VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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Addition of SGLT2 inhibitors in type 2 diabetes is associated with persistent and significant weight loss: a real-world study from Eastern India

ABSTRACT

Background: The obesity pandemic is triggering the tsunami of type 2 diabetes mellitus (T2DM) worldwide. Sodium-glucose transport protein 2 inhibitors (SGLT2i) have demonstrated weight loss in clinical trials. This retrospective study aims to look at long-term effects on body weight, body mass index (BMI), and glycemic control (HbA1c), when SGLT2i are added to existing glucose-lowering drug (GLD), in real-world settings.

Methods: The hospital database of endocrinology outpatient was searched in whom one of the three SGLT2i was prescribed over and above the preexisting antidiabetic regime. Anthropometric parameters, HbA1c, and blood pressure data were captured for analysis at the onset of the therapy and at the last visit. Subjects with interruption or termination of therapy including hospitalization or non-availability of requisite data were excluded.

Results: Forty-five of 417 subjects were lost to follow-up. The subjects of the three groups of SGLT2i (viz canagliflozin, dapagliflozin, empagliflozin) were fairly matched with respect to age, height, body weight, BMI, blood pressure, and HbA1c. All the groups achieved a mean weight loss of 1 kg over an average of 12 months of therapy. Decrease in weight, BMI, and HbA1c were statistically significant. There was weight gain in 16.93%, less than 5% weight loss in 35.21%, 5–10% weight loss in 11.55%, more than 10% weight loss in 13.17%, while no change in 23.11%. Nearly 25% of subjects had more than 5% weight loss irrespective of accompanying drugs, suggesting the benefits of SGLT2i across the spectrum of T2DM.

Conclusions: The addition of SGLT2i causes persistent and significant weight loss along with improvement in glycemic control, independent of background GLD and duration of diabetes. Weight loss was not so significant but HbA1c reduction from baseline and blood pressure changes was more as compared to previous trials with SGLT2i. (Clin Diabetol 2022, 11; 1: 26–32)

Keywords: body weight, glycemic control, SGLT2 inhibitors, type 2 diabetes mellitus

Introduction

Diabetes is considered as one of the fastest-growing metabolic disorders affecting most of the global population which was estimated in 2017 as many as 451 million people worldwide and by 2045 almost 693 million people will be projected to be affected by diabetes [1]. Among the Southeast Asian region India is considered to have the greatest number of people affected with diabetes which is as much as 74 million within the age group of 18–99 years 9.8% age-adjusted comparative prevalence and in the age group of 20–79 years 50.7% premature mortality [2]. In a population-based cross-sectional study done by Indian Council of Medical Research-India Diabetes (ICMR- INDIAB) where

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Clinical Diabetology 2022, 11; 1: 26–32
DOI: 10.5603/DK.a2022.0008
Received: 27.01.2021 Accepted: 3.04.2021

samples were taken across 15 Indian states, the overall prevalence of diabetes was 7.3% [3].

The obesity pandemic is triggering the tsunami of type 2 diabetes mellitus (T2DM) worldwide. Obesity is becoming one of the most important health issues which is growing by pandemic proportions and growth is such high that even it appears in double the growth rate than estimated in the last 15 years. According to the World Health Organization (WHO), 40% of the global adult population were overweight or obese [4]. Obesity along with diabetes is one of the major concerns as atherosclerotic cardiovascular disease, various musculoskeletal, gastrointestinal, renal, respiratory, dyslipidemia, hypertension, stroke, and psychiatric complications are linked with it [5–8]. It has been also observed that especially for subjects with diabetes significant weight loss either by exercise or by oral medication or even by surgery led to significant improvement in cardiovascular outcomes [9–12].

Sodium-glucose transport protein 2 inhibitors (SGLT2i) have demonstrated weight loss in clinical trials. SGLT2i (e.g., dapagliflozin, canagliflozin, and empagliflozin) improves blood glucose level by an insulin-independent mechanism thus are approved for the treatment of T2DM. In the proximal tubule in the kidney by inhibiting glucose reabsorption from urine SGLT2i promotes urinary glucose excretion up to about 50% [13–15]. Several trials have already confirmed that apart from tight glycemic control, SGLT2i largely accounted for by body fat reduction and thus lead to bodyweight loss and what is existing that these beneficial effects are sustained over several years [16–19].

