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Comparison of canagliflozin and teneligliptin on energy intake and body weight in Japanese patients with Type 2 diabetes: a subanalysis of the CANTABILE study

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Abstract

Background While the Sodium-glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) are widely used for the glycemic control in type 2 diabetes mellitus, the differences in the effects of SGLT2 inhibitors and DPP4 inhibitors on energy intake and diabetes-related indicators are unclear.

Methods This was a subanalysis of the CANTABILE study which compared the effects of canagliflozin and teneligliptin on metabolic factors in Japanese patients with Type 2 diabetes. The changes at 24 weeks from the baseline of the diabetes-related indicators including Hemoglobin A1c (HbA1c), energy intake and body weight were compared between the canagliflozin and teneligliptin groups.

Results Seventy-five patients in the canagliflozin group and 70 patients in the teneligliptin group were analyzed. A significant decrease in HbA1c was observed in both groups. In the teneligliptin group, although energy intake was significantly reduced, there was no significant change in body weight. Conversely, in the canagliflozin group, although energy intake tended to increase, body weight significantly decreased.

Conclusion Canagliflozin and teneligliptin have different effects on the dietary status of patients with Type 2 diabetes. Our result suggests that canagliflozin can manage blood glucose without weight gain, even with increased energy intake.

Keywords Body weight, Sodium-glucose co-transporter 2 inhibitor, Energy intake, Dipeptidyl peptidase-4 inhibitor, Type 2 diabetes

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Background

Weight loss is associated with a reduction in mortality in overweight patients with type 2 diabetes, can improve glycaemia and related comorbidities [1]. The effects of antidiabetes drugs on body weight vary depending on the type of drugs. Although dipeptidyl peptidase 4 (DPP4) inhibitors have been shown to have less effect on body weight [2, 3], increased fat intake has also been shown to worsen glycemic control and weight control, and thus the therapeutic effect of DPP4 inhibitors on Type 2 diabetes may be affected by dietary conditions [4]. On the other hand, patients receiving sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown weight loss in many clinical studies [5–8], and overseas, Ferrannini et al. reported that 90-week administration of SGLT2 inhibitors in patients with Type 2 diabetes resulted in decreased blood glucose and body weight even with increased calorie intake [9]. These results are considered to be related to the calorie loss due to the urinary glucose excretion by SGLT2 inhibitors and SGLT2 inhibitors may be able to control blood glucose and body weight regardless of dietary adherence. It has also been reported that calorie loss by SGLT2 inhibitors leads to improvement of liver function markers through reduction of liver fat [10–13] and that the effect of SGLT2 inhibitors on liver function may also be less affected by dietary adherence. However, the effects of SGLT2 inhibitors on energy intake and the relationship between energy intake and body weight, blood glucose, and liver function markers has not been fully elucidated. Thus, we compared the effects of CAN and TNL on energy intake and the associations between energy intake and diabetes-related parameters and liver function markers in the Japanese patient with Type 2 diabetes in the CANTABILE study.

Methods

Design

The CANTABILE study was a prospective, multicenter, open-label, randomized, parallel-group comparison study conducted across 38 sites in Japan (UMIN000030343). The study rationale, design, and methods have been reported previously [14]. This study was conducted in compliance with the articles of the Declaration of Helsinki (revised in October 2013) and in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labor, and Welfare in Japan. The investigator provided sufficient explanation to the patients before obtaining written informed consent. In accordance with the laws on clinical research in Japan, the protocol of this study was approved by the Nara Medical University Certified Review Board (approval number: nara0002).

Intervention

Eligible participants were dynamically assigned to either the CAN group or the TNL group, based on the following assignment factors: HbA1c, fasting triglyceride, BMI, systolic blood pressure, and whether or not metformin treatment. In each group, 100 mg of CAN or 20 mg of TNL was orally administered once a day for 24 weeks in addition to their ongoing diabetes treatment. If necessary, the TNL dose was increased up to a maximum of 40 mg/day. The concomitant and ongoing diet and exercise therapies prior to the study were continued without modification from at least 8 weeks before the date of informed consent until week 24 of treatment.

