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Safety and efficacy of dapagliflozin versus empagliflozin as add-on therapy in type 2 diabetes mellitus management

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ABSTRACT

Objectives: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are drugs used as the oral hypoglycaemic that have a significant effect in lowering blood glucose, glycated haemoglobin (HbA1c), weight and blood pressure in patients of type 2 diabetes mellitus (T2DM). SGLT-2 inhibitors, such as empagliflozin and dapagliflozin, are used in addition to diet and exercise to help persons with T2DM improve their glucose control. The drugs are combined with other antidiabetic medications or used as monotherapy.

Materials and Methods: The aim of this study was to evaluate the efficacy and the safety of the drug dapagliflozin against empagliflozin in individuals with T2DM as an add-on treatment. The study is carried out in a Tertiary Care Hospital in Coimbatore using a prospective observational research design. T2DM patients with a HbA1c level of >7% are included in the study. Patient information was collected by patient interviews and from the patient file. Participants in the study are categorised into two groups: one group consists of patients taking oral dapagliflozin in doses of 5 mg or 10 mg alongside other oral hypoglycemic agents (OHAs), while the other group comprises patients taking oral empagliflozin in doses of 10 mg or 20 mg alongside other OHAs. The endpoints were to assess the safety and effectiveness of each SGLT-2 inhibitor by monitoring changes in the diabetic profile, body weight, body mass index (BMI), blood pressure and cardiovascular risk.

Results: The study included 100 patients, with 56 males and 44 females. Most participants were aged 51–60 years. In both treatment groups, A and B, significant reductions in body weight Group A: 3.14 kg and Group B: 2.29 kg and BMI Group A: 0.65 kg/m^2 and Group B: 0.84 kg/m^2 were observed after 6 months of treatment follow-up. Both groups experienced decreases in HbA1c levels from baseline to 6 months of treatment. The mean differences in HbA1c were 0.36% in Group A and 0.55% in Group B; empagliflozin led to a more significant reduction in HbA1c (0.19%) compared to dapagliflozin. Significant reductions were noted in fasting blood sugar (FBS) and postprandial blood sugar (PPBS) levels in both groups. Both dapagliflozin and empagliflozin were associated with reductions in systolic blood pressure (SBP) after 6 months of therapy. Dapagliflozin showed a greater reduction in SBP of 10.26 mmHg compared to 4.2 mmHg with empagliflozin. In addition, dapagliflozin increases diastolic blood pressure (DBP) by 2.25 mmHg, while empagliflozin reduces DBP by 3.61 mmHg. While both groups experienced reductions in SBP, only the group using empagliflozin showed a significant reduction in DBP. The Framingham risk score showed significant reductions in mean differences observed in both groups after 6 months of treatment, with a mean difference of 1.08% in Group A and 2.17% in Group B. However, the score is not statistically different between the groups. Both drugs exhibited equal effects on the prevention of cardiovascular risk. Both drugs exhibited a similar safety profile, with mild-to-moderate adverse events reported, including urinary tract infections (Group A: 18% and Group B: 12%) and hypoglycaemia (Group A: 24% and Group B: 20%) during the study period.

Conclusion: SGLT-2 inhibitors dapagliflozin and empagliflozin have favourable efficacy and safety in the management of T2DM; both drugs show equal effects on HbA1c, FBS, PPBS, body weight and BMI. Empagliflozin led to a more significant reduction in HbA1c compared to dapagliflozin. In both hypertensive and non-hypertensive patients, dapagliflozin exhibited greater systolic blood pressure reduction compared to empagliflozin, whereas empagliflozin exhibited greater reduction in diastolic blood pressure compared to dapagliflozin; in contrast, dapagliflozin has shown to increase DBP. Further investigation is required to explore the blood pressure effects of SGLT-2 inhibitors in a large population. In addition, these drugs decreased cardiovascular risk. Both medications exhibited fewer instances of hypoglycaemic episodes and urinary tract infections.

