Original Article

Characterization of Metabolic Parameters in Responders and Nonresponders Treated with Canagliflozin Monotherapy in Drug-naive Subjects with Type 2 Diabetes

Eiji Kutoh[1,2,3], Asuka Wada[2], Teruma Murayama[1], Jyunka Hayashi[2]

[1]Division of Clinical Research, Biomedical Center, Tokyo, [2]Department of Internal Medicine, Division of Endocrinology and Metabolism, Gyoda General Hospital, Saitama, [3]Department of Internal Medicine, Division of Diabetes and Metabolism, Higashitotsuka Memorial Hospital, Yokohama, Japan

Abstract

Objectives: The aim of this project is to compare the effect of canagliflozin monotherapy on metabolic parameters between responders and nonresponders with this drug. This study is a prospective, unblinded, observational study. **Subjects and Methods:** Drug-naïve patients with type 2 diabetes mellitus received only 50–100 mg/day canagliflozin for 3 months ($n = 39$). They were divided into two groups according to the novel "A1c index" to assess glycemic efficacies; responders ($n = 24$) and nonresponders ($n = 15$). **Results:** At baseline, glycated hemoglobin (HbA1c) and fasting blood glucose (FBG) were significantly higher and homeostatic model assessment (HOMA)-B and body mass index (BMI) were significantly lower in responders. In both groups, similar, significant reductions of BMI (−1.9% with responder and −1.8% with nonresponder) and HOMA-R (−35.8% for responder and –31.5% for nonresponder) were observed. However, differences were seen with other parameters as follows: 1) responders: significant reductions of HbA1c (10.95%–8.44%), FBG (−29.6%) or free fatty acid (FFA) (−16.2%), and significant increases of HOMA-B (79.7%) were observed. 2) Nonresponders: significant reductions of serum uric acid (UA) (−8.6%) levels were seen. Significant correlations were observed between the baseline levels of serum UA and those of HOMA-B ($R = 0.7259$). However, this link became uncorrelated with the treatment with canagliflozin. **Conclusions:** These results suggest that (1) responders with canagliflozin have lower BMI and beta-cell function. Reductions of body weight with canagliflozin were not associated with its glycemic efficacy, (2) reduced FFA levels and enhanced insulin sensitivity/beta-cell function could be a potential mechanism of good glycemic efficacy of canagliflozin, and (3) serum UA might be involved in modulating beta-cell function during canagliflozin treatment.

Keywords: Canagliflozin, responders and nonresponders, sodium-glucose co-transporter 2 inhibitors

Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of orally administered drugs for type 2 diabetes mellitus (T2DM).[1-3] Canagliflozin is one of the SGLT-2 inhibitors available in many countries including Japan, USA, and Europe. Similar glycemic and nonglycemic efficacies were reported in comparison to other SGLT-2 inhibitors.[4-6] With the simple mechanism of discarding glucose into the urine (correcting glucotoxicity),[7] canagliflozin was shown to ameliorate impaired beta-cell function and insulin resistance.[4-6] Canagliflozin has been shown to possess some nonglycemic benefits such as weight reduction, blood pressure control, diuretic action, renal protection, and uric acid (UA) reduction.[4-6] However, as expected from its mechanism of action, this drug is associated with higher incidence of certain adverse events including genital mycotic infections, urinary tract infections, osmotic diuretic-related adverse events, and volume depletion-related adverse events.[8] Canagliflozin and other SGLT-2 inhibitors are currently used as add-on therapy to metformin or other drugs as part of dual or triple therapy. However, it could also be used as alternative first-line options in patients with contraindications or intolerance to metformin.[9]

Regarding its glycemic efficacy, physicians often experience distinct response (responders and nonresponders) with

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_578_17

Address for correspondence: Dr. Eiji Kutoh, Division of Clinical Research, Biomedical Center, Tokyo, Japan. E-mail: ekuto@excite.com

How to cite this article: Kutoh E, Wada A, Murayama T, Hayashi J. Characterization of metabolic parameters in responders and nonresponders treated with canagliflozin monotherapy in drug-naive subjects with Type 2 diabetes. Indian J Endocr Metab 2018;22:185-90.

canagliflozin or other oral hypoglycemic drugs.[10] However, it remains unclear whether other nonglycemic parameters (e.g., body weight, UA) are regulated according to its glycemic efficacy. This study was initiated to explore the effect of canagliflozin on metabolic parameters in relation to that on glycemic control. It makes sense to perform this kind of study with drug-naïve patients as monotherapy to eliminate the influences of other drugs as much as possible. As an initial step toward investigating this question, canagliflozin 50–100 mg/day monotherapy was performed with drug-naïve patients with T2DM, and the effects on a number of glycemic and nonglycemic parameters were investigated in two groups representing distinct response to canagliflozin (responders and nonresponders). Since the response to canagliflozin was shown to be baseline glycated hemoglobin (HbA1c) dependent,[9] we used a novel index called A1c index[10] to evaluate the glycemic efficacy of canagliflozin.