Endpoints

The changes at 24 weeks from the baseline of the diabetes-related indicators below were compared between the two groups: ΔHbA1c, ΔHOMA-IR, Δbody weight, Δketone body, Δenergy intake, Δprotein intake, Δfat intake, Δcarbohydrates intake, and Δsucrose intake assessed by the brief-type self-administered diet history questionnaire (BDHQ). The BDHQ has an acceptable level of validity in Japanese population and has been used in several studies. [15–18]

Patients

Patients who met the eligibility criteria and did not meet the exclusion criteria were enrolled. The inclusion criteria were as follows: 1) written informed consent provided, 2) age ≥ 20 y.o. and < 85 y.o, 3) HbA1c ≥ 7.0% and < 10.0%, 4) has at least one of the following metabolic risk factors: a) BMI ≥ 25 kg/m^2, b) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or c) serum triglyceride ≥ 150 mg/dL or HDL-C < 40 mg/dL, and 5) has not taken antidiabets medication for 8 weeks before consent or has not changed metformin monotherapy 8 weeks before consent. The exclusion criteria were as follows: 1) Type 1 diabetes, 2) BMI < 22 kg/m^2, 3) hypersensitivity to TNL or CAN, 4) requirement for insulin therapy for blood glucose management, 5) congestive heart failure (New York Heart Association functional classification III or IV), 6) pregnant, breast feeding, or possibly pregnant, 7) malignant tumors diagnosed or suspected, 8) taking prohibited medications or therapy defined in the study protocol.

Statistics

This study was a subanalysis of the CANTABILE study [14], and the full analysis set (FAS) defined in the study was used for the analysis. The FAS population included patients whose data was collected, at least, one point other than baseline. The Wilcoxon rank sum test was

used to compare continuous variables, and the chi-square test was used to compare categorical variables. The Wilcoxon signed-rank test was used to compare various data at week 0 and week 24. The significance level was set to be <0.05 on both sides. Statistical analyses were performed using SAS® software.

Results

Patient characteristics

Of the 187 enrolled patients, 162 patients were eligible (Fig. 1). Eighty-two patients were assigned to the CAN group, and 75 of them were included in the analysis as FAS. Eighty patients were assigned to the TNL group, and 70 of them were included in the analysis. There was no significant difference in patient characteristics between the CAN and TNL groups (Table 1).

Diabetes-related indicators

A significant decrease in HbA1c was observed in both groups (Table 2). Body weight and HOMA-IR were not significantly changed in the TNL group, but were significantly reduced in the CAN group. Ketone body and Ht were not significantly changed in the TNL group, but were significantly increased in the CAN group. Regarding

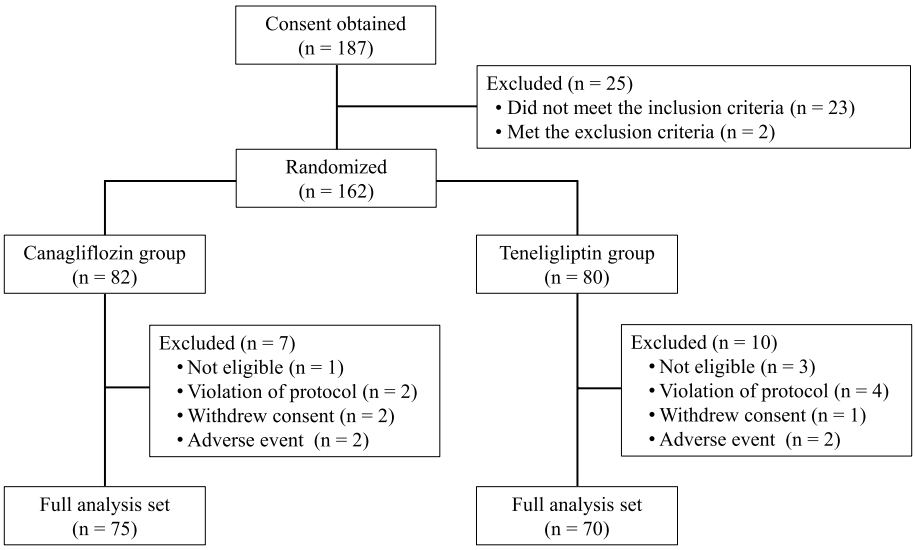


Fig. 1 Patient flow. The full analysis set (FAS) population included patients whose data was collected, at least, one point other than baseline

