Research Article

A Prospective Observational Study on Safety, Efficacy and Cardiovascular Risk Assessment of SGLT2 Inhibitors (Dapagliflozin and Empagliflozin) in Obese Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Aim: To compare the Safety, Efficacy and Cardiovascular risk assessment of sodium glucose co- transporter2 (SGLT2) inhibitors in Obese patients with Type-2 Diabetes Mellitus.

Introduction: Type 2 diabetes mellitus is a prevalent, progressive disease with a need for innovative therapeutic agents to continue to advance disease management. Sodium glucose co- transporters (SGLT2) inhibitors are recent oral hypoglycemic agents which has major advantages in terms of reducing HbA1c, FBS, PPBS, B.P and weight. These two drugs are compared in terms of efficacy and safety in Obese Patients with Type-2 Diabetes Mellitus. Many recent studies revealed that use of SGLT2 inhibitors in type-2 diabetes reduces the risk of cardiovascular death.

Materials and Methods: This study was a prospective observational study done in department of endocrinology and general medicine in Tertiary care Hospital, Coimbatore. Patients with uncontrolled glycated hemoglobin (HbA1c) level of >7 % are included. Study participants are randomly divided into two groups. Group A patients received oral Dapagliflozin 5, 10 mg and Group B patients received oral Empagliflozin 10, 20 mg for 6 months. The primary end points were the efficacy profile of each SGLT-2 agent in terms of body weight changes, BMI, FBS, PPBS, HbA1c and assessment of Cardiovascular Risk score. The secondary end point was to determine the safety profiles of each SGLT-2 inhibitors.

Results: After 6 months of treatment, both drugs showed significant reduction in HbA1c, FBS, PPBS, Blood pressure and Body weight with P value <0.001 within the individual Treatment groups which it is statistically significant. When comparing the Hip Waist Ratio in within the individual Treatment groups the P Value 0.299 is statistically not significant. The statistical analysis was performed by using unpaired t-test for both Treatment A and Treatment B found that FBS, PPBS, HbA1c, Weight, BMI, SBP, DBP in Non hypertension patients and CV risk score shows no significant difference and SBP and DBP in hypertensive patient's shows significant difference. The safety profile of both SGLT2 agents was observed during the study period and no major AEs were reported in the study groups UTIs, hypoglycemic episodes and Vomiting occurred more often in patients who received both Dapagliflozin and Empagliflozin. UTIs was more commonly seen in the patients who received Empagliflozin than Dapagliflozin.

Conclusion: Our study demonstrated that SGLT2 inhibitors can be effectively used as an add on therapy to conventional OHAs in patients with T2DM. Both Empagliflozin and Dapagliflozin were effective in reducing glycemic parameters and both drugs showed better safety outcomes in Obese Patients with Type-2 Diabetes Mellitus.

Keywords: Diabetes Mellitus, Empagliflozin, Dapagliflozin, Hypoglycemics, UTIs.

INTRODUCTION

Obesity is a chronic complex disease defined by excessive deposition of fat accumulation in the adipose tissue due to chronic over nutrition reduced physical activity and Imbalanced diet or hereditary reasons is called as obesity. People who are Obese have high risk in developing of type 2 diabetes and heart disease along with this obesity can affect sturdy bone health and in few obese populations it increases the risk of certain cancers. Obesity influences the quality of living, such as sleeping or moving in the people.[1]

One of the main causes of obesity is an imbalance between the excess energy stored and the energy utilized by the body, which can disrupt nutrient signals and result in insufficient energy expenditure.[2]

Diabetes is a chronic disease occurs when pancreas no longer able to make insulin, or when the body cannot make good use of the insulin it produces. Insulin is a hormone made by the pancreas that act like a key to let glucose from the food we eat pass from the blood stream into the cells in the body to produce energy. The body breaks down all carbohydrate foods into glucose in the blood, and insulin helps glucose move into the cells.[3]

T2 DM is most commonly seen in persons older than 45 years; still it is increasingly seen in children's, adolescents and younger adults due to rising level of physical inactivity and energy dense diets and obesity.[12] Where T2 DM is strongly associated with obesity and the prevalence of obesity related diabetes is expected to double to 300 million by 2025. [4]

SGLT2 inhibitors are a class of prescription medications approved by FDA to use along with diet and exercise to lower blood sugar in patients with type-2 diabetes. Drugs in this class includes Dapagliflozin, Empagliflozin, Ipragliflozin these drugs are available as active ingredient products and also in combination with other oral hypoglycemic agents. [5]

