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Effect of canagliflozin on the overall clinical state including insulin resistance in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Information on the clinical efficacy of SGLT2 inhibitors in the Japanese population is limited. The aim of this single-arm, single-center, open-label study was to confirm the body weight- and fat mass-lowering effects of canagliflozin (CANA) and the accompanying improvement in insulin resistance in Japanese patients with Type 2 diabetes mellitus (T2DM).

Methods: Thirty-eight patients were enrolled and administered 100 mg CANA once daily for 24 weeks. Blood and anthropometric parameters were examined before and after treatment. In a subset of patients, insulin sensitivity was assessed based on the glucose infusion rate (GIR) during a hyperinsulinemic euglycemic clamp test.

Results: CANA treatment significantly decreased hemoglobin A1c, fasting plasma glucose, and plasma liver enzyme levels, and increased plasma adiponectin levels. In addition, a significant reduction in body weight, visceral and subcutaneous fat area, fat and lean mass, and liver steatosis was also observed. The change in plasma adiponectin levels significantly correlated with the changes in both body fat mass and visceral fat area. GIR increased from 3.25 ± 1.53 to 4.11 ± 1.30 mg/kg/min ($P < 0.05$).

Conclusions: CANA improved insulin resistance and decreased visceral fat mass in Japanese patients with T2DM.

1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of oral agents for the treatment of Type 2 diabetes mellitus (T2DM) that act via the suppression of glucose reabsorption in the proximal tubule and an increase in urinary glucose excretion [1]. Many studies have demonstrated the favorable effects of SGLT2 inhibitors in patients with T2DM [2]. The administration of SGLT2 inhibitors not only improved glycemic control but also reduced body weight [3–5]. Moreover,

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approximately two-thirds of body weight reduction was due to a decrease in body fat [6,7]. In addition, the visceral fat area-lowering effects of SGLT2 inhibitors were reported to be slightly greater than their effects on the subcutaneous area [7], fatty liver [8,9], and insulin resistance [10–12]. However, the previous studies that reported these findings were mostly conducted in groups of Western subjects with a mean body mass index (BMI) of more than 30.

Japanese patients with T2DM have a characteristic pathogenesis; the BMI of Japanese patients is lower than that of Caucasians, and East Asian people including the Japanese tend to have excessive visceral fat compared to that in other BMI-matched ethnic groups, and show insulin resistance from the initial stage of an increase in visceral fat [13–15]. Many studies of SGLT2 inhibitors have been carried out in Japan; however, information regarding their effects on body fat and insulin resistance is limited. It is unclear whether SGLT2 inhibitors can have similar effects on body fat and insulin resistance in Japanese patients as those seen in Western patients so far. Therefore, we conducted a 24-week study to investigate the effects of an SGLT2 inhibitor, canagliflozin (CANA), on glycemic control, body weight, body composition, and insulin resistance using an insulin clamp technique in Japanese patients with T2DM.

2. Material and methods

2.1. Patients

Patients older than 20 years and younger than 70 years who regularly visited the H.E.C Science Clinic (Yokohama, Japan) and had a diagnosis of T2DM according to the criteria of the Japan Diabetes Society were recruited. The patients were required to have hemoglobin A1c (HbA1c) levels between 7.0 and 10.0%, a BMI equal to or greater than 23 kg/m^2, and serum creatinine levels of 1.0 mg/dL or less for men and 0.8 mg/dL or less for women. Patients who were on a very low-carbohydrate diet, who showed one or more contraindications as outlined in the latest version of the package insert for CANAGURU® Tablets 100 mg, and who were judged by the physician to be inappropriate for the study, were excluded.

2.2. Study design

This was a single-arm, single-center (H.E.C Science Clinic), open-label study that examined the effect of CANA on blood glucose control and body fat in Japanese patients with T2DM. We planned to enroll 40 subjects, which was deemed sufficient for the assessment of blood glucose-lowering and body weight-reducing effects of CANA, and considering the feasibility of the study. CANA (100 mg) was administered once daily for 24 weeks. The subjects were instructed not to change their diet and exercise regimen during the study. The dosage and administration of all concomitant medications were also kept as constant as possible. It was permissible to change the doses and even to discontinue the concomitant medications, if necessary, at the physician's discretion. This study was conducted between November 2014 and November 2016 in accordance with the Declaration of Helsinki (revised in October 2013). Written informed consent was obtained from all individuals before participation in this study. The protocol was approved by the Institutional Ethics Review Committee of H.E.C Science Clinic (approval number: 140801) and was registered in the UMIN Clinical Trial Registry as UMIN0000166359.