Table 1 Patient characteristics

	Canagliflozin group (*n* = 75)	Teneligliptin group (*n* = 70)	*p* value
Sex (male), n (%)	51 (68.0%)	47 (67.1%)	1.000
Age, mean ± SD	57.2 ± 11.5	55.2 ± 11.4	0.5277
Height (cm), mean ± SD	165.5 ± 9.2	165.5 ± 9.5	0.9984
Body weight (kg), mean ± SD	79.0 ± 15.2	79.2 ± 16.7	0.7848
BMI, mean ± SD	28.7 ± 4.7	28.8 ± 4.8	0.854
HbA1c (%), mean ± SD	7.7 ± 0.6	7.8 ± 0.8	0.3706
HDL-C (mg/dL), mean ± SD	52.1 ± 12.1	53.6 ± 11.4	0.3532
Triglyceride (mg/dL), mean ± SD	202.1 ± 195.0	169.7 ± 115.5	0.5336
Systolic blood pressure (mmHg), mean ± SD	140.7 ± 19.0	137.8 ± 14.7	0.4580
Diastolic blood pressure (mmHg), mean ± SD	83.4 ± 10.5	82.7 ± 9.9	0.7454
Dyslipidemia, n (%)	34 (45.3%)	31 (44.4%)	1.000
Hypertension, n (%)	55 (73.3%)	50 (71.4%)	0.8536
Duration of diabetes mellitus (years), mean ± SD	5.9 ± 4.9	6.7 ± 6.3	0.7889
Metformin treatment, n (%)	44 (58.7%)	44 (62.9%)	0.6148

Table 2 Changes in variables

	Canagliflozin			Teneligliptin		
	Baseline	24 weeks	p	Baseline	24 weeks	p
HbA1c (%), mean ± SD	7.7 ± 0.6	7.0 ± 0.6	< 0.0001	7.8 ± 0.8	7.2 ± 0.7	< 0.0001
HOMA-IR, mean ± SD	4.9 ± 6.1	3.5 ± 6.4	< 0.0001	4.0 ± 3.6	3.7 ± 2.8	0.2451
Ketone body (μmol/L), mean ± SD	110.0 ± 113.8	206.4 ± 186.3	< 0.0001	110.2 ± 94	109.8 ± 80.3	0.7946
Body weight (kg), mean ± SD	79.0 ± 15.2	76.6 ± 15.2	< 0.0001	79.2 ± 16.7	79.1 ± 16.4	0.0899
Ht (%), mean ± SD	44.6 ± 3.5	47.2 ± 3.5	< 0.0001	44.9 ± 4.0	44.9 ± 4.3	0.7740
Energy intake (kcal/day), mean ± SD	1747.7 ± 634.3	1859.7 ± 639.8	0.0872	1789 ± 601.7	1620.9 ± 516.9	0.0354
Protein intake (g/day), mean ± SD	66.1 ± 26.9	69.9 ± 29.1	0.1032	67.8 ± 28.4	64.3 ± 26.1	0.2634
Fat intake (g/day), mean ± SD	50.1 ± 18.4	53.1 ± 19.0	0.1355	54.4 ± 23.2	47.9 ± 19.3	0.0105
Carbohydrate intake (g/day), mean ± SD	216 ± 73.2	236.5 ± 83.8	0.1072	230.1 ± 90.8	209.7 ± 75.8	0.1632
Sucrose intake (g/day), mean ± SD	7.8 ± 6.2	8.7 ± 6.6	0.0889	9.0 ± 7.4	8.3 ± 6.0	0.8843
AST (IU/L), mean ± SD	32.1 ± 19.7	25.5 ± 12.0	< 0.0001	30.3 ± 17.7	30.6 ± 20.5	0.9764
ALT (IU/L), mean ± SD	40.4 ± 28.0	30.1 ± 19.6	< 0.0001	41.1 ± 33.1	40.4 ± 36.0	0.4180
γ-GTP (IU/L), mean ± SD	67.6 ± 96.9	47.4 ± 43.9	< 0.0001	54.3 ± 52.6	51.8 ± 51.3	0.2547
Fib 4 index, mean ± SD	1.3 ± 0.8	1.2 ± 0.6	0.1047	1.2 ± 0.6	1.2 ± 0.7	0.2362