However, the efficacy and safety of SGLT2i in patients with obesity and T2DM in a real-world setting, where patients often have multiple co-morbidities and are treated with several drugs, have not been established. This retrospective study aims to look at long-term effects on body weight, body mass index (BMI), and glycemic control (glycated hemoglobin [HbA1c]), when SGLT2i are added to the existing anti-diabetic regime, in real-world settings.

Methods

This is a real-world retrospective investigator-initiated study done in a teaching hospital that has the facility of endocrinology department. The hospital database of Endocrinology out the patient was searched in whom one of the three SGLT2i was prescribed over and above the preexisting anti-diabetic regime.

In this study major inclusion criteria were uncontrolled T2DM with HbA1c > 8%, body weight > 70 kg and age > 20. Major exclusion criteria were patients with a known history of complicated micro or macrovascular disease, patients with any type of disability, patients who were not willing to give consent. Subjects with interruption or termination of therapy including hospitalization or non-availability of requisite data were excluded. Dosage formulations used in this study were as per optimum treated dosage range. 10 mg dapagliflozin, 100 mg canagliflozin, and 5 mg empagliflozin were used in this study.

Initially, 417 patients were screened to initiate the retrospective analysis. Among these patients 68 patients were on canagliflozin, 174 patients were on dapagliflozin and 175 were on empagliflozin. But at the end of the study 45 patients were lost to follow-up due to many reasons which include patients didn't turn out for follow-up regular intervals, patients shifted to some other hospital in between, administrative issues to maintain documents, etc. All selected patients have continued their respective medication which was initiated before enrolment throughout the study without any modification.

Anthropometric parameters, HbA1c, and blood pressure data were captured for analysis at the onset of the therapy and at the last visit. The study protocol was approved by the ethics review committees of the participating medical centers. Informed consent was obtained from all subjects.

Statistical analysis was carried out with SAS (Statistical Analysis System) version 9.2 (SAS Institute Inc. Cary, NC USA). Results on continuous measurements are presented as Mean ± standard deviation (SD) and results on categorical measurements are presented in numbers (%). Significance is assessed at a level of 5%. Paired t-test was used to find the significance of study parameters within groups of patients measured on two occasions.

Results

Baseline characteristics

Though 417 patients were initially screened only 317 patients were able to complete the study. Table 1 demonstrated the baseline characteristics of patients after initial screening. 58.8% of patients were male with an average age of 54.81 ± 9.45 years and body weight of 77.11 ± 12.32 kg. These patients were also having a long duration (> 12 years) of T2DM with an average mean HbA1c of 8.37 ± 0.57%.

Baseline characteristics depend upon pharmacotherapy. Four hundred and seventeen subjects of the three groups of SGLT2i (viz canagliflozin [n = 68], dapagliflozin [n = 174], empagliflozin [n = 175]) were fairly matched with respect to age, height, body weight, BMI, blood pressure and HbA1c (Tab. 2). It has also been noticed that despite all parameters being similar

Table 1. Baseline characteristics of the patients (n = 417)

Demographic and clinical profile	Values
Male, n (%)	245 (58.8)
Female, n (%)	172 (42.2)
Age [years], mean ± SD	54.81 ± 9.45
Height [cm], mean ± SD	161.64 ± 9.46
Body weight [kg], mean ± SD	77.11 ± 12.32
SBP [mmHg], mean ± SD	131.58 ± 13.04
DBP [mmHg], mean ± SD	85.34 ± 14.19
BMI [kg/m^2], mean ± SD	28.77 ± 0.76
HbA1c [%], mean ± SD	8.37 ± 0.57
Duration of follow-up [months], mean ± SD	12.68 ± 8.37

BMI — body mass index; DBP — diastolic blood pressure; HbA_{1c} — glycated hemoglobin; SBP — systolic blood pressure; SD — standard deviation

in the canagliflozin group, patients were diagnosed with T2DM long back, as compared to the two other subgroups, which means in the canagliflozin group patients had a long duration of diabetes,

Table 3 summarizes the change in study parameters during the follow-up period. It had been noticed that there was a significant drop ($p < 0.001$) in BMI and HbA1c after treating with SGLT2i in 372 subjects who completes the study.

