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Original Research Article

Efficacy And Safety Of Sodium Glucose Co- Transporter 2 Inhibitors In Type 2 Diabetes Mellitus Patients.

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ABSTRACT

Type 2 Diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia. It affects millions of people worldwide and is the fourth leading cause of death in India. One of the most important and effective treatment to achieve glycemic control in diabetic patients are various oral hypoglycemic agents with adequate lifestyle modifications and physical activities. Sodium glucose cotransporter 2 inhibitors are one such emerging oral hypoglycemic agents that achieve the desired goal with some complimentary benefits. This prospective observational study using four different SGLT2 inhibitors amongst 68 patients with Type II diabetes namely Canagliflozin 100 mg, Dapagliflozin 10 mg, Empagliflozin 25 mg, Remogliflozin 100mg has shown promising results in managing glycemic control along with complimentary benefits including weight loss.

Keywords: SGLT2inhibitors, Diabetes, Kidney disease, Canagliflozin, Empagliflozin, Remogliflozin, Dapagliflozin, Glycated hemoglobin.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM), a metabolic disease is characterized by high blood sugar level in blood (hyperglycemia) due to defect in secretion of insulin, action of insulin or both. This chronic condition inflicts millions of people all over the world and is the fourth leading cause of death in India (1).

Older oral hypoglycemic drugs like sulfonylureas, metformin, thiazolidinedione, and even dipeptidyl peptidase inhibitors (DPP4i) though cause lowering of the blood sugar level and reduced incidence of microvascular complications, usually don't cause weight loss in contrast to the novel drug used in the study as an oral hypoglycemic agent (OHA) i.e. sodium-glucose co-transporter 2 inhibitors (SGLT2i) which not only reduces HbA1C significantly but also causes weight loss as well as prevents micro and macrovascular complications in patients with T2D (2).

The SGLT2 inhibitors namely Canagliflozin, Empagliflozin, Dapagliflozin and Remogliflozin has gained popularity due to its unique mechanism of action i.e., by decreasing the glucose level without affecting insulin release or insulin sensitivity. Hence, it can be used without much dose alteration in patients with renal impairment (eGFR > 30 ml/min/1.73m2). (3) (4).

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The kidney reabsorbs 99% of the daily (~180 g/day) glucose that is filtered in the kidneys. This reabsorption mechanism of filtered glucose in the kidneys are mediated by two transporters viz. the facilitative glucose transporters (GLUTs) and active sodium-glucose co-transporter (SGLTs). SGLT2 is one amongst the different SGLTs that is expressed mainly in the kidneys. The SGLT2 inhibitors act by decreasing the renal threshold for reabsorption of glucose resulting in urinary glucose excretion (UGE) and thereby net caloric loss, which in turn causes lowering of blood glucose level and diminishing of body weight. SGLT2i cause approximately 30–80 g of loss of glucose in 24 h (2) (5).

SGLT2 inhibitors has been included in 1st line therapy by the American diabetes association (ADA) for T2DM patient whose sugar level is not controlled or in patients in whom Metformin is contraindicated although there is an increased risk of adverse effects like genital-urinary tract infection (4). Other adverse effects which are closely associated with SGLT2 inhibitors are euglycemic ketoacidosis, dehydration, polyuria at initiation, fracture, and leg amputation, but these are very less and don't overcome the beneficial effect of the SGLT2i class of drugs (2) (6) (7).

Type 2 diabetes increases the risk of cardiovascular disease (CVD) and the control of glucose will be important to prevent cardiac disease, but other factors like weight, blood pressure, renal functions are also important to maintain good heart health. So, the focus on reducing glucose levels is not the main target of Sodium glucose co-transporter 2 (SGLT2) inhibitors but rather they have a pleiotropic beneficial effect too in lowering the blood pressure (BP) and weight of an individual (8) (9) (10).

With this background this prospective observational study has been done to evaluate the efficacy and safety.

MATERIALS AND METHODS

An observational prospective study was conducted in a tertiary care hospital for assessment of safety as well as efficacy of SGLT2 inhibitors. Institutional ethical committee approval was obtained before commencement of the study.

