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Original Research Article

Effect of add on therapy of SGLT 2 inhibitors on glycaemic parameters

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ABSTRACT

Background: Glycaemic control in type 2 diabetes mellitus can be difficult to attain, even with a combination of multiple oral agents as well as Insulin. SGLT2 inhibitors are potential novel agents inhibits the sodium glucose co transporters operated in the kidney tubules independent of the action on insulin resistance or secretion. This study aimed to evaluate the effect on the mean reduction of HbA1c levels. Also, to evaluate the effect of gliflozins on the mean reduction of FBS and PPBS values at the end of 3rd and 6th months and to find out the ADR profile over 6 months.
Methods: Prospective observational study conducted on the patients with type 2 diabetes mellitus with HbA1c >7% not controlled on metformin in the outpatient over a period of 15 months. An initial visit and thereafter follow up visits at 3rd and 6th month. HbA1c, FBS and PPBS was noted. ADR profile was also noted.
Results: Significant mean reduction in the glycemic parameters among 90% study population with 0.5% reduction in mean HbA1c from the baseline. Also, the reduction in FBS and PPBS were statistically significant by 3rd month of the treatment. Incidence of genital itching was more compared with conventional drugs. Hypotension and polydipsia were rare.
Conclusions: SGLT 2 inhibitors are found to be a promising new category of antidiabetic medications with better control of FBS, PPBS and HbA1c.

Keywords: Gliflozins, Glycosuria, HbA1c, Type 2 diabetes mellitus, Weight loss

INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease in which hyperglycemia results from insulin resistance and reduced insulin secretion. It accounts for almost 90% of cases of diabetes in adults.[1,2] Lifestyle modifications such as diet and exercise are the cornerstone of therapy, pharmacotherapy is added to reach glycemic targets.

The use of current agents for T2DM is often limited by their potential to induce significant adverse effects. For instance, metformin can cause gastrointestinal effects such as diarrhoea and nausea, and rarely, lactic acidosis, whereas sulphonylureas or insulin can induce hypoglycaemia as well as weight gain.[3] Newer drugs, such as the incretin mimetics, may produce nausea, vomiting and diarrhoea.[4] Glycaemic control can be difficult to attain, even with a combination of multiple oral agents, and with insulin added.[4,5]

The kidney has a key role in regulating glucose levels by mediating the reabsorption of glucose from the proximal tubules into the circulation and this is a crucial evolutionary adaptation to maintaining glucose homeostasis and to retaining calories. This process contributes to the sustained elevated serum glucose levels

observed in individuals with diabetes, as they have an increased capacity for renal glucose reabsorption.[6] Inhibiting this glucose reabsorption, thereby allowing its excretion in the urine (glycosuria), is therefore emerging as a potential new approach to the treatment of diabetes.

Sodium-glucose cotransporter-2 (SGLT2) inhibition is a novel mechanism that reduces hyperglycemia independent of insulin secretion or action. In addition, this inhibitory action can induce mild osmotic diuresis and increase urinary excretion of glucose with modest caloric elimination leading to weight loss. Dapagliflozin, an SGLT2 inhibitor, has been shown to improve glycemic control in patients with type 2 diabetes as monotherapy and in combination with metformin sulfonylurea, or insulin, but not yet with a thiazolidinedione.[7] Hence, the present study was aimed at evaluating the effect of gliflozins (SGLT2 inhibitors) on HbA1c levels when used as an add on therapy in patients with type 2 diabetes mellitus not controlled with metformin with or without sulfonylurea, with the primary objective of evaluating the mean reduction of HbA1c levels at the end of 3rd and 6th months of the treatment and secondary objectives of evaluate the effect of gliflozins on the mean reduction of FBS and PPBS values at the end of 3rd and 6th months and ADR profile over 6 months.