Table 4 further clarified the changes in study parameters during the follow-up periods among each group. It has All the groups achieved a mean weight loss of 1 kg over an average of 12 months of therapy. Decrease in weight, BMI, and HbA1c were statistically significant. It has also been noticed that despite similarity dapagliflozin and empagliflozin had higher significant statistical values as compared to canagliflozin.

Table 5 demonstrates the proportion of patients who had achieved a weight loss of a specific percentage. There was weight gain in 16.93%, less than 5% weight loss in 35.21%, 5–10% weight loss in 11.55%, more than 10% weight loss in 13.17%, while no change in 23.11%.

Table 6 has further demonstrated the proportion of patients who achieved a specific percentage of weight loss in subgroups. In subgroup analysis, it has been observed that SGLT2i canagliflozin and dapagliflozin have the highest impact on weight reduction as compared to empagliflozin.

Table 7 summarizes the major side effects that have been noticed during the 12-month follow-up. There was no discontinuation of study medication due to the severity of side effects.

Table 2. Baseline characteristics of the patients-subgroup (n = 417)

Demographic and clinical profile	Canagliflozin (n = 68)	Dapagliflozin (n = 174)	Empagliflozin (n = 175)
Male, n [%]	43 (63.2)	88 (50.5)	114 (65.1)
Female, n [%]	25 (36.8)	86 (49.5)	61 (34.9)
Age [years], mean ± SD	53.83 ± 8.31	52.08 ± 8.85	57.91 ± 9.58
Height [cm], mean ± SD	163.31 ± 10.34	160.6 ± 9.01	162.03 ± 9.46
Body weight [kg], mean ± SD	77.79 ± 13.47	74.71 ± 10.76	74.47 ± 13.19
SBP [mmHg], mean ± SD	128.44 ± 13.04	133.94 ± 13.79	130.31 ± 12.09
DBP [mmHg], mean ± SD	81.37 ± 6.85	83.9 ± 9.65	89.14 ± 19.77
BMI [kg/m^2], mean ± SD	29.28 ± 4.41	28.93 ± 3.49	28.43 ± 4.73
HbA1c [%], mean ± SD	8.49 ± 0.24	8.52 ± 0.44	8.20 ± 0.30
Duration of follow-up [months], mean ± SD	18.61 ± 10.34	10.34 ± 7.2	12.11 ± 6.89

BMI — body mass index; DBP — diastolic blood pressure; HbA1c — glycated hemoglobin; SBP — systolic blood pressure; SD — standard deviation

Table 3. Changes in study parameters during the follow-up period (n = 372)

Parameter	Baseline Mean ± SD	Follow-up Mean ± SD	P
Body weight [kg]	75.02 ± 12.41	74.06 ± 12.20	< 0.001
BMI [kg/m^2]	28.66 ± 4.21	26.91 ± 7.07	< 0.001
SBP [mmHg]	131.24 ± 12.84	124.93 ± 19.80	< 0.001
DBP [mmHg]	85.89 ± 15.07	80.25 ± 7.81	< 0.001
HbA1c [%]	8.37 ± 0.57	5.76 ± 0.89	< 0.001

$p < 0.05$ considered as statistically significant; p computed by paired-t-test; BMI — body mass index; DBP — diastolic blood pressure; HbA1c — glycated hemoglobin; SBP — systolic blood pressure; SD — standard deviation

Table 4. Changes in study parameters during the follow-up period — subgroup analysis (n = 372)