SGLT2 inhibitors offer several putative advantages:

- Acting independent of insulin, these agents should not confer a risk of hypoglycemia and could be employed as monotherapy or in combination with other drugs.
- As per the mechanism of action, these drugs should be effective in patients with insulin resistance or β-cell function.
- They should also be associated with weight loss regarding from the loss of glucose in urine and glucose induced osmotic diuresis and in prescribed to obesity patients with T2 DM.
- Their mild osmotic diuretic effect could potentially reduce blood pressure and have a beneficial impact on cardiovascular outcomes, more over this newer class of anti- hyperglycemic medications have beneficial effects in the Diabetes patients who are with Overweight and having cardiovascular diseases.[6]

Dapagliflozin and Empagliflozin are a relatively novel SGLT-2 class of drug for treating type 2 diabetes mellitus (T2DM) that inhibits glucose reabsorption in the renal proximal convoluted tubule to promote glucosuria and reduce blood glucose levels. These drugs are clinically prescribed for treating T2DM, and for both primary and secondary prevention of cardiovascular and renal events in Type 2 diabetic patients.[7] These drugs approved by the FDA for the treatment of cardiovascular disease as it showed a dramatic beneficial effect on cardiovascular outcomes and reduce the incidence of cardiovascular death and heart failure hospitalization in people with and without diabetes, and those with and without prevalent heart failure.[8]

Empagliflozin (Jardiance, Gibtulio), is an SGLT-2 inhibitor approved by FDA in 2014 administered as oral tablets with recommended doses 10 mg, 25 mg. It has a low side effects profile when used in combination with other anti-diabetic medications, but it produces a little[9]. In 2016, the FDA (United States food and drug administration) approved a new indication for Empagliflozin, which was to reduce the risk of cardiovascular death in adult patients with type-2 diabetes and cardiovascular disease.[10]

Dapagliflozin (Farxiga) is an SGLT2 inhibitor approved by FDA in 2014 administrated as oral tablets with recommended doses 5mg and 10mg. Dapagliflozin is a highly potent, reversible sodium-glucose cotransporter-2 inhibitor indicated for the treatment of type-2 diabetes mellitus[11]. This drug was approved for the treatment of type-2 diabetes in many countries. Dapagliflozin is a selective SGLT2 inhibitor approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 Diabetes mellitus it will increase the amount of glucose excretion in the urine and improved both fasting and post- prandial plasma glucose levels in patients with T2 DM[12].

Empagliflozin has a low side effects profile when used in combination with other anti-diabetic medications, but it produces a little risk of hypoglycemia because of its mechanism of action is independent of beta-cell function and insulin pathway.[13] When prescribed to T2 DM patients with overweight it will improve the glycaemic control in conjunction with diet and exercise and this drug given either as monotherapy or add-on therapy reported to be reduce glycated hemoglobin levels in Obesity patients with type-2 diabetes.[14]

Dapagliflozin can cause dehydration, hypoglycemic episodes, serious urinary tract infections and genital yeast infections. People with kidney problems, those with low blood pressure, and people on diuretic should be assessed for their volume status and kidney function[15].

MATERIALS AND METHODS

Study Design

The study is planned and conducted as a prospective observational study in two groups by enrolling obese patients with T2 DM patients.

Inclusion Criteria

- Both male and female patients diagnosed with obesity and Type 2 DM with age above 18 years with excess weight, poor diabetic control, Greater BMI (Inclusive of both) and prescribed with SGLT-2 inhibitors as add-on therapy to control Overweight in type 2 diabetes mellitus along with other class of oral Hypoglycemic Agents.
- Patients with HbA1c > 7% are included.
- Obese patients with cardiovascular diseases and patients who are with chronic kidney disease.

Exclusion Criteria

- Patients with the history of type 1 diabetes mellitus.
- History is evidence of gestational diabetes, significant hepatic disease, unstable/rapidly progressing renal disease.
- History or evidence of predispose to ketoacidosis including pancreatic insulin deficiency from any cause, pancreatic surgery and acute febrile illness.
- History or evidence of serious urinary tract infections including urosepsis and pyelonephritis.
- History or evidence of significant systemic diseases, seizures, psychiatric disorders, neurological disorders, metabolic disorders, nutritional disorders and/or allergic rash.
- History of addiction to any steroid use.