AST aspartate transaminase, *ALT* alanine aminotransferase, *FIB4 index* fibrosis-4 index, *γ-GTP* γ-glutamyl transpeptidase, *HOMA-IR* homeostasis model assessment of insulin resistance

the amount of change in each marker, there were significant differences between the two groups for ΔHOMA-IR, Δbody weight, and Δketone body (Fig. 2a). Δ Body weight was not significantly differences between CAN group with metformin use and CAN group without metformin use (-2.9 ± 2.5 kg vs. -2.3 ± 2.6 kg; $p = 0.294$) and between TNL group with metformin use and TNL group without metformin use (0.7 ± 2.1 kg vs. 0.2 ± 2.2 kg; $p = 0.356$).

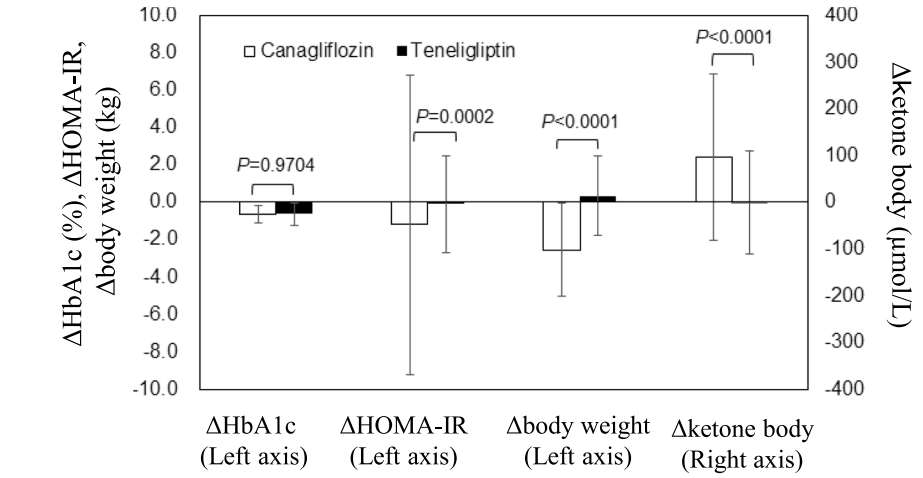
Diet-related indicators

Energy intake was significantly decreased in the TNL group ($p = 0.0354$) and tended to increase in the CAN group ($p = 0.0872$) (Table 2). Therefore, regarding relationship between changes in energy intake and body weight, in the TNL group, although energy intake was significantly reduced, there was no significant change in body weight. In the CAN group, although energy intake tended to increase, body weight significantly decreased. Regarding the intake of the major nutrients, the TNL group showed a significant decrease in fat intake ($p = 0.0105$), and there were no significant changes in other nutrients. In the CAN group, sucrose intake tended to increase ($p = 0.0889$), but there was no significant change in any of the nutrients. Regarding changes in energy and major nutrient intake, Δenergy intake, Δfat intake, and Δcarbohydrate intake showed significant differences between the two groups and all of these measurements decreased in the TNL group and increased in the CAN group. (Fig. 2b). Δenergy intake was not significantly different between CAN group with metformin use and CAN group without metoformin use (161.8 ± 516.2 kcal/day vs. 67.6 ± 403.8 kcal/day; $p = 0.402$) and between TNL group with metformin use and TNL group without metformin use (-15.0 ± 591.9 kcal/day vs. -158.9 ± 314.4 kcal/day; $p = 0.211$).