Cohort	Parameter	Baseline Mean ± SD	Follow-up Mean ± SD	P
Canagliflozin	Body weight [kg]	78.01 ± 13.68	76.95 ± 13.07	0.006
n = 63	BMI [kg/m^2]	29.41 ± 4.52	26.72 ± 8.14	0.012
	SBP [mmHg]	128.49 ± 12.58	127.76 ± 16.61	0.801
	DBP [mmHg]	81.71 ± 6.98	81.51 ± 8.42	0.874
	HbA1c [%]	8.49 ± 0.24	7.21 ± 0.39	< 0.001
Dapagliflozin	Body weight	74.25 ± 10.41	73.27 ± 10.47	< 0.001
n = 147	[kg]			
	BMI [kg/m^2]	28.88 ± 3.48	28.38 ± 3.42	< 0.001
	SBP [mmHg]	133.44 ± 13.43	126.56 ± 15.79	< 0.001
	DBP [mmHg]	83.91 ± 10.44	80.08 ± 7.64	0.001
	HbA1c [%]	8.52 ± 0.44	6.58 ± 0.78	< 0.001
Empagliflozin				
n = 162	Body weight [kg]	74.55 ± 13.44	73.64 ± 13.17	< 0.001
	BMI [kg/m^2]	28.27 ± 4.64	25.62 ± 8.68	< 0.001
	SBP [mmHg]	130.23 ± 12.03	121.66 ± 24.51	0.001
	DBP [mmHg]	90.26 ± 20.53	79.78 ± 7.66	< 0.001
	HbA1c [%]	8.20 ± 0.30	6.64 ± 0.69	< 0.001

p < 0.05 considered as statistically significant, p computed by paired-t-test
BMI — body mass index; DBP — diastolic blood pressure; HbA1c — glycated hemoglobin; SBP — systolic blood pressure; SD — standard deviation

Table 5. Proportion of patients achieving weight loss 5%, 5%–10%, 10% and beyond (n = 372)

Weight loss (in %)	Number of subjects	Percent of subjects
Weight gain	63	16.93
No change	86	23.11
0–5%	131	35.21
5–10%	43	11.55
> 10%	49	13.17

Table 6. The proportion of patients achieving weight loss 5%, 5–10%, 10% and beyond — subgroup analysis

Weight loss (in %)	Number of subjects	Percent of subjects
Canagliflozin, n = 63		
Weight gain	6	9.52
No change	11	17.46
< 5%	23	36.51
5–10%	7	11.11
> 10%	16	25.4
Dapagliflozin, n = 147		
Weight gain	27	18.37
No change	24	16.33
< 5%	61	41.5
5–10%	18	12.24
> 10%	17	11.56
Empagliflozin, n = 162		
Weight gain	30	18.52
No change	51	31.48
< 5%	47	29.01
5–10%	18	11.11
> 10%	16	9.88

There were patients who went on to hypoglycemia but didn't require any further medical intervention or support.

Discussion

Sodium-glucose cotransporter-2 inhibitors with their novel, the insulin-independent mechanism is a major turning point in the management of T2DM.

Sodium-glucose cotransporter-2 inhibitors lower plasma glucose through the inhibition of SGLT2-mediated reuptake of filtered glucose in the kidney, thus resulting in other beneficial effects in addition to tighter glycemic effects, such as significant weight loss during the treatment period. There was around 1kg to 3 kg weight loss observed in several randomized clinical trials (RCTs) and real-world trials by the treatment with various SGLT2i that is currently available [20–24].

Table 7. Side effects observed during 12 months follow-up

Types	Number of patients
Weight gain	63
GTI	28
Nausea	2
Dyspepsia	3
Weakness	4
Vertigo	2
Generalized itching	3
Back pain	2
Hypoglycemia	1

