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Beneficials Effects of Canagliflozin in a Weight-Centered Management in Patients with Type 2 Diabetes Mellitus in Real Practice

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Abstract

Objective: Evaluate the real-world efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus (T2DM), associated to a weight-loss intensive lifestyle intervention program (WLIP), to achieve weight loss greater than 5% at 12 months.

Methods: Retrospective review of patients with T2DM included in a WLIP, who were prescribed canagliflozin from June 2015 to December 2016 at four endocrinology clinics in the south of Spain within routine clinical practice context. Changes during 12 months in anthropometric variables, HbA1c, uric acid and adverse events were assessed.

Results: 201 patients with T2DM (45.8% women, 60.3 ± 9.4 years old and BMI: 34.9 ± 8.7 kg/m^2) were studied. Patients treated with canagliflozin lost an average weight and reduced an average of waist circumference of -4.0 ± 4.2 kg and -3.2 ± 8.4 cm, -5.4 ± 5.7 kg and -4.9 ± 9.9 cm and -5.3 ± 8.0 kg and -7.0 ± 14.6 cm, achieving weight loss greater than 5%: 29.0%, 47.9% and 42.7% of patients at 3, 6 and 12 months, respectively. HbA1c levels were average reduced by -1.2%, -1.3% and -1.3% and 68.8% reached an HbA1c level ≤ 7% at 12 months. 17.9% (36 patients) experienced mild adverse events and canagliflozin treatment was suspended in 23 patients (11.4%).

Conclusion: The addition of canagliflozin to the treatment of overweight or obese patients with T2DM, as a complement of a weight-loss intensive lifestyle intervention, was associated with improvement in body weight and glycemic control with relative mild adverse events.

Keywords: Canagliflozin; Obesity; Type 2 diabetes; Glycosylated hemoglobin; Uric acid

Introduction

The obesity epidemic is driving the increased prevalence of type 2 diabetes mellitus (T2DM), and approximately 85% patients with T2DM are overweight or obese [1]. In overweight and obese patients with T2DM, modest weight loss, defined as sustained reduction of 5% of initial body weight, can reduce HbA1c levels, improve fitness and cardiovascular disease (CVD) risk factors, and decrease the use of anti-diabetic, antihypertensive, and lipid-lowering medications. Additional benefits of weight loss include reduction of depression symptoms and remission or decrease severity of obstructive sleep apnea [2-5].

Patients with T2DM have greater difficulty to lose weight than individuals without diabetes for several reasons. In insulin-resistant states, skeletal muscle and liver are the predominant organs responsible for glucose disposal. Hyperinsulinemia promotes triglyceride synthesis and storage while inhibits lipolysis in adipocytes, resulting in an expansion of adipose tissue. Patients with diabetes use to have more sedentary lifestyles and less physical activity. Importantly, some of the commonly used antihyperglycemic agents (AHAs) are associated with weight gain, which further complicates successful weight management. Finally, weight regain can result from compensatory response to hormonal and metabolic changes following initial weight loss, where or exigenic mediators that stimulate appetite persist [4].

Longitudinal cohort studies indicate changes in BMI among patients with T2DM are significant predictors of changes in HbA1c [5], and patients who lose weight are more likely to achieve target HbA1c values than those with stable weight or weight gain [6,7]. As a result, when health behavior modification fails to achieve glycemic and metabolic goal targets, priority should be given to AHAs that are associated with weight loss without increasing the risk of hypoglycaemia, as glucagon-like peptide-1 (GLP-1) receptor agonists and the sodium glucose co-transporter 2 (SGLT2) inhibitors [8].

Canagliflozin is a SGLT2 inhibitor that offers an anti-diabetic effect by increasing urinary glucose excretion equates to a loss of approximately 308-476 calories per day [9]. While initial weight loss may reflect fluid loss due to osmotic diuresis, weight loss by canagliflozin is largely result of reduction of subcutaneous and visceral fat [10,11]. Multiple studies have demonstrated that treatment with canagliflozin result in significant reductions of HbA1c from baseline by −0.58% and −1.03% and in body weight by −3.3% and −4.4% after

52 weeks with 100 and 300 mg, respectively, in patients with diabetes [12]. However, at present there is little information in real world relating about benefits and safety of canagliflozin in a weight-centered management in specialty diabetes practice settings [13-17]. The aim of this study was to evaluate the real-world efficacy and safety of canagliflozin in patients with T2DM, associated to a weight-loss intensive lifestyle intervention program, to achieve weight loss greater than 5% at 12 months.