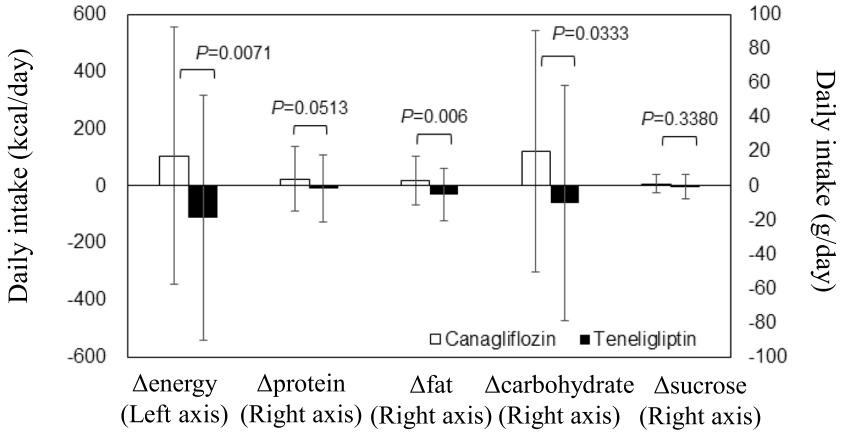
The change in urinary ketones from baseline to 24 weeks were significantly higher in the group of patients who lost more than 3% of their body weight than in the group that did not lose more than 3% (156.7 ± 203.5 μmol/L, $n = 36$ and 22.2 ± 105.7 μmol/L, $n = 34$) ($p = 0.001$). Conversely, there was no significant difference in energy intake (135.0 ± 460.2 kcal/day, $n = 36$ and 66.7 ± 446.2 kcal/day, $n = 34$) ($p = 0.548$).

Liver function markers

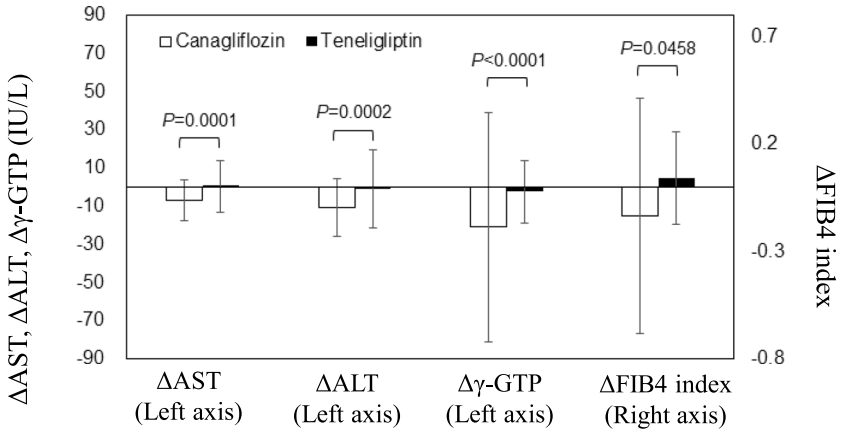
No significant changes were found in any liver function markers in the TNL group (Table 2). In the CAN group, AST, ALT, and γ-GTP were all significantly reduced (all $p < 0.0001$). Regarding the amount of change in liver function markers, there were significant differences in all of ΔAST, ΔALT, Δγ-GTP, and ΔFib4 index between the two groups (Fig. 2c). The decrease in the CAN group was examined in patients with a pre-treatment FIB-4 index of 1.3 or greater and those with a pre-treatment FIB-4 index of less than 1.3, based on the cutoff value of 1.3, which is defined as a risk factor for fibrosis in the NAFLD/NASH Diagnostic Guideline [19]. The results showed a trend toward greater change in the group with a pre-treatment FIB-4 index of 1.3 or greater compared to those with a pre-treatment FIB-4 index of less than 1.3 (-0.28 ± 0.80 and -0.03 ± 0.19 $p = 0.0556$).



a. Changes in diabetic indicators



b. Changes in daily energy and nutrient intake



c. Changes in liver function markers

Fig. 2 Changes in various variables in both groups. Δ: amount change form baseline to 24 weeks, AST: aspartate transaminase, ALT: alanine aminotransferase, FIB4 index: fibrosis-4 index, γ-GTP: γ-glutamyl transpeptidase, HOMA-IR: homeostasis model assessment of insulin resistance

