ORIGINAL ARTICLE

COMPARISON OF EFFICACY AND SAFETY PROFILE OF EMPAGLIFLOZIN VERSUS DAPAGLIFLOZIN AS ADD ON THERAPY IN TYPE 2 DIABETIC PATIENTS

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Background: SGLT-2 (sodium-glucose cotransporter-2) inhibitors are a novel class of oral hypoglycemic agents for the management of type 2 diabetes mellitus (T2DM). Herein, we aimed to assess the efficacy and safety profile of empagliflozin versus dapagliflozin in type 2 diabetic patients **Methods:** In this randomized controlled trial, type 2 diabetic patients with inadequate glycaemic control HbA1c 7.5–11% with different first line anti diabetic medications were randomly divided in to two groups. Group A were given tablet Empagliflozin 25 mg while Group B were given tablet Dapagliflozin 10mg over a period of 12 weeks. The primary end point was to measures efficacy profile in terms of changes in body weight, BMI, fasting blood sugar and HbA1c. The secondary end point was to determine safety and tolerability profile. **Results**: After 12 weeks of treatment body weight was reduced significantly in both groups empagliflozin -2.9±6.4 kg (p=0.002) versus dapagliflozin -1.7±2.4 (p=0.007). However, comparison between two groups was non-significant (p=0.032). FBS was reduced in both study groups empagliflozin -75.6±43.5 mg/dl versus dapagliflozin -63.5±60.5 mg/dl with p<0.01. However, empagliflozin caused a significant reduction in fasting blood sugar as compared to dapagliflozin (p=0.001). HbA1c was also significantly reduced in both groups empagliflozin -1.7±0.9% versus dapagliflozin -1.2±1.4% with p<0.01. However, empagliflozin caused a more significant reduction in HbA1c as compared to dapagliflozin (p=0.002). The tolerability profile of both drugs was quite good and no major adverse effects were reported in both study groups. However minor adverse effects were observed in both study groups. There was low risk of urinary and genital infection with empagliflozin (2.34% & 3.1%) as compared to dapagliflozin (7.08% and 8.66%) with p-value 0.003 and 0.005 respectively. **Conclusion:** Both empagliflozin and dapagliflozin has excellent efficacy and safety profile. They can be used as add on therapy in type 2 diabetic patients.

Keywords: Dapagliflozin; Empagliflozin; BMI; HbA1c; Safety Profile; Adverse Effect

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INTRODUCTION

Diabetes mellitus a chronic metabolic disorder is escalating at an alarming rate worldwide. One out of eleven people has diabetes. Current prediction reveals that the number of diabetic patients will be expected to rise from 450 million to 642 million over a period of 20 years. Pakistan stands at 7th position in world diabetic ranking. There were about 7.5 million diabetic patients in Pakistan in 2017. This number will be expecting to reach 11.4 million in 2030. This will add significant morbidity as well as mortality and pose an enormous economic burden.[1,2]

Seeing this global burden of type 2 diabetes, there is also significant advancement in the treatment of diabetes. Oral anti diabetics usually consider first regarding type 2 diabetes management in addition to life style modification. Currently there are seven groups of anti-diabetic medications up till now and various others are under consideration. These groups are Biguanides, Sulphonyl-ureas, Alpha glycosidase inhibitors, thiazolidinediones, GLP receptor agonist, DPP-4 and SGLT-2 inhibitors. These drugs are acts through multiple mechanisms to control blood sugar.[3] Sodium glucose co transport (SGLT-2) inhibitors are the latest anti diabetic drugs with unique mechanism of action than conventional anti diabetic agents. The anti-diabetic effect of SGLT-2 inhibitors is medicated by inhibiting the glucose reabsorption from the proximal convoluted tubule of the kidney. This effect causes increase excretion of glucose in urine. SGLT-2 inhibitors are considering ideal in this stance that about 90% of the filtered load of glucose is reabsorbed in the proximal convoluted tubule. The FDA approved drugs of this group are canagliflozin, dapagliflozin and empagliflozin.[4,5]

Various Studies have shown that SGLT-2 inhibitors have excellent efficacy, safety and tolerability profile with no risk of hypoglycaemia. Moreover SGLT-2 inhibitors have promising effect on body weight, blood pressure, dyslipidaemia and fatty liver.[6] Clinical trials are under consideration with positive results regarding their safety in cardiovascular and kidney disease.[7,8] SGLT-2

inhibitors usually recommended as 2nd line anti diabetic drug when there is inadequate glycaemic control with the first line anti diabetic drugs. However, they are also recommended monotherapy as well.[9]

The present study was conducted to assess the safety and tolerability profile of SGLT-2 inhibitors (dapagliflozin & empagliflozin) as add on therapy in type 2 diabetic patients over a period of 3 months.