2.3. Clinical and biochemical analysis

Clinical and biochemical measurements were performed before and after CANA treatment for 24 weeks. Body weight, BMI, waist circumference, blood pressure, and HbA1c were measured at H.E.C Science Clinic. Measurements of plasma parameters, including fasting plasma glucose (FPG), aspartate transaminase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γGTP), interleukin (IL)-6, tumor necrosis factor (TNF)-α, and adiponectin level, were carried out by Health Sciences Research Institute, Inc. (Yokohama, Japan). Total fat mass and total lean mass were assessed with dual-energy X-ray absorptiometry (DEXA). The areas of visceral fat and subcutaneous fat at the level of the umbilicus were measured using computed tomography (CT). The liver-to-spleen CT attenuation ratio (L/S ratio) was also calculated for the evaluation of fatty liver. The above parameters were assessed in all patients, and a euglycemic hyperinsulinemic study was conducted in 10 of these patients to evaluate insulin sensitivity.

2.4. Euglycemic hyperinsulinemic clamp technique

Patients were examined in the morning after overnight fasting (for over 12 h). The euglycemic hyperinsulinemic glucose clamp examination was performed using an artificial pancreas (STG22, Nikiso, Shizuoka, Japan) as described previously [11,16,17]. We cannulated both the left and right antebrachial veins, and human regular insulin (Novolin R 100 IU/mL; Novo Nordisk, Denmark) was infused through one antebrachial vein and 20% glucose was infused through the other. The artificial pancreas controlled the insulin infusion rate and glucose infusion rate (GIR) so as to maintain the plasma insulin level at 200 μU/mL and plasma glucose level at 95 mg/dL. Ninety to 150 min after starting the clamp study, GIR became stable and the mean of the steady-state GIR for a 30-min period was determined as an index of peripheral glucose uptake. All patients were allowed to urinate before the test, and the urine was discarded. Urine was collected from the subjects immediately after the test. When urination occurred during the study, the urine was also collected and combined. Urine volume and urine glucose levels were determined, and the urinary glucose excretion rate was calculated as follows: Urine volume (mL) multiplied by the urine glucose concentration (mg/mL) divided by time (min) and body weight (kg) = urinary glucose excretion rate (mg/kg/min). GIR was corrected by subtracting the respective glucose excretion rate.

2.5. Statistical analysis

Data are presented as the mean ± SD. Changes from baseline to 24 weeks were analyzed by two-tailed paired *t*-test. Associations between variables were assessed using Pearson's correlation coefficients. A *P*-value less than 5% was considered

statistically significant. All statistical analyses were performed using R software (ver. 3.2.3) by SRD Co., Ltd. (Tokyo, Japan).

3. Results

3.1. Baseline characteristics of the study patients

Initially, we planned this study with 40 participants. However, one participant withdrew consent while another was excluded due to a deviation from the eligibility criteria (the participant could not fast before the examination). Eventually, 38 eligible subjects were enrolled in this study. All participants completed the study without any severe side effects, such as severe hypoglycemia, severe dehydration, genital and urinary infections needing medical treatment, stroke, and myocardial infarction that require a hospital visit or hospitalization. Their concomitant anti-diabetic medications were not changed from at least 3 months prior to baseline evaluation to the end of the study, except in the cases of two insulin-treated patients. For one participant, the dose of long-acting insulin was reduced from 12 U/day to 10 U/day, and for the other, the dose of long-acting insulin was reduced from 23 U/day to 22 U/day. We adjusted the doses of insulin as these participants were concerned about hypoglycemia. Baseline characteristics of all patients (left column) and the patients who were a part of the euglycemic hyperinsulinemic clamp study (right column) are shown in Table 1, which were generally similar except for the prescription rates of anti-diabetic medications such as DPP4 inhibitors, insulin, and GLP-1 agonists.

3.2. Effects of CANA on HbA1c, FPG, body weight, BMI, and waist circumference

Twenty-four weeks of treatment with CANA significantly reduced HbA1c and FPG (Table 2). Body weight, BMI, and waist circumference also significantly decreased (Table 2).

3.3. Effects of CANA on fat mass, lean mass, abdominal visceral fat area, abdominal subcutaneous fat area, and L/S ratio

CANA also significantly reduced both fat mass and lean mass by −1.31 kg and −1.15 kg, respectively (Table 2), indicating each accounted for roughly one-half of the body weight loss induced by CANA. Abdominal visceral fat area and abdominal subcutaneous fat area assessed by CT also decreased by −8.7% and −7.7%, respectively (Table 2). In addition, as shown in Fig. 1, L/S ratio, an index of fatty liver, changed from 0.90 ± 0.24 to 1.02 ± 0.20 ($P < 0.001$).

