e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(4); 147-153

Original Research Article

A Study of Glycemic Control and Weight Reduction in Diabetic Patients on SGLT2 Inhibitors in Delhi, India

Aman Tuli[1], Nusrat Nabi[2], Aishwarya Kimmatkar[3], Vineet Jain[4], Sunil Kohli[5]

[1]MD, Senior Resident Department of Medicine, Hamdard Institute of Medical Sciences and Research, Delhi

[2]Assistant Professor, Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, Delhi

[3]MBBS Intern, Department of Medicine, Hamdard Institute of Medical Sciences and Research, Delhi

[4]Professor, Department of Medicine, Hamdard Institute of Medical Sciences and Research, Delhi

[5]Professor, Department of Medicine, Hamdard Institute of Medical Sciences and Research, Delhi

Received: 25-01-2024 / Revised: 23-02-2024 / Accepted: 26-03-2024

Corresponding Author: Dr. Aman Tuli

Conflict of interest: Nil

Abstract:

Introduction: The increasing prevalence of type 2 diabetes has prompted the search for effective therapies to manage the disease and improve glycemic control. One class of drugs that has emerged as a promising option is Sodium-glucose cotransporter 2 inhibitors (SGLT2i). These drugs work by inhibiting the reabsorption of glucose by the renal tubules, leading to its excretion in the urine. This mechanism of action not only improves glycemic control but also has the added benefit of promoting weight loss. Many trials demonstrate that use of SGLT2 inhibitors reduces HbA1c levels and promotes weight loss. This study is aimed at assessing the glycemic control and changes in weight with the use of SGLT2i.

Methods: After due clearance from the institutional ethics committee, screening and enrolment was done for 440 participants attending medicine OPD at the institute with 220 assigned to the SGLTi group and 220 to control group. The study duration was approximately 1 year. In the SGLT2i group participants were started on Dapagliflozin 10 mg, Canagliflozin 100 mg once daily or Empagliflozin 25 mg once daily. Control group was receiving oral hypoglycemic agents other than SGLT2i. Demographic details, weight, height, BMI, were recorded. HBA1C was recorded at baseline and 6 months. Weight and BMI were recorded at each follow up visit at 1, 3 and 6 months. Collected data was analyzed using SPSS and help from a qualified statistician.

Results: There was a statistically significant decrease of 2.16Kg in the mean weight in the SGLT2i group at 6 months compared to an increase in mean weight by 0.7 Kg in the control group at 6 months. Mean FPG was lower by a statistically significant 34mg/dl at 6 months among the SGLT2i group compared to a reduction of 8.45 mg/dl in the control group.

Keywords: SGLT2 inhibitors, Glycemic Control Diabetes Mellitus.

Introduction

Type 2 diabetes (T2DM) continues to pose a significant challenge in terms of management, despite the various treatment options available. Currently, metformin is considered the first line of therapy; however, its effectiveness is limited by its adverse effects and the fact that up to 10% of patients cannot tolerate it at any dose. With T2DM being a progressive condition, patients often require ongoing treatment as their beta cell function declines, making it necessary to explore alternative treatments. [1]

Alternatives and supplements to metformin also have limitations, such as weight gain and a higher risk of hypoglycemia with meglitinides, sulfonylureas, and insulin. As a result, the need for more therapeutic alternatives persists. The ideal diabetic medication would have a strong and lasting impact on HbA1c, be well-tolerated, simple to administer, with minimal or no risk of hypoglycemia, have good long-term safety, and have additional benefits such as a positive effect on beta cell function, blood pressure, and weight. [1]

The kidney has recently been identified as a target for the treatment of diabetes, as it plays a significant role in maintaining glucose homeostasis and the Sodium-glucose cotransporter 2 (SGLT2) is a transporter protein that mediates most of the glucose reabsorption from glomerular filtrate [1]. SGLT2 inhibitors are derived from phlorizin, a naturally occurring compound found in apples and

other fruits, and have been developed and tested as potential treatments for type 2 diabetes since the late 1990s. SGLT2 inhibitors work by blocking the reabsorption of glucose in the kidneys and causing glucose to be excreted in the urine instead of being reabsorbed into the bloodstream. [2]