Keywords: Dapagliflozin, Empagliflozin, Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM), the highly prevalent form of diabetes, makes up more than 90% of all cases. Its defining traits include insulin resistance in tissues, inadequate compensatory insulin release and insufficient synthesis of insulin by pancreatic islet β-cells.[1] The increasing rates of obesity, sedentary lifestyles, high-calorie diets and ageing populations are contributing to the global increase in the incidence of T2DM. This has led to a four-fold increase in T2DM incidence and prevalence, posing a significant public health concern.[2]

Injectable therapy such as insulin, oral antidiabetic drugs, lifestyle modifications and more recent pharmacological medicines are all part of the multimodal approach that is the current standard of care for T2DM. By increasing insulin sensitivity and glycaemic control, lifestyle adjustments, including controlling weight, getting regular exercise and eating differently, are essential for the management of type 2 diabetes.[3]

Various oral antidiabetic drugs, such as metformin, sulfonylureas, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase 4 (DPP-4) inhibitors, among others, are frequently recommended to maintain blood sugar within target ranges.

SGLT-2 inhibitors, including dapagliflozin and empagliflozin, were approved by the Food and Drug Administration (FDA) in 2014 to help improve glycaemic control in adults with T2DM when used alongside diet and exercise. These medications can be used alone or with other antidiabetic drugs. Dapagliflozin and empagliflozin increase the urine excretion of glucose through SGLT-2 inhibition in the kidneys, thereby decreasing blood glucose levels. These medications provide additional treatment options for individuals with T2DM.[4,5] These medications work by preventing glucose reabsorption in the kidney's proximal renal tubule epithelial cells, which lowers blood glucose and glycated haemoglobin levels. Research has demonstrated that dapagliflozin lowers the chance of a lupus flare in randomised controlled trials.[6] In T2DM patients, dapagliflozin and empagliflozin have both shown a considerable decrease in cardiovascular events. SGLT-2 inhibitors have been shown to be nephroprotective in non-diabetic chronic kidney disease. This makes them appealing candidates for treating patients with systemic lupus erythematosus, particularly those with lupus nephritis.[6]

SGLT-2 inhibitors have been demonstrated to have direct and indirect physiological mechanisms that support their nephroprotective and cardiovascular protective effects in addition to their glucose-lowering actions. These include lowering lipotoxicity, raising insulin sensitivity, enhancing lipid metabolism, lowering intraglomerular pressure and lowering kidney hypoxia. Moreover, mild osmotic diuretic effects have been connected to SGLT-2 inhibitors, which may help lower blood pressure. Since this impact is distinct from insulin, it can be administered to people with different levels of insulin resistance or β-cell activity. As a result, SGLT-2 inhibitors become a highly flexible therapeutic option that can be used to treat comorbidities like hypertension in addition to controlling hyperglycaemia. This allows patients with T2DM and its associated cardiovascular risk factors to receive comprehensive care.[7] This study aimed to assess the efficacy and the safety of drugs SGLT-2 inhibitors (dapagliflozin and empagliflozin) when combined with existing treatments such as DPP-4 inhibitors, biguanides and sulfonylureas in T2DM patients.

MATERIALS AND METHODS

Our prospective observational study was conducted at PSG Hospital in Coimbatore, spanning 9 months from July 2021 to March 2022. The research focused on patients with T2DM who were prescribed dapagliflozin and empagliflozin in addition to other classes of anti-diabetic medications to manage their condition. The study received approval from the Institutional Human Ethics Committee (IHEC, PSG IMSR) under proposal number PSG/IHEC/2021/Appr/Exp/159, dated 2 July 2021, and adhered strictly to the principles outlined in the Declaration of Helsinki.

Study participants

Study participants are patients of individuals aged 18 years and above who were prescribed dapagliflozin and empagliflozin in addition to biguanides, DPP-4 inhibitors or sulfonylureas for managing T2DM and those with HbA1c levels above 7%. Type 1 diabetes patients, gestational

diabetes, renal disease, ketoacidosis, liver diseases, pancreatic disorders or ongoing steroid therapy patients are excluded from the study.

