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A real-world retrospective evaluation of glycaemic control and weight loss in patients with type 2 diabetes mellitus treated with canagliflozin 100 mg and canagliflozin 300 mg in an Indian setting

ABSTRACT

Background. Canagliflozin is a sodium glucose co--transporter 2 (SGLT2) inhibitor that improves glycaemia in patients with type 2 diabetes mellitus (T2DM) by enhancing urinary glucose excretion (UGE). Indian data regarding comparative efficacy of canagliflozin 300 mg over canagliflozin 100 mg in reduction of body weight are scanty.

Objectives. To evaluate and compare the efficacy of canagliflozin 100 mg versus canagliflozin 300 mg regarding loss of body weight retrospectively, in patients with T2DM inadequately controlled with other antihypergycaemic agents (AHA) in a real world setting in India.

Material and methods. T2DM patients inadequately controlled (HbA$_{1c}$ > 8.5%) with diet, exercise and AHA who were prescribed canagliflozin 100 mg (n = 62) or canagliflozin 300 mg (n = 36) once daily, between May 2016 to May 2019 and were followed for at least 20 weeks, are included in the analysis. Changes in blood pressure and glycaemic parameters and body weight are studied.

Results. Results show that addition of canagliflozin 100 and 300 mg provided statistically significant improvements in glycaemic control associated with weight loss. However no superiority of canagliflozin 300 mg to canagliflozin 100 mg is established.

Conclusion. The present study shows that addition of canagliflozin 300 mg has no advantage over canagliflozin 100 mg on body weight when added on existing therapy with other AHA. (Clin Diabetol 2020; 9; 5: 300–305)

Key words: canagliflozin, SGLT2 inhibitors, T2DM

Background

The substantial increase in the incidence of type 2 diabetes mellitus (T2DM) over the past decade is associated with a marked increase in the prevalence of obesity, which contributes greatly to insulin resistance, a key pathophysiologic parameter observed especially in individuals at risk. Given the role of obesity and sedentary lifestyles in contributing to the progression of T2DM, the first step in T2DM management is lifestyle modification, exercise and weight loss [1]. With progressive deterioration in β-cell function (βCF) and mass, T2DM management progresses from non-pharmacological treatment to monotherapy (metformin being the preferred first line drug), to the need for combination drugs. Drugs that can provide glycaemic control independent of βCF while having beneficial effects on weight are now preferred second line agent after metformin [2].

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of patients with T2DM. SGLT2 found in the proximal renal tubule is a low affinity, high capacity transporter responsible for the majority (90.0%) of renal glucose reabsorption [3, 4]. Canagliflozin by inhibiting the SGLT2 co-transporter lowers the renal threshold for glucose (RT_G range 4.4–5.0 mmol/l),thereby increasing urinary glucose excretion (UGE) and resulting in decreased plasma glucose, a mild osmotic diuresis and increased caloric loss (4 kcal/g of glucose), with a low potential for hypoglycaemia [5–9]. The loss of glucose with attendant caloric loss contributes to weight loss; in addition, improvements in βCF have been seen [5, 8].

The recommended starting dose of canagliflozin is 100 mg once daily, taken before the first meal of the day. Dose can be increased to 300 mg once daily in patients tolerating canagliflozin 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycaemic control [10]. Several randomized controlled studies have found that canagliflozin 300 mg is superior to sitagliptin and glimepiride as add-on therapy to metformin in achieving more effective glycaemic control [11–13].

The weight reducing effect of canagliflozin is an important therapeutic consideration for patients with T2DM who are overweight or obese. The incremental efficacy of canagliflozin 300 mg on reducing postprandial plasma glucose peaks, is consistent with the hypothesis that it transiently inhibits intestinal SGLT1-mediated glucose absorption-the major intestinal glucose transporter, with perhaps a small contribution of delayed gastric emptying, possibly related to the increased glucagon-like peptide-1 (GLP-1) levels that assist in glycaemic and appetite control [14, 15]. Interestingly, canagliflozin 300 mg was found to significantly reduce body weight in obese and overweight patients without diabetes compared to placebo [16]. However there is paucity of real world data regarding superiority of canagliflozin 300 mg over canagliflozin 100 mg in reduction of body weight in Indian setting. This study compared the efficacy and weight loss benefit of two doses of canagliflozin (100 and 300 mg) as an add-on therapy in patients with T2DM inadequately controlled with other antihyperglycaemic agent (AHA).