The first SGLT2 inhibitor, Dapagliflozin, was approved by the US Food and Drug Administration (FDA) in 2013, and since then several others, including empagliflozin, canagliflozin, and ertugliflozin, have been developed and approved for use. These drugs have been shown to effectively reduce HbA1c between 0.4% to 1.1% depending on baseline HbA1c and type of SGLT2-inhibitor used along with body weight, and blood pressure by increasing urine glucose excretion (UGE) and lowering plasma glucose levels without the need for insulin. SGLT2 inhibitors exhibit pleiotropic effects, such as improving kidney and cardiovascular outcomes in diabetic patients. [3]

They have been shown to reduce HbA1c levels between 0.4% to 1.1%, with canagliflozin, which also has modest SGLT1-inhibitory activity, appearing to have a slight advantage over other agents.[4]

A meta-analysis of 39 trials involving 25,000 individuals showed canagliflozin 300mg, empagliflozin 25mg and dapagliflozin 10mg all at a once daily dosing resulted in a weight loss of 2.66kg, 1.80kg and 1.81kg respectively compared to placebo. [5]

SGLT2 inhibitors have also been shown to effectively lower blood glucose levels and improve glycemic control in people with type 2 diabetes, although a meta-analysis of clinical trials found that they were less effective in reducing hemoglobin A1c levels in Asian populations compared to non-Asian populations.

The present study was designed and to assess the glycemic control, weight reduction and changes in BMI in diabetic patients on SGLT2 in the population of Delhi NCR, India.

Methods

A GCP-ICH guideline compliant, descriptive-analytical study was carried out in a medical college, in Delhi, for a period of 1 year starting November 2021. T2DM patients aged, 18-75 years, receiving oral hypoglycemic agents, attending diabetes and endocrinology OPD were included in the study.

Enrollment of a total 440 participants was done over a period of 3 months, patients were screened for major exclusions such as HbA1c greater than 9%, immunocompromised status, history of urinary stones or recent genitourinary procedures including urethral catheterization, pregnant females, GFR< 45 mL/min/1.73 m^2. The participants were categorized into patients on anti-diabetic Regimens with SGLT 2 inhibitors and those on anti-diabetic regimens without SGLT 2 inhibitors. The two arms were named as SGLT 2 Inhibitors Arm and Non-SGLT 2 Inhibitors Arm. In the SGLT2i group 3 drugs namely Dapagliflozin 10 mg once a day, Canagliflozin 100 mg once a day, and Empagliflozin 25 mg once a day were used.

The 6 months follow-up period of the participants included a baseline visit and 3 subsequent visits at 1 month, 3 month and 6 month from enrolment. Fasting Plasma Glucose (FPG), Blood pressure and weight were recorded at each follow up visit. HbA1c levels were measured at baseline and at 6 months. BMI was recorded at baseline at each follow- up.

Results

Most of the enrolled participants in the SGLT2i and control groups in the present study were between the age group of 41- 60 years with mean age of the participants being 52.6 ±9.9 in the SGLT2i and 53.3 ±12.1 in the control group. So the present study was age matched.

Majority; 61.8 % (N=136) participants were females in the SGLT2 group whereas, males at 51.4% (N= 113) formed the majority in the control group. Out of the 136 female participants in the SGLT2i group, 42.7% (N=94) were menopausal females compared to 31.8% (N= 70) in the control group. The mean duration of DM was 7.1 ±4.8 years in the SGLT2i group vs 5.6 ±3.9 years in the control group. Table 1 mentios the distribution of different SGLT2i molecules among the study population.

Table 1: Different SGLT2I Molecules among SGLT2I Group

SGLT2i Molecule	Number of Participants	Percentage
Dapagliflozin 10 mg OD	111	50.40%
Empagliflozin 25 mg OD	81	36.81%
Canagliflozin 100 mg OD	28	12.72%

Changes in Weight and BMI: The SGLT2 group had 29.1% individuals in the normal weight category, 38.6% were overweight, 32.3% participants were obese with 26.8% and 1.4% belonging to obesity class 1 and 3 respectively. (See table 2) The control group comprised of 39.1% participants having normal weight, 45.9% was overweight and 13.2% and 1.8% participants in the obesity class 1 and 2 respectively.