Sample size

The sample size of 100 participants was determined by Cochrane Equation, N = Z^2 * p * q/e^2, where e represents the margin of error set at 0.05, Z is 1.96 for a 95% confidence interval, q is calculated as 1-p and p denotes the estimated population proportion of patients previously reported with T2DM.

Study procedure

This study starts with screening patients according to the inclusion and exclusion criteria. The study details were explained, and the patient's informed consent was obtained. The demographics details (age, sex and comorbidities), physical profile (weight, body mass index [BMI]), diabetic profile (HbA1c, fasting blood sugar [FBS] and postprandial blood sugar [PPBS]) and hypertensive profile (Systolic blood pressure [SBP] and diastolic blood pressure [DBP]) were collected by patient interview and from the patient file.

Assessment of study

Regular follow-up assessments of patients were conducted over a 6-month period. During these assessments, both the safety and efficacy of the treatment groups were evaluated and compared using biochemical parameters and observed adverse effects. In addition, cardiovascular risk was assessed using the Framingham risk score.

RESULTS

The study's initial recruitment of 109 participants was determined by the inclusion and exclusion criteria. Of these, nine patients were excluded due to incomplete follow-up data, leaving 100 patients included in the study. The demographic breakdown included 56 males and 44 females, with an average age of study participants found to be 54 years. The age group of 51–60 years was the most prevalent among the patients, representing a significant portion of the study population. Of these, 73% of the participants were elderly. Out of 50 patients, 25 males and 25 females made up Group A and 31 men and 19 women made up Group B. In both groups, the patient's age category 51–60 is more predominant than other age groups. In Group A, 78% of patients have hypertension, while in Group B is 60%. The number of patients taking other anti-diabetic medications is shown in Table 1.

Table 1: Demographic profile.

	Group A (*n*=50) (%)	Group B (*n*=50) (%)
Gender-based classification		
Male	25 (50)	31 (62)
Female	25 (50)	19 (38)
Age-based classification		
30–40 age category	9 (18)	3 (6)
41–50 age category	8 (16)	7 (17.4)
51–60 age category	18 (36)	20 (40)
>60 age category	15 (30)	20 (40)
Comorbidity		
Hypertension patients	39 (78)	30 (60)
Non-hypertension patients	11 (22)	20 (40)
Drugs given as add-on therapy		
Biguanides	8 (16)	8 (16)
DPP-4 inhibitors	12 (24)	11 (22%
Sulfonyl ureas (alone)	10 (20)	10 (20)
Sulfonyl urea's+DPP-4 inhibitors	5 (10)	7 (14)
Sulfonyl ureas+Metformin	14 (28)	14 (28)

DPP-4: Dipeptidyl peptidase 4

After 6 months, the effectiveness of treatments in Group A and Group B was evaluated. Both groups showed notable decreases in body weight, with mean reductions of 3.14 kg in Group A and 2.29 kg in Group B compared to baseline. However, the difference was not statistically significant (P = 0.385). Similarly, reductions in BMI were observed in both groups, with mean differences of 0.65 kg/m^2 in Group A and 0.84 kg/m^2 in Group B. When comparing body weight and BMI levels between the two groups, the differences were not significant. Both drugs were equally effective in reducing body weight as well as BMI.

After 6 months of treatment, both Group A and Group B experienced significant reductions in HbA1c, FBS and PPBS levels. In Group A, the mean reductions in HbA1c were 0.36%, whereas in Group B, they were 0.55%. Empagliflozin demonstrated a more pronounced decrease in HbA1c compared to dapagliflozin. For FBS, the reductions were 19.6 mg/dL in Group A and 17.4 mg/dL in Group B, and for PPBS, the reductions were 10.93 mg/dL in Group A and 21.9 mg/dL in Group B. However, the difference in FBS and PPBS was not statistically significant between the groups, indicating both medications were equally effective in lowering these parameters.