Materials and methods
Study design

This retrospective, real-world observational study was conducted in a tertiary care setting in Kolkata to evaluate and compare the efficacy of two doses of canagliflozin 100 and 300 mg regarding weight loss potential in T2DM patients who were inadequately controlled ($HbA_{1c} > 8.5\%$) with diet, exercise and other AHAs. The patients underwent minimum 20 weeks treatment from May 2016 to May 2019.

Protocol characteristics

Eligible patients were adult ($\geq$ 18 years) men and women with T2DM who had inadequate glycaemic control on diet, exercise and AHAs including oral antidiabetic drugs (OAD), non-insulin injectable agents and insulin injections at maximally or near-maximally effective doses. Patients not adequately controlled were defined as either having one or more of the following parameters: fasting glucose (FPG) > 150 mg/dL, post prandial plasma glucose (PPPG) > 200 mg/dL, HbA_{1c} > 8.5% despite receiving optimal dose of two or three antihypergycaemic agents [17]. Subjects were excluded if they had a history of type 1 diabetes, diabetic ketoacidosis, alcohol or drug dependence, recent or multiple hospitalization for reasons other than hyper glycaemia within past six months, nursing women, history of urinary tract or other systemic infections, haematuria, decompensated heart failure, liver failure, debilitating illness that may adversely affect renal function or on drugs that may adversely affect renal function. Total 98 patients who came to the study setting during the study period fitted the above mentioned criteria and were prescribed canagliflozin for a minimum period of 20 weeks. As weight change can also be affected by lifestyle therapy (diet and exercise), the subjects were advised at the beginning not to alter these and at subsequent visits the same was ensured. Comparability between the two groups of patients receiving canagliflozin 100 and 300 mg was ensured. Decision on prescribing canagliflozin 100 mg or 300 mg was taken by examining physician based on patient's body weight.

Data collection

Baseline data of various parameters on the day of starting treatment with canagliflozin were collected from previous records. Data included all patients' demographic records with respect to age, gender, anthropometric measurements like height, weight, body mass index (BMI) and clinical parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP). Laboratory investigations data included HbA_{1c}, FPG, PPPG, serum creatinine (Cr). Weight was recorded for each patient using an electronic weighing scale in the study setting following proper standardization procedure. BP was measured by mercury sphygmomanometer. Cuff size of 16 × 30 cm was chosen while measuring BP for non-obese patients and larger cuff (16 × 36 cm) was used for obese patients. Plasma glucose was measured by hexokinase method and

HbA$_{1c}$ was measured by high performance liquid chromatographic (HPLC) method (Bio-RAD D-10, Bio-RAD, and Hercules, CA, USA) in the institute. Data were collected from only those patients who completed at least 20 weeks of treatment period with canagliflozin 100 mg or 300 mg.

Recordings of body weight, SBP, DBP, HbA$_{1c}$, FPG, PPPG, Cr in the study group at last follow-up were collected from records. The primary parameter was change in weight from baseline at last follow up. Other secondary parameters studied included change in HbA$_{1c}$, FPG, PPPG and SBP from baseline at final follow up. To evaluate safety profile of canaglifozin adverse events due to genital mycotic infections were noted.

Statistical analysis

The data were analysed using SPSS statistics version 21. Comparability of both groups at baseline was assessed by independent t-test and nonparametric counterpart Mann-Whitney U test. Before treatment and after treatment efficacy data of canagliflozin within groups were analysed by paired sample t-test. To compare the efficacy of canagliflozin 300 mg with canagliflozin 100 mg in regards to body weight and BMI, ANCOVA was done. P value less than 0.05 was considered as statistically significant.