Patients who are not willing to participate in the study and patients who lost their follow up are excluded from the study.

Study Procedure:

The study is conducted by randomly selecting the patients from Department of General medicine and Endocrinology having obesity and type 2 DM. Data collection form is designed according to the requirement for the study to be conducted. Subjects are identified and recruited based on the inclusion and exclusion criteria. Sample size of the subject is n=100 patients (50 in each arm) which is divided into two groups, Group 1 is receiving Both Treatment A: Dapagliflozin 5mg, 10mg with other OHAs and Treatment B: Empagliflozin 10mg, 25mg with other OHAs. Group 2: 100 patients receiving Treatment B - Patients receiving Empagliflozin with other OHA agents and Treatment C - Patients receiving Canagliflozin with other OHA agents

Patient's demographic details are collected as a baseline of the study. Physical profiles include Weight, BMI, Hip waist ratio, diabetic profile includes HbA1c, FBS, PPBS and safety profiles includes adverse reaction caused after the treatment given to the patient.

Regular follow up of patients was done and data was collected in every 12 weeks for 6months. Assessment and comparison of safety and efficacy of both groups (By using biochemical parameters and adverse effects) and cardiovascular risk assessment was done by using Framingham Risk score.

Statistical Analysis

Statistical Analysis was performed by using ANOVA MODEL (Student's t test) in a SPSS Software latest version 22.0. The results were tabulated as mean ± standard deviation (SD) and analyzed. The level of significance was determined as its 'p' value with $p > 0.001$ taken as not significant and $p < 0.05$ taken as significant at 1% significance level, $p < 0.01$ taken as significant at 1% significance level and $p < 0.001$ taken as highly significant.

RESULTS

A total of 100 patients were enrolled in the study and data analysis was completed. These patients were divided based on the Treatment intervention they were prescribed by the physician i.e. For **Treatment A: 50 patients who were prescribed with Dapagliflozin** and **Treatment B: 50 patients who were prescribed with Empagliflozin** in combination with other Oral hypoglycemic agents (OHA'S).

Table 1: Efficacy Parameters - Demographic Profile: Comparison of Weight and BMI of group 1 patients who received Treatment A & B

Parameters	Treatment A (Reduction difference)	Treatment B (Reduction difference)	P Value
Weight	3.14	2.29	**0.385**
BMI	0.65	0.84	**0.407**

Demographic and clinical data of patients were recorded. HbA1c, FBS, PPBS, BMI, HWR, BP (systolic and diastolic) were documented for 6 months' period. ADR's were also recorded during the follow up period in the hospital.

Table 2: Diabetic Profile - Comparison of HbA1c, FBS, PPBS levels of group 1 patients who received Treatment A & B.

Parameters	Treatment A (Reduction difference)	Treatment B (Reduction difference)	P Value
HbA1c	0.36	0.55	**0.980**
FBS	19.6	17.4	**0.781**
PPBS	10.93	21.9	**0.207**

Table 3: Clinical Profile - Comparison of SBP, DBP in hypertensive and non-hypertensive patients and CV Risk Score of group 1 patients who received Treatment A & B.

Parameters	Treatment A (Reduction difference)	Treatment B (Reduction difference)	P Value
Systolic BP in hypertensive patients	10.26	4.2	**0.023**
Diastolic BP in hypertensive patients	-2.25	3.61	**0.076**
Systolic BP in non-hypertensive patients	3.22	1.47	**0.176**
Diastolic BP in non-hypertensive patients	-5.83	4.63	**0.282**
CV Risk Score	1.08	2.17	**0.225**

When Treatment A and Treatment B were compared using unpaired t test, FBS, PPBS, HbA1c, Body Weight, BMI, SBP, DBP in Non-hypertension patients and CV risk score shows **no significant difference** and SBP and DBP in hypertensive patient's shows **significant difference.**

Table 4: Safety Profile - The incidence of adverse drug reactions is mentioned in below table.

Drug Name	Treatment A	Treatment B	P value
Hypoglycemic Episodes	12	10	0.720
Hypo + Nausea	4	7	0.343
Hypo + Weight gain	4	2	0.405
Weight Gain	6	4	1.000
Vomiting	6	8	0.510
Abdominal pain	4	5	0.730
UTI	6	9	0.406
Hypo + UTI	0	3	0.80
Hypo + Abdominal pain	1	0	0.320
Nausea + Abdominal pain	0	2	0.156
No ADR'S	1	5	0.940

Adverse reactions seen in Treatment A & B:

When comparing the adverse events in Treatment A and Treatment B there were no statistically significant difference seen.