Furthermore, significant reductions in SBP were seen in hypertensive patients in both groups from the beginning to the end of the 6-month period. Dapagliflozin showed a greater reduction in SBP of 10.26 mmHg compared to 4.2 mmHg with empagliflozin. In addition, dapagliflozin increases DBP by 2.25 mmHg, while empagliflozin reduces DBP by 3.61 mmHg. While both groups experienced reductions in SBP, only the group using empagliflozin showed a significant

reduction in DBP. In non-hypertensive, we observe that SBP shows reduction in both groups. Dapagliflozin showed a greater reduction in SBP of 3.22 mmHg compared to 1.47 mmHg with empagliflozin. In addition, dapagliflozin increases DBP by 5.83 mmHg, while empagliflozin reduces DBP by 4.63 mmHg, empagliflozin showed a significant reduction in DBP as illustrated in Table 2. In addition, large sample sizes need to be proven for the non-hypertensive patients.

Over the 6-month study duration, cardiovascular risk assessment was done using the Framingham risk score, revealing notable decreases in mean differences in both Group A (1.08%) and Group B (2.17%). However, the difference was not statistically significant (P = 0.225), indicating that dapagliflozin and empagliflozin had similar effects in preventing cardiovascular diseases, as depicted in Table 3.

After 6 months of treatment, differences in the occurrence of adverse events between Group A and Group B were not significant. Both medications demonstrated similar safety profiles, with only mild-to-moderate adverse events and no severe adverse were reported during the study. The most observed adverse events were urinary tract infections (UTIs) and hypoglycaemia. In Group A, UTIs were observed in 18% of patients, compared to 12% in Group B. Hypoglycaemia occurred in 24% of Group A participants and 20% in Group B participants, as indicated in Table 4.

DISCUSSION

We found that treatment with dapagliflozin and empagliflozin led to significant reductions in body weight and BMI in patients diagnosed with T2DM. This outcome is similar to the findings of a study conducted on the Italian population by Mirabelli *et al.*,[8] which investigated the long-term effectiveness and safety of SGLT-2 inhibitors. This suggests that treatment with SGLT-2 inhibitors directly induces weight loss by excreting glucose (or) calories through the kidneys.

Regarding glycaemic control, significant reductions were noted in HbA1c, FBS and PPBS levels in both groups. Empagliflozin led to a more significant reduction in HbA1c compared to dapagliflozin. When comparing FBS and PPBS levels between the two groups, the differences were not significant. These findings align with a study conducted in China by Lee *et al.*[9]

In addition to decreasing blood sugar, these drugs also function as osmotic diuretics, which help people with type 2 diabetes decrease their blood pressure. Our findings also align with previously reported meta-analysis by Li *et al.*[10] which assessed both short-term and long-term effectiveness of SGLT-2 inhibitors, whether used alone or in combination with other therapies. Both patients with hypertension and those without hypertension experienced a decrease in SBP when treated with dapagliflozin, while DBP increased in both groups. These findings are consistent with a study conducted by Sjöström *et al.*,[11] which reported significant reductions in

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

Parameters	Group A (Dapagliflozin) *n*=50			Group B (Empagliflozin) *n*=50		
	Baseline	6th Months	*P*-value	Baseline	6th Months	*P*-value
BMI (kg/m^2)	26.90±4.60	26.35±4.70	<0.001	26.54±4.70	25.70±5.12	<0.001
Weight (kg)	71.97±10.83	68.83±10.83	<0.001	71.74±13.89	69.45±12.70	<0.001
Diabetic profile						
HbA1c (%)	9.13±1.81	8.77±1.83	<0.015	9.09±1.91	8.77±1.83	<0.001
FBS (mg/dL)	185.60±58.15	166.33±51.60	<0.001	174.24±61.20	156.84±4.20	<0.006
PPBS (mg/dL)	268.48±75.41	257.54±63.14	<0.001	259.0±84.70	235.21±83.60	<0.001
Blood pressure status in hypertension patients						
	n=39			*n*=30		
SBP (mmHg)	137.40±14.97	127.48±10.39	<0.001	135.22±13.42	131.0±16.78	<0.001
DBP (mmHg)	80.14±10.20	82.39±9.28	<0.115	78.89±9.28	75.28±9.34	<0.029
Blood pressure status in non-hypertension patients						
	n=11			*n*=20		
SBP (mmHg)	111.75±7.70	108.53±6.07	<0.341	110.0±5.14	108.53±6.07	<0.012
DBP (mmHg)	68.0±6.46	73.83±7.63	<0.004	73.83±7.63	69.2±10.39	<0.420
Framingham CV risk score						
CV Risk score (%)	12.28±8.08	12.68±7.88	<0.001	11.32±7.22	10.51±6.94	<0.001

Values are given in mean±standard deviation. BMI: Body mass index, HbA1c: Glycated haemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CV: Cardio vascular, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar

Table 3: Reduction difference of Group A and Group B.