All the patients attending as outpatient in Endocrinology department of the hospital, between January 2020 to December 2020, with a history of T2DM were initiated with SGLT2 inhibitors. Total of 68 patients were enrolled initially but later 61 of them were followed up till the end of the study.

Table A-

TABLE A - Demographics of Diabetes patient				
S. No.		**Category**	**Number of subjects**	**Percentage**
1	**Gender N=61**	Male	42	68.9
		Female	19	31.1
2	**Age N=61**	Less than 50	26	42.6
		50-65 years	35	57.4
3	**BMI (Kg/m2)**			
		Between 18.5 and 24.9	39	63.9
		Between 25 and 29.9	6	9.8
	N=61	Above 30	16	26.2

During initial evaluation basic demographic details, details of medications taken were noted and lab investigations relevant for the patient were done to assess the patient's condition accordingly. The baseline HbA1c was noted to be compared on consecutive visits for evaluation of SGLT2 inhibitors efficacy. Compliance of patient was checked by cross-checking the empty blister of medicines.

Patients were requested to get the HbA1C done on each follow-up visit, which was scheduled every

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3 months for 2 times. On second and third visits patients were also analyzed for any adverse effect and patients were also contacted through phone for any notable adverse effect.
SGLT2i drugs used for the study included Canagliflozin 100 mg (Cana or C), Dapagliflozin 10 mg (Dapa or D) ,Empagliflozin 25 mg (Empa or E) and Remogliflozin 100mg (Remo or R).
The data gathered were collated in Microsoft office excel worksheet. Qualitative variable was expressed in numbers and percentages while quantitative variable was expressed in mean and standard deviations. Paired t-test was performed to find a significant difference between parameters. P-value <0.05 were considered significant statistically and p-value < 0.001 were considered highly significant statistically.

RESULTS & OBSERVATIONS

A total of 68 patient was enrolled in the study, out of which 61 were followed up, of which 42 were males and 19 were females. Of the 61 number of patients, 43% were below the age of 50 years and the remaining were between 50 to 65 years of age. Body Mass Index (BMI) was calculated along with other baseline characteristics of patient. BMI of 18.5 – 24.9 was taken as normal, 25.0 – 29.9 as overweight and above 30.0 as obese. Only a single strength and type of SGLT2 inhibitor was used i.e. either canagliflozin 100 mg (16 nos.), dapagliflozin 10 mg (18 nos.), empagliflozin 25mg (13 nos.) or remogliflozin (14 nos.).

The follow-up duration for each patient was six months, during which they were to visit the endocrinology department OPD at least two times with a three-month gap period.
The overall baseline HbA1C was taken to check the efficacy of SGLT2 inhibitors on consecutive visits and thereby compared. An apparent reduction in average mean from 8.56 to 8.25 on 2nd visit (SD 1.011) was observed on second visit and then a reduction to the level of 7.92 was observed on the third visit (SD 1.085). Thus, there was an average reduction in 0.64 % of HbA1C within 6 months.
Paired T-test was used to calculate p-value of all drugs used as SGLT2 inhibitors, to show their efficacy in HbA1c (A1c) reduction. Baselines mean at the first visit, in Cana treated patient was 9.0 and 8.56 (±1.590) & 8.44(±1.632) in second and third visits respectively, with a p-value of 0.014 in second visit and 0.007 in third visit, which is of statistical significance. There was an absolute 0.56% reduction of HBA1C from the baseline in 6 months duration.
Similarly, in Empa treated patients a significant reduction of A1c, approximately 0.77%, was observed between initial evaluation and after 6 months, with a p-value of 0.018 & 0.001 respectively in second and third visits.
Dapa and Remo treated group of patients didn't show statistically significant results in the second visit but in their third visit they also showed a significant reduction of A1c, approximately 0.76 %, in patients on Dapa and 0.5% in patients on Remo.

