body weight, glycaemic control (blood sugar and HbA1c) and safety profile of both drugs.[15] The secondary end point of our study was to determine the extra glycaemic effects (BMI, blood pressure and lipid profile) of dapagliflozin and empagliflozin. A digital weighing machine and Microtoise stature meter were used to determine body weight and height respectively. A standard formula weight in Kg divided by height in m^2 (Kg/m^2) was used to calculate BMI. Blood pressure was measured with a mercury sphygmomanometer in supine position twice over a period of 15 minutes. Blood sugar, HbA1c and serum lipid profile were analysed by Microlab 300 following standards protocols.

SPSS-22 was used to analyse the data. Data was presented as Mean±SD, frequencies and percentages. A paired *t*-test and Chi-square test were used to analyse percentage changes and secondary end-point from baseline. Differences within groups measured at baseline and week 12 were analysed using independent samples *t*-test. Differences within group measured at baseline and week 12 were analysed using a paired-sample *t*-test, and $p \leq 0.05$ was considered statistically significant.

RESULTS

The baseline demographic characteristics of study subjects at the start of study are shown in Table-1 which shows no significant statistical differences among various study parameters. Patients taking antidiabetic medication as monotherapy as well as combination therapy are shown in Table-1. The safety and tolerability profiles of both drugs were quite good, and no major adverse effects were recorded during the study period. However, minor adverse effects in the form of nausea and increased urination were reported in 5 patients in dapagliflozin and 8 in empagliflozin group. These adverse effects settled without any intervention after first week of therapy.

A significant improvement in body weight and BMI was seen in both groups of SGLT-2 inhibitors after 12 weeks of treatment. Empagliflozin significantly reduced body weight from 86.7±18 to 78±16.5 Kg, (p=0.001), and Dapagliflozin significantly lowered body weight from 89.8±12 to 83±10 Kg (p=0.005). BMI in Group A was significantly reduced from 29.6±4.2 to 25.7±5.8 Kg/m^2 (p=0.002) while that in Group B was reduced from 28±5.5 to 26.5±4.2 Kg/m^2 (p=0.003).

A comparison between empagliflozin and dapagliflozin in terms of body weight and BMI was not significant. Both drugs significantly reduced fasting blood sugar (empagliflozin from 180±32 to 140±44 mg/dL, p=0.003; dapagliflozin from 190±48 to 150±33 mg/dL, p=0.005) and HbA1c (empagliflozin from 9.7±2.6 to 7.5±1.8%, p=0.004; dapagliflozin from 9.0±1.82 to 7.0±2.2%, p=0.001). No significant changes were observed between two groups based on blood sugar and HbA1c. There was no significant improvement in blood pressure and serum lipid profile by both drugs within and between groups (Table-2).

Table-1: Baseline and clinical Characteristics at the start of study in groups

Demographic Characteristics	Empagliflozin Group A (n=110)	Dapagliflozin Group B (n=110)	*p*
Age (Years)	52±9.5	58±7.8	0.71
Gender (M/F)	80 (72.7%)/30 (27%)	78 (71.0%)/32 (29.0%)	0.52
Body weight (Kg)	86.7±18	89.8±12	0.42
BMI (Kg/m^2)	28.0±5.5	29.6±4.2	0.66
Diabetes duration (Years)	10.3±3.2	12.4±4.2	0.82
Laboratory Parameters			
Serum glucose Fasting (mg/dL)	180±32	190±48	0.62
HbA1c (%)	9.7±2.6	9.0±1.82	0.32
SBP (mmHg)	135±14	140±8.6	0.45
DBP (mmHg)	88±10	86±12	0.54
Total Cholesterol (mg/dL)	180±20.5	175±19.8	0.82
Triglycerides mg/dL)	136±24.5	165±20.2	0.72
LDL-Cholesterol (mg/dL)	128±19.5	129±15.6	0.33
HDL-Cholesterol (mg/dL)	36.4±5.5	38±7.4	0.93
Concomitant antidiabetic drugs [n (%)]			
Metformin	8 (7.2%)	10 (9.0%)	0.32
Sitagliptin	10 (9.0%)	8 (7.2%)	0.67
Vildagliptin	10 (9.0%)	7 (6.3%)	0.49
Glimepiride	20 (18.0%)	21 (19.0%)	0.27
Metformin+Glimepiride	22 (28.0%)	24 (21.8%)	0.87
Sitagliptin+Metformin	21 (19.0%)	23 (20.9%)	0.92
Vildagliptin+Metformin	19 (17.2%)	17 (15.4%)	0.42