METHODS

This was prospective observational study conducted at Department of Pharmacology in collaboration with Department of Endocrinology, Government Medical College and Indian Institute of Diabetes (IID), Thiruvananthapuram for 15 months from April 2018 to June 2019.

Inclusion criteria

Patients of either gender, aged between 18 to 70 years, diagnosed with type 2 diabetes mellitus patients with HbA_1c >7.0% not controlled even on metformin ± sulphonyl urea and are started on one of the gliflozins (Empa/Dapa) as an add on therapy and willing to be part of our study were included.

Exclusion criteria

Pregnant women, patients with systemic illnesses other than diabetes and those with S. creatinine clearance <60ml/min were excluded from the study.

Sample size

By using the formula,

$$n \geq \frac{\left(Z\,1-\frac{\alpha}{2}+Z\,1-\beta\right)^2}{\Delta^2} + \frac{(Z\,1-\frac{\alpha}{2})^2}{2}$$

where, n = sample size

$$\Delta = \frac{(\mu_2-\mu_1)}{\sigma}, \quad \sigma = \frac{\sigma_1+\sigma_2}{2}$$

μ_1 = pre test mean, μ_2 = post test mean, σ_1 = SD in the pre test, σ_2 = SD in the post test, Δ = effect size, α = significance level, 1-β = power, n = 40.

Study procedure

Ethical clearance (IEC.No.12/15/2017/MCT) was obtained from the Institutional Human Ethics Committee prior to the study. Confidentiality and anonymity of the patient's information was maintained during and after the study. The study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines.

The study population included the patients with type 2 diabetes mellitus with HbA1c >7% not controlled on metformin with or without sulfonylurea and were started on one of the gliflozins as an add on therapy and who obeyed inclusion and exclusion criteria. Each patient was seen 3 times, an initial visit and thereafter follow up visits at 3rd and 6th month. At the initial visit, the baseline data like demographic profile, clinical diagnosis, comorbid conditions, treatment history, current treatment with dosage of each drug and the lab values: HbA1c, FBS and PPBS were recorded. Follow up done at 3rd and 6th months. ADR profile was also noted during the follow up visits. No invasive investigation was done as a part of the study. Rechallenge and rechallenge were not done.

Statistical analysis

Data was entered in Microsoft excel software and analysed using SPSS 16 statistical software. Qualitative variables were described by percentage distribution. Quantitative variables were described by mean, standard deviation, minimum and maximum. Pre-test and post-test comparison of quantitative variables were analysed by paired t' test. A p value of less than 0.05 was taken as level of significance.

RESULTS

The data was collected during the first visit and also during the follow up visits which were conducted at the end of third and sixth months. The data were entered into an structured proforma.

The age of the patients included in the study was between 18 to 70 years. The mean age of the patients included in this study was 56.18±8.614 years. The minimum age 37 years and the maximum was 70 years. Analysis of gender distribution shows that out of 40 patients, 18 (45%) were females and 22 (55%) were males.

Analysis shows that out of 40 patients 25% were taking metformin alone and 75% of patients were taking

metformin along with sulfonylurea which was shown in the Table 1.

Table 1: Patients on first line drugs (n=40).

Drugs	Frequency	Percent (%)
Metformin	10	25.0
Metformin+sulfonylurea	30	75.0

Analysis of patients taking gliflozins shows that out of 40 patients 7.5% patients were taking dapagliflozin 10 mg, 27.5% were taking empagliflozin 10 mg, 60% were taking empagliflozin 12.5 mg and 5% were taking empagliflozin 25 mg shown in the depicted in Figure 1.

