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Original Research Article

A 12 week prospective clinical evidence of empagliflozin efficacy in uncontrolled type 2 diabetes mellitus treated with metformin and a sulfonylurea

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ABSTRACT

Background: The main aim of the study is to evaluate the efficacy of empagliflozin 10 mg once daily over 12 weeks as add-on therapy to metformin plus sulfonylurea in patients with type 2 diabetes mellitus with inadequate glycemic control.
Methods: It is a prospective, observational, study conducted in patients of Sri Badhrakali Diabetic Center located in Warangal, Telangana, India. The efficacy of empagliflozin 10 mg was assessed by measuring the change in the glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), body mass index (BMI) at the baseline and 12 weeks, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the baseline and after 24 hours of treatment.
Results: In the present study, the addition of empagliflozin to metformin and Sulfonylurea therapy for 12 weeks provided 0.87 % reduction in HbA1c. The mean changes of FPG from baseline to 12-week is -26 mg/dl. At 24 hours empagliflozin significantly reduced blood pressure with mean changes of SBP and DBP -4.147 and -1.526 mmHg respectively. The mean changes in BMI from baseline to week 12 is -0.638 kg/m^2.
Conclusions: Empagliflozin 10 mg provided ancillary reduction in HbA1c outside of metformin and sulfonylurea. Controlled body weight, HbA1c, blood pressure decreases diabetes progression, decreased risk of diabetic complications and reduced risk for cardiovascular disorders.

Keywords: Type 2 diabetes mellitus, HbA1c, FPG, BMI, Sodium glucose co-transporter 2 Inhibitor, Sulfonylurea, Metformin, DBP, SBP

INTRODUCTION

The world prevalence of diabetes among adults (aged 20–79 years) will be 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7%, and 439 million adults by 2030. There will be a 20% increase in developed countries and a 69% increase in numbers of adults with diabetes in developing countries between 2010 and 2030.[1] The population of diabetes is increasing due to growth of population, urbanization, aging, and increasing prevalence of obesity and torpidity. In 2013, 382 million people throughout the world had diabetes and it is expected to rise to 592 million by 2035.[2] In conjunction with lifestyle interventions, the use of metformin as a first-line treatment for type 2 diabetes is well established. However, when additional treatment is required to achieve or maintain glycosylated hemoglobin (HbA1c) levels at <7%, the update to a position statement of the American Diabetes Association and the European Association for the study of diabetes recommends concomitant treatment with sulfonylurea, a thiazolidinedione (TZD), a dipeptidyl peptidase 4 inhibitor, a sodium/glucose co transporter 2 inhibitor, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin.[3]

Furthermore, as type 2 diabetes progresses, with deterioration of beta cell function and increased insulin resistance, the use of agents utilizing pathways dependent on insulin becomes increasingly difficult. In addition, steady increases in weight are observed in patients with type 2 diabetes.[4,5] Thus, there is still a great unmet need

for effective and well-tolerated anti-diabetes agents that can be used in combination with existing treatments to improve glycemic control in patients with type 2 diabetes, in particular without the risk of hypoglycemia and weight gain. Metformin is the recommended first line pharmacotherapy for patients with type 2 diabetes, but most patients will ultimately require additional therapies to maintain glycemic control. Maintaining intensive glucose control early in the disease process may lead to legacy benefits that persist beyond the period of treatment. Therefore, when metformin fails to achieve glycemic control, add-on combination therapy with two oral anti-diabetes agents may be beneficial.[6]

Empagliflozin is a potent and selective inhibitor of sodium-glucose co-transporter 2 (SGLT2).[7] Their mechanism of action involves inhibiting the SGLT2 in the proximal nephron, thereby reducing glucose reabsorption and increasing urinary glucose excretion by up to 80 g/day.[8]Because this action is independent of insulin, SGLT2 inhibitors may be used at any stage of type 2 diabetes, even after insulin secretion has waned significantly. Additional potential advantages include modest weight loss (-2 kg, stabilizing over 6–12 months) and consistent lowering of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the order of -2 to 4/-1 to 2 mmHg.[9,10] Their use is also associated with reductions in plasma uric acid levels and albuminuria.[11]

Empagliflozin, a selective SGLT2, reduces hyperglycemia in patients with type 2 diabetes by reducing the renal reabsorption of glucose, thereby increasing urinary glucose excretion.[12] The use of empagliflozin has been associated with a lowering of glycated hemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease, and with reductions in weight and BP, without increases in heart rate.[13-18] Empagliflozin has been shown to reduce intraglomerular pressure and improve hyperfiltration in patients with type 1 diabetes.[19,20] and it has been suggested that these effects may translate into improved renal outcomes.[21]

Primary objective of this study is to procure real-time clinical outcomes of empagliflozin 10 mg once daily over 12 weeks when added as third line oral hypoglycemic agent in patients with uncontrolled diabetes. Empagliflozin, a selective SGLT2, reduces glucose absorption and increases urinary glucose excretion. Pleotropic effects of empagliflozin include weight loss, decreasing BP are also monitored in this prospective study along with glycated haemoglobin.