Table-2: Changes in the parameters from baseline to end point in study groups

Group A Empagliflozin (n=110)				Group B Dapagliflozin (n=110)				
Parameters	0 weeks	12 weeks	*p**	Parameters	0 weeks	12 weeks	*p**	*p***
Body weight(Kg)	86.7±18	78±16.5	0.001	Body weight (Kg)	89.8±12	83±10	0.005	0.76
BMI (Kg/m^2)	28.0±5.5	26.5±4.2	0.003	BMI (Kg/m^2)	29.6±4.2	25.7±5.8	0.002	0.23
FBG (mg/dL)	180±32	140±45	0.003	FBG (mg/dL)	190±48	150±33	0.005	0.52
HbA1c (%)	9.7±2.6	7.5±1.8	0.004	HbA1c (%)	9.0±1.82	7.0±2.2	0.001	0.67
SBP (mmHg)	135±14	138±12	0.86	SBP (mmHg)	140±8.6	136±10	0.23	0.44
DBP (mmHg)	88±10	90±8.6	0.33	DBP (mmHg)	86±12	83±9.7	0.42	0.92
Total Cholesterol (mg/dL)	180±20.5	182±25	0.78	Total Cholesterol (mg/dL)	175±19.8	165±22	0.32	0.88
Triglycerides (mg/dL)	136±24.5	146±22	0.62	Triglycerides (mg/dL)	165±20.2	155±25	0.21	0.72
LDL-Cholesterol (mg/dL)	128±19.5	126±25.5	0.42	LDL-Cholesterol (mg/dL)	129±15.6	135±18	0.33	0.92
HDL-Cholesterol (mg/dL)	36.4±5.5	36±4.1	0.34	HDL-Cholesterol (mg/dL)	38±7.4	37±5.5	0.72	0.98

*Differences within group measured at baseline and week 12, **Differences within groups measured at baseline and week 12

DISCUSSION

This study investigated the glycaemic and nonglycaemic effects of SGLT-2 inhibitors. We observed the impact of dapagliflozin and empagliflozin as adjunct therapy in patients with type 2 diabetes mellitus (T2DM) who had inadequate glycaemic control despite conventional antidiabetic drugs. Our findings demonstrate that both drugs significantly enhanced glycaemic control over 12 weeks, leading to significant reductions in body weight and BMI. However, neither medication showed significant improvements in blood pressure or lipid profile.

Many studies recommend use of anti-diabetic drugs that have a potential benefit against traditional and nontraditional risk factors of cardiovascular disease in diabetic patients. Currently, studies are focusing more on GLP-1 analogues, DPP-4, and SGLT-2 inhibitors regarding their cardiovascular safety profile.[16]

In our study, there was a significant reduction in HbA1c and body weight by dapagliflozin and empagliflozin over a period of 12 weeks. Similar findings were observed in a randomized controlled trial in which empagliflozin significantly reduced body weight and HbA1c over a period of 12 and 24 weeks respectively.[17] In another controlled clinical trial, dapagliflozin as add-on therapy significantly reduced body weight (-1.21 Kg, $p<0.0001$) and HbA1c (-0.60%, $p<0.0001$) in patients with type 2 diabetes who had inadequate glycaemic control, without any episodes of severe hypoglycemia.[18] In our study, a comparison was done between two SGLT-2 inhibitors while in above mentioned studies comparison was done between SGLT-2 inhibitors and placebo.

An open-label prospective study demonstrated that over 52 weeks, empagliflozin led to a significant reduction in fasting blood sugar and HbA1c compared to dapagliflozin.[19] Both drugs significantly reduced body weight and blood pressure while increased HDL-C was observed in empagliflozin group only. In our study both drugs significantly reduced body weight, blood sugar and HbA1c over a period of 12 weeks. No significant findings were recorded regarding blood pressure and serum lipid profile by both drugs. In our

study efficacy and safety profile of both SGLT-2 inhibitors was quite good and no major adverse effects were reported during the study.