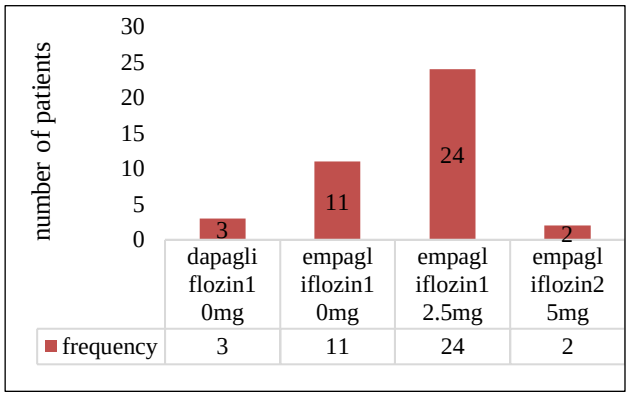

Figure 1: Frequency distribution of gliflozins taken by the study sample.

Out of 40 patients, 26 (65%) were having hypertension alone or in association with other diseases and 1 (2.5%) with CAD. 13 (32.5%) had no other coexisting diseases.

Table 2: Distribution of comorbid conditions.

Co morbidity	Frequency	Percentage (%)
Hypertension	26	65
Coronary artery disease	1	2.5
Nil	13	32.5

The glycemic parameters analysed were HbA1c, FBS, PPBS.

Table 3: Mean HbA1c values (n=40).

H visits	Mean (%)	Mean reduction	P value
Baseline	9.57±1.47	-	
3rd month	8.71±1.73	0.86 ± 1.41	<0.001
6th month	8.04±1.24	1.53 ± 1.17	<0.001

Table 3 shows that the mean baseline value was 9.57±1.47%. After three months of treatment, this value got reduced to 8.71±1.73% with the mean reduction of -0.86±1.41%. On analysis, it was statistically significant with the P value of <0.001. At the end of 6 months the mean value dropped to 8.04±1.24% with the mean reduction of -1.53±1.17%. This reduction was also found to be statistically significant.

Figure 2 depicts the fall in HbA1c levels from the baseline. Figure 3 shows the mean reduction at the end of 3rd and 6th month.

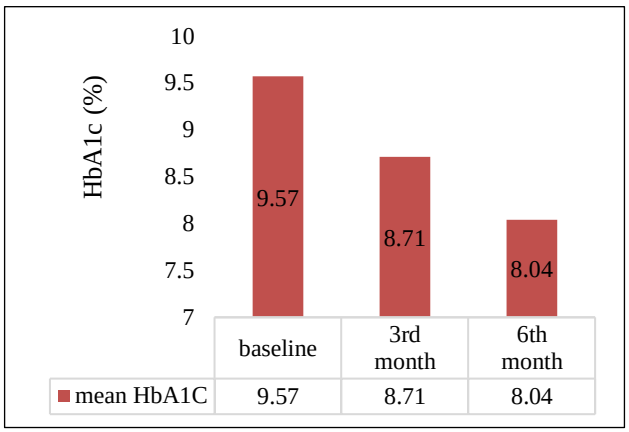

Figure 2: Mean HbA1c values.

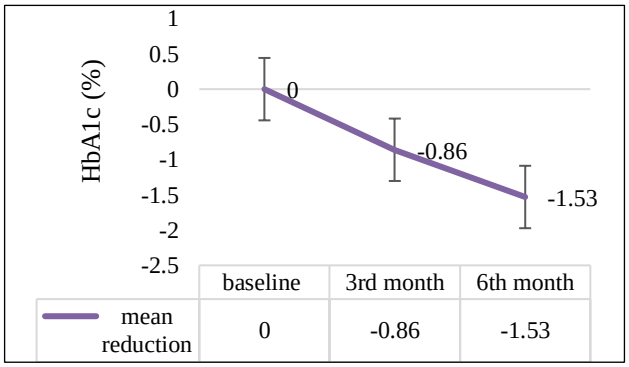

Figure 3: Mean reduction in HbA1c.

Figure 4 shows that 19 (47.5%) patients were showing mean reduction of 0.5% or more at the end of 3rd month and 36 (90%) patients were showing 0.5% reduction in mean HbA1c at the end of 6th month.

