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ORIGINAL ARTICLE

To compare the efficacy and safety profile of empagliflozin and sitagliptin as an add on therapy to metformin in T2DM patients.

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ABSTRACT… Objective: To compare the efficacy and safety and profile of empagliflozin and sitagliptin as an add on therapy to metformin in T2DM patients. **Study Design:** Randomized Controlled Trial. **Period:** January to March 2024. **Setting:** Sheikh Zayed Medical College & Hospital, Rahim Yar Khan. **Methods:** A total of 280 T2DM patients with inadequate glycemic control on metformin were randomly assigned to receive either empagliflozin or sitagliptin. The primary outcomes included changes in body weight (BW), body mass index (BMI), fasting blood glucose (FBG), HbA1c, systolic and diastolic blood pressure (SBP, DBP), and lipid profile. Secondary outcomes involved monitoring adverse effects throughout the study. **Results:** After 12 weeks, both groups showed significant reductions in BW and BMI, with empagliflozin showing greater improvements (BW: 92.5±13.5 to 79±14.5 kg, BMI: 29.4±4.2 to 27.5±3.8) compared to sitagliptin (BW: 89±16.6 to 81±12.5 kg, BMI: 28.5±5.6 to 27.3±4.2). Similarly, empagliflozin more effectively reduced FBG (240±60.5 to 130±35.5 mg/dL) and HbA1c (8.35±1.9% to 7.2±1.6%) compared to sitagliptin. Both drugs were well-tolerated with no major adverse effects. **Conclusion:** Empagliflozin demonstrated superior efficacy and safety compared to sitagliptin as an add-on therapy to metformin in T2DM management.

Key words: BMI, Empagliflozin, Efficacy, HbA1c, Sitagliptin, Safety, T2DM.

INTRODUCTION

T2DM is one of the most prevalent metabolic disorder and substantial health issue. T2DM is spread like a pandemic in recent years. According to IDF 2021, 537 million people are living with diabetes. This number is projected to rise to 643 million by 2030 and 783 million by 2045. The burden is more (75%) in middle and lower income counties. This will add significant morbidity and mortality and pose a significant burden on health system. There is an urgent need to take necessary action in order to prevent and manage this escalating metabolic disorder.[1]

Asia is the epicenter of global diabetes burden. Asian countries including China, India and Pakistan have the highest number of diabetic individuals (248 million) in the world. The number of diabetic patients rises significantly in Pakistan in last 10 years. The number of diabetes population is projected to become almost double from 33 million in 2021 to 62.2 million in 2045. Pakistan stands at the 3rd position in world diabetes ranking after China and India. In 2021, Pakistan has the highest diabetes prevalence 30.8% in the world. This increase burden poses significant impact on diabetes related comorbidities.[2-3]

The lifestyle modification in the form of diet and exercise usually consider first in the management of diabetes. Currently 9 anti diabetics drug groups are available and various are under consideration. The oral antidiabetic drugs groups include biguanides, sulphonylurea, alpha-glucosidase inhibitors, thiazolidinediones, DPP-4 inhibitors and SGLT-2 inhibitors. The parenteral antidiabetic medications include insulin, GLP-analogs and Amylin analogs.[4]

Sodium glucose cotransport-2 (SGLT-2) inhibitors are the latest group of antidiabetic with different mechanism of action than conventional

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antidiabetic drugs. They inhibit sodium-glucose cotransport in the proximal convoluted tubules that result in loss of glucose in urine with reduction in serum blood glucose.[5] SGLT2 inhibitor also have a beneficial effect on anthropometric parameters (BW, BMI), hypertension, blood pressure, NAFLD, uric acid, dyslipidemia, inflammation and oxidative stress.[6] Current guidelines recommend SGLT2 inhibitors as 1st line antidiabetic drug in renal and CVD patients. The SGLT2 inhibitors have strong potential to improve cardiovascular and renal outcome in T2DM patients.[7] The Empa-reg Outcome trial, Canavas Program, Declare-TIMI-59 and Credence Trial showed the cardiovascular and renal safety profile of SGLT2 inhibitors.[8]

Dipeptidyl peptidase-4(DPP-4) inhibitors are class of oral antidiabetic that potentiate the effects of glucagon like peptide-1(GLP-1) and glucose dependent insulinotropic peptide (GIP) by inhibiting the enzyme DPP-4. They stimulate insulin release, inhibits glucagon secretion, reduce satiety and inhibit glucose absorption from intestine They are used as monotherapy as well as combination therapy in T2DM patients.[9] DPP-4 inhibitors lower body weight, BMI, lipid profile, NAFLD, inflammation and oxidative stress.[10] The DPP-4 inhibitors also have a cardiovascular benefit. These cardiovascular benefits were clearly demonstrated in the Examine study for alogliptin, SAVOR-TIMI-53 study for saxagliptin, TECOS trial for sitagliptin, and Carmelina study for linagliptin.[11]

Seeing these potential properties of empagliflozin and sitagliptin, we conducted a study to compare the efficacy and safety profile of both drugs as add on to metformin in T2DM patients.