Patients and Methods

Study design and sample selection

This study is a retrospective review of 201 patients with T2DM who were prescribed canagliflozin from June 2015 to December 2016 at four endocrinology clinics in the south of Spain within the context of routine clinical practice. Patients are referred to this specialty office by regional and local specialist and primary care providers for advanced diabetes management, generally because poor metabolic control. Records searches were realized identifying those patients with inclusion criteria: patients with T2DM, over 18 years of age, who started treatment with canagliflozin in the study period and had received initial and regular follow-up in the clinic at least during 12 months. Exclusion criteria were: patients with type 1 diabetes mellitus, pregnant women, patients receiving treatment with systemic corticosteroids during the study period, not having enough information in clinical records or patients who failed two or more programmed visits. Selected patients were included in a database and each one was identified by a unique study number assigned to ensure confidentiality.

Outpatient diabetes treatment protocol

All patients included in the study were attended in one of four endocrinology outpatient clinics within the context of routine clinical practice. Habitually patients overweight or obese, in order to promote the improvement of metabolic control and weight loss, were included in a weight-loss intensive lifestyle intervention program that includes: i) Personalized low-calorie diet. Majority of women were given diets of approx. 1200-1500 Kcal. and men diets were of approx. 1500 to 1800 Kcal; ii) Physical activity recommendations tailored to each patient of at least 45 minutes of walking 4 days a week; iii) AHAs were adjusted individually to achieve metabolic control objectives (HbA1c ≤ 7%). Usually, in obese or overweight patients with T2DM anti-diabetic regimens with sulfonylureas, metiglinides, pioglitazon or acarbose were suspended and treatment with metformin was maintained or initiated whenever was well tolerated. GLP-1 receptor agonist usually was maintained and initiation was proposed in obese patients. Recommendations were given to patients to optimize basal insulin dose in order to achieve and maintain fasting blood glucose levels between 80 and 130 mg/dl and prandial insulin dose was adjusted to achieve postprandial blood glucose below 180 mg/dl.

Data Collection

Most patients with T2DM were attended every 3 months, with the possibility of mid-term reviews to assess tolerance and efficacy of the treatments. At baseline, data on demographic variables (gender, age and smoking), history of diabetes (date of diagnosis, current treatment and HbA1c level), comorbidities (hypertension, dyslipidemia) and complications (retinopathy and cardiovascular disease) were collected. Every 3 months visit patient's weight and waist circumference (WC), diabetes treatment variables (basal and rapid insulin doses and other anti-diabetic treatments), HbA1c and uric acid levels, common SGLT2 inhibitors adverse events (mainly osmotic diuresis -polyuria and pollakiuria-, genital candidiasis and urinary tract infection), severe hypoglycemia episodes (defined as those episodes requiring the help of a third person for resolution) and diabetic ketoacidosis were recorded.

Statistical Methodology

Every data collected in the study was coded, entered, and analyzed using the SPSS Statistics for Windows 12.0 version program. Qualitative variables descriptive analysis was performed by calculating frequencies and percentages, and for quantitative variables mean, standard deviation, median, and range were determined. Each patient served as his/her own control. Paired t-tests were performed on primary and secondary outcomes. P values <0.05 were considered statistically significant.

IRB approval

This study was conducted in accordance with the good clinical practice guidelines and with the Helsinki Declaration principles. Study was approved by the independent Institutional Review Board (IRB) of Viamed Hospital.

Results

201 patients with T2DM (54.2% males, 45.8% females) mean age of 60.3 ± 9.4 years old and an average time of diabetes disease in years of 10.4 ± 8.8, body weight and BMI mean of 94.2 ± 18.2 kg and 34.9 ± 8.7 kg/m^2, respectively, were included in the study. Overall, 93.6% of the sample reported having at least one comorbidity, most common comorbidities reported were hyperlipidemia (75.6%) and hypertension (74.6%) (Table 1). Only 5 patients (2.5%) had a normal BMI, 44 patients (21.9%) were overweight (BMI between 25 and 29.9 kg/m^2) and 152 patients (75.6%) were obese (BMI ≥ 30 kg/m^2). Most patients showed inadequate metabolic control at baseline (69.7% of patients with HbA1c> 7.0%).

Clinical Characteristics	**Results**
Mean Age (years-old)	60.3 ± 9.4
Female (%)	92 (45.8)
Mean time diabetes evolution (years)	10.4 ± 8.8
Patients with antidiabetic drugs (%)	179 (89.1)
Metformin	152 (75.6)
Sulfonilureas or Metiglinides	39 (19.4)
DPP-4 inhibitors	80 (39.8)
GLP-1 receptor agonist	33 (16.4)
Insulin	92 (45.8)
Physical Examination	
Body weight (kg)	94.2 ± 18.2
BMI (kg/m^2)	34.9 ± 8.7

Waist Circunference (cm)	113.7 ± 14.0
Comorbidities and Chronic complications	
Smoking habit (%)	33 (16.4)
Dyslipemia (%)	152 (75.6)
Hypertension (%)	150 (74.6)
Diabetic Retinopathy (%)	25 (12.4)
Cardiovascular disease (%)	51 (25.4)

Table 1: Patients Characteristics (n = 201). Results are expressed as mean ± standard deviation. BMI: Body mass index; Kg: Kilograms; cm: centimeters; IU: Units.