Table 2: BMI and Weight Category at Baseline of the Study Participants

BMI baseline	SGLT inhibitor		Controls		Chisquare test P value
	N	%	N	%	
Underweight	0	0.0%	0	0.0%	**0.001**
Normal	64	29.1%	86	39.1%	
Overweight	85	38.6%	101	45.9%	
Obesity Class 1	59	26.8%	29	13.2%	
Obesity Class 2	9	4.1%	4	1.8%	
Obesity Class 3	3	1.4%	0	0.0%	

Baseline means height and weight (fig.1) and BMI (fig. 2) at baseline and follow up is shown in table 3. Changes from baseline in mean weight and BMI are depicted in table 4.

Table 3: Mean Height, Weight, BMI At Baseline and Follow Up Visits

Variables	SGLT inhibitor		Controls		Unpaired t test p value
	Mean	SD	Mean	SD	
Height	158.87	9.25	157.03	8.84	**0.034**
Weight baseline	70.48	11.93	64.78	11.02	**<0.001**
Weight 1 month	70.26	11.80	64.96	11.01	**<0.001**
Weight 3 month	69.71	11.91	64.70	10.88	**<0.001**
Weight 6 month	68.32	13.96	64.87	10.80	**0.004**
BMI baseline	27.90	4.19	26.26	3.70	**<0.001**
BMI 1 month	27.81	4.06	26.41	3.84	**<0.001**
BMI 3 month	27.62	4.11	26.23	3.54	**<0.001**
BMI 6 month	27.55	4.15	26.3	3.60	**<0.001**

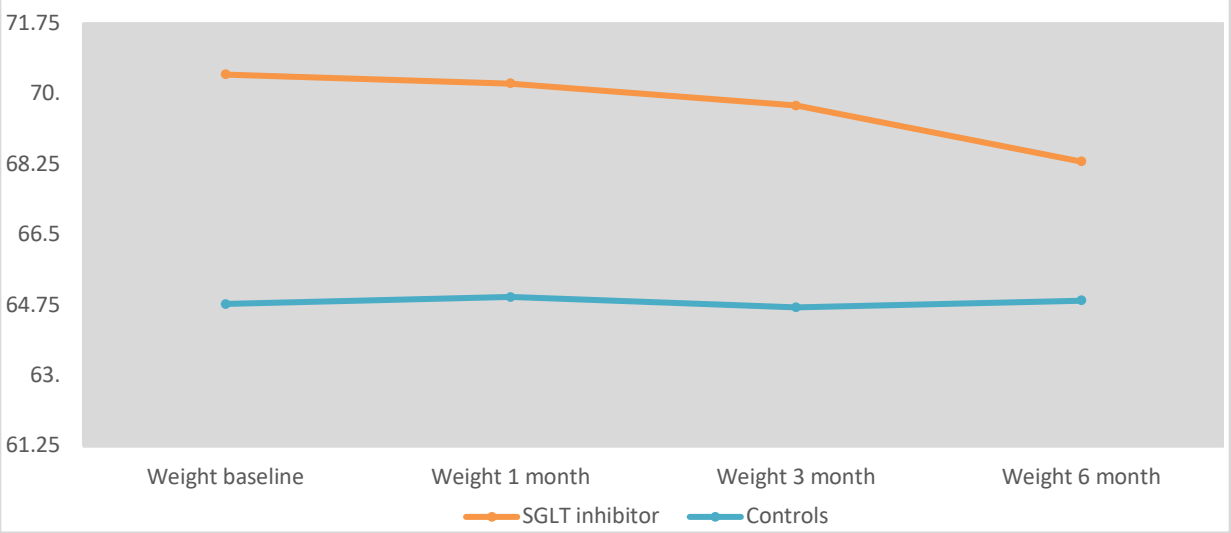

Figure 1: Mean Weight at Baseline and Follow Up

Table 4: Changes in Mean from Baseline in Weight and BMI of Participants in both SGLT2I and Control Groups

Changes from baseline	SGLT inhibitor		Controls		Unpaired t test p value
	Mean	SD	Mean	SD	
Weight 1 month	-0.22	1.75	+0.18	1.73	**0.017**
Weight 3 month	-0.78	2.38	-0.09	1.74	**0.001**
Weight 6 month	-2.16	7.38	0.08	1.93	**<0.001**
BMI 1 month	-0.09	0.69	+0.14	0.66	**<0.001**
BMI 3 month	-0.28	0.85	-0.03	0.74	**0.001**
BMI 6 month	-0.35	1.18	0.04	0.70	**<0.001**