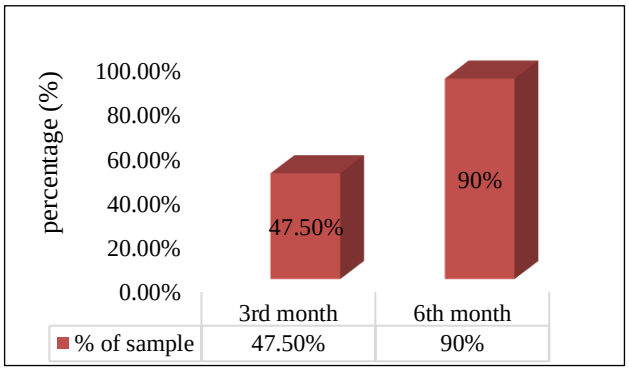

Figure 4: Percentage population showing 0.5% reduction in mean at 3rd and 6th month.

Table 4: Comparison of mean fasting blood sugar.

FBS (mg/dl)	Mean (mg/dl)	Mean reduction (mg/dl)	P value
Baseline	202.20±64.77	-	-
3rd month	168.65±53.25	-33.55±62.12	0.002
6th month	156.7±43.22	-45.5±63.14	<0.001

The Table 4 explains that the mean baseline value was 202.2±64.77 mg/dl. After 3 months of treatment this value got reduced to 168.65±53.25 mg/dl with the mean reduction of 33.55±62.12 mg/dl with statistically significant p value of 0.002. At the end of 6th month the mean value significantly dropped to 156.7±43.22 mg/dl with the mean reduction of 45.5±63.14 mg/dl (p =<0.01). Figure 5 shows the mean reduction at the end of 3rd and 6th month.

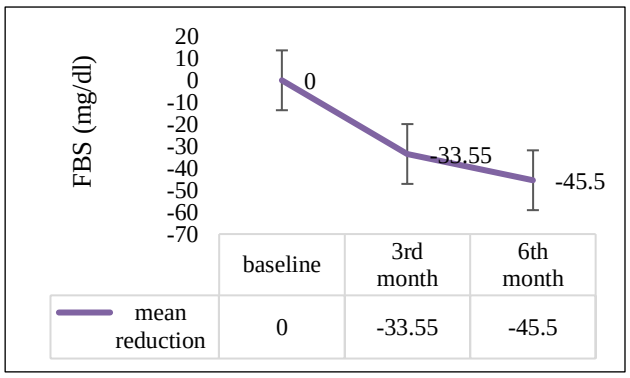

Figure 5: Mean reduction in FBS.

At the time of recruitment 95% of patients had fasting blood glucose of >126 mg/dl which was considered as diabetic as per ADA recommendation. By 3rd month only 82.5% had a value of >126 mg/dl and at the end of 6 months 67.5% of patients has FBS value of >126 mg/dl. At the baseline no patients were having Impaired Glucose Tolerance (IGT), at the end of 3rd month 10 % had IGT and at the end of 6 months 20 % had IGT. 5% had normal FBS value at the baseline whereas it increases to 7.5% and 12.5% at the end of 3rd and 6th month respectively.

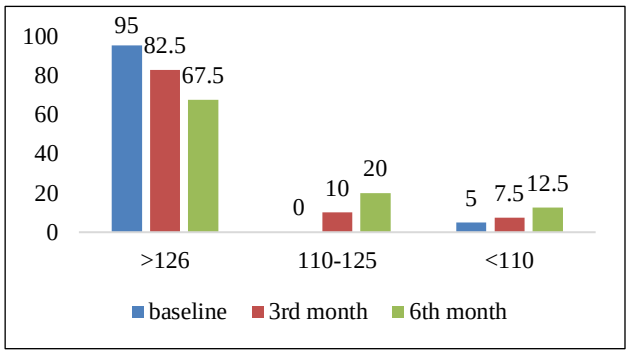

Figure 6: Percentage population showing difference in mean FBS over 6 months.