Demographic Profile:

Total n=100 patients were included in this study for Group -1 where n=56 was male and n=44 was female. Gender is categorized for two treatments i.e., group 1 For Treatment A: Among 50 patients, 50% were male (n=25) and 50% (n=25) were female and for Treatment B: Among 50 patients, 62% were male (n=31) and 38% (n=19) were female.

BMI were included and it is categorized with weight of the patient. BMI range were categorized with patients' weight. Obese (30.0 to 35.0) patients were 23 in Treatment A and 19 in Treatment B. BMI mean difference were taken in groups 1 for both treatments, both showed significant reduction in BMI after 6 months and mean difference in Treatment A is 0.43 and in Treatment B is 0.64. As P value is <0.001 in both Treatments it is statistically significant.

Weight of the patients were taken in Group 1 for Treatment A & B for baseline and after 6 months' data are compared. Initially Treatment A has 74.37±9.45 and Treatment B has 72.39±12.92. After 6 months Treatment A reduced to 72.01±10.04 and Treatment B reduced to 70.15±11.92. In both Treatments showed significant reduction in weight after 6 months and mean difference in Treatment A is 2.35 and in Treatment B is 2.24. As P value is <0.001 in both groups it is statistically significant.

Clinical Profile:

Blood Pressure of the patients are also taken in Group 1 for both Treatment A and B for baseline and after 6 months, data are then analyzed. Blood Pressure of the patients are categorized in hypertension and non-hypertension patients and their systolic and diastolic blood pressure (SBP and DBP). In hypertension patients, Treatment A, mean baseline SBP 137.7±14.97 was reduced to 127.48±10.39 and mean baseline DBP 80.14±10.20 was increased to 82.39±9.28. In Treatment B, mean baseline SBP 135.22±13.42 was reduced to 131±16.78 and mean baseline DBP 78.89±9.28 was reduced to 75.28±9.34.

In Non-hypertension patients, Treatment A, mean baseline SBP 111.75±7.70 was reduced to 108.53±6.07 and mean baseline DBP 68±6.46 was increased to 73.83±7.63. In Treatment B, mean baseline SBP 110±5.14 was reduced to 108.53±6.07 and mean baseline DBP 73.83±7.63 was reduced to 69.2±10.39.

Diabetic Profile:

Diabetic profile was analyzed by taking HbA1c, FBG, PPBG levels in both Treatment A and Treatment B as baseline and after 6 months are collected and evaluated.

Table 5: Mean ± SD values of Diabetic parameters HbA1C, FBS, PPBS:

Parameters	Treatment A (N=50) mean ± SD		Treatment B (N=50) mean ± SD	
	Baseline	After 6 months	Baseline	After 6 months
HbA1c	9.139±1.812	8.778±1.83	9.09±1.91	8.77±1.838
FBS	185.6±58.15	166.33±51.69	174.24±61.2	156.84±4.2
PPBS	268.48±75.41	257.54±63.14	259.8±84.7	235.21±83.6

In both Treatment A & B showed significant reduction in HbA1c, FBS, PPBS levels after 6 months of treatment and mean difference of HbA1C for Treatment A is 0.36 and Treatment B is 0.55 for FBS the mean difference in Treatment A is 19.6 and in Treatment B is 17.4 and for PPBS the mean difference in Treatment A is 10.93 and in Treatment B is 21.9. As P value is <0.001 in both groups it is statistically significant.

Safety Profile:

The safety parameters are also assessed for this group and both the drugs showed better safety outcomes with fewer incidences of Hypoglycemic Episodes and UTI's are more commonly seen in the patients who are treated with SGLT-2 inhibitors (Dapagliflozin and empagliflozin). When statistically comparing the safety profile between two treatment groups (A Vs B) there were no statistically significant difference seen.