Discussion

In this study, a significant decrease in HbA1c level was observed in both the CAN group and the TNL group; however, there were differences between the two groups in the change in energy intake and in body weight. In the TNL group, there was a significant decrease in energy

intake, but no significant change in body weight. Conversely, in the CAN group, the energy intake tended to increase, but the body weight significantly decreased. In both groups, there was no significant relationship between results with and without metformin. It has been shown that DPP4 inhibitors have no apparent effect on body weight [2, 3] and SGLT2 inhibitors cause body weight loss [5–9]. Our study showed a difference in the effects of DPP4 and SGLT2 inhibitors on body weight in the head-to-head comparison. Regarding energy intake, the TNL group showed a significant decrease, but the CAN group showed a tendency to increase. This suggests that adherence to the diet was relatively strict in the TNL group compared to the CAN group. Kuwata et al. reported that glycemic control by DPP4 inhibitors was influenced by energy intake [4]. The reason for the reduced energy intake in the TNL group may be that dietary adherence was maintained in cases of inadequate glycemic control. For SGLT2 inhibitors, an increase in food intake has been reported in both basic [20, 21] and clinical studies [9, 22, 23]. The reason for this may be a physiological compensatory response to calorie loss due to the urinary glucose excretion caused by SGLT2 inhibitors [9, 24]. Another possibility is that patients receiving SGLT2 inhibitors may not be on a strict diet because glycemic control is maintained. The mechanism by which SGLT2 inhibitors stimulate energy intake is not yet fully understood.

Nakamura et al. showed that Canagliflozin administration to obese and diabetic mice may increase blood ketone levels by activating AMPK activity and enhancing fatty acid oxidation [25].

Increased energy intake may be through the phosphorylation of AMP-activated protein kinase (AMPK) is a cellular energy sensor [26].

In relation to weight loss with canagliflozin, several studies have reported that patients treated with canagliflozin experience a weight loss of approximately 1–3% from baseline [27–29]. However, one report suggests weight gain with dapagliflozin [30], In the study of the integrated CANVAS Program and CREDENCE trials, weight gain and weight stability were observed in some CAN patients [31], Our study suggests that the weight gain observed in the SGLT2 group is not due to compensatory overeating but rather to a lesser increase in ketone production despite SGLT2 use. Conversely, the weight loss observed in the other group is due to an increase in ketones rather than food intake.

The results of this study also suggests that SGLT2 inhibitors can manage blood glucose without weight gain, even with increased energy intake. Some patients with Type 2 diabetes have difficulty adhering to the diet, and SGLT2 inhibitors may benefit the treatment of these patients. Additionally, adherence to diet may contribute to further improve glycemic control in the patients with Type 2 diabetes who are prescribed SGLT2 inhibitor.

In this study, a significant decrease in AST, ALT, and γ-GTP was observed in the CAN group. These results were similar to previous reports of CAN [10–13]. Liver fibrosis is the most important factor in the prognosis of life in patients with nonalcoholic fatty liver disease (NAFLD). The FIB-4 index is a method to evaluate the progress of fibrosis based on data calculated from four blood test parameters (AST, ALT, platelet count, and age). In a relatively small scale study, a decrease in FIB-4 index values was showed in NAFLD patients administered canagliflozin for 6 months [13]. This study showed a significant decrease in FIB4 index was observed in the CAN group compared to that in TNL group in Japanese patients with Type 2 diabetes in the multicenter clinical trial.

In the present results, there was a trend towards a greater effect of Canagliflozin in Fib4 ≥ 1.3 where fibrosis was suspected.

This result suggests that it may be possible to suppress the progression of liver fibrosis in nonalcoholic fatty liver (NAFL) by CAN administration. Studies using MRI have shown a significant reduction in liver fat fraction with CAN administration [12]. Since SGLT2 inhibitors promote the utilization of fatty acids instead of glucose [32], the decrease in liver fat associated with fatty acid oxidation may be involved in the improvement of liver function markers [12, 13]. On the other hand, Inoue et al. reported that there was no correlation between changes in liver fat fraction and changes in liver function markers when CAN was administered [12]. Although it is difficult to clarify, the results of this study suggest the improvement of liver function markers by SGLT2 inhibitors involve mechanisms other than hepatic fat loss.