Subjects and Methods

Subjects

This study is a prospective, un-blinded, observational study. The protocol was approved by the Institutional Review Board of Gyoda General Hospital, and informed consent was obtained from the patients. Anti-glutamic acid decarboxylase (GAD) antibody was measured in some suspected patients to exclude those with type 1 diabetes mellitus (T1DM) (Mitsubishi BML, Tokyo, Japan). Inclusion criteria were those who were newly diagnosed with T2DM or those who were previously diagnosed but were untreated. The diagnosis was made according to the criteria of the Japan Diabetes Society.[11] All the patients had not received any regularly prescribed drugs in the past 6 months before the study initiation. Exclusion criteria were those with clinically significant impaired renal (creatinine [CRE] >1.5 mg/dl) or hepatic (glutamic oxalacetic transaminases/glutamic pyruvic transaminases [AST/ALT] >70/70 IU/l) functions, history of heart disorders, severe hypertension (blood pressure above 160/100 mmHg), T1DM, and pregnancy. Other exclusion criteria were those who require other medical treatments (e.g., peripheral vascular disease, fracture, urosepsis, catabolic state, or other serious disorders). No patients had a previous or recent history of amputations.

These patients were recruited from the Outpatient Department of Diabetes and Endocrinology of Gyoda General Hospital (Saitama, Japan) and other related hospitals. Initially, 53 patients were enrolled in this study. Nine patients had stopped visiting the hospitals without any reasons. Five out of 44 patients dropped out due to tolerability problems and/or adverse events. These dropout patients were excluded from data analysis. The final analysis was performed with 39 patients. Female patients ($n = 10$) took 50 mg/day due to adverse events that frequently occur with women (e.g., urogenital infections), while male patients ($n = 29$) took 100 mg/day. The patients were encouraged to follow the exercise and diet suggested by the American Diabetes Association.[12] Compliance of diet and exercise was monitored by the authors of this manuscript once a month when they visited the hospital. This study was conducted in accordance with principles of Good Clinical Practice. A novel index called "A1c index" where the changes of HbA1c levels (ΔHbA1c) were adjusted by the baseline HbA1c levels (ΔHbA1c/baseline HbA1c),[10] was used to assess the glycemic efficacy of canagliflozin. Patients with A1c index ≤−0.0975 were termed as responders while those with A1c index >−0.0975 were termed as nonresponders. This cutoff value was the borderline where the changes of HbA1c levels become significant or nonsignificant.

Laboratory measurements

The primary end point was the changes in HbA1c levels from baseline to 3 months. HbA1c values were shown with National Glycoprotein Standardization Program standardization.[13,14] The secondary end point included fasting blood glucose (FBG), insulin, homeostatic model assessment (HOMA)-R, HOMA-B, body mass index (BMI), serum UA, urine UA excretion, total cholesterol (T-C), triglyceride (TG), nonhigh-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and free fatty acid (FFA). For the assessment of the urine UA excretion levels, spot urine UA/CRE ratio (u-UA/u-CRE mmol/mmol) was used.[15] Blood and urine samples were collected at the fasting state before breakfast, and standard techniques were used to measure these parameters as described previously.[16] Measurements of HbA1c and FBG were performed once a month. Insulin (measured by the kit from Abbott Japan, Tokyo) was measured at the start (baseline) and at the end (3 months) of the study. HOMA-R and HOMA-B were calculated as described;[17] HOMA-R = insulin × FBG/405, HOMA-B = insulin × 360/(FBG-63).

Hepatic (AST, ALT, alkaline phosphatase, and gamma-glutamyl transpeptidase) and renal (blood urea nitrogen and CRE) functions were also monitored 1 month after administration of canagliflozin. In the case of any significant increases of these parameters, administration of these drugs was planned to discontinue. None of the patients dropped out due to the elevations of hepatic or renal parameters.