3.4. Effects of CANA on laboratory data

Plasma ALT, AST, γGTP, and adiponectin levels significantly decreased, whereas no significant differences were detected in plasma IL-6 and TNF-α levels (Table 2).

3.5. Correlations between changes in adiponectin levels and body composition parameters

The change in adiponectin level inversely correlated with the changes in both body fat mass ($r = -0.371$, $P = 0.0219$; Fig. 2a) and abdominal visceral fat area ($r = -0.369$, $P = 0.0225$; Fig. 2b). However, there were no significant associations between adiponectin levels and other body composition parameters.

3.6. Euglycemic hyperinsulinemic clamp study

As shown in Fig. 3, there was a significant increase in GIR during the euglycemic hyperinsulinemic clamp study, from 3.25 ± 1.53 to 4.11 ± 1.30 mg/kg/min ($P < 0.05$).

4. Discussion

Accumulation of visceral fat induces insulin resistance [18] and is an independent risk factor for the onset of T2DM

Table 1 – Baseline characteristics of all and clamp study patients.

	All patients	Clamp study patients
Number of patients	38	10
Male/female	17/21	3/7
Age (years)	59.2 ± 8.5	59.0 ± 9.3
Duration of diabetes (years)	12.4 ± 7.3	13.1 ± 9.7
BW (kg)	72.08 ± 11.64	72.53 ± 13.12
BMI (kg/m^2)	27.07 ± 3.28	27.97 ± 3.12
HbA1c (%)	7.94 ± 0.69	8.29 ± 0.65
FPG (mg/dL)	154.1 ± 33.8	155.10 ± 47.53
Anti-diabetic medications		
Biguanide	33 (87%)	7 (70%)
DPP4 inhibitor	26 (68%)	2 (20%)
Sulfonylurea	25 (66%)	4 (40%)
Insulin	8 (21%)	7 (70%)
GLP-1 agonist	6 (16%)	5 (50%)
Thiazolidine	2 (5%)	1 (10%)

Data are expressed as n, mean ± standard deviation (SD), or n (%). BW: body weight; BMI: body mass index; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; DPP4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1.

Table 2 – Effects of CANA on anthropometric and laboratory data.

	Baseline	Week 24	P-value
BW (kg)	72.08 ± 11.64	69.67 ± 11.87	<0.001
BMI (kg/m^2)	27.07 ± 3.28	26.13 ± 3.28	<0.001
Waist circumference (cm)	95.30 ± 8.86	93.06 ± 8.40	0.0199
HbA1c (%)	7.94 ± 0.69	7.18 ± 0.64	<0.001
FPG (mg/dL)	154.1 ± 33.8	130.2 ± 29.6	<0.001
Plasma ALT (U/L)	36.8 ± 26.2	24.3 ± 6.8	<0.001
Plasma AST (U/L)	49.7 ± 43.7	30.3 ± 18.3	<0.001
Plasma γGTP (U/L)	48.2 ± 37.0	32.2 ± 20.6	<0.001
Plasma Adiponectin (μg/mL)	6.77 ± 2.65	7.33 ± 2.81	0.0028
Plasma IL-6 (pg/mL)	2.21 ± 1.60	2.32 ± 1.74	0.6689
Plasma TNF-α (pg/mL)	1.16 ± 0.31	1.11 ± 0.37	0.2765
Subcutaneous fat area (cm^2)	205.02 ± 81.63	189.19 ± 79.10	<0.001
Visceral fat area (cm^2)	125.58 ± 42.35	114.70 ± 40.51	<0.001
Body fat mass by DEXA (kg)	21.06 ± 5.56	19.75 ± 5.51	<0.001
Lean body mass by DEXA (kg)	49.57 ± 9.48	48.43 ± 9.41	<0.001

Data are expressed as mean ± standard deviation (SD) and P-value obtained using paired t-test. BW: body weight; BMI: body mass index; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; γGTP: γ-glutamyl transpeptidase; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; DEXA: dual-energy X-ray absorptiometry.