Results

In the present study, total 62 patients received canagliflozin 100 mg and were followed up a for a mean period of 25 weeks whereas 36 patients received canagliflozin 300 mg and were followed up a for a mean period of 24 weeks; patients were advised to take canagliflozin once daily before the first meal of the day.

Table 1 shows the baseline characteristics of the study subjects in the two groups receiving canagliflozin 100 mg and canagliflozin 300 mg. Baseline patient demographic and disease characteristics were similar across the two groups except body weight which was significantly higher in the canagliflozin 300 mg treatment group (Mann-Whitney U test, P = 0.0001). Overall the mean age of the patient was 52.12 years, 53.1% were male. Mean body weight was 78.81 kg and mean BMI was 29.68 kg/m^2 with 45.9% patients classified as obese (according to WHO classification of obesity BMI $\geq$ 30 kg/m^2) [18]. Mean FPG and PPPG level were 164.82 mg/dL and 214.18 mg/dL respectively. Baseline mean HbA$_{1c}$ was 8.33%.

Table 2 shows that both doses of canagliflozin significantly reduced bodyweight from baseline to final follow up (P < 0.001). Analysis of BMI also showed significant reduction in both canagliflozin groups (P value 0.001 and 0.002 respectively).

As the baseline body weight differed significantly in the two groups, ANCOVA was done for adjustment for the baseline body weight and BMI. After adjustment of baseline body weight and BMI estimated mean treatment differences between CANA 300 & CANA 100 with 95% confidence interval were 1.41 (–0.902 to 1.878) and 0.40 (–0.112 to 0.922) respectively which were not statistically significant (P value 0.957 and 0.123 respectively).

Table 3 shows glycaemic efficacy of the two doses of canagliflozin. HbA$_{1c}$ was significantly reduced from baseline with canagliflozin100 and 300 mg (P < 0.0001 and 0.01 respectively). Subgroup analysis showed substantially greater reductions in HbA$_{1c}$ (P < 0.01) with both canaglizolin doses in patients with higher (HbA$_{1c}$ > 9%), relative to those with lower, baseline HbA$_{1c}$. Proportion of patients who achieved HbA$_{1c}$ < 7.0% at final follow up with canagliflozin 100 mg and 300 mg were 31.1% and 27.8% respectively. Significant improvement from baseline in FPG was observed; P < 0.001 for both canagliflozin doses. PPPG reduction was also noted to be significant (P $\leq$ 0.001 for both canagliflozin doses).

Reductions from baseline in SBP and DBP at week 25 seen with canagliflozin 100 mg were statistically significant (P = 0.024 and 0.041 respectively). However reductions in SBP and DBP with canagliflozin 300 mg were found to be statistically insignificant.

Over the time, both canagliflozin doses were associated with higher rates of adverse events consistent with genital mycotic infections in the study groups. Frequency of genital mycotic infection associated with canagliflozin 100 mg and 300 mg was 21% and 11.1% respectively and the difference was statistically non-significant (chi square, P > 0.05) (Table 4).

Discussion

In this study of subjects with T2DM who had inadequate glycaemic control with other AHA, treatment with canagliflozin 100 and 300 mg provided statistically significant improvements in glycaemic control over 25 weeks and 24 weeks respectively; these improvements were associated with weight loss with both doses of canagliflozin.