Data analyses

The change was calculated as the values at 3 months (posttherapy) minus those at baseline (pretherapy). When the data were normally distributed, paired Student's *t*-test was used to analyze the changes in each group (intragroup differences). When the data were not normally distributed, Wilcoxon signed-rank test was employed. Unpaired Student's *t*-test was used to compare the baseline values in these two groups (responders and nonresponders). Simple regression analysis was performed to analyze the correlations of the changes of measured parameters. The results were expressed as the mean ± standard deviation. Throughout the statistical analysis, values of $P < 0.05$ were regarded as being statistically significant. Values of $0.05 \leq P < 0.1$ were considered to be statistically insignificant but to have a tendency to possess differences or correlations. Statistical analysis was performed

with PAST program from the University of Oslo (https://folk.uio.no/ohammer/past/).

Results

Effect of canagliflozin monotherapy on glycemic and nonglycemic parameters in overall subjects

At 3 months, significant reductions of FBG and HbA1c levels with canagliflozin monotherapy were observed in overall patients (for each value and statistical significance, [Table 1]). To assess the effect of canagliflozin on insulin resistance and beta-cell function, changes of HOMA-R and HOMA-B levels were measured. Significant reductions of HOMA-R and increases of HOMA-B levels were seen [Table 1]. Effects of canagliflozin on nonglycemic parameters including lipid, UA, and body weight were investigated. Among the parameters tested, significant reductions of BMI and serum UA levels were observed. Insignificant reductions of TG and increases of urine UA excretion levels were noted [Table 1]. Blood pressure was also monitored. At least, reduced levels of blood pressure were noted with canagliflozin. However, the variations were so large; therefore, no solid data have been obtained regarding the effect of canagliflozin on blood pressure (results not shown).

Baseline characteristics of metabolic parameters between responders and nonresponders treated with canagliflozin.

Then, the patients were divided into two groups according to the novel "A1c index" as described in Subjects and methods; responders (A1c index ≤ -0.0975) and nonresponders (A1c index > -0.0975). Baseline characteristics were compared between these two groups. As indicated in Table 2, HbA1c and FBG levels were significantly higher in responders, while insulin, HOMA-B or BMI levels were significantly higher in nonresponders. HOMA-R levels had a tendency to be lower in responders. Other parameters showed no statistically significant differences between these two groups.

Differential regulation of metabolic parameters between responders and nonresponders treated with canagliflozin.

At 3 months, in both groups, significant reductions of HOMA-R and BMI levels were observed [Table 3a and b]. No intergroup differences were noted in the changes of these parameters between the two groups (results not shown). Significant increases of HOMA-B and decreases of FFA levels were seen in responders [Table 3a]. Little, if any, changes of lipid parameters including T-C, HDL-C, non-HDL-C, or LDL-C were noted in these two groups except that insignificant decreases of TG levels were seen in nonresponders [Table 3a and b]. Regarding UA, significant decreases of serum UA levels were observed in nonresponders, whereas little changes in serum UA levels were noted in responders [Table 3a and b]. Significant increases of urine UA excretion levels were seen in responders, whereas insignificant increases of urine UA excretion levels were noted in nonresponders [Table 3a and b]. Significant correlations were observed between the baseline levels of serum UA and HOMA-B in responders [Figure 1a]. However, at 3 months with canagliflozin, the correlations had been lost [Figure 1a]. By contrast, no correlations were noted between serum UA and HOMA-B levels at baseline or at 3 months in nonresponders [Figure 1b].

Table 1: Changes of glycemic and nonglycemic parameters with 3 month's treatment with canagliflozin monotherapy in drug-naïve overall patients with type 2 diabetes mellitus (*n*=39). Paired Student's *t*-test was used to analyze the changes