After adding canagliflozin to treatment, a significant reduction of HbA1c was observed from mean baseline value (± SD) of 8.0 ± 1.7% to 6.8± 1.0% to 6.7± 0.9% and 6.6 ± 0.9% at the third, sixth and twelfth month visits, respectively (Table 2). At 3, 6 and 12 month, HbA1c levels were significantly reduced by an average of -1.2%, -1.3% and -1.3%, respectively, and 68.8% reached an HbA1c level ≤ 7% at 12 months (Table 2). Patients treated with canagliflozin 300 mg/day (30 patients) showed more HbA1c reductions at 3 months (-1.8 ± 1.7% *Vs* -1.1 ± 1.4%; p=0.046), 6 months (-2.2 ± 1.4% *Vs* -1.2 ± 1.5%; p=0.06) and 12 months (-2.0 ± 1.8% *Vs* -1.1 ± 1.3%; p=0.03) than patients treated with canagliflozin 100 mg/day.

	Basal	3 months	6 months	12 months	P
Body weight (Kg)	94.2 ± 18.2	91.1 ± 16.5	88.7 ± 15.9	90.3 ± 16.7	<0.011
Waist circumference (cm)	113.7 ± 14.0	110.1 ± 12.6	109.0 ± 12.8	108.4 ± 16.5	<0.011
HbA1c (%)	8.0 ± 1.7	6.8 ± 1.0	6.7 ± 0.9	6.6 ± 0.9	<0.011
Patients with HbA1c ≤ 7% (%)	30.3	60.7	67.3	68.8	<0.011
Uric acid levels (mg/dl)	5.3 ± 1.6	4.8 ± 1.6	4.8 ± 1.6	4.8 ± 1.3	<0.011

Table 2: Changes in clinical and metabolic variables at 3, 6 and 12 months. Kg: Kilograms; cm: centimeters; 13, 3 and 12 months vs. basal

Weight-loss intensive lifestyle intervention program and canagliflozin treatment was associated with a significant weight and waist circumference reduction (Table 2). Patients treated with canagliflozin had lost an average weight of -4.0 ± 4.2 kg (-4.1 ± 3.9%), -5.4 ± 5.7 kg (-5.6 ± 5.4%) and -5.3 ± 8.0 kg (-5.4 ± 7.7%), achieving weight loss greater than 5% the 29.0%, 47.9% and 42.7% at 3, 6 and 12 months, respectively. Similarly, waist circumference and uric acid levels were reduced an average of -3.2 ± 8.4 cm and -0.5 ± 1.1 mg/dl, -4.9 ± 9.9 cm and -0.6 ± 1.2 mg/dl and -7.0 ± 14.6 cm and -0.7 ± 1.1 mg/dl at 3, 6 and 12 months, respectively. There was no difference in HbA1c reductions or reaching HbA1c level ≤ 7% between patients with or without weight loss greater than 5% (Table 3).

	Weight loss ≥ 5% at 12 months		p
	Yes (n=86)	No (n=115)	
Age (years)	61.8 ± 8.1	59.2 ± 9.3	0.2
Females (%)	51.5	48.5	0.4
Basal body weight (Kg)	97.5 ± 17.2	90.1 ± 18.9	0
Basal BMI (kg/m^2)	34.6 ± 6.0	35.4 ± 13.6	0.7
Basal HbA1c (%)	7.8 ± 1.4	7.8 ± 1.5	0.9
HbA1c (%) at 12 months	6.6 ± 0.9	6.7 ± 0.9	0.1
HbA1c ≤ 7% at 12 months (%)	61.4	71.7	0.2
Insulin users (%)	47.2	52.8	0.5
Initial insulin doses (UI/kg/day)	0.66 ± 0.45	0.60 ± 0.33	0.5
Canagliflozin 300 mg users (%)	51.1	48.9	0.4
GLP-1 agonist users (%)	45.8	54.2	0.3

Table 3: Clinical different between patients who losses more or less than 5% of weight. Kg: Kilograms; m: meter; UI: Unit.

During follow-up, 17.9% (36 patients) experienced mild adverse events. More frequent were genital candidiasis (20 patients; 10.0%), urinary tract infection (9 patients; 4.5%), pollakiuria (5 patients; 2.5%) and hypotension (2 patients; 1%). No patients reported severe hypoglycemia or ketoacidosis. Canagliflozin treatment was suspended because of them in 23 patients (11.4%).