Both treatment groups showed reductions in all glycaemic parameters — HbA$_{1c}$, FPG, and PPPG. A large proportion of subjects reached HbA$_{1c}$ < 7.0% with canagliflozin. These results are consistent with reports from randomised controlled trials (RCT) conducted previously [13, 14, 19]. In the high glycaemic group (HbA$_{1c}$ > 9%), both canagliflozin doses substantially improved glycaemic parameters similar to results from previous study. Because UGE is proportional to the glucose concentration above RT$_G$, subjects with higher

Table 1. Baseline demographic and disease characteristics of the overall study subjects (n = 98)

Study parameter	CANA 100 mg (n = 62)	CANA 300 mg (n = 36)	Total (n = 98)
Gender, n (%)			
Male	35 (56.45)	17 (47.22)	52 (53.1)
Female	27 (43.55)	19 (52.78)	46 (46.9)
Age (years)	52.68 ± 8.79	51.17 ± 10.55	52.12 ± 9.45
Body weight [kg]	74.06 ± 10.62	86.99 ± 14.88	78.81 ± 13.78
BMI [kg/m^2]	28.16 ± 3.92	32.31 ± 4.88	29.68 ± 4.72
SBP [mm Hg]	130.65 ± 13.69	131.00 ± 13.02	130.78 ± 13.38
DBP [mm Hg]	83.40 ± 8.38	83.56 ± 8.47	83.46 ± 8.37
HbA$_{1c}$ (%)	8.45 ± 1.65	8.16 ± 1.20	8.33 ± 1.50
FPG [mg/dL]	164.90 ± 46.14	164.68 ± 56.78	164.82 ± 50.02
PPPG [mg/dL]	214.50 ± 71.88	213.64 ± 63.27	214.18 ± 68.51
Serum Cr [mg/dL]	0.89 ± 0.20	0.87 ± 0.20	0.88 ± 0.20
Obesity, n (%)	18 (29.0)	27 (75.0)	45 (45.9)

Table 2. Changes from baseline in bodyweight and BMI at final follow up*

Canagliflozin doses	Baseline		Final follow up		Mean differences	t	P value diff. within the groups	P value diff. between the groups
	Mean	SD	Mean	SD				
Body weight changes [kg]								
CANA 100 mg (n = 62)	74.06	10.62	72.69	10.26	1.37	4.063	< 0.001	0.957
CANA 300 mg (n = 36)	86.99	14.88	85.08	14.58	1.91	3.839	< 0.001	
BMI changes [kg/m^2]								
CANA 100 mg (n = 62)	28.16	3.92	27.62	3.79	0.54	3.646	0.001	0.123
CANA 300 mg (n = 36)	32.31	4.88	31.72	4.58	0.59	3.444	0.002	

*Canagliflozin 100 mg — 25 weeks, canagliflozin 300 mg — 24 weeks. P < 0.05 considered as statistically significant, p value within the groups computed by paired sample t-test, P value between the groups computed by ANCOVA

Table 3. Summary of changes from baseline in glycaemic parameters and blood pressure at final follow up*

Canagliflozin doses	Baseline		Final follow up		Mean differences	t	p
	Mean	SD	Mean	SD			
FPG [mg/dL]							
CANA 100 mg (n = 62)	164.90	46.14	138.49	42.78	26.41	3.706	< 0.001
CANA 300 mg (n = 36)	164.68	56.78	128.36	25.63	36.32	4.113	< 0.001
PPPG [mg/dL]							
CANA 100 mg (n = 62)	212.39	70.53	176.22	52.31	36.17	4.033	< 0.001
CANA 300 mg (n = 36)	213.64	63.27	173.39	42.24	40.25	3.581	0.001
HBA$_{1c}$ [%]							
CANA 100 mg (n = 62)	8.435	1.6619	7.655	1.3143	0.78	4.834	< 0.0001
CANA 300 mg (n = 36)	8.115	1.2032	7.543	1.0058	0.572	2.581	0.014
SBP [mm Hg]							
CANA 100 mg (n = 62)	130.65	13.69	127.92	11.19	2.73	2.261	0.024
CANA 300 mg (n = 36)	131.00	13.02	128.03	10.61	2.97	1.525	0.136
DBP [mm Hg]							
CANA 100 mg (n = 62)	83.40	8.38	81.27	7.04	2.13	2.088	0.041
CANA 300 mg (n = 36)	83.56	8.47	81.42	7.87	2.14	1.423	0.164

*Canagliflozin 100 mg — 25 weeks, canagliflozin 300 mg — 24 weeks. P < 0.05 considered as statistically significant, p computed by paired sample T-test

Table 4. Frequency of genital mycotic infection of canagliflozin 100 and 300 mg over the treatment period*

Adverse effect	CANA 100 mg (n = 62)	CANA 300 mg (n = 36)
Genital mycotic infection [n (%)]	13 (20.97%)	4 (11.1%)

*Canagliflozin 100 mg — 25 weeks, canagliflozin 300 mg — 24 weeks

baseline glucose level might be expected to show greater UGE and osmotic diuresis resulting in greater glycaemic efficacy of canagliflozin [14].