	Baseline	3 months	*P*	% changes
Age	53.1±14.0	-	-	-
F/M	10/29	-	-	-
A1c index	-	-0.144±0.517	-	-
HbA1c (%)	-	8.33±1.66	<0.00001	-16.3
FBG (mg/dl)	193.4±66.7	147.1±32.4	<0.00001	-23.9
Insulin (mU/ml)	9.45±7.17	8.42±6.26	0.077	-10.8
HOMA-R	4.50±9.15	2.99±2.17	<0.00001	-33.5
HOMA-B	31.91±30.12	41.52±38.20	<0.03	30.1
BMI	26.84±5.56	26.34±5.50	<0.00001	-1.8
UA (mg/dl)	5.35±1.21	5.07±1.19	<0.05	-5.2
u-UA/u-CRE	0.474±0.643	0.653±0.643	NS	37.7
T-C (mg/dl)	219.1±38.7	215.1±39.1	NS	-1.8
TG (mg/dl)	187.2±134.8	165.6±95.8	0.057	-11.5
HDL-C (mg/dl)	52.4±13.3	54.4±12.2	NS	3.8
Non-HDL-C (mg/dl)	166.6±38.3	160.7±39.6	NS	-3.5
LDL-C (mg/dl)	140.2±37.8	137.1±34.6	NS	-2.2
FFA (eE/l)	0.771±0.330	0.665±0.348	NS	-13.7

Table 2: Comparison of baseline characteristics of glycemic and nonglycemic parameters between nonresponders (*n*=15) and responders (*n*=24) treated with canagliflozin monotherapy. Unpaired Student's *t*-test was used to compare the baseline values in these two groups (responders and nonresponders)

	Non-responders	Responders	*P*
Age	53.2±14.0	53.0±14.0	NS
F/M	6/9	5/19	NS
HbA1c (%)	8.38±1.42	10.95±2.39	<0.0002
FBG (mg/dl)	166.6±38.9	210.2±71.5	<0.002
Insulin (mU/ml)	14.03±8.89	6.59±4.56	<0.02
HOMA-R	5.93±4.22	3.60±3.28	0.058
HOMA-B	53.37±37.47	18.51±14.01	<0.0002
BMI	27.92±5.84	26.17±5.47	<0.05
UA (mg/dl)	5.76±1.27	5.10±1.19	NS
u-UA/u-CRE	0.526±0.801	0.440±0.801	NS
T-C (mg/dl)	215.3±25.8	221.4±46.2	NS
TG (mg/dl)	216.7±128.2	168.7±141.8	NS
HDL-C (mg/dl)	50.1±11.5	53.9±14.6	NS
Non-HDL-C (mg/dl)	165.2±25.5	167.5±45.8	NS
LDL-C (mg/dl)	136.2±32.5	142.7±41.7	NS
FFA (eE/l)	0.765±0.425	0.776±0.251	NS

Table 3a: Changes of glycemic and nonglycemic parameters with 3 month's treatment with canagliflozin monotherapy in nonresponders and responders. Responders (*n*=24). Paired Student's *t*-test was used to analyze the changes in each group (intragroup differences)

	Baseline	3 months	*P*	% changes
Age	53.0±14.0	-	-	-
F/M	5/19	-	-	-
A1c index	-	-0.219±0.146		-
HbA1c (%)	10.95±2.39	8.44±1.89	<0.00001	-22.9
FBG (mg/dl)	210.2±71.5	147.8±38.0	<0.00001	-29.6
Insulin (mU/ml)	6.59±4.56	6.56±4.72	NS	-0.4
HOMA-R	3.60±3.28	2.31±1.51	<0.01	-35.8
HOMA-B	18.51±14.01	33.28±33.07	<0.03	79.7
BMI	26.17±5.47	25.67±5.36	<0.002	-1.9
UA (mg/dl)	5.10±1.19	4.96±1.26	NS	-2.7
u-UA/u-CRE	0.440±0.801	0.581±0.801	<0.05	32
T-C (mg/dl)	221.4±46.2	217.3±47.7	NS	-1.8
TG (mg/dl)	168.7±141.8	152.7±85.8	NS	-9.4
HDL-C (mg/dl)	53.9±14.6	56.8±12.7	NS	5.3
Non-HDL-C (mg/dl)	167.5±45.8	160.5±45.4	NS	-4.1
LDL-C (mg/dl)	142.7±41.7	137.1±41.6	NS	-3.9
FFA (eE/l)	0.776±0.251	0.650±0.397	<0.05	-16.2

Table 3b: Changes of glycemic and nonglycemic parameters with 3 month's treatment with canagliflozin monotherapy in nonresponders and responders. Nonresponders (*n*=15). Paired Student's *t*-test was used to analyze the changes in each group (intragroup differences)