METHODS

It is a six months prospective, observational study conducted in 136 diabetic patients from August 2018 to January 2019 at out-patient department of Sri Badrakali Hospital located in Warangal, Telangana state.

Patient eligibility

Inclusion criteria

This study enrolled patients [aged ≥18 years; body mass index (BMI)≤45 kg/m^2] with inadequately controlled BP>140/90 mmHg, type 2 diabetes (HbA1c ≥7 to ≤10%) despite a diet and exercise program and a stable regimen (unchanged for ≥12 weeks prior to randomization) of metformin plus a sulfonylurea.

Exclusion criteria

Pregnant and lactating females, patients on insulin therapy, history of type 1 diabetes mellitus, signs of diabetic complications (nephropathy, neuropathy, and retinopathy) and patients with clinical signs and symptoms of acute myocardial infarction, liver failure, chronic heart failure and renal failure were excluded. Treatment with anti-obesity drugs 3 months prior to consent, use of any treatment at screening that leads to unstable body weight, treatment with systemic steroids at time of consent, change in dosage of thyroid hormones within 6 weeks of consent, alcohol or drug abuse within 3 months of consent, and investigational drug intake within 30 days of the trial. Treatment with additional antihypertensive drug, TZDs, GLP-1 analogues or insulin within 3 months.

Study measurements

The primary endpoint was the change in HbA1c from baseline to week 12 with empagliflozin 10 mg. Secondary endpoints include changes in fasting plasma glucose (FPG), BMI, SBP and DBP from baseline.

Statistical analysis

All parameters were expressed as mean±SE [or standard deviation (SD) where indicated]. Data analyses were performed using the GraphPad prism 7.0. Student's paired t-test was used to assess significant differences between values obtained before and after the addition of empagliflozin, p value <0.001 was considered statistically significant. Pearson correlation coefficient was used to measure the correlation between HbA1c and FPG.

RESULTS

The mean age of the patients included was 52.55±9.99 (Figure 2) with 61 males and 75 females (Figure 1).

Effect of empagliflozin on glycemic levels

The mean HbA1c levels at the beginning of the study was 9.305±1.220. At the end of the study, HbA1c levels reduced by -0.87±0.115 mg/dl (p<0.0001) by empagliflozin when added to metformin plus sulfonylurea (Figure 3). The mean FPG levels at the baseline and 12-week were 147.082±42.282 and

120.9836±44.763 respectively. The changes from baseline was -26.099 mg/dl (p<0.0001) which is significant (Figure 4).

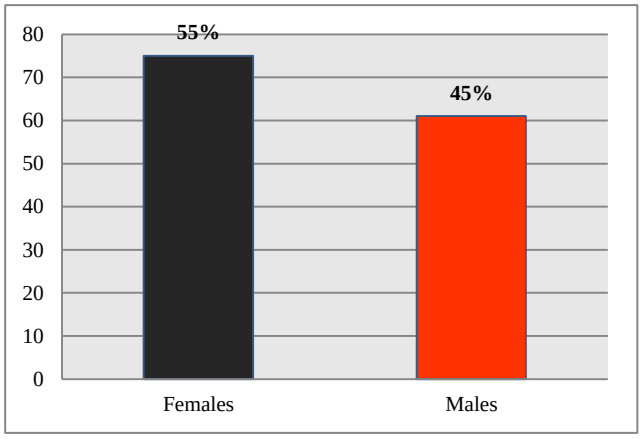

Figure 1: Gender distribution.

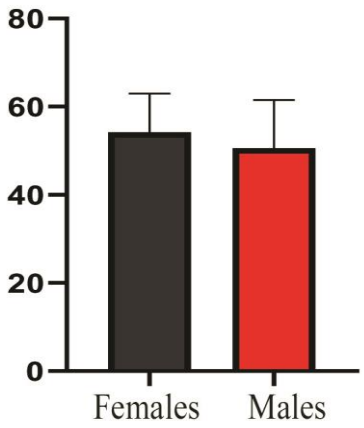

Figure 2: Age distribution.