METHODS

This RCT was carried out at four private hospitals and medical outdoor of Sheikh Zayed Medical College/ Hospital of district Rahim Yar Khan. A total of 450 T2DM patients were screened at diabetic clinic and private clinic set up of district Rahim Yar Khan. Out of which, 380 patients were enrolled in this clinical study on the basis of inclusion and exclusion criteria. Inclusion criteria was T2DM patients diagnosed for at least 06 months' duration of either sex with inadequate glycemic control (HbA1C >7%) with metformin. These patients were randomly allocated in to two groups, each group comprising of 140 patients. over a 12-week period (from January to March 2024). patients in group A received tab empagliflozin and patients in group B received tab sitagliptin. Both medication doses were adjusted based on FBG level: however, the metformin dose remained unchanged. The dose of empagliflozin varies between 12.5 to 25mg while dose of sitagliptin varies between 50-100mg. The process of randomization was done through computed generated software in a random block of 1:1 to receive either empagliflozin and sitagliptin. Patients. A flow chart of patient's recruitment for randomized controlled trial has shown in (Figure-1).

Patients with insufficient data, renal impairment, T1DM, gestational diabetes, secondary diabetes, HbA1c > 9%, malignancy, lactation, hepatic disease, pancreatitis, autoimmune disease and cancers on the basis of medical records and history were excluded from study. Patients who were taking steroids, anti- obesity, oral contraceptives, beta blockers, thiazide diuretics and atypical antipsychotic drugs were also excluded from the study. The study was approved by the ethical committee of the Institutional Review Board (26/IRB/SZMC/SZH) of Sheikh Zayed Medical College/Hospital Rahim Yar Khan. All participants told a through explanation of the study perspectives prior to giving their informed consent. The research protocols were performed according to the Declaration of Helsinki and good principle practice (GCP) guidelines.

Measuring changes in BW, BMI, blood pressure, HbA1c and lipid profile between baseline and 12 weeks was one of the study primary end point. The secondary end points to record any adverse effects from start to end of study.

Both weight and height were measured by wearing light cloths and without shoes. Body weight was measured in a standing position by digital weight machine. Height was measured in

a standing position by stadiometer. The standard formula was used to calculate BMI i.e weight in kg divided by height in m^2. Blood pressure was measured in supine position in both arms twice to avoid errors at interval of fifteen minutes by mercury sphygmomanometer apparatus.

A fasting venous blood sample (5ml) were collected by a venipuncture using disposable syringe. Sample was used to analyze FBG, lipid profile and HbA1C. The FBG was determined via standard glucose oxidase method using automated analyzer. An automated biochemical analyzer using an enzymatic method was used to measure the lipid profile. The HbA1c was measured using high performance liquid chromatography (HPLC) following standard protocols.

Statistical Analysis

Statistical package for social sciences (SPSS 21) was used to analyze data. Continuous and categorical variable was expressed as mean ± SD and n (%). A student T was used for the comparison of quantitative parametric value between two groups. The Pearson Chi-square test was used to compared categorical variables. A p-value < 0.05 will be considered statistically significant. The number of adverse effects reported by both were documented. In order to achieve 90% power and detect a difference in HbA1c of 0.5% using the two-sided t test, a sample size of 140 patients were required in each group. Assuming a standard deviation of 1.2%, level of significance 0.05 and loss to follow up 20%.

RESULTS

The mean age of patients in empagliflozin and sitagliptin group was 50.6 ±6.24 and 49.26 ±8.53 respectively. The percentage of male in empagliflozin group was 58.57% and in sitagliptin group was 53.5%. The percentage of female in empagliflozin group was 41.4% and in sitagliptin group was 46.4%. The baseline anthropometric, clinical and biochemical characteristics of study groups are shown in Table-I. There was no significant statistical difference at baseline among study variables between two groups.