Table 5: Mean PPBS values.

Visits	Mean(mg/dl)	Mean difference	P value
Baseline	276.10±87.9	-	-
3rd month	247.82±75.61	28.27±103.3	0.091
6th month	233.45±58.23	42.65±91.78	0.006

Table 5 shows that the mean baseline value was 276.10±87.9 mg/dl. After 3 months of treatment this value got reduced to 247.82±75.61 mg/dl with the mean reduction of 28.27±103.3 mg/dl (p 0.091). At the end of 6th month, the mean value significantly dropped to with the mean reduction of 42.65±91.78 mg/dl, p=0.006.

Figure 7 shows that the % of patients with post prandial blood glucose level at the baseline was 85% which then reduced to 72.5% and 65% at 3rd and 6th month respectively. The patients with IGT were 10% at the baseline, 20% and 35% at the end of 3rd and 6th month respectively. 5% of patients had normal PPBS level at the baseline and at the end of 3rd month 7.5% had normal PPBS values and none had normal PPBS at the end of 6th month.

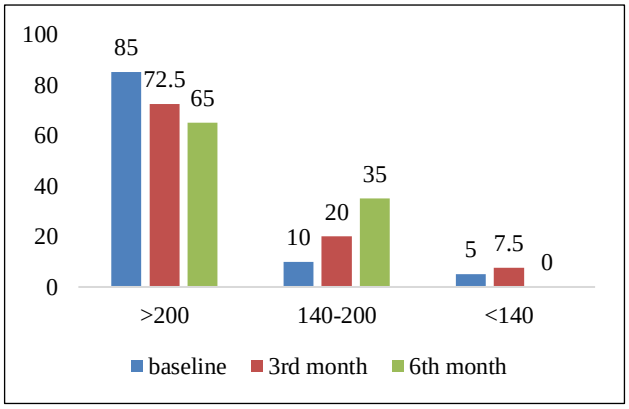

Figure 7: Percentage population showing reduction in PPBS over 6 months.

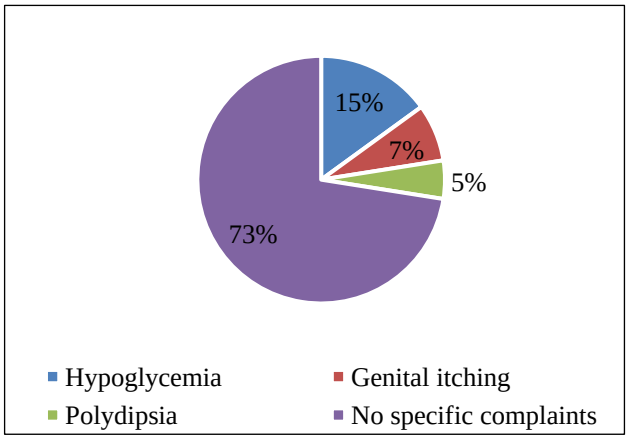

Figure 8: Percentage distribution of adverse drug reactions.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a progressive chronic disease characterized by insulin resistance and a progressive insulin secretory defect associated with severe microvascular and macrovascular complications and it has been a focus of active clinical and therapeutic research for many decades.[8] Many large randomized control trials have demonstrated a significant reduction in microvascular events in patients treated with hypoglycemic agents leading to a reduced HbA1c.[9] The progressive nature of the disease makes the patients to take combination of multiple class of antidiabetic medications. Given this issue, the American Diabetes Association (ADA) guidelines recommend HbA1c therapeutic goals <7% to reduce morbidity and complications in T2DM.[10]

Fortunately, there have been numerous medical advances made in this regard, such as the discovery of SGLT2 inhibitors. Sodium glucose co-transporter type 2 inhibitors are becoming a promising therapy for T2DM. These drugs reduce hyperglycemia by blocking renal glucose reabsorption, in the proximal tubule of the kidney. This induces glycosuria which lowers serum glucose and also induces diuresis. This class of medicine has brought new hope for patients with diabetes and clinicians treating this condition due to the remarkable glycemic and non-glycemic benefits.[11]

The primary objective of the present study was to evaluate the effect on the mean reduction of HbA_1c levels at the end of 3rd and 6th months. The secondary objective were to evaluate the effect of gliflozins on the mean reduction of FBS and PPBS values at the end of 3rd and 6th months and also to find out the ADR profile over 6 months.