Table 1: Drug effects on HbA1c parameter after 3 & 6-months of treatment

HbA1c (%)	1.Canagliflozin (n=16)			2.Dapagliflozin (n=18)			3.Empagliflozin (n=13)			4.Remogliflozin (n=14)		
	Mean	SD	p-value	Mean	SD	p-value	Mean	SD	p-value	Mean	SD	p-value
Baseline	9.0	1.633	-	8.47	0.874	-	8.46	0.776	-	8.29	0.914	-
First follow-up	8.56	1.590	0.014	8.18	0.809	0.056	8.08	0.641	0.018	8.14	0.663	0.165
Second follow-up	8.44	1.632	0.007	7.71	0.772	0.000	7.69	.855	0.001	7.79	0.914	0.013

It was observed that 21 (34.5%) patients have lost weight ranging from 1 kg to 3 kg in SGLT2 inhibitor users with mean weight loss of 0.5 kg (p value = 0.009) in 6 months' time.
The base line weight was taken, and 16 patients had weight in between 68-72kg, 10 had weight between 60- 64 kg and another 10 had weight between 72-76 kg (fig 2a). On the third visit again, weight was measured and there was significant decrease in weight. Mean baseline weight were 70.2

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± 7.68 and on follow up after 6 months were 69.7 kg ± 7.38.

Table 2: Change in Weight after 6-months of treatment

Timepoint	Weight (N=61)		
	Mean	SD	p-value
Baseline	70.2	7.68	-
Second follow- up	69.7	7.38	0.009

Second follow-up taken after six months. SD=Standard Deviation

During follow up, four patients were found to suffer from UTI and the same number of patients also had urinary discomfort, nearly 5% of patients had GI symptoms, Back pain, myalgia, and polyuria. Other side effects noted were genital infection (4.92%), Dehydration (4.92%) & flu-like symptoms.

DISCUSSION

Diabetes Mellitus Type 2 is a progressive disease and is associated with severe complications especially in patients with poor glycemic control in the long run.

The safety and efficacy of various SGTL2 inhibitors were evaluated in this study. The single strength of SGTL2 inhibitors included in the study was Canagliflozin 100 mg, Dapagliflozin 10mg, Empagliflozin 25 mg, and Remogliflozin 100mg.

The study found a significant reduction in the HbA1C and body weight in six months with SGTL2 inhibitors treatment.

Efficacy of SGLT2 inhibitors in lowering HbA1c levels

The study analyzed the effect of SGTL2 inhibitors in 61 number of patients with T2DM. The baseline assessment of the patient found that 21 patients had HbA1c between 7 and 8% while the remaining patients had levels above 8. The mean HbA1c value of the patients at baseline was 8.56% ± 1.118.

The study has found a decrease in the mean HbA1c value from 8.56% baseline to 8.25% ± 1.011 (in the first visit after 3 months) and finally to 7.92 ± 1.085 (in the second visit i.e., 6 months. Several similar studies have found a similar significant reduction in HbA1c with SGLT2 inhibitors, indicating the high efficacy of this class of drugs. This effect can be attributed to its unique mode of action in which it does not require beta cells' function.

Some studies also evaluated the cellular mechanism for weight loss due to SGLT2 inhibitors.

Sawada et al. proposed a mechanism that involves inhibition of signals in the liver that occurred due to SGLT2 triggering glycogen depletion and liver-brain-adipose axis activation that may cause lipolysis in adipose tissues (11). This might induce a reduction in fat and weight loss (ZHENG et al) (12).

The results of this study are similar to the results obtained by other studies. Bashier et al. reported a significant HbA1c reduction from a mean of 8.9±1.7% to 8±1.5% at 6 months, while Kitada et al. who studied on 29 patients for 48 weeks, concluded that additional treatment with SGTL2 inhibitors causes improvement in the glycemic control (13)(14). Mirabelli et al found a significant HbA1c reduction from 8.4% to 7.5% (6.9 to 8.2) (15).

In the present study, 11 patients were already taking OHA other than SGLT2i. Panikar et al, who administered SGLT2 inhibitors as add-on therapy, reported a significant HbA1c reduction by -1.63 ± 0.99%, while Hussain et al. reported a similar significant reduction in HbA1c in the range of -1.4% to -2.1% levels after being treated with SGLT2 inhibitors in patients already on oral anti-hyperglycemic drugs combinations (16) (17).