	Baseline	3 months	*P*	% changes
Age	53.2±14.0	-	-	-
F/M	6/9	-	-	-
A1c index	-	-0.033±0.052	-	-
HbA1c (%)	8.38±1.42	8.16±1.38	NS	-2.6
FBG (mg/dl)	166.6±38.9	146.0±23.4	<0.02	-12.3
Insulin (mU/ml)	14.03±8.89	11.39±7.67	<0.05	-18.8
HOMA-R	5.93±4.22	4.06±2.76	<0.02	-31.5
HOMA-B	53.37±37.47	54.71±44.36	NS	2.5
BMI	27.92±5.84	27.40±5.85	<0.0002	-1.8
UA (mg/dl)	5.76±1.27	5.26±1.10	<0.05	-8.6
u-UA/u-CRE	0.526±0.801	0.761±0.801	NS	44.6
T-C (mg/dl)	215.3±25.8	211.6±23.2	NS	-1.7
TG (mg/dl)	216.7±128.2	186.3±110.9	0.071	-14
HDL-C (mg/dl)	50.1±11.5	50.5±11.7	NS	0.7
Non-HDL-C (mg/dl)	165.2±25.5	161.1±20.5	NS	-2.4
LDL-C (mg/dl)	136.2±32.5	137.0±22.1	NS	0.5
FFA (eE/l)	0.765±0.425	0.687±0.378	NS	-10.1

Discussion

Different response to canagliflozin

With respect to responders and nonresponders with hypoglycemic drugs, the patients are traditionally divided into two groups according to the reduction of HbA1c ≥1% or <1%, respectively.[10,18] Simply, dividing the patients in this fashion may constitute a fundamental problem since the changes of HbA1c levels were shown to be dependent on the baseline HbA1c levels in many drugs including canagliflozin.[9] Thus, we previously used a novel index called "A1c index" to overcome this problem.[10,18] However, the validity of A1c index would require further well-designed studies. Approximately, 38% (15 out of 39 patients) of the drug-naïve patients with T2DM were nonresponders with canagliflozin according to our analysis [Table 2]. In spite of the high rate of nonresponders, the glucose-lowering efficacy of canagliflozin is rather strong with responders (HbA1c reduced from 10.95% to 8.44% in 3 months). Baseline BMI levels were significantly lower in responders. Thus, this drug may be more effective and useful with lean populations including Asians. It is of interest to investigate whether any differences exist between responders and nonresponders in glycemic and nonglycemic efficacies among different SGLT-2 inhibitors. Since canagliflozin is widely used worldwide, efficacy across different ethnicities will be of great interest.

Nonglycemic efficacies of canagliflozin in responders and nonresponders

One of the most beneficial nonglycemic efficacies of SGLT-2 inhibitors including canagliflozin is the reduction of body weight [Table 1].[19] Many diabetes drugs, including insulin, sulfonylureas, and thiazolidinediones cause weight gain.[9] Therefore, drugs that possess reducing effects on body weight are particularly important. So far, few studies report the relationship between the body weight reductions with canagliflozin and its effects on glycemic control. Our investigation on this issue unexpectedly revealed that the glycemic efficacies of canagliflozin were not associated with the degrees of body weight reductions (responders and nonresponders have similar weight reductions and insulin-sensitizing capacities [Table 3a and b]).

Serum and urine UA levels displayed an interesting pattern. Serum UA levels significantly decreased in nonresponders, while they had no changes in responders [Table 3a and b]. Urine UA excretion levels significantly increased in responders, whereas they insignificantly decreased in nonresponders [Table 3a and b]. These results suggest that, in responders, UA synthesis and/or production may be upregulated. In responders, significant correlations between the baseline levels of serum UA and those of HOMA-B were seen, while this is not the case with nonresponders [Figure 1a and b]. These observations might support our previous hypothesis that UA may enhance beta-cell function through its antioxidant effect.[20] Interestingly, significant correlations (between the baseline levels of serum UA and those of HOMA-B) had been lost on treatment of canagliflozin in responders [Figure 1a]. One potential explanation for this phenomenon is that, with canagliflozin, beta-cell function is enhanced through relieving glucotoxicity,[7,9] thereby beta-cell activation by UA is no