Limitations

This study has the following limitations. This was an open-label, 24-week study, and the long-term effects of the drug are unknown. Calorie intake is estimated using BDHQ validated in Japan, not measured values. The results of this study need to be interpreted in consideration of these factors. The use of metformin may have an additive effect on canagliflozin energy intake and weight loss. Blood ketone levels were not measured in this study. It is worth noting that Canagliflozin does not affect urine volume [33], a phenomenon that may be due to the activation of ketone body production in the liver.

Conclusions

CAN and TNL have different effects on the dietary status of patients with Type 2 diabetes. Our result suggests that CAN can manage blood glucose without weight gain, even with increased energy intake. SGLT2 inhibitors may benefit in patients with Type 2 diabetes who have difficulty adhering to the diet. On the other hand, it is suggested that appropriate nutritional guidance should be provided to prevent excessive increase in calorie intake when SGLT2 is administered. Moreover, this study suggested that CAN offered a favorable effect on improvement in the FIB-4 index as a surrogate marker of liver fibrosis. Further studies are required to investigate whether SGLT 2 treatment improves the prognosis and prevents liver-related and extrahepatic complications in patients with NAFLD complicated by T2DM.

Abbreviations

ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AST	Aspartate transaminase
BDHQ	Brief-type self-administered diet history questionnaire
BMI	Body mass index
CAN	Canagliflozin
DPP4	Dipeptidyl peptidase-4
FIB4 index	Fibrosis-4 index
FAS	Full analysis set
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
γ -GTP	γ- Glutamyl transpeptidase
LDLC	Low-density lipoprotein cholesterol
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
SGLT2	Sodium-glucose co-transporter 2
TNL	Teneligliptin

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The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MI interpreted data and prepared and finalized manuscript HM, CS, YM and MK contributed to the study design, interpretation of data and manuscript preparation. CS contributed to data acquisition. KN contributed to statistical analysis. TH, SK and MN contributed to data interpretation and manuscript preparation. MK helped to draft the manuscript. KH made substantial contributions to the study concept and project management. All authors have read and approved the final version of the manuscript for publication.

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Availability of data and materials

Clinical data presented in this paper is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nara Medical University (Reference no. CRB5180011). All the experiment was conducted according to the Helsinki Declaration. All participants gave written informed consent before participants' enrollment.

Consent for publication

Not applicable.

Competing interests

HM received grants from Eli Lilly Japan K.K. and Novartis Pharma K.K. CS received grants and personal fees from MSD, Mitsubishi Tanabe Pharma Corporation, Sanofi K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Takeda Pharmaceutical, Taisho Toyama Pharmaceutical Co, Fujifilm Pharma, Abbott Japan, AstraZeneca, Kowa Co, Ono Pharmaceutical Co, and Sumitomo Dainippon Pharma. KN received grants from Philips Japan Co., Terumo Co., and Daiichi Sankyo Co. SK received grants from Mitsubishi Tanabe Pharma Corporation. MN received grants from MSD, Sanofi, Eli Lilly, Novartis and Takeda. MK received compensation as an advisor of the medical consulting firm Reason Why, Inc., payments for lectures from Fuji Yakuhin, Pfizer, Daiichi Sankyo Co., Teijin, Fuji Film, Baxter, and Otsuka Pharmaceutical, and grants from Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., and Fuji Yakuhin. KH received grants, personal fees, and non-financial support from Mitsubishi Tanabe Pharma Co., MSD, Sanofi, Eli Lilly, Novartis, Takeda, Astellas, Daiichi Sankyo, Amgen, Novo Nordisk Pharma, Kyowa Hakko Kirin, Ono, Sumitomo Dainippon, AstraZeneca, Taisho Pharma, Boehringer Ingelheim, and OMRON HEALTHCARE, MSD, Sanofi, Eli Lilly, and Takeda. MI, TH and YM declare no competing interests.

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