Discussion

Almost all patients with T2DM are overweight or obese, and weight loss is a recommended treatment strategy that probably is associated with reductions in mortality (18). A recent systematic review and meta-analysis showed majority of weight-loss intensive lifestyle interventions in overweight or obese adults with T2DM (17 of 19 studies) resulted in weight loss <5% at 12 months (-3.2 Kg; 95% IC: -5.9 to -0.6) and did not result in beneficial metabolic outcomes [3]. In this meta-analysis, only two study groups with 12-month weight loss of >5% (the Mediterranean-style diet in the Esposito trial [18,19] and the intensive lifestyle intervention in the Look AHEAD trial [20]) had significant decreases in HbA1c, as well as significant improvements in lipids and blood pressure (BP). Authors concluded weight loss for many overweight or obese patients with T2DM might not be a realistic primary treatment strategy to improve glycemic control [3].

In our study, patients with T2DM included in a weight-loss intensive lifestyle intervention program and treated with canagliflozin during a year showed an average weight loss of -5.4 ± 7.7% and 42.7%

lost ≥ 5% of initial weight at 12 month (85.1% patients lost weight). These results are consistent with CANATA trials [21], which reported mean weight loss of 2.2–4.2% at 52 weeks, and with Blonde et al (10) that showed 85% of patients treated with canagliflozin 100 and 300 mg had a decrease in body weight at week 104 (35-40% patients lost ≥ 5% body weight), with reductions in waist circumference, fat mass (two-thirds of canagliflozin-associated weight loss) and lean mass compared with glimepiride [10]. Weight loss demonstrated in our study is higher than others studies conducted within the context of routine clinical practice [11-13] and occurred despite the fact large portions of patient population concomitantly received therapies with AHAs known to be associated with weight gain, including insulin (45.8%) and sulfonylurea (19.4%).

In clinical trials with canagliflozin weight loss demonstrated an association with improvements in weight-related quality of life and satisfaction with physical and emotional health, and probably contribute to reduce healthcare cost [22]. In this way, in a retrospective observational study conducted in our country with 738 patients with T2DM during 12 months of follow up, it was found patients with a decrease of one point in BMI had lower health spending (especially pharmacy costs) as compared with those patients who increased their BMI during the follow up [23]. Finally, findings of the Look AHEAD study suggest patients are more likely adhere to treatment regimens that offer benefits from their own perspective (e.g., convenience, avoidance of hypoglycaemic episodes, weight loss) than to regimens do not [1-2].

This study reports a significant decrease in mean HbA1c of 1.3% at 12 months with the addition of canagliflozin to anti-diabetic therapy, superior to Phase III trials (where canagliflozin 100 mg and 300 mg reduced HbA1c from –0.58% to –1.03%) [12] and others real-world studies [12-17]. Probably weight loss over a short-term period (12 months) is associated with a positive impact on attainment of HbA1c goals [19,20], but our patients with weight loss ≥ 5% or ≥ 10% at 12 months did not result in additional reductions in HbA1c levels (Table 3). In the present study, there was a significant decrease in mean uric acid levels. Decrease in uric acid levels might be attributable to osmotic diuresis or to direct suppression of uric acid reabsorption at the tubular level by SGLT2 inhibitors and bring additional benefits for patients with diabetes and hyperuricaemia. Clinical relevance of hypouricaemic effects of SGLT2 inhibitors, extended to blood pressure-reducing and renoprotective benefits which could be attributable to those effects, warrant further studies [24,25]. As expected, some patients discontinued treatment before 12 months. All of these discontinuations were associated with treatment-related adverse events, specifically related to genital candidiasis, and were consistent with those seen in clinical trials [12]. However, nor serious adverse events occurred.

The present study has several limitations. First, sample size of this study is relatively small and patients were evaluated for a short period of time (12 months) without an associated control group. Second, our study was conducted on a particular study group and is possible that clinical results observed in our patients could be different in another countries or type 2 diabetes patient groups. Third, despite availability of a treatment protocol and uniform monitoring, it is possible that in some cases it has not been strictly followed. Fourth, data were collected by retrospective review of an electronic medical record and only documented adverse events were captured. It is possible more adverse events occurred than the ones reported. Fifth, no patient received treatment with orlistat or other anti-obesity medications, which could have contributed to further improve in metabolic control and body weight of our patients. Finally, it has not assessed the impact on other important clinical parameters such as lipid profile or blood pressure levels, among others.

Conclusion

In conclusion, our data support the idea that the addition of canagliflozin to the treatment of overweight or obese patients with T2DM, as a complement of a weight-loss intensive lifestyle intervention program, is associated with an improvement in glycemic control, body weight and uric acid levels with relative mild adverse events. Authors consider health care practitioners should prioritize weight-reducing medications (such Canagliflozin) as a complement of a weight-loss intensive lifestyle intervention program in overweight or obese patients with T2DM.

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Disclosures

The authors report no conflicts of interest.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

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