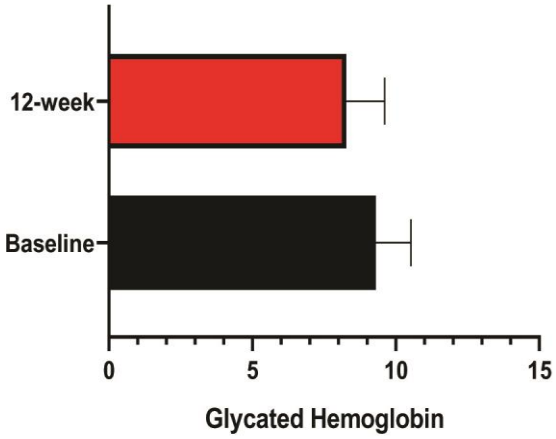

Figure 3: Effect of empagliflozin on glycated hemoglobin.

Effect of empagliflozin on BP

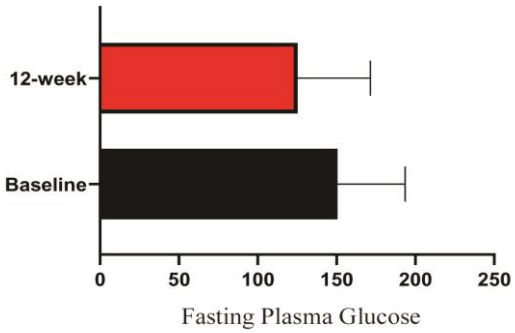

Figure 4: Effect of empagliflozin on FPG.

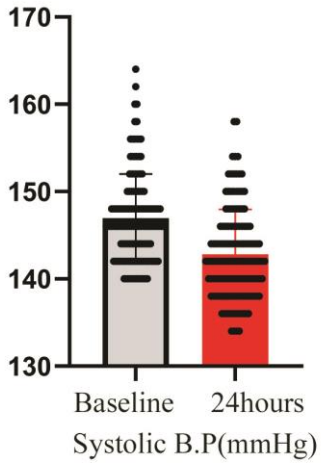

Figure 5: Effect of empagliflozin on SBP.

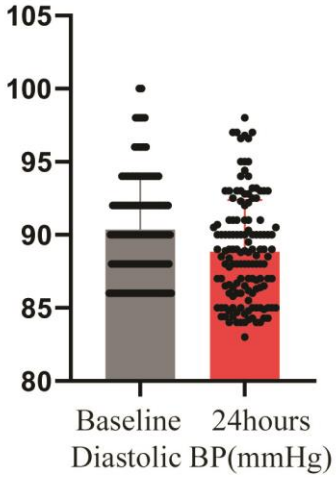

Figure 6: Effect of empagliflozin on DBP.

The baseline means of SBP and DBP were 146.955±5.04 and 90.367±3.474. After 24 hours they were significantly reduced to 142.808±5.118 and 88.841±3.529 (p<0.0001) (Figures 5 and 6).

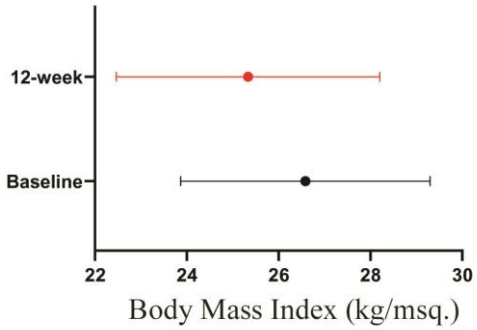

Figure 7: Effect of empagliflozin on BMI.

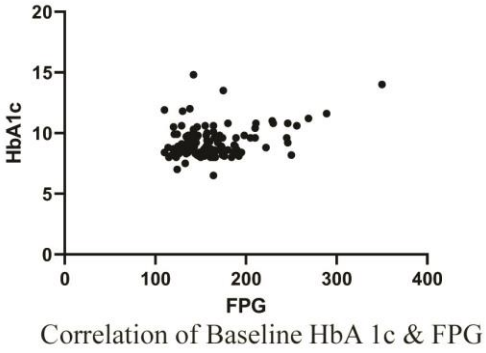

Figure 8: Correlation of baseline HbA1c and FPG.

