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BRIEF REPORT

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Favourable effect of the sodium-glucose co-transporter-2 inhibitor canagliflozin plus the dipeptidyl peptidase-4 inhibitor teneligliptin in combination on glycaemic fluctuation: An open-label, prospective, randomized, parallel-group comparison trial (the CALMER study)

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Abstract

This multicentre, prospective, randomized, open-label, blinded-endpoint, parallel-group, short-term (4–5 weeks) controlled trial was conducted to investigate the superiority of the effect of reducing mean amplitude of glycaemic excursions (MAGE) during meal tolerance tests (MTTs) for the combination of dipeptidyl peptidase-4 (DPP-4) inhibitor and sodium-glucose co-transporter-2 (SGLT2) inhibitor compared with SGLT2 inhibitor monotherapy. Ninety-nine patients with type 2 diabetes who were taking teneligliptin (20 mg/d) were randomized to one of the following two groups: those who switched to 100 mg/d of canagliflozin (SWITCH group) or those who added 100 mg/d of canagliflozin (COMB group). MAGE in the COMB group was significantly decreased compared with that in the SWITCH group (COMB 117.5 ± 39.8 to 92.2 ± 28.0 mg/dL vs SWITCH 110.7 ± 29.8 to 104.2 ± 27.6 mg/dL; $P<0.01$). Mean blood glucose decreased significantly during MTTs in both groups,

although the extent of the reduction was significantly greater in the COMB group (COMB 142.3 ± 28.7 to 119.5 ± 25.1 mg/dL vs SWITCH 146.4 ± 25.5 to 135.5 ± 22.4 mg/dL; $P < 0.01$). SGLT2 inhibitor combined with DPP-4 inhibitor therapy strongly reduced glycaemic fluctuation compared with SGLT2 inhibitor monotherapy.

KEYWORDS
continuous glucose monitoring, DPP-4 inhibitor, randomized trial, SGLT2 inhibitor, type 2 diabetes.

1 | INTRODUCTION

Glycaemic variability and postprandial hyperglycaemia induce oxidative stress[1] and damage endothelial cells. Decreasing the daily glycaemic variability would have a beneficial influence on cardiovascular events and cognitive decline[2] over the long term. Dipeptidyl peptidase-4 (DPP-4) inhibitors have a blood glucose-lowering effect induced via blood glucose-dependent secretion of insulin and suppression of glucagon, and they also suppress glycaemic fluctuation well and are associated with a lower risk of hypoglycaemia. Additionally, sodium-glucose co-transporter-2 (SGLT2) inhibitors have a blood glucose-lowering effect with a low risk of hypoglycaemia via kidney function and blood glucose-dependent urinary glucose excretion.[3] Clinical research showed that the ability of SGLT2 inhibitors to reduce glucose variability was comparable to that of DPP-4 inhibitors in patients with type 2 diabetes (T2DM) who were treated with insulin therapy.[4]

Although both DPP-4 and SGLT2 inhibitors suppress glycaemic variability, there has been little evidence showing their additive effects on daily glucose fluctuation using a glucose monitoring system. The aim of the present study, therefore, was to conduct a multicentre, prospective, randomized, controlled trial using continuous glucose monitoring (CGM) and meal tolerance tests (MTTs) to evaluate changes in daily blood glucose fluctuation when switching to SGLT2 inhibitors or when adding SGLT2 inhibitors in people with T2DM being treated with a DPP-4 inhibitor.

2 | METHODS

2.1 | Study participants

Japanese people with T2DM, aged 20–80 years, with glycated haemogobin (HbA1c) level of 47.5 mmol/mol–74.9 mmol/mol (6.5%–9.0%), body mass index (BMI) ≥23 kg/m^2 and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2, who were treated with 20 mg/d of teneligliptin for ≥12 weeks before enrolment, were eligible for this study. Full details of the inclusion and exclusion criteria are provided in Appendix S1.

2.2 | Study design

We conducted a prospective, randomized, open-label, blinded-endpoint, parallel-group comparison trial at 10 sites that treat people with diabetes in Hokkaido, Japan. Screening started in November 2017 and recruitment was completed in September 2018. Participants were assigned randomly to switch from teneligliptin (20 mg/d) to canagliflozin (100 mg/d; SWITCH group) or to add canagliflozin (100 mg/d) to teneligliptin (COMB group). Dose adjustments were not allowed during the trial. Other anti-hyperglycaemic agents were similarly continued at a constant dose. However, the dose of sulphonylureas and insulin could be reduced if there was a risk of hypoglycaemia.[5] Participant randomization and allocation was performed by a specialized centre that was independent of the participating sites. Allocation factors included age, BMI, HbA1c and eGFR.

This study was performed for 4 to 5 weeks from visit 1 to visit 2. At visit 1 (baseline), blood and urine samples after an overnight fast were collected and CGM (Freestyle Libre Pro®, Abbott Laboratories, Chicago, Illinois) was started. Daily glycaemic control was monitored for the first 14 consecutive days using CGM. The first MTT was performed with four consecutive meals (dinner, breakfast, lunch and dinner) on days 2 to 4, while the participant was taking teneligliptin, after wearing a CGM device. The allocated medication (canagliflozin or a combination of canagliflozin/teneligliptin) was subsequently started instead of teneligliptin in each group. Seven days later, an identical four-meal MTT (second MTT) was performed. At 4 to 5 weeks after visit 1, blood and urine samples were collected again at the end of the study (visit 2; Figure S1). Calories in the meals used for the MTTs were determined based on the participant's ideal body weight (height [m]^2 × 22 kg). Other food, alcohol and drinks, except for water, were prohibited during the MTTs. Participants had to maintain a lifestyle as similar as possible between the first and second MTTs.