DISCUSSION

The present study was conducted to determine the efficacy and safety profile of Dapagliflozin and Empagliflozin as an add-on therapy in obese patients with type-2 Diabetes mellitus experiencing inadequate glycemic control. In this study the patients are divided into two Groups, Group 1 total 50 patients who receive Treatment A: Dapagliflozin with other OHAs and Treatment B: Empagliflozin with other OHAs and Group 2 total 50 patients who receive Treatment B: Empagliflozin with other OHAs and Treatment C: Canagliflozin with other OHAs. Although three of the drugs tested in this study demonstrates their beneficial effect to improve blood glucose control.

In this study all the subject's data were collected during the initial visit (Base line values) and remaining two follow ups (with in a period of every three months once). By analysing the Data of group 1 patients we observed that

Empagliflozin (Treatment B) was relatively superior to Dapagliflozin (Treatment A) with respect to decreasing glycemic control, body weight, and Blood pressure from baseline to follow up.

Management of overweight/obese patients with T2 DM poses a challenge because of there being fewer therapeutic options available for both glycemic control and weight reduction. SGLT-2 inhibitors are novel oral GLDs that promote weight loss, decrease adiposity, and improve CV outcomes. As most of the T2 DM patients are overweight/obese and at high risk of CVD, SGLT-2 inhibitors offer an effective therapeutic option for the management of these patients, and due to complex nature of type 2 diabetes mellitus, many diabetes patients have difficulty to achieve efficient control of their glycemic index using monotherapy alone, so this leads to the recommended use of a combination therapy of either two or even three different class of OHAs.

At present in our study, we found that male patients are more risk to diabetes and age category 51-60 was more predominant and same results was seen in the study conducted by the **Hussain, Mazhar, et al.**[16] This implies that these subjects develop T 2 DM in the most productive year of their life, because of their lifestyle modification, increase in stress rate and various physical changes in the body. So, this age group also has a great chance of developing various other chronic complications associated with diabetics.

In our study we found that after treatment with Dapagliflozin and Empagliflozin there was a significant reduction in body weight and BMI in the patients with type 2 DM. This finding was similar to the study conducted in Italian population by **Mirabelli, Maria, et al.,**[17] who conducted a long-term effectiveness and safety study on SGLT2 inhibitors. This signifies that treatment with SGLT-2 inhibitors directly cause body weight loss via glucose excretion (or) calorie loss in the kidney.

In terms of the glycemic control with Empagliflozin and Dapagliflozin HbA1c, FBS levels was reduced and maintained consistently throughout the end of the study. In our study Empagliflozin treated group had a significantly better glycemic control from baseline to end follow up for 6 months, but in this study both drugs maintained relatively constant glycemic control throughout the study period.

Encouragingly, we observed a decrease in SBP, DBP and cardiovascular risk in T2 DM patient when treated with Empagliflozin and Dapagliflozin and the results was similar to the meta-analysis study. In treatment with Empagliflozin the SBP, DBP and cardiovascular risk was reduced and these results are found be similar in the study **(EMPA-REG trials, DECLARE-TIM 58 trial)** which was conducted by **Imprialos, Konstantinos P., Pantelis A. Sarafidis, and Asterios I. Karagiannis.**[18] In their study SGLT-2 inhibitors treated group improved cardiovascular morbidity and mortality and found that the use of these drugs was associated with decreased risk of cardiovascular death and cardiovascular hospitalization.

Currently as per our research study results both the drugs of SGLT2 inhibitors Dapagliflozin and Empagliflozin showed a better safety and efficacy parameters in treatment for obese patients with T2 DM, but eventually when comparing the two Treatments Empagliflozin showed a better outcome in all the aspects like safety, efficacy and cardiovascular risk assessment. On further we will evaluate the other drugs like Canagliflozin and we conclude the safety, efficacy and cardiovascular profile upon treatment with SGLT2 inhibitors in obese patients with T2 DM.

CONCLUSION

SGLT-2 inhibitors are safe and effective in treating uncontrolled type 2 diabetes mellitus patients. When obese patients with T 2 DM treated with Empagliflozin and Dapagliflozin showed some reduction in glycemic parameters like FBS, PPBS, HbA1c levels and additionally Body weight reduction was seen in obese patients. Both the drugs showed better safety outcomes with fewer incidences of hypoglycemic episodes, UTIs and Weight gain. In obese patients with T2 DM these drugs reduced cardiovascular risk and are producing promising results by decreasing the death and hospitalization due to CVD. Both Empagliflozin and Dapagliflozin have shown good efficacy and safety profiles and they can be used as an adjuvant therapy to conventional OHAs in obese patients with T2DM.

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