Addressing obesity is an important part of T2DM management. Because many of the traditional therapies for T2DM result in weight gain, the added benefit of weight loss with canagliflozin is clinically useful [20]. In the present study canagliflozin 100 and 300 mg both showed significant body weight reduction from baseline similar to findings noted with other studies [13, 14, 19]. While body composition measurements were not performed in this study, analyses conducted in other phase 3 studies in patients with T2DM showed that approximately two-thirds of the reduction in body mass seen with canagliflozin was from fat mass and one-third was from lean body mass [13]. In clinical studies of weight loss, modest reductions in body weight have been associated with favourable improvements in cardiovascular risk factors, including lipids, BP, and inflammatory markers [21].

In the present study canagliflozin 100 mg was associated with a statistically significant reduction in SBP and DBP from baseline; however no such association was found in case of canagliflozin 300 mg though BP reduction was similar in both groups (mean differences in SBP –2.73 mm Hg in canagliflozin 100 mg, –2.97 mm Hg in canagliflozin 300 mg group and mean differences in DBP –2.13 mm Hg in canagliflozin 100 mg, –2.14 mm Hg in canagliflozin 300 mg group). This is in contrary to the previous studies which reported favourable improvements in SBP with both doses of canagliflozin [14]. The above finding can be due to smaller sample size in canagliflozin 300 mg group.

Relative to canagliflozin 100 mg an incremental efficacy on glycaemic endpoints, body weight and systolic BP of canagliflozin 300 mg was observed in a randomised controlled trial (RCT) conducted previously [14]. Clinical mechanism of action studies [15, 22] have confirmed delayed gastrointestinal glucose absorption with canagliflozin 300 mg in healthy volunteers and subjects with T2DM. However in the present study, despite absolute weight reduction was higher in the canagliflozin 300 mg group (mean differences 1.91

vs. 1.37 kg), this difference appeared to be insignificant. No significant difference was also found between the two doses of canagliflozin in respect to change of BMI although in this case difference was smaller (mean differences 0.59 *vs.* 0.54 kg/m^2). This lack of significance can probably be attributed to small study groups.

The observed frequencies of genital mycotic infection in this study in both canagliflozin groups were higher than in previous RCTs; these were generally mild or moderate in severity and treated by antifungal therapies [8, 19, 23, 24].

Finally the limitations of this study must be considered. One limitation of the study is small number of participants which may explain a lack of significance of some of the findings. Besides this is a real world study (RWS) and propensity score matching of the confounding factors between the two groups were not done due to limited sample size. Randomisation and placebo controlling was not possible in RWS. In addition, the treatment period under observation was short; a longer duration of observation with a larger sample size is needed to understand the comparative benefits and risks of these drugs and the durability of response. Finally, we did not assess the other potential adverse effects of canagliflozin like hypoglycaemia, postural dizziness and changes in eGFR. These issues might have implication in the result and outcome of the study.

Conclusion

The present study showed that canagliflozin 100 and 300 mg significantly improved glycaemic control, reduced body weight in subjects with T2DM inadequately controlled with diet, exercise and other AHA. Canagliflozin 100 mg additionally caused reduction in SBP and DBP. This the only Indian real world study is thus consistent with RCTs and real world studies of western world. However no superiority of canagliflozin 300 mg to canagliflozin 100 mg in respect to body weight was established in this study.

Conflict of interest

The authors report no conflicts of interest in this study.

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