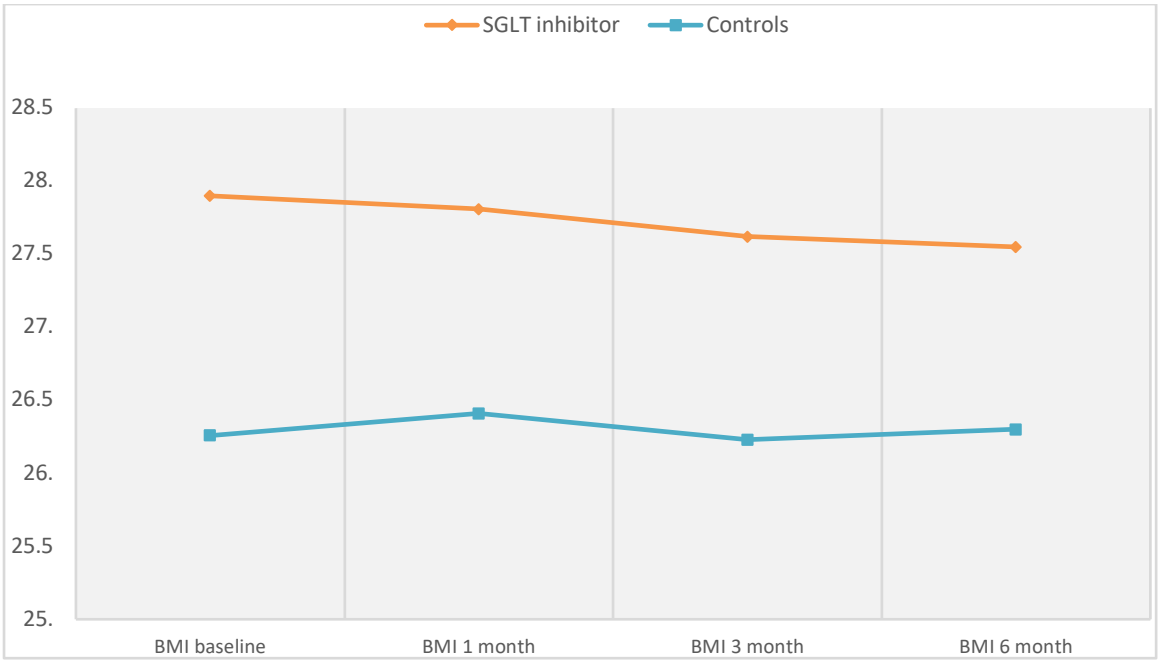

Figure 2: Mean BMI of Participants in both Sglt2 and Control Groups at Baseline and Follow up Visits

Mean FPG (fig.3) and HbA1c (fig. 4) at baseline and follow up is shown in table 5. Changes from baseline in FPG and HbA1c are depicted in table 6.

Table 5: Mean Fasting Blood Sugar and Hba1c at Baseline and Follow Up

Parameters	SGLT inhibitor		Controls		Unpaired t test p value
	Mean	SD	Mean	SD	
FBS baseline (mg/dL)	164.8	51.7	158.2	48.5	0.163
FBS 1 month (mg/dL)	155.8	53.2	156.0	54.1	0.968
FBS 3 month (mg/dL)	135.0	38.2	151.3	52.4	**<0.001**
FBS 6 month (mg/dL)	130.1	38.5	149.7	45.1	**<0.001**
HBA1C baseline (%)	7.75	1.01	7.54	1.24	0.055
HBA1C 6 month (%)	7.15	.91	7.34	1.02	**0.046**