A review study[20] revealed that empagliflozin is one of the safest drugs and can be prescribed in patients with renal impairments. However, both dapagliflozin and empagliflozin showed excellent safety and tolerability profile in our study.

Canagliflozin at a dose of 300 mg as an add on therapy caused a significant reduction in HbA1c as compared to empagliflozin 25 mg and dapagliflozin 10 mg in a 26 weeks study[21] in United Arab Emirates. Our study duration was 12 weeks and both empagliflozin and dapagliflozin significantly improved glycaemic control as a combination therapy with different antidiabetic drugs. The results of our study are similar to a study conducted in China in which both SGLT-2 inhibitors reduced body weight, fasting blood sugar, and HbA1c over a period of 6 months. Moreover, both drugs demonstrated beneficial effects on liver impairment and insulin resistance.[22] A study showed that empagliflozin has a beneficial effect on body weight and glycaemic control with good safety and tolerability profile. However, no significant improvement was observed in systolic and diastolic blood pressure and serum lipid profile similar to our study.[22]

In a systematic review[23] and meta-analysis of 48 randomized controlled trials SGLT-2 inhibitors significantly increased total cholesterol, LDL-C, HDL-C, non-HDL-C, and decreased serum triglycerides level. However, no significant changes were recorded in LDL/HDL ratio. In another narrative review[24] SGLT-2 inhibitors had beneficial effects on body weight and glycaemic control while they had moderate effects on blood pressure and serum lipid profiles similar to our study.

Another study[25] demonstrated a significant reduction in HbA1c levels ($p<0.01$) and BMI ($p<0.001$) with 6 months treatment of 10 mg daily dose of dapagliflozin. That study also showed a significant decrease in the levels of TC and LDL-C but HDL-C and TG levels were not changed significantly. The present study did not find any significant changes in TC and LDL-C levels, but changes in HDL-C levels were relatively similar to Hong *et al*[25].

In a systematic review[26] and meta-analysis of 12 randomized trials, empagliflozin 10 mg and 25 mg significantly reduced body weight, BMI, fasting blood sugar, HbA1c, serum uric acid, systolic and diastolic blood pressure. That data supports that empagliflozin has beneficial effects on cardiovascular risk factors in type 2 diabetic patients.

In a retrospective cohort study[27] (249 T2DM patients) six SGLT-2 inhibitors (tofogliflozin, canagliflozin, empagliflozin, ipragliflozin, dapagliflozin and luseogliflozin) significantly reduced body weight, BMI, fasting blood sugar, HbA1c, serum uric acid, liver functions, HDL-cholesterol, non-HDL cholesterol, systolic and diastolic blood pressure. In another retrospective cohort study[28], six SGLT-2 inhibitors as above significantly reduced HbA1c, body weight and liver function while no significant effects were observed on serum lipid profile and blood pressure.

In a systematic review[29] and meta-analysis of 08 randomized trial including cohort of 5,233 nondiabetic patients, SGLT-2 inhibitors significantly reduced blood sugar, HbA1c, body weight, BMI, and systolic blood pressure while no significant effects were seen on LDL-cholesterol and diastolic blood pressure. Moreover, there was 20% relative risk reduction of cardiovascular deaths and heart failure hospitalization by SGLT-2 inhibitors.

CONCLUSION

Empagliflozin and dapagliflozin both demonstrated reductions in body weight and blood glucose levels. However, their impact on serum lipid profile and blood pressure did not reach statistical significance. While SGLT-2 inhibitors give benefits in T2DM patients, their effects on cardiovascular disease risk factors are limited.

DISCLOSURE

All authors agree to take responsibility for the work and confirm that all questions related to the accuracy and integrity of the research have been properly and thoroughly resolved.

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MH: Concept of study, data collection, manuscript writing
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AQA: Concept of study, abstract writing and critical review
AA: Data analysis and interpretation
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