Several such systematic reviews and meta-analyses have been done by several researchers to evaluate the efficacy of SGLT2 inhibitors. Another meta-analysis reported that SGLT2 inhibitors

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reduced the HbA1c level by 1.35% (18).
In an analysis by Despoina Vasilakou et al. includes 11 trials with 3,51,476 patients, 2 trials were related to Empagliflozin, while 4 trials were of canagliflozin. Dapagliflozin was evaluated in 3 trials and the remaining 2 were observational studies involving various SGLT2 inhibitors. It concluded that SGLT2 inhibitors caused significant reduction in the HbA1c level with weighted mean difference (WMD) of −0.39% ((95% CI, −0.52 to −0.26) (19).
In a meta-analysis done in 2013 by Vasilakou et al, the reduction in HbA1c caused by SGLT2i in T2D patients without any severe renal impairment with a baseline of 6.9–9.2%, was 0.79% [95% CI, -0.96% to -0.62%]; as monotherapy and 0.61% [CI, -0.69% to -0.53%]; as add-on therapy (19).

Efficacy of SGLT2 inhibitors in reducing weight.

The BMI of the patients was also considered in the present study. It was found that approximately 10 percent were overweight with BMI between 25 – 29.9 and 26% were overweight with a BMI of more than 30.
It was observed that 21 (34.5%) patients amongst the SGLT2 inhibitor users lost weight ranging from 1 kg to 3 kg with mean weight loss of 0.5 kg in 6 months' time (SD 7.38). The weight loss was statistically significant (p= 0.009) as compared to the baseline weight data. These findings coincided with previous studies done by Vasilakou et al (19).
The weight loss effect of the SGLT2 inhibitors may be due to the increased amount of glucose excreted through the kidneys. The drug may cause the excretion of about 60 -100 gm. of glucose daily and act in a glucose-dependent manner. The excretion of glucose not only assists in glycemic control but also minimizes the risk of complications associated with diabetes, such as neuropathies and diseases of the cardiovascular system.
A study was conducted to determine the reason behind the weight loss induced by SGLT2 inhibitors and found that it might be due to increased fat catabolism and the resultant increase in glucose elimination or loss of excessive fluid, resulting in increased glucose elimination in the urine, which may be the factor responsible for weight loss. The study concluded that weight loss is the net effect of both these factors, which occur at different points in time (20) . The observations of the present study concerning weight change are consistent with the previous findings.
Basher et al reported a reduction in 1.5 kg weight which was highly significant. The baseline value was 85.7 ± 17 kg and the measurement at 6 months was 84.2 ± 16.6 kg, (P = 0.0001) (13). Kitada et al also reported a reduction in body weight by 4.1 kg in 48 weeks (from baseline of 80.1 ± 21.4 kg to 76.0 ± 20.6 at 48 weeks; p=0.01)(14). This study also concluded that SGLT2 inhibitors reduce body weight. The weight loss in Kitada et al. was higher than what was found in this study. This might be due to the smaller sample size and short follow-up period (14).
Some studies have concomitantly measured the impact of weight loss on BMI, due to SGLT2 inhibitors. Mirabelli et al reported decrease in body weight from 83 kg (75 to 92) to 80 kg (73 to 91) (P = 0:008), and in turn caused reduction in BMI from 30.2 kg/m2 (27.8 to 33.0) to 29.4 kg/m2 (26.8 to 32.2) (P = 0:009) (15).
An interesting meta-analysis was done by Zheng et al. to analyze the effects of SGLT2 inhibitors on weight loss (12). However, the study only included overweight or obese patients and not patients with diabetes. It reported that the group on SGLT2 inhibitors showed reductions in body weight which was statistically significant (MD: -1.42 kg, 95% CI: -1.70 to -1.14; P<0.00001) and the BMI too was lowered (MD: - 0.47 kg/m2, 95% CI: -0.63 to -0.31; P<0.00001). Further, the hypoglycemia reported in the analysis was similar to the placebo indicating that SGLT2 did not significantly lower the plasma glucose levels even in euglycemic patients.