After 12 weeks' therapy with empagliflozin and sitagliptin, body weight and BMI was significantly reduced in both study groups Empagliflozin (BW: from 92.5**±13.5 to 79± 14.5 kg** p=0.001; BMI: from 29.4**±4.2 to** 27.5**±3.8** p=0.001. Sitagliptin (BW: from 89**±16.6 to 81±12.5** p=0.001 BMI: from 28.5**±5.**6 to 27.3**±4.2** p=0.001. Empagliflozin, however, significantly decreased body weight and BMI when compared to sitagliptin with p<0.001.

Regarding glycemic control, both empagliflozin and sitagliptin significantly reduced FBG and HbA1c. Empagliflozin (FBG from 240**±60.50 to** 130**±35.5** p=0.001, HbA1c: from 8.35**±1.9** to 7.2± 1.6 p=0.001) Sitagliptin (FBG from 255**±46.60 to** 165± **40.5** p=0.001; HbA1c from 8.5**±1.5 to** 7.9**±1.8** p=0.001) However, in comparison with sitagliptin, empagliflozin have more pronounced effect on FBG and HbA1c with p<0.001.

Although SBP and DBP was decreased in empagliflozin group but it not reaches statistical significance. No significant changes were recorded in SBP and DBP in sitagliptin group.

Regarding lipid profile, both drugs failed to demonstrated any significant changes in serum lipid profile empagliflozin. The lipid profile comparison between the two groups was also not statistically significant. The safety profile of both drugs was excellent and no major adverse effcts were recorded during coarse of therapy. However minor adverse effcts in the form headache 4(2.5%), urinary tract infection 5(3.5%), genital infection 8(5.7%) and nausea/vomiting 7(5%) were recorded in empagliflozin group while headache 8(5.7%), allergy/rashes 2(1.4%) and nausea/ vomiting 10(7.14%) in sitagliptin group. Most of these adverse effects were settled itself during 1st week and did not lead to discontinuation of therapy. These results are shown in Table-III.

DISCUSSION

In this study, we compared two groups of antidiabetic medication empagliflozin and sitagliptin used as adjuvant therapy to metformin in T2DM patients.

Variables	Empagliflozin(n=140)	Sitagliptin(n=140)	P-Value
Age(years)	50.6 ±6.24	49.26 ±8.53	0.82
Male(n%)	82(58.57%)	75(53.57%)	0.45
Female(n%)	58(41.42%)	65(46.42%	0.32
Body weight(kg)	92.5±13.5	89±16.6	0.56
BMI(kg/m2)	29.4±4.2	28.5±5.6	0.12
FBG(mg/dl)	240±60.50	255±46.60	0.16
HBA1c%	8.35±1.9	8.5±1.5	0.31
SBP(mmHg)	132±15.5	125±18.5	0.98
DBP(mmHg)	75±8.5	80±6.5	0.32
TC(mg/dl)	188±20.5	195±18.5	0.55
TG(mg/dl)	209.5±30.5	220±25.5	0.27
LDL-C(mg/dl)	126±22.5	132±28.5	0.54
HDL-C(mg/dl)	44±8.5	46.5±9.2	0.71

Table-I. Baseline study variables of both study groups

Data are presented as means ± standard deviation except the gender. P

Variables	Empagliflozin (n=140)	P-Value	Sitagliptin (n=140)	P-Value	P-Value*
Body weight(kg)	79± 14.5	0.001	81±12.5	0.002	< 0.001
BMI(kg/m^2)	27.5±3.8	0.001	27.3±4.2	0.001	<0.001
FBG(mg/dl)	130±35.5	0.001	165± 40.5	0.001	<0.001
HBA1c%	7.2± 1.6	0.002	7.9±1.8	0.003	<0.001
SBP(mmHg)	127±15.2	0.246	130±10.42	0.231	0.921
DBP(mmHg)	78.4±8.2	0.412	81.5±6.5	0.876	0.142
TC(mg/dl)	192±32.5	0.434	212±40.2	0.126	0.561
TG(mg/dl)	147.5±40.5	0.821	160.5±54.5	0.448	0.329
LDL-C(mg/dl)	125±32.4	0.266	143±28.5	0.323	0.213
HDL-C(mg/dl)	46±6.6	0.321	47±8.5	0.321	0.488

Table-II. Changes in variables from baseline to end point in study groups.

Data are presented as means ± standard deviation. * comparison between empagliflozin and sitagliptin.

In, comparison with sitagliptin, empagliflozin significantly improved glycemic control (FBG, HbA1C) and anthropometric parameters such as body weight and BMI while no significant changes were recorded in blood pressure and serum lipid profile by both drugs.