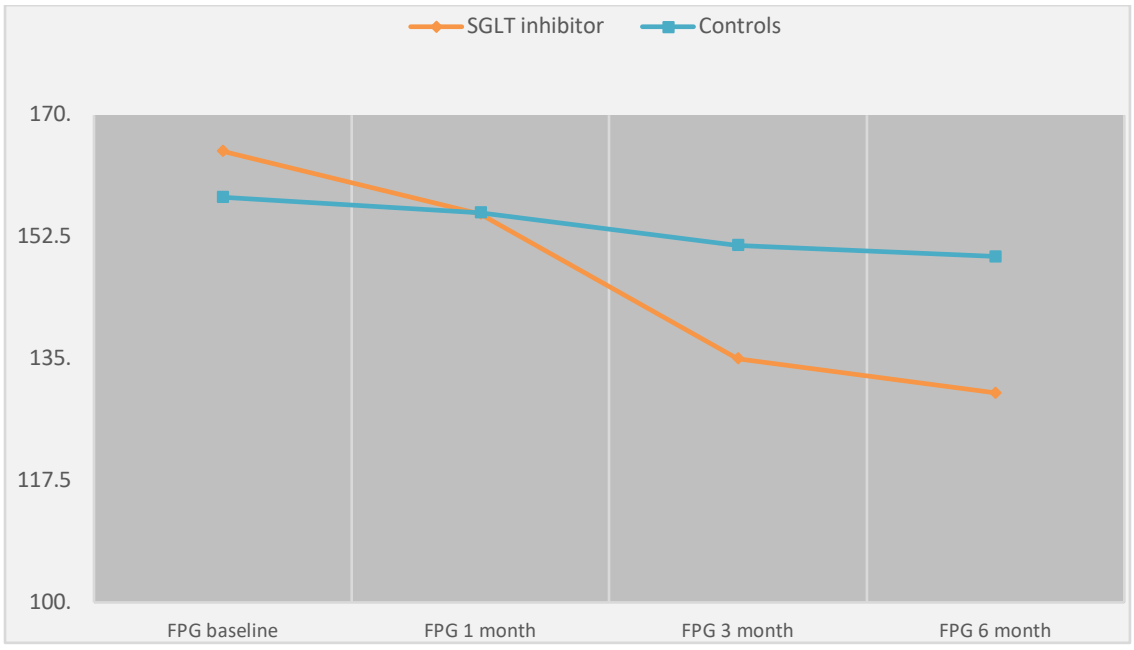

Figure 3: Mean Fasting Plasma Glucose (FPG) At Baseline and Follow Up

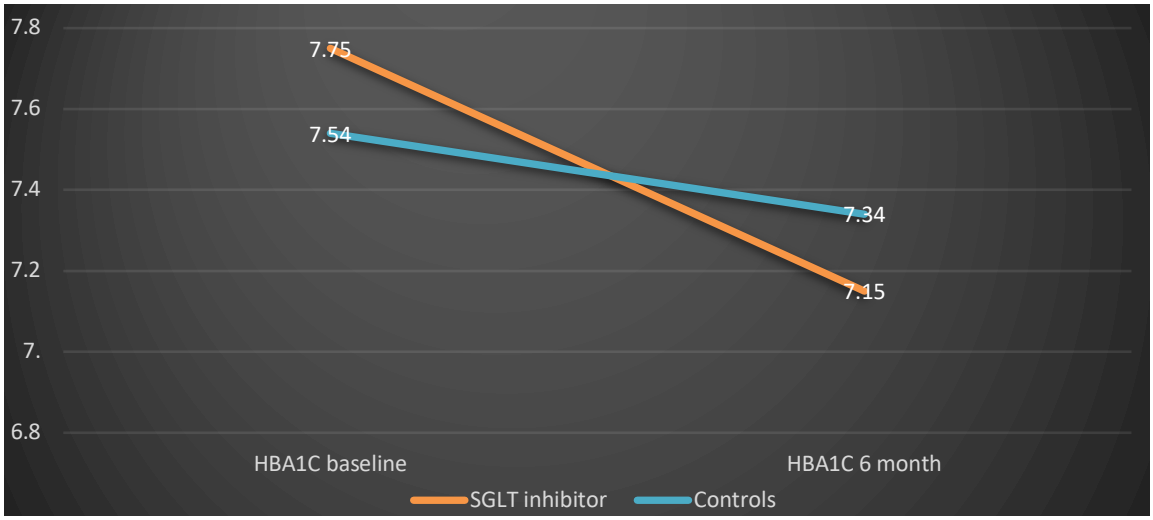

Figure 4: Mean, Hba1c at Baseline and Follow Up

Table 6: Changes from Baseline in Mean FBS and HBA1C

Changes from baseline	SGLT inhibitor		Controls		Unpaired t test p value
	Mean	SD	Mean	SD	
FBS 1 month	9.03	45.92	2.15	33.71	0.074
FBS 3 month	29.82	46.33	6.90	41.67	**<0.001**
FBS 6 month	34.70	51.52	8.45	37.38	**<0.001**
HBA1C 6 month	0.60	0.99	0.21	0.65	**<0.001**

Discussion

This study was done with the objective to study glycemic control and changes in weight among diabetic patients on SGLT2i. A total of 440 patients were enrolled in the study, 220 in each SGLT2i and control group.