Parameters	Group A (Reduction Difference)	Group B (Reduction difference)	*P*-value
Weight (kg)	3.14	2.29	0.385
BMI (kg/m^2)	0.65	0.84	0.407
HbA1c (%)	0.36	0.55	0.980
FBS (mg/dL)	19.60	17.40	0.781
PPBS (mg/dL)	10.93	21.90	0.207
SBP in hypertensive patients	10.26	4.2	0.023
DBP in hypertensive patients	-2.25	3.61	0.076
SBP in non-hypertensive patients	3.22	1.47	0.176
DBP in non-hypertensive patients	-5.83	4.63	0.282
CV risk score (%)	1.08	2.17	0.225

BMI: Body mass index, HbA1c: Glycated haemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CV: Cardiovascular, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar

Table 4: Adverse drug reaction seen in Group A and Group B.

S. No.	Adverse effect	Group A (*n*=50) (%)	Group B (*n*=50) (%)	*P*-value
1.	Hypoglycaemic	12 (24)	10 (20)	0.720
2.	Nausea	6 (12)	4 (8)	0.510
3.	UTI	10 (20)	6 (12)	0.406

UTI: Urinary tract infections

both SBP and DBP among patients treated with dapagliflozin, irrespective of hypertension status.

We noted decreases in SBP, DBP and cardiovascular risk among T2DM patients treated with empagliflozin and dapagliflozin. These results align with a meta-analysis study. Treatment with empagliflozin led to decreases in SBP, DBP and cardiovascular risk, consistent with findings from the (EMPA-REG trials and the DECLARE-TIM 58) trial conducted by Imprialos *et al.*[12] Their study showed that SGLT-2 inhibitors improved cardiovascular morbidity and mortality and decreased risk of cardiovascular death and hospitalisation.

Both empagliflozin and dapagliflozin were well tolerated in terms of adverse effects, with mild cases of hypoglycaemia and UTIs observed regardless of the treatment group. Other similar adverse events were noted in both groups, including nausea reported by some patients. These findings are consistent with those of a study conducted by Ku *et al.*[13]

CONCLUSION

SGLT-2 inhibitors dapagliflozin and empagliflozin have favourable efficacy and safety in management of T2DM. Both drugs show equal effects in reducing HbA1c level when added to oral antihyperglycemic agents. Empagliflozin has the upper hand in reducing HbA1c level when compared to dapagliflozin. Furthermore, both dapagliflozin and empagliflozin resulted in significant reductions in the FBS and PPBS levels and decreased the body weight and BMI. In both hypertensive and non-hypertensive patients, dapagliflozin exhibited greater systolic blood pressure reduction compared to empagliflozin, whereas empagliflozin exhibited greater reduction in diastolic blood pressure compared to dapagliflozin. In contrast, dapagliflozin has shown to increase DBP. Further, investigation is required to explore the blood pressure effects of SGLT-2 inhibitors in a large population.

Both medications exhibited favourable safety profiles, with fewer instances of hypoglycaemic episodes and UTIs. In addition, in patients with T2DM, using the Framingham risk score, these drugs show decreases in cardiovascular risk. The safety and efficacy profile of dapagliflozin and empagliflozin establish them a suitable add-on therapy with conventional oral hypoglycaemic agents for T2DM patients.

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Ethical approval

The research/study approved by the Institutional Review Board at Institutional Human Ethics Committee (IHEC, PSG IMSR), number PSG/IHEC/2021/Appr/Exp/159, dated 2 July 2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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