GTI — genito-urinary tract infection

In our study, we had also observed a mean weight loss of 1 kg over an average of 12 months of therapy in real-world clinical setting. Decrease in weight, BMI, and HbA1c were statistically significant. There were several reasons why weight loss is a significant process during treatment with almost all different types of SGLT2i. A known phenomenon in weight loss is mainly because of slowing in resting metabolic rate which is beyond that expected from changes in body composition. In the natural process, during weight loss or reduced energy stores which led to negative energy balance, a significant attempt was made to maintain homeostasis between hormonal signaling (e.g. leptin and insulin) and another signaling so that information to the hypothalamus (brain) are maintained to stimulate appetite and weight gain. Potentially because of up-regulation of SGLT2 or SGLT1 or both during T2DM leads to excessive renal glucose reabsorption exacerbating hyperglycemia [25–27]. SGLT2i drugs inhibit glucose reabsorption, promoting approximately 75 g of urinary glucose excretion with an associated caloric loss (approximately 300 kcal/day), further understanding of this is needed in order to maximize glycosuria, but, explaining the weight loss [28]. In this study, nearly 25% of subjects had more than 5% weight loss irrespective of accompanying drugs, suggesting the benefit of SGLT2i across the spectrum of T2DM.

It has also been noticed in the study that weight loss was generally modified by metabolic compensation which will also likely vary between individuals and this only partially explains weight loss variability and weight regain in long term. This is one of the main reasons why a significant number of patients are weight neutral and even in some cases weight has increased. In the rat model intensified treatment with SGLT2i like dapagliflozin leads to result in a compensatory increase in caloric intake [29, 30].

It will be beneficial to stop the intervention if metabolic compensation which includes appetite and energy expenditure does offset a negative energy balance thereby limiting weight regain with SGLT2i. But this monitoring was not possible in real-world setting which leads to the experience of weight gain among SGLT2i treated patients. Epidemiology of childhood overweight and obesity in India was passed in several studies in which Harish Ranjani made an attempt to review the data on trends in childhood overweight and obesity reported from India from 1981 to 2013. Even in this study, 64 patients were gained their weight. The median value for the combined prevalence of childhood and adolescent obesity showed that it was higher in the north, compared to south India. The pooled data after 2010 estimated a combined prevalence of 19.3% of childhood overweight and obesity which was a significant increase from the earlier prevalence of 16.3% reported in 2001–2005 [31].

Nearly 25% of subjects had more than 5% weight loss irrespective of accompanying drugs, suggesting the benefit of SGLT2i across the spectrum of T2DM. Several RCTs have established the beneficial role of SGLT2i with significant weight loss ranging from −1.6 to −5 kg versus placebo [18, 19, 32] and this reduction was confirmed even in long-term trials [16, 23, 33]. Several trials also demonstrate the efficacy of various SGLT2i in terms of reduction in HbA1c by 0.6–1.0% as compared with the placebo [34–36]. In a large scale RCT which confirms the superiority of SGLT2i as per cardiovascular (CV) outcome other oral glucose-lowering agents, it has been observed that dapagliflozin reduced weight by 1.8 kg (95% confidence interval 1.7–2.0) with HbA1c reduction of 0.42% [37], Canagliflozin reduced weight by 1.6 kg with HbA1c reduction of 0.58% [38] and empagliflozin reduces HbA1c by 0.45% with 2 kg weight loss [39, 40]. In our study, we have noticed a 1 kg weight reduction over a year of time frame which seems to be a little lesser as compared to above-mentioned trials but our study demonstrated a better HbA1c reduction as compared to those. Lesser weight reduction may be justified as the food habit, nature, and time was not monitored strictly and there was a high chance that undisciplined food habits can influence the weight reduction outcome.

Along with many trials which established strong potency of SGLT2i to reduce blood glucose parameters, this study also showed a statistically significant reduction in HbA1c ($p < 0.001$) after follow-up. This effectiveness to reduce HbA1c was equally observed in all three groups of SGLT2i. The main limitation of the study is a smaller number of subjects and properly follow-up. But this type of effect can be seen even in clinicians' day-to-day practice and bias was avoided as during initial selection patients were selected randomly.

Conclusions

Addition of SGLT2i causes persistent and significant weight loss along with improvement in glycemic control, independent of background glucose-lowering drugs and duration of diabetes. However, weight gain has also been observed in some groups of patients irrespective of having good glycemic control. HbA1c reduction is comparable to various RCTs but weight reduction was much less with our real-world study compared to other real-world data available as already discussed.

Conflict of interest

None declared.

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