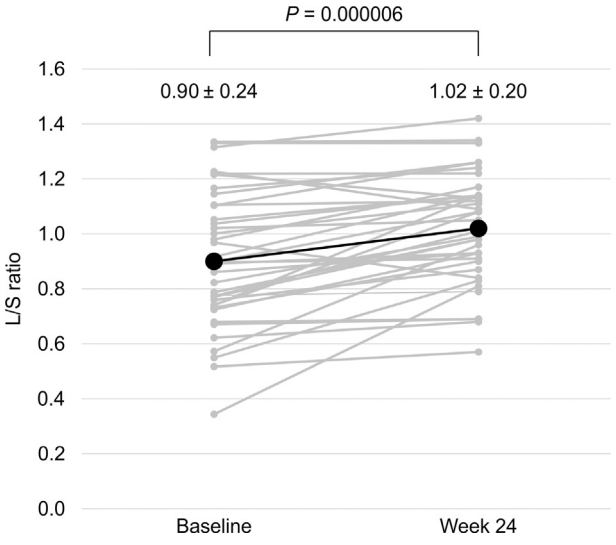

Fig. 1 – Change in the liver-to-spleen computed tomography (CT) attenuation ratio (L/S ratio) from baseline to week 24. Data are expressed as individual measurements (gray circle), mean (black circle), mean ± standard deviation (SD) (value in the figure), and P-value obtained using paired t-test.

[19]. Meanwhile, it is well-known that Asians, including the Japanese, are more likely to have metabolic syndrome despite the lower degree of obesity than in Westerners [14]. Asians have larger areas of visceral adipose tissue than do Westerners with the same waist circumference or obesity, which is considered to be one of the causes of the greater incidence of metabolic syndrome in the former [13,14]. Japanese people who have at least one risk factor for hyperglycemia, hypertension, or dyslipidemia accumulate visceral fat in skeletal muscles and show insulin resistance even if their BMI ranges from 23 to 25 kg/m^2 [15]. Therefore, more intensive interventions to prevent visceral fat accumulation are recommended for Asians [14]. In this study, administration of CANA for 24 weeks to Japanese patients with T2DM resulted in not only glycemic control but also a reduction in visceral fat, possibly through energy loss due to an increase in urinary glucose excretion, and improvement of insulin resistance.

As a mechanism by which visceral fat accumulation causes insulin resistance, the involvement of adipocytokines secreted from adipose tissue is well established. In particular, lower levels of the anti-diabetic, anti-arteriosclerotic, and anti-inflammatory adipocytokine, adiponectin, which are caused by visceral fat accumulation, are thought to be most important for the pathogenesis [20,21]. In this study, administration of CANA increased blood adiponectin levels. In addition, a significant negative correlation was found between the change in blood adiponectin level and changes in body fat mass or visceral fat area. These results suggest that CANA could reduce visceral fat, resulting in improved insulin resistance. Therapy of Japanese patients treated with DPP4 inhibitors with an SGLT2 inhibitor was recently reported to improve peripheral insulin resistance, and the improvement in insulin resistance and the decrease in body fat mass were inversely correlated [12], which also strongly supports our hypothesis.

Other adipocytokines, TNF-α and IL-6, are also considered to play an important role in the pathogenesis of metabolic syndrome [22]. However, CANA treatment did not result in a significant reduction in the blood levels of these cytokines. Adiponectin is specifically expressed and secreted by adipocytes, while TNF-α and IL-6 are also produced by many cells other than adipocytes and macrophages infiltrating the adipose tissues [23,24]. Thus, this may be the reason changes in these factors could not be detected.

Treatment with CANA significantly increased GIR (after correction by subtracting the loss due to urinary glucose excretion) in the clamp test. Since more than 80% of glucose utilization occurs in skeletal muscles under the conditions of the hyperinsulinemic euglycemic clamp technique used in this study [25], the results indicate that CANA improved skeletal muscle insulin resistance. However, the degree of fatty liver evaluated using L/S ratio revealed that CANA improved fatty liver, and decreased plasma liver enzymes