In our study both drugs reduce significantly reduce BW, BMI, FBG and HbA1c over a period of 12 weeks. However, in comparison with sitagliptin, empagliflozin significantly improved BW, BMI, FBG and HbA1c level as an add on therapy to metformin. Most of the T2DM patients are overweight and obese and weight loss either by exercise, diet and drugs have a potential role to overcome the insulin resistance.[12] A number of clinical studies revealed that empagliflozin in combination with metformin significantly improved BW, BMI and improved glycemic control as compared to other combination therapies. In comparison to sitagliptin and glimepiride, empagliflozin monotherapy significantly reduced HbA1c in T2DM patients according to a study by DeFrtonzo et al.[13] This trial compared the effects of empagliflozin vs sitagliptin for 24 weeks and empagliflozin vs glimepiride for 52 weeks as adjuvant therapy to metformin. However, our study duration was 12 weeks and empagliflozin

showed significant reduction in HbA1c level as compared to sitagliptin as add on therapy to metformin.

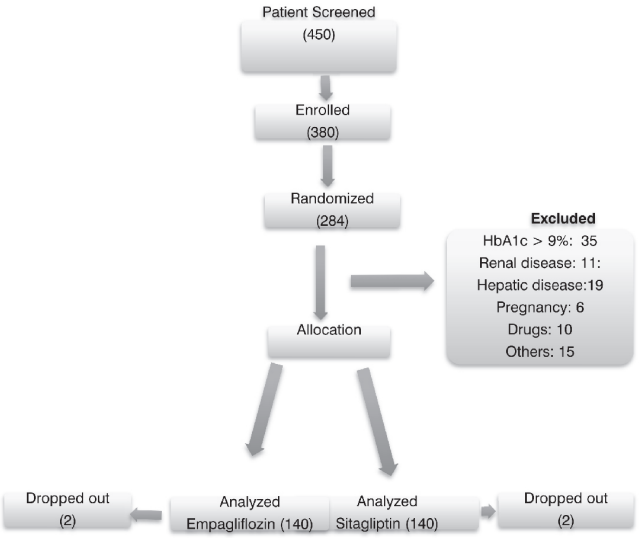

Figure-1. Flow char of patient's recruitments for placebo controlled trial

Adverse Effects	Empagliflozin (n=140)	Sitagliptin (n=140)
Adverse effects leads to discontinuation	0(0%)	0(0%)
Headache	4(2.85%)	8(5.71%)
Nasopharyngitis	0(0%)	0(0%)
Urinary tract infection	5(3.5%)	0(0%)
Genital infection	8(5%)	0(0%)
Allergy/rashes	0(0%)	2(1.4%)
Pancreatitis	0(0%)	0(0%)
Nausea/vomiting	7(5%)	10(7.14%)
Hypoglycemia	0(0%)	0(0%)
Dehydration	0(0%)	0(0%)
Total	24(17%)	20(14.2%)

Table-III. Adverse effects recorded in both study groups

A meta-analysis of 7 clinical trials by Mishriky et al[14], 2018 demonstrated that SGLT-2 inhibitors significantly lowered HbA1c at 52 weeks but not at 26 weeks in contrast to DPP-4 inhibitors. However, more weight loss was seen at both 26 and 52 weeks of treatment in contrast to DPP-4 inhibitors. More weight loss but with more genital infection were also seen with SGLT-2 inhibitors. A data of 25 randomized trial analysis showed that, in comparison to DPP-4 inhibitors, SGLT-2 inhibitors significantly reduced BW, FBG and HbA1c with no risk of hypoglycemia.[15] Our findings closely resemble those of study conducted by Mubashir et al, 2022[16] which showed that empagliflozin was more beneficial in maintaining glycemic control versus sitagliptin as adjunctive treatment to metformin in T2DM patients over a period of 12 weeks. A study in Faisalabad, Pakistan also showed similar results in which empagliflozin had a pronounced effect on glycemic control and body weight as add on therapy to metformin in T2DM patients over a period of 12 weeks.[17] Similarly, a study conducted in India showed that empagliflozin is superior to sitagliptin for the improvement in glycemic control as an adjuvant treatment to metformin in 300 T2DM subjects over a period of 3 months.[18]

SA meta-analysis encompassing 116 randomized controlled trials conducted over a period of 20 years clearly demonstrated the weight and BMI reduction properties of SGLT-2 inhibitors.[19] Similarly, in a meta-analysis of 18 studies, SGLT2 inhibitors significantly improved body weight, waist circumference, BMI, visceral and subcutaneous fat.[20] The main mechanism by which SGLT2 inhibitors reduce body weight include calorie loss (glucose) in urine, decrease in leptin/adiponectin ratio and increased lipolysis.[21]