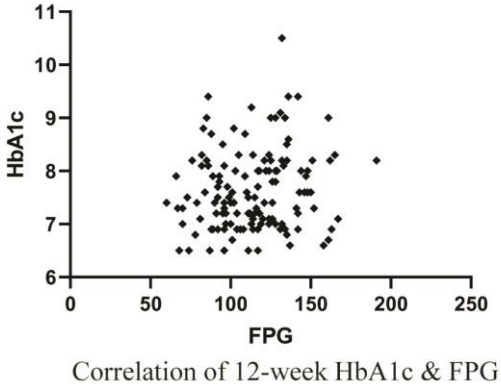

Figure 9: Correlation of 12-week HbA1c and FPG.

Effect of empagliflozin on body weight

The mean of body weight at baseline was 26.58±2.705, at week 12 was 25.89±2.739 (p<0.638) (Figure 7).

Relation between HbA1c and FPG

Pearson correlation coefficient of baseline HbA1c and FPG was found to be r=0.7 which indicates high correlation and Pearson correlation coefficient for 12-week HbA1c and FPG was r=0.4 indicating moderate correlation (Figures 8 and 9).

Table 1: Clinical characteristics.

Characteristics	Baseline (mean±SD)	Week 12 (mean±SD)	Changes from baseline (LS±SE)	P value
BMI (kg/m^2)	26.58±2.705	23.816±2.739	2.764±0.034	<0.0001
HbA1C (%)	9.305±1.220	8.435±1.335	0.87±0.115	<0.0001
FPG (mg/dl)	147.082±42.282	120.9836±44.763	26.099±2.481	<0.0001
SBP (mmHg)	146.955±5.04	142.808±5.118	4.147±0.078	<0.0001
DBP (mmHg)	90.367±3.474	88.841±3.529	1.526±0.055	<0.0001

BMI: Body Mass Index, HbA1c: Glycated Hemoglobin, FPG: Fasting Plasma Glucose, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SD: Standard Deviation, LS: Least Squares, SE: Standard error.

DISCUSSION

We have evaluated add-on therapy of empagliflozin among patients having inadequately controlled T2DM even after treatment with dual therapy of metformin and sulfonylurea. Add-on therapy with empagliflozin provided a significant reduction in HbA1c, FPG, BMI, SBP, DBP.

In the present study, the addition of empagliflozin to metformin and sulfonylurea therapy for 12 weeks provided 0.87% reduction in HbA1c. The mean changes of FPG from baseline to 12-week is -26 mg/dl. At 24 hours empagliflozin significantly reduced BP with mean changes of SBP and DBP -4.147 and -1.526 mmHg respectively. The mean changes in BMI from baseline to week 12 were -0.69 kg/m^2. A 24-week, randomized, double-blind, placebo-controlled trial investigated that The percentage of patients with uncontrolled BP at baseline who had controlled BP (SBP 130 mmHg and DBP 80 mmHg) at week 24 was higher with empagliflozin 10 mg, furthermore it reduced HbA1c by -0.70%, BMI by -2.08 kg and FPG by -19.98 mg/dl at the end of 24 week. An active-controlled, open-label extension study in patients with type 2 diabetes concluded that empagliflozin provided 0.34 HbA1c mmol/mol, -30 mg/dl FPG, -2.2 kg body weight, SBP mmHg by -0.1 and DBP by -1.6 mmHg respectively.[22]

A 12-week study concluded that empagliflozin as an add-on therapy decreased HbA1c by -0.94%. A reduction of -30.3 mg/dl in FPG, -2.1 kg in body weight, -4.7 mmHg of systolic and -1.3 mm Hg of DBP were significantly improved by empagliflozin.[23] An investigation on

effectiveness of SGLT2 inhibitors have shown a significant reduction in mean weight and HbA1c reduction 3.2 kg and 1.26%, respectively.[24] Based on four months follow-up, a study reported 0.7 % HbA1c reduction, weight dropped for an average −2.0 kg, SBP dropped significantly, but no change in DBP were observed.[25]

Limitation

Limitation of this study includes small sample size, absence of control group and short duration. Although the measurement of HbA1c at three months is reliable, studies to measure parameters other than glycemic control of longer duration are required.

CONCLUSION

Empagliflozin 10 mg provided ancillary reduction in HbA1c outside of metformin and sulfonylurea. Controlled body weight, HbA1c, blood pressure decreases diabetes progression, decreased risk of diabetic complications and reduced risk for cardiovascular disorders. These evidence of efficacy in clinical parameters along with additional benefits and usability will be beneficial. With the increasing obesity and diabetic rates globally in the coming years leads to increased costs in healthcare, decreased quality of life and increased complications. Therefore, hypoglycemic agents with additional benefits are the pressing need for the treatment.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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