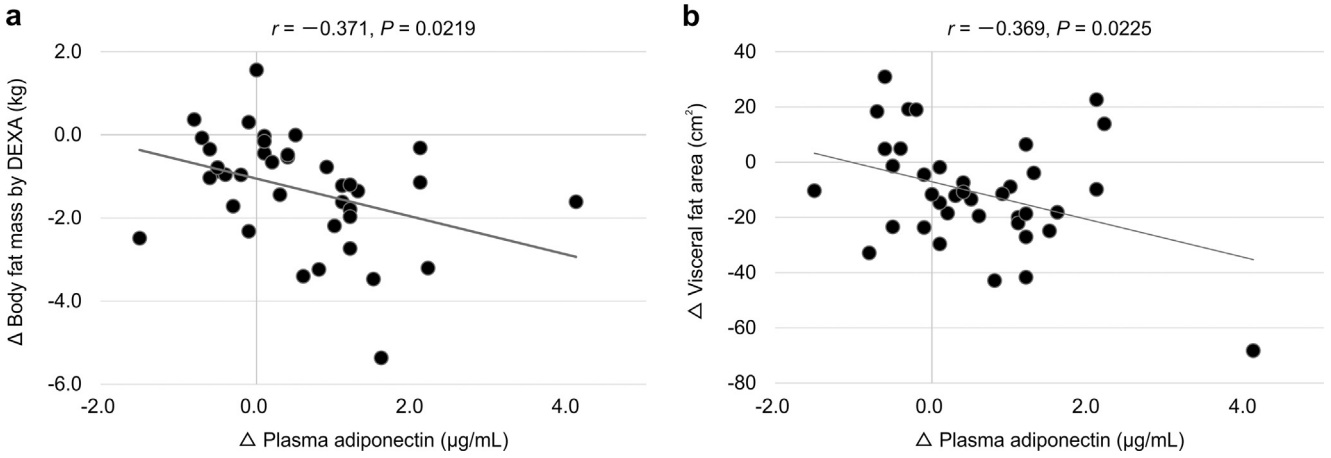

Fig. 2 – Correlation between change in plasma adiponectin level and changes in body fat mass (a) or visceral fat area (b). The relationship between the changes was assessed using Pearson's correlation coefficient.

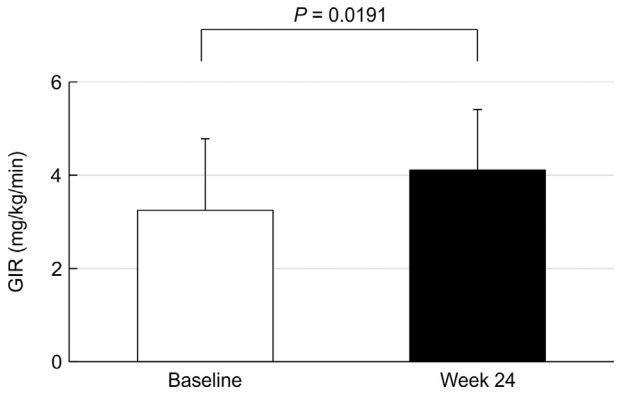

Fig. 3 – Glucose infusion rate during the euglycemic hyperinsulinemic clamp studies performed before (baseline) and after 24-week treatment with CANA (week 24). Data are expressed as mean + standard deviation (SD) and P-value obtained using paired t-test.

were also observed. The accumulation of ectopic fat in the liver and skeletal muscle has been found to play an important role in the development of insulin resistance in each tissue [26]. Taken together, the findings suggest that CANA improves hepatic insulin resistance and decreases the fat content in skeletal muscles.

Several studies in Western patients reported that approximately two-thirds of the weight loss by SGLT2 inhibitors is due to a decrease in adipose tissue mass [6,7]. However, decreases in body fat mass and lean body mass in this study were found to be almost similar. A subset of patients in our study whose BMI was 30 kg/m^2 or more was selected as the population with BMI comparable to that of the subjects in Western studies (n = 6, mean BMI is 33.43) and analyzed; however, the decreases in body fat mass and lean mass were still similar (data not shown). Therefore, the difference does not depend on the difference in the degree of obesity of the participants, but the exact mechanisms underlying remain unclear. Although the proportion of skeletal muscle mass in the decreased lean mass is not known, because the reduction in skeletal muscle mass is also associated with the aggravation of insulin resistance [27,28], a possible negative impact on insulin sensitivity cannot be ruled out. Thus, concomitant diet or exercise therapy fully optimized both in quality and quantity could minimize the decrease in lean body mass, and could make the insulin-sensitizing action of the drug more apparent.

There are some limitations to this study that must be taken into consideration. First, we conducted the study in a single-site, single-arm, and open-label manner. Second, the observation period was relatively short, 24 weeks. Therefore, to ensure sufficient reliability of the findings obtained in this, we believe that confirmation by a longer-term multicenter randomized controlled trial is necessary.

In conclusion, the present results revealed that CANA not only improves glycemic control but also improves insulin resistance in Japanese T2DM patients who are less obese compared to Westerners. The improvement in insulin resistance is probably mediated by reduction in visceral adipose tissue and ectopic fat accumulation. Therefore, SGLT2 inhibitors including CANA are useful therapeutic agents for Asian T2DM patients whose insulin resistance is caused by mild increase of visceral fat.

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Author contributions

All authors were involved in the design of the study. Y.K. was responsible for data collection, data analysis, interpretation of the results, and writing of the first draft of the manuscript. S.S., H.M., A.Y., K.A., A.K., and K.H. contributed to data collection, data interpretation, and critical revision of the manuscript. Y.T. supervised the study. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of the manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.029.

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