Weight Reduction: Oral hypoglycaemic agents cause weight gain (thiazolidinediones, sulfonylureas, and insulin), others are weight-neutral (metformin, dipeptidyl peptidase-4 inhibitors, acarbose), and only a few [glucagon-like peptide (GLP)-1 analogues] reduce weight. [6] The starting weight (kg) for the control group was 64.78 11.02 and was 70.48 11.93 in the SGLT2i group. In the SGLT2i group, the mean weight dropped from 70.48 to 68.32 ($p = 0.004$). It was noted that the mean weight in the control group increased from 64.78 kg at baseline to 64.87 kg at six months. Mean BMI at baseline was 27.90 +/- 4.19 Kg/m^2 in the SGLT2i group and 26.26 +/-3.7 Kg/m^2 in the control group.

Mean BMI was 27.55 Kg/m^2 and 26.3 Kg/m^2 in the SGLT2i and control group at 6 months respectively. There was a reduction in the mean BMI: 0.35 Kg/m^2 ($p = 0.006$) in the SGLT2 group at 6 months in contrast, there was an increase in mean BMI at 6 months in the control group by 0.04 Kg/m^2 ($p=<0.001$). Cai et al also reported Weight loss in a meta-analysis with dapagliflozin 10 mg. A placebo adjusted weighted mean difference of -1.79 Kg ($p< 0.001$) was reported by them. [7] Kaku et al reported significantly greater mean reductions in total body weight from baseline across all doses of dapagliflozin compared with the placebo group ($p < 0.0001$).

A mean reduction of -1.91 Kg from baseline was reported at 12 weeks by them with 10 mg dapagliflozin compared to -0.5Kg among controls. [8] Roden et al conducted a randomized multicentre placebo-controlled trial with 224 patients receiving Empagliflozin 25mg and 228 receiving placebo. At 24 weeks, a change of -2.48 Kg from baseline bodyweight was reported in the Emapagliflozin group compared to -0.33 Kg among the placebo group at. [6] Inagaki et al through there double blind, mulitcenter study on Japanese patients receiving Canagliflozin reported, a significantly greater reduction of -3.76 Kg in mean bodyweight from baseline in the Canagliflozin 100mg group comparted to -0.76Kg in placebo group, at 24 weeks. [9]

Reduction in body weight is likely a consequence of caloric loss via glucosuria and potentially some initial fluid loss. In a body composition study performed in Europe, two thirds of the weight loss associated with dapagliflozin treatment was explained by a reduction in fat mass. [6] SGLT2 inhibitor-induced glycosuria decreases plasma glucose and insulin levels in persons with T2DM or obesity without diabetes while increasing fasting and post-meal glucagon concentrations. Lipid storage is mobilized as a result of these hormonal changes and the drop in blood glucose concentration. [10] Adipose tissue lipolysis increases under conditions of decreased portal insulin-to-glucagon

ratio, releasing non-esterified fatty acids that are then converted to ketone bodies in the liver through mitochondrial beta oxidation and ketogenesis , creating a metabolic state resembling a prolonged fast. [11]

Glycaemic Control

The SGLT2i group had a baseline mean Fasting blood sugar levels 164.8 ±51.7 mg/dl, mean FBS was 155.8 ±53.2 mg/dl at 1 month, 135 ±38.2 mg/dl at 3 month, 130.1 ±38.5 mg/dl at 6 month follow up. The mean reduction in mean Fasting blood sugar levels at 6 months was 34.70 mg/dl. Also the SGLT2i group had a mean HbA1c of 7.75 ±1.01 percent at baseline that reduced to mean of 7.15 ±0.91 percent at 6 months. The change in mean HbA1c from baseline was 0.6 percent. The control group had baseline mean Fasting blood sugar (FBS) level of 158.2 ±48.5 mg/dl, mean FBS was 156.0 ±54.1 mg/dl at 1 month, 151.3 ±52.4 mg/dl at 3 month, 149.7 ±45.1 mg/dl at 6 month follow ups. The mean reduction in mean Fasting blood sugar levels at 6 months was 8.45 mg/dl. The control group had a mean HbA1c of 7.54 ±1.24 percent at baseline that reduced to mean of 7.34 ± 1.02 percent at 6 months. The change in mean HbA1c from baseline was 0.21 percent.