Adverse effects of SGLT2 inhibitors

It has been observed that SGLT2 inhibitors are more likely to increase genital mycotic infection both in males and females with diabetes (4). As the main mechanism of SGLT2i is urinary glucose excretion the chances of infection also rise. In the present study however only 6.56 % cases of

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Genito-urinary tract infections were reported which were not so serious and hence the patients did not discontinue SGLT2i, and necessary treatments were given to these affected patients.
Certain other side effects were reported in this study viz. 4 patients (6.56%) had hypoglycemia and a similar number of patients had flu-like symptoms and dehydration. 3 patients also had GI (gastro-intestinal) symptoms like nausea and vomiting and 3 patients (4.92%) had polyuria. Back pain and leg ulcer was also seen in approx. 5 % patients. None of the adverse effects were serious enough to discontinue their medication. Necessary treatments were given as per their complaints.
Results in contrast to the present study related to some adverse events were reported by Mirabelli et al (15). The adverse events reported in Mirabelli et al were nausea, dizziness, hypotension, acute coronary event, and rapid deterioration in renal function. Further, while no patient discontinued medication due to adverse effects in the present study, almost 24% of the participants discontinued SGLT2 inhibitors in Mirabelli et al. The primary reason for discontinuation was chronic or recurring genital yeast infections followed by persistent or recurrent urinary tract infections. Worsening of glycemic control status was also a reason for discontinuation in patients on SGLT2 inhibitors in Mirabelli et al (15).
Jeong also mentioned the side effects that occurred in patients with SGLT2 inhibitors. Some of the side effects, such as hypotension, reported by Jeong were not reported in the current study. However, similar to the study by Jeong, some of the patients had developed genital infections (21).
Similar to the adverse effect profile reported in the present study, Hussain et al also concluded that SGLT2 inhibitors were safe and tolerated well by the patients. Hypoglycemia occurred in 6.56 % of patients in the present study, while only 3.3% of the patients in the study reported by Hussain et al developed hypoglycemia. Although 4% of patients discontinued SGLT2 inhibitors due to adverse effects in the study conducted by Hussain et al, in the present study the medicine was continued. Like the findings of the present study, common adverse effects like dehydration, urinary tract infection and genital infection were reported by Hussain et al too (17).
A pooled analysis of 4 placebo-controlled trials on canagliflozin showed 10.4 % of GTI vs 3.2 % in females. (Ajay Agarwal study) the risk is also high in males (3.7%-4.2% vs 0.6%). Similarly study of Dapa with the strength of 10 mg shows an almost similar result in the case of GTI 4.1%-5.7% vs 0.9 % in the placebo group (22).
The higher rate of GTI in other studies is probably due to inadequate pretreatment counseling wherein in the present study proper instruction and guidance were provided to the patients for maintenance of hygiene and regular telephonic updates were taken. One of the important factors for GTI and UTI in male counterparts was probably due to non-circumcision.
With the development of SGLT2 inhibitors, clinicians have found newer possibilities in the treatment of type 2 diabetes. These drugs were initially developed for the management of hyperglycemia. But soon their additional advantages began to appear through several safety trials. These drugs are now one of the most popular classes of drugs that manage hyperglycemia without increased risk of hypoglycemia. The additional advantages include reduced secondary cardiovascular events risk, favorable weight reduction, and managing the progression of renal disease.

Limitations & Future Recommendations

The major limitation in this study is the relatively small sample size which may be attributed to the corona pandemic at the time of the study. This study also did not evaluate the other parameters like blood pressure, lipid profiles which could have given a better cardiometabolic prediction of SGLT2i. Also, individual drug comparisons couldn't be done due to fewer patients.
In this study, single strength of SGLT2i has been taken; but to determine the overall efficacy different strengths should be used for a longer duration to determine the risk versus benefit ratio.
Further, larger number of patients are required for better assessment and more research is needed in this area to practice evidence-based medicine and this will help prepare guidelines for prescribing SGLT2 inhibitors in Indian phenotype.

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CONCLUSION

The present study was a prospective observational study where the objective was to assess the efficacy and safety of SGLT2inhibitors on T2DM patients. The study was for a total of 18 months duration only.

This study concluded that SGLT2 inhibitors are effective in significantly reducing the HbA1c level when compared with the baseline (0.64% ± 1.085). Owing to its mechanism of action, which involves less glucose reabsorption in the kidneys and thereby increased elimination of glucose through urine weight loss was theoretically expected.

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