MATERIAL AND METHODS

This 12 weeks randomized controlled trial was conducted at four private clinical setting as well as diabetic clinic of Sheikh Zayed Medical College from March to May 2020. A total of 410 patients were recruited from these clinical setting. Out of which 280 were enrolled in the study following inclusion and exclusion criteria. Inclusion criteria was type 2 diabetic patients with inadequate glycaemic control, i.e., HbA1c 7.5–11% with different first line anti-diabetic drugs combinations such as metformin, glimepiride, sitagliptin, vildagliptin. Patients with history of pregnancy, lactation, type 1 diabetes, gestational diabetes, pancreatitis, hepatic insufficiency, renal dysfunction, hypothyroidism, Cushing syndrome, cancer, genitourinary infection, oral contraceptive and steroids were excluded from the study. A written informed was taken from all patients and study perspectives were clearly explained to them. A study protocol was approved by the Institutional Review Board (IRB) of Sheikh Zayed Medical College.

Patients were randomly divided in to two groups. Randomization was done through simple random sampling. Patients in group A were given tab empagliflozin 10–25 mg while patients in group B were given tab dapagliflozin 5–10 mg daily as add on therapy over a period of 12 weeks. The doses of SGLT-2 inhibitors, DPP-4 inhibitors and metformin were maintained while dose of glimepiride was reduced if patients developed hypoglycaemic episodes. The primary end point was to measure changes in efficacy between two group, i.e., body weight, BMI, fasting blood sugar and HbA1c from baseline. The secondary end point was to observe the safety and tolerability profile between two group, i.e., adverse effects from baseline. All the parameters were measured before start and at the end of study. Body mass index BMI was measured by using standard formula weight in kg divided by height in m^2 (kg/m^2). Fasting blood sugar was analysed by glucose oxidase peroxidase method. HbA1c was measured by liquid chromatography while fasting serum lipid profile was measured by enzymatic end point method.

Data were analysed by using SPSS-16. Numeric data values body weight, BMI, blood sugar and HbAIC were expressed as mean± SD. The frequency data were expressed as percentage. The difference in primary end point from baseline was done by paired t test while difference in secondary end point from baseline was determined by Chi-square test. *p*-value <0.05 was considered to be statistically significant and *p*-value <0.01 was considered to be highly significant.

RESULTS

A total of 410 type 2 diabetic patients were recruited, out of which 356 were enrolled in the study. 76 Patients were excluded and 280 were randomized in to two groups. Ten patients in Empagliflozin and 15 patients in dapagliflozin group were drop out, 128 patients were analysed in empagliflozin and 127 in dapagliflozin group has shown in flow chart Figure-1**.**

There is no difference in baseline demographic characteristics and clinical study parameters in both study groups at the start of study. The number (%) of patients taking other anti-diabetic medications has shown in (Table 1).

After 12 weeks of treatment body weight was reduced significantly in both groups empagliflozin -2.9±6.4kg (p=0.002) versus dapagliflozin -1.7±2.4 (p=0.007). However, comparison was found to be non-significant between groups (p=0.032). Similarly fasting blood sugar level was reduced in both study groups empagliflozin -75.6±43.5 mg/dl versus dapagliflozin -63.5±60.5 mg/dl with p<0.01. However, empagliflozin caused a more significant reduction in fasting blood sugar as compared to dapagliflozin (p=0.001) at 12 weeks. HbA1c was also significantly reduced in both groups empagliflozin -1.7±0.9% versus dapagliflozin -1.2±1.4% with p<0.01. However, empagliflozin caused a more significant reduction in HbA1c as compared to dapagliflozin (p=0.002) at 12 weeks (Table-2).

The tolerability profile of both drugs was quite good and no major adverse effects were reported in both study groups. However minor adverse effects were observed in both study groups (Table 3). There was low risk of urinary and genital infection with empagliflozin (2.34% & 3.1%) as compared to dapagliflozin (7.08% and 8.66%) with p value 0.003 and 0.005 respectively.