Inagaki et al reported a mean -31.6 ± 2.8 mg dl reduction in fasting plasma glucose with canagliflozin 100 mg and a mean reduction of -0.74 ±0.07 percent in HbA1c at 24 weeks. [9]

A reduction of -0.066 (95% CI: -0.76 to -0.56) percent in HbA1c compared to 0.08% change in placebo with Empagliflozin was reported, along with a reduction of -24.48 (95% CI: 28.26 to 20.52) mg/dL in fasting plasma glucose from baseline at 24 weeks by Roden et al. [6]

In a pan Indian observational study with Dapagliflozin reported a mean HbA1c reduction of ~1.5 % reduction in HbA1c was reported. [12]

This is in contrast to the findings of the present study and Other global studies including a 24 week double blinded placebo- controlled phase 3 trial reported a mean HbA1c change of -0.89%(P< 0.0001) with Dapagliflozin 10 mg vs -0.23% with placebo. The study also reported a mean reduction from baseline in Fasting plasma glucose of – 28.8 ± 4 mg/dL with dapagliflozin 10 mg compared to -4.1 ±3.9 mg/dL in the placebo arm. [13]

Kaku et al conducted a multicentre, randomized, double-blind, placebo-controlled study conducted at 26 centres in Japan; Placebo-corrected adjusted mean reductions from baseline in HbA1c at week 12 for the dapagliflozin 5- and 10-mg groups were (0.74 and 0.80%, respectively) and a mean reduction in FPG of -31.94 ±3.57 mg/dL vs – 15/61 ±3.43 mg/dL in placebo group. [8]

Conclusion

In this age matched, prospective analytical study it was observed that a 6 month long treatment with SGLT2 inhibitors namely Dapagliflozin, Canagliflozin, Empagliflozin is associated with a significant reduction in fasting plasma glucose, HbA1c, body weight and BMI compared to controls.

Bibliography

1. Scheen AJ. An update on the safety of SGLT2 inhibitors. Expert Opin Drug Saf [Internet]. 2019;18(4):295–311.
2. Jörgens V. The roots of SGLT inhibition: Laurent-Guillaume de Koninck, Jean Servais Stas and Freiherr Josef von Mering. Acta Diabetol [Internet]. 2019;56(1):29–31.
3. Kaze AD, Zhuo M, Kim SC, Patorno E, Paik JM. Association of SGLT2 inhibitors with cardiovascular, kidney, and safety outcomes among patients with diabetic kidney disease: a meta-analysis.
4. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab [Internet]. 2013;15(4):372–82.
5. Pinto LC, Rados DV, Remonti LR, Kramer CK, Leitao CB, Gross JL. Efficacy of SGLT2 inhibitors in glycemic control, weight loss and blood pressure reduction: a systematic review and meta-analysis. Diabetol Metab Syndr 2015 71 [Internet]. 2015 Nov 11;7(1):1–2.
6. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol [Internet]. 2013;1(3):208–19.
7. Cai X, Yang W, Gao X, Chen Y, Zhou L, Zhang S, et al. The Association Between the Dosage of SGLT2 Inhibitor and Weight Reduction in Type 2 Diabetes Patients: A Meta-Analysis. Obesity. 2018;26(1):70–80.
8. Kaku K, Inoue S, Matsuoka O, Kiyosue A, Azuma H, Hayashi N, et al. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: A phase II multicentre, randomized, double-blind, placebo-controlled trial. Diabetes, Obes Metab. 2013;15(5):432–40.
9. Inagaki N, Nangaku M, Sakata Y, Sasaki K, Mori-Anai K, Iwasaki T, et al. Real-World Safety and Effectiveness of Canagliflozin Treatment for Type 2 Diabetes Mellitus in Japan: SAPPHIRE, a Long-Term, Large-Scale Post-Marketing Surveillance. Adv Ther [Internet]. 2022;39(1):674–91.

10. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97(3):1020–31.
11. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs [Internet]. 2019;79(3):219–30.
12. Viswanathan V, Singh KP. Use of dapagliflozin in the management of type 2 diabetes mellitus: A real-world evidence study in indian patients (FOREFRONT). Diabetes Technol Ther. 2019;21(8):415–22.
13. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care [Internet]. 2010 Oct;33(10):2217–24.