The sample of the study was 40 patients who was prescribed with one of the gliflozins when not controlled with metformin with or without sulfonylurea for the treatment of type 2 diabetes mellitus. The age of the patients included in this study was 18-70 years with mean age 56.18±8.6 years in which males are about 55% and females are 45%. it was comparable to List, Wheeler DC and James J et al in which mean age group was 54±9 years with males about 53% and females about 47%. Among the 40 patients 25% were taking metformin alone and 75% were taking metformin with sulfonylurea along with one of the gliflozins.[12]

The treatment was considered effective when the patient attained the mean reduction in HbA1c of 0.5% from the baseline value at the end of the 6th month. The mean reduction of HbA1c at the end of the 6 months was 1.53±1.71. This was similar to the study conducted by Rosenstock et al which showed dapagliflozin added to patients already taking metformin and sulfonylurea showed a decrease in HbA1c of -0.86% compared to a decrease in HbA1c of -0.17% in the placebo group at 24 weeks. Out of 40 patients 90% of patients showed the reduction of 0.5% at the end of 6th month.[13]

The mean FBS at the baseline was 202.2 mg/dl and at the end of 6 months was 156.7 mg/dl. The mean reduction was about 45.5±63.14mg/dl at the end of 6 months. This was comparable to the study by Clar et al in which mean reduction of about 35.25 to 56.84 mg/dl is observed. Out of 40 patients 5% was having normal FBS levels and 95% were having diabetes, whereas at the end of the 6th month, the patients with normal FBS has increased to 12.5% and the persons with diabetes were reduced to 67.5%. The mean PPBS at the baseline and at the end of 6th month was 276.1 mg/dl and 233.45 mg/dl respectively.[14] Out of 40 patients 5% were having normal PPBS values, 10% were having IGT and 85% were having diabetes. At the end of 6 months, the persons having diabetes had reduced to 65%.

Regarding ADR 15% of the study sample complaints of hypoglycemia at the starting of the gliflozins. None of them required discontinuation of the drug. 7.5% complaints of genital itching relieved by excessive intake of water, 5% complaints of polydipsia. No other serious drug reactions were observed during the study period. Similar studies were conducted by van Erik et al.[15] Higher ALP should raise suspicion of increased bone loss and caution may be advised in post-menopausal women and those with other diseases or medications which may predispose to osteoporosis.

This study has some limitations. A randomised controlled trial would have been preferred for a better assessment. The sample size was small. Study population should be large for the proper assessment of effectiveness and safety profile. The study period was short. Long term follow up was needed to evaluate long term efficacy and adverse effects. Patients having creatinine clearance < 60ml/min and with serious systemic illnesses were excluded from the study.

CONCLUSION

With the above observation and discussion, we would like to conclude that out of 40 patients 90% shows mean reduction of 0.5% of HbA1c or more from the baseline at the end of 6 months with maximum reduction of 1.53%. FBS and PPBS values are also found to be significantly reduced with the mean reduction of 45.5mg/dl and 42.5mg/dl respectively from the baseline at the end of 6 months. Overall, the drug is found to be useful in patients with uncontrolled type 2 diabetes mellitus with comparatively lesser side effects than the older drugs. However, long term study with larger sample population with wider age distribution and different demographic area will yield comparatively better comparative results.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee
(IEC.No.12/15/2017/MCT)

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