A study investigate the effects of empagliflozin and sitagliptin on glycemic control and metabolic parameters in T2DM patients as an adjunct to metformin therapy. In comparison with our study, no significant difference was recorded between empagliflozin and sitagliptin on glycemic control in T2DM patients over a period of 12 weeks. Regarding lipid profile, both drugs significantly improved serum TGs and HDL-C, but empagliflozin caused a more improvement as compared to sitagliptin. However, we did not find any significant effect on serum lipid profile by both drugs.[22]

A study conducted in Egypt by Zakaraia et al, 2023[23] showed that empagliflozin significantly reduced HbA1c, FBG and TGs while drastically

increased LDL-C, HDL-C and total cholesterol. On the other hand, sitagliptin significantly lower FBG, body weight and TGs while significantly increase HDL-C over a period of 12 weeks. The adverse effects were also reported by both drugs empagliflozin 11.8% vs sitagliptin 8.2%. We also noticed a significant improvement in glycemic control but did not find any significant effects on serum lipid profile by both drugs over a period of 12 weeks. The adverse effects reported in our study was 24(17%) by empagliflozin 20(14%) by sitagliptin.

In our study, both drugs had not any discernible effects on blood pressure as add on therapy to metformin. Although some studies postulated that SGLT2 inhibitors have significant impact on blood pressure.[24-28] A data of fifteen clinical trial revealed that SGLT-2 inhibitors have blood pressure lowering properties, for both SBP and DBP SGLT-2 inhibitors had a greater impact than DPP4 inhibitors. While DPP-4 inhibitors have mild blood pressure lowering effects.[29] A meta-analysis of 10 randomized controlled trial comprising 9913 participants suggested that SGLT-2 inhibitors should be consider as an adjuvant drug with 1st line antihypertensive regimen.[30]

Similarly, we did not find that either medication had a noteworthy impact on lipid profile in T2DM patients when used in addition to metformin. Although a lot of studies showed that SGLT2 inhibitors significantly improved serum lipid profile in T2DM patients.[31-34] On the other hand, a meta-analysis of 48 randomized controlled trials by Garica et al, 2020[35] showed that SGLT-2 inhibitors significantly increase TC, LDL-C, HDL-C while showed a significant decrease in TGs.

Similarly, DPP4 inhibitors also reduced blood pressure and improved serum lipid profile in various clinical studies. The results of 14 randomized controlled trials showed that sitagliptin monotherapy as well as combination therapy significantly reduced TC and LDL-C while no considerable difference was noted in TGs and HDL-C.[36-37]

Both drugs had a satisfactory safety profile, and there were no significant adverse effects reported during the study. However, some patients were complaint of increase urine frequency during 1st week of therapy with empagliflozin. The increase urine frequency resolve itself without any intervention. At 12 weeks of medical records, no evidence of any urine and genital infection were detected. The risk of urogenital infection with SGLT2 inhibitors varies from to % A 3% patient's complaints of headache with sitagliptin which also settle itself without any intervention. A double blinded placebo controlled trial was conducted in 15 countries to determine the efficacy and safety profile SGLT2 inhibitor versus DPP-4 inhibitors in young people with T2DM. This study showed that in comparison with linagliptin, empagliflozin offered better efficacy in reduction of HbA1c level.[38] Similarly, a lot of studies showed a good safety profile of both drugs.[15,20,23]

LIMITATION

Our study's main limitation is its small sample size. To acquire broader perspectives, it is necessary to conduct more studies with a large sample size. Second our study duration was short, in order to understand the effects of both drugs on anthropometric, metabolic and chemical parameters in T2DM patients, it is necessary to conduct a prospective cohort follow-up studies. A lot of studies documented beneficial effects of empagliflozin and sitagliptin on blood pressure and serum lipid profile. On the other hand, we failed to exhibit any favorable effects on blood pressure and lipid profile. The reason might be that both blood pressure and lipid profile was not significantly deranged in our study. Moreover, small sample size and short study duration might be other reason.

Moreover, the effect of both drugs should be explored in co-morbidities of diabetes such as renal, heart and liver diseases.

CONCLUSION

Empagliflozin as combination therapy with metformin is superior to sitagliptin plus metformin

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	**Asif Hussain:** The conception, design, analysis, interpretation of results.
3	**Haroon Aziz:** The conception, design, analysis, interpretation of results.
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