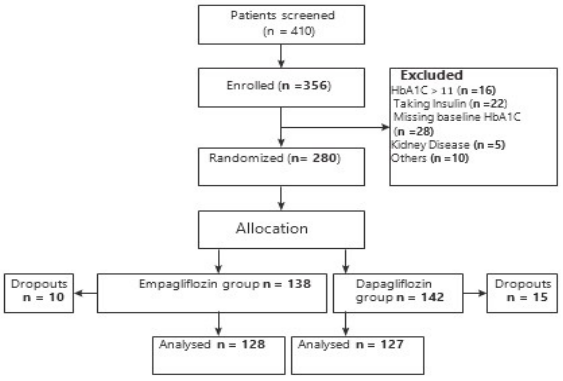

Figure-1: Flow chart of study design

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

Demographic Characteristics	Empagliflozin (n=128)	Dapagliflozin (n=127)	*p*-value
Age (years)	48.7±10.2	55±15.8	0.82
Gender (M/F)	84 (66%) 44 (34%)	91 (72%/36 (28%)	0.44
Body weight (kg)	82.4±16	81.6±18	0.36
BMI (kg/m2)	27.0±8.0	27.8±6.8	0.22
Diabetes duration (years)	8.6±4.2	10.2±6.5	0.65
Parameters Lab (mean ± SD)			
Serum glucose F(mg/dl)	177±44.6	201.4±58	0.44
HbA1c (%)	9.8±2.2	8.9±0.82	0.62
Total Cholesterol (mg/dl)	176±24.4	182.2±28.4	0.37
Triglycerides (mg/dl)	166±33.4	175±29.5	0.81
LDL-Cholesterol (mg/dl)	122±22.2	132±14.4	0.54
HDL-Cholesterol (mg/dl)	39.4±7.2	42±6.4	0.73
Concomitant Antidiabetic drugs (%)			
Metformin	14 (11%)	16 (12.5%)	0.21
Sitagliptin	11 (8.5%)	8 (6.2%)	0.45
Vildagliptin	11 (8.5%)	8 (6.2%)	0.64
Glimepiride	22 (17%)	25 (19.6%)	0.79
Metformin+ Glimepiride	36 (28%)	30 (23.6%)	0.56
Sitagliptin +Metformin	22 (17%)	25 (19.6%)	0.54
Vildagliptin+ Metformin	12 (9.3%)	15 (11.8%)	0.29

Values are given ±standard deviation

Table-2: Changes in the parameters from baseline in both study groups

Group A Empagliflozin(n=128)				Group B Dapagliflozin (n=127)				*p*-value‡
Parameters	**0 weeks**	**12 weeks**	***p* value†**	**Parameters**	**0 weeks**	**12 weeks**	***p* value†**	
Body weight (kg)	82.4±16	79.2±10	0.002	**Body weight(kg)**	81.6±18	80.5±4	0.007	0.032
BMI (kg/m2)	27.0±8.0	26.8±6.4	0.001	**BMI (kg/m2)**	27.8±6.8	26.6±5.6	0.001	0.016
FBG (mg/dl)	177±44.6	125.4±655	0.004	**FBG (mg/dl)**	201.4±58	140±5.8	0.008	0.001
HbA1c (%)	9.8±2.2	7.62±1.9	0.006	**HbA1c (%)**	8.9±0.82	7.5±1.4	<0.007	0.002

†Differences within groups measured at baseline and week 12. ‡Differences within group measured at baseline and week 12.

Table-3: Adverse effects reported in both study group.

Adverse Effects	Group A Empagliflozin(n=128)	Group B Dapagliflozin(n=127)	*p*-value*
Serious adverse effect leading to discontinuation	0	0	
Severe Hypoglycaemia (glucose < 70mg/dl)	2 (1.6%)	4 (3.14%)	0.32
Genital Infection	3 (2.34%)	15 (7.08%)	0.003
Urinary infection	4 (3.1%)	11 (8.66%)	0.005
Urgency	2 (1.6%)	3 (2.36%)	0.82
Frequency	5 (3.9%)	4 (3.14%)	0.56
Nocturia (3times/night)	3 (2.3%)	3 (2.36%)	0.72
Total Adverse effects	19	40	0.002

*Chi-square test was performed for comparison between groups.

DISCUSSION

The present study was conducted to determine the efficacy and safety profile of empagliflozin in comparison with dapagliflozin as add on therapy in type 2 diabetic patients, with inadequate glycaemic control with first line anti diabetic therapies. The results of our study showed that both drugs have excellent efficacy and safety profile. However, in comparison with dapagliflozin, empagliflozin caused a more significant improvement in body weight, fasting blood sugar and HbA1c over a period of 12 weeks. Similarly, in comparison with dapagliflozin, there were less adverse effects reported in empagliflozin group over a period of 3 months.