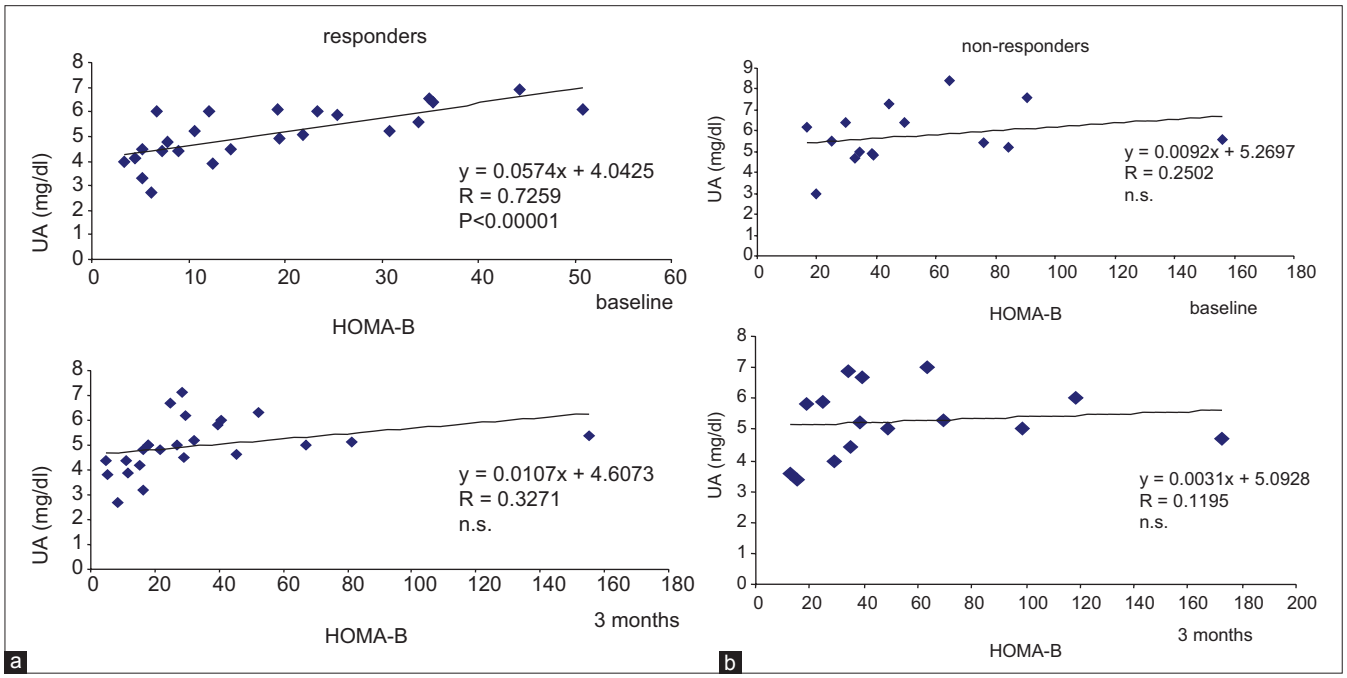

Figure 1: Link between serum uric acid and beta-cell function. Simple regression analysis was performed between the serum uric acid and homeostasis model assessment-B levels at baseline and at 3 months. (a) Responders ($n = 24$). (b) Nonresponders ($n = 15$). Values of $P < 0.05$ were regarded as being statistically significant

longer required. Emerging evidence has suggested that UA is beneficial through its antioxidant effect.[20-22] Molecular and cellular approaches are required to further consolidate this issue.

In this study, no significant effects on lipid profiles were noted with canagliflozin, though TG levels have a tendency to decrease in nonresponders [Tables 1 and 3a, b]. Effects on lipid parameters with SGLT-2 inhibitors, in general, are inconsistent and nonsignificant.[1-3]

Significant reductions of FFA levels were observed in responders [Table 3a]. Elevated FFA levels are known to increase insulin resistance[23,24] and to decrease beta-cell function through lipotoxicity.[25,26] In responders, modulation of insulin resistance and beta-cell function through the decreased FFA levels could be one of the potential mechanisms of good glycemic efficacies of canagliflozin.

The limitations and strengthens of the study

There are a number of limitations with this study. It is an observational (though prospective) study with small numbers of patients and with short study duration (3 months). Dropout rate due to adverse events (5 out of 44 patients) or without any reasons (9 out of 53 patients) is high. Further, male patients took 100 mg/day while female patients received 50 mg/day. This can result in inaccurate evaluation of its efficacy. However, one can assume that the observed changes were caused exclusively by canagliflozin based on the design of the study (monotherapy with drug-naïve patients). Further randomized, double-blind, placebo-controlled, and longer period study with increased number of patients will be required to strengthen the finding of this study.

Conclusions

The conclusions of this study are (1) responders with canagliflozin have lower BMI and beta-cell function. Reductions of body weight with canagliflozin were not associated with its glycemic efficacy, (2) reduced FFA levels and enhanced insulin sensitivity/beta-cell function could be a potential mechanism of good glycemic efficacy of canagliflozin, and (3) serum UA might be involved in modulating beta-cell function during canagliflozin treatment.

Acknowledgment

The authors would like to thank Mitsuru Hirate, Takashi Suzuki, Rika Kusudo, Yui Takizawa, Mai Kaneko, and Hiroshi Kawashima, for help and valuable discussions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011;32:515-31.
2. Whalen K, Miller S, Onge ES. The role of sodium-glucose co-transporter 2 inhibitors in the treatment of type 2 diabetes. Clin Ther 2015;37:1150-66.
3. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in

glucose homeostasis: A new path towards normalizing glycaemia. Diabetes Obes Metab 2012;14:5-14.
4. Rosenthal N, Meininger G, Ways K, Polidori D, Desai M, Qiu R, *et al.* Canagliflozin: A sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann N Y Acad Sci 2015;1358:28-43.
5. Brunton S, Reid TS. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, for the management of type 2 diabetes. Hosp Pract (1995) 2014;42:96-108.
6. Kuriyama C, Ueta K, Arakawa K. Pharmacological and clinical profile of a novel SGLT2 inhibitor canagliflozin hydrate (CANAGLU®). Nihon Yakurigaku Zasshi 2015;146:332-41.
7. Takahara M, Shiraiwa T, Matsuoka TA, Katakami N, Shimomura I. Ameliorated pancreatic β cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. Endocr J 2015;62:77-86.
8. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes Metab 2014;40:S28-34.
9. Kutoh E, Wada A, Murayama T, Takizawa Y. Canagliflozin as an initial therapy in drug-naïve subjects with type 2 diabetes mellitus: A potential involvement of atherogenic lipids in its glycemic efficacy. Drugs R D 2017;17:313-20.
10. Kutoh E, Kaneoka N, Hirate M. Alogliptin: A new dipeptidyl peptidase-4 inhibitor with potential anti-atherogenic properties. Endocr Res 2015;40:88-96.
11. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, *et al.* Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010;1:212-28.
12. Ma Y, Olendzki BC, Merriam PA, Chiriboga DE, Culver AL, Li W, *et al.* A randomized clinical trial comparing low-glycemic index versus ADA dietary education among individuals with type 2 diabetes. Nutrition 2008;24:45-56.
13. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE, *et al.* The national glycohemoglobin standardization program: A five-year progress report. Clin Chem 2001;47:1985-92.
14. Miedema K. Towards worldwide standardisation of HbA1c determination. Diabetologia 2004;47:1143-8.
15. Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Ka T, Fukuchi M, *et al.* A simple method of selecting gout patients for treatment with uricosuric agents, using spot urine and blood samples. J Rheumatol 2002;29:1937-41.
16. Kutoh E, Fukushima T. Insulin-dependent actions of pioglitazone in newly diagnosed, drug naïve patients with type 2 diabetes. Endocrine 2009;35:333-40.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC, *et al.* Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
18. Kutoh E. Differential regulations of lipid profiles between Japanese responders and nonresponders treated with pioglitazone. Postgrad Med 2011;123:45-52.
19. Scheen AJ, Paquot N. Metabolic effects of SGLT-2 inhibitors beyond increased glucosuria: A review of the clinical evidence. Diabetes Metab 2014;40:S4-S11.
20. Kutoh E, Hori T. Effect of pioglitazone on serum uric acid levels in newly diagnosed, drug-naïve patients with type 2 diabetes. Endocr Res 2012;38:151-9.
21. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: A hypothesis. Proc Natl Acad Sci U S A 1981;78:6858-62.
22. Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med 1993;14:615-31.
23. Boden G. Fatty acids and insulin resistance. Diabetes Care 1996;19:394-5.
24. Olson AL. Insulin resistance: Cross-talk between adipose tissue and skeletal muscle, through free fatty acids, liver X receptor, and peroxisome proliferator-activated receptor-α signaling. Horm Mol Biol Clin Investig 2013;15:115-21.
25. Giacca A, Xiao C, Oprescu AI, Carpentier AC, Lewis GF. Lipid-induced pancreatic β-cell dysfunction: Focus on *in vivo* studies. Am J Physiol Endocrinol Metab 2011;300:E255-62.
26. Unger RH. Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Genetic and clinical implications. Diabetes 1995;44:863-70.