The drug management of diabetes also changes a lot with the passage of time. It is very difficult to achieve optimal glycaemic control with monotherapy due to complex and progressive nature of type 2 diabetes. This leads to use two to four anti diabetic drugs as combination therapy in type 2 diabetic patients. This combination therapy is also recommended as guideline by both American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in type 2 diabetic patients with inadequate glycaemic control with monotherapy.[10]

In our study both empagliflozin and dapagliflozin significantly reduced body weight. This was favoured by study conducted in two different cohort at 12 and 24 weeks by Neeland *et al*[11], who

demonstrated that empagliflozin significantly reduced HbA1c (-0.61%) and body weight -1.7 (−2.1 to −1.4kg) at 12 weeks while reduced HbA1c-0.73%) and body weight 1.9 (−2.1 to −1.7kg) at 24 weeks. Similarly in another clinical study dapagliflozin reduced HbA1c 0.3% and body weight -4.54kg over a period of 152 weeks with inadequate glycaemic control with metformin.[12] In above mentioned studies the comparison was done with placebo while in our study comparison was done between two SGLT-2 inhibitors.

Our results were similar to study conducted by et al revealed in comparison with dapagliflozin, empagliflozin reduced body weight, blood sugar and HbA1c. Moreover, there were low chances of genitor urinary infection with empagliflozin. However, the duration of study was 52 weeks in comparison with our study. Moreover empagliflozin also improved others cardiometabolic risk factor more significantly as compared to dapagliflozin as we did not investigate these parameters.[13] A review regarding efficacy, safety and tolerability of different SGLT-2 inhibitors demonstrated that empagliflozin is one of the safest and can be prescribe in type 2 diabetic patients with renal impairment.[14] While our study demonstrated that the tolerability, efficacy and safety profile of both drugs were quite good but empagliflozin showed a better edge statistically . However, we did not assess their safety in renal impairment patients.

A study conducted in United Arab Emirates pointed out that canagliflozin 300mg provide a greater reduction in HbA1C (-0.79%) as compared to empagliflozin 25 mg (-0.64) and dapagliflozin 10mg (-0.41%) as add on therapy to metformin in type 2 diabetic patients over a duration of 26 weeks. Our study yields similar result but we did comparison between empagliflozin and dapagliflozin only and our study duration was 12 weeks.[15] Moreover we used SGLT-2 inhibitors as add on therapy with different anti diabetic drugs combinations. A study conducted in Chinese type 2 diabetic patients pointed out that empagliflozin and dapagliflozin reduced body weight, fasting blood sugar and HbA1c similar to our study. In addition, both drugs ameliorate hepatic dysfunction and improve insulin resistance over a period of 6 months.[16]

The efficacy, safety and tolerability profile of empagliflozin[17–20] and dapagliflozin[21–25] as add on therapy was investigated in various clinical studies and yield similar results to our study. These results determined that both drugs reduce body weight and excellent glycaemic control effect with no risk of severe hypoglycaemia similar to our study. Moreover, the risk of urogenital infection varies in these studies from 1–9%. However, in our study the cases of urinary and genital infections were quite lower in most of the above-mentioned studies.

The risk of atherosclerotic disease is very high in type 2 diabetic patients. Treatment with dapagliflozin provides cardiovascular safety with low rate of cardiovascular death and hospitalization due to heart failure.[26] Empagliflozin also reduces cardiovascular events and delays the progression of kidney disease in type 2 diabetes mellitus patients with CVD history. The systematic review and meta-analysis of 27 studies also showed that SGLT-2 inhibitors reduce risk of renal and cardiovascular disease impairment in patients with chronic kidney disease and in patients with diabetes.[27]

CONCLUSION

Both empagliflozin and dapagliflozin has excellent efficacy, safety, and tolerability profile. They can be safely used as add on therapy in type 2 diabetic patients.

There is further need to explore the efficacy and safety of SGLT-2 inhibitors in diabetic patients with cardiovascular disease and renal impairment. Moreover, large sample size and longer study duration will require for their safety and tolerability profile.

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AUTHORS' CONTRIBUTION

MH: Conceived the idea, designed the study, manuscript review and Statistical analysis. MA: Designed the study, preparing the manuscript and data analysis. MB: Search the literature, collected the clinical data and manuscript editing LA: Interpreted the data with final editing and drafting of manuscript. All members hereby agree to take responsibility of the work and confirm that all questions related to the accuracy and integrity of the research has been properly and thoroughly resolved.

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