The trial was registered with the University Hospital Medical Information Network centre (UMIN000029628) before beginning enrolment. The study protocol was approved by the Ethics Review Board of Hokkaido Hospital, and the study was performed in accordance with the principles of the Declaration of Helsinki and its amendments. All participants provided written informed consent before enrolment.

2.3 | Endpoints and assessments

The primary endpoint was the superiority of the change in mean amplitude of glycaemic excursions (MAGE) during the first and the second MTT (ΔMAGE) in the COMB group compared with the SWITCH group. The secondary endpoints consisted of changes in the other CGM data during MTTs between the groups and between before and after changing medications. The mean blood glucose, M-value, which is also a fluctuation indicator for daily blood glucose, the rate of blood glucose

<70 mg/dL, the rate of blood glucose >180 mg/dL, and the other variables were evaluated using the CGM data. Details and principles for calculating MAGE and the M-value are described in Appendix S2. Subjective symptoms and interstitial glucose levels lower than 54 mg/dL for at least 20 min were defined as an episode of clinically significant hypoglycemia.[6] The sample size calculation and statistical analysis methods are described in Appendix S3.

3 | RESULTS

3.1 | Participant characteristics

A total of 101 people were screened, of whom two withdrew their consent before starting the trial. Ninety-nine participants were assigned randomly to the SWITCH group (n = 48) or the COMB group (n = 51; Figure S2). Table 1 provides the participants' baseline characteristics, showing a similar profile between the two groups. Body weight, waist circumference, blood pressure, diabetic complications, and medication at baseline showed no significant differences between the groups. One participant had a reduced sulphonylurea dose and one had decreased insulin units in the SWITCH group, while two participants had a reduced sulphonylurea dose and one had decreased insulin units in the COMB group. All 99 participants completed the trial. At the end of the trial, body weight, systolic blood pressure and uric acid levels were significantly decreased in both groups ($P < 0.01$), and the extent of the reduction was comparable (Table S1). Although HbA1c decreased in both groups during the trial ($P < 0.01$), the extent of the reduction was significantly larger in the COMB group compared with the SWITCH group ($P < 0.01$). Fasting plasma glucose and glycoalbumin levels were significantly decreased only in the COMB group ($P = 0.02$ and $P < 0.01$, respectively). Waist circumference and alanine transaminase and aspartate aminotransferase levels (liver function tests) significantly decreased only in the COMB group, but these changes were not significantly different between the groups.

3.2 | Improvement of glycaemic fluctuation with the combination of SGLT2 and DPP-4 inhibitor therapy

The daily glycaemic profile obtained by CGM in both groups is shown in Figure 1. Daily blood glucose levels were decreased by switching or adding canagliflozin in both groups. The improvement in MAGE, the primary endpoint, was significantly greater in the COMB group compared with the SWITCH group (COMB 117.5 ± 39.8 to 92.2 ± 28.0 mg/dL vs SWITCH 110.7 ± 29.8 to 104.2 ± 27.6 mg/dL; $P < 0.01$ [Figure S3 and Table S2]). MAGE was significantly improved in the COMB group ($P < 0.05$), although there was only a trend toward an improvement in the SWITCH group. M-value, the other daily glycaemic fluctuation marker, also showed similar changes (COMB 2299.4 ± 462.1 to 1968.3 ± 439.7 mg/dL vs SWITCH 2369.6 ± 407.9 to 2196.1 ± 356.5 mg/dL; $P < 0.01$ for the changes in the M-value from the first to the second MTT).

TABLE 1 Clinical characteristics of the study cohort

Variables	SWITCH (n = 48)	COMB (n = 51)	P
Age, years	62.3 ± 9.9	62.3 ± 10.4	0.98
Men, n (%)	27 (56.3)	34 (66.7)	0.29
Length, cm	162.3 ± 9.2	163.0 ± 9.5	0.40
Body weight, kg	69.7 ± 11.9	69.8 ± 10.9	0.96
BMI, kg/m^2	26.4 ± 3.2	26.2 ± 3.0	0.77
Duration of diabetes, n (%)*			0.79
5 years	12 (25.0)	11 (21.6)	
>5 to 10 years	12 (25.0)	11 (21.6)	
>10 to 15 years	15 (31.3)	20 (39.2)	
>15 years	9 (18.8)	7 (13.7)	
Smoking status, n (%)			0.74
Current smoker	8 (16.7)	11 (21.6)	
Former smoker	18 (37.5)	24 (47.1)	
Alcohol drinking status, n (%)	12 (25.5)	10 (19.6)	0.48
Diabetic retinopathy, n (%)	8 (16.7)	6 (11.8)	0.48
Diabetic nephropathy, n (%)	15 (31.3)	13 (25.4)	0.53
Microalbuminuria	12 (25.0)	10 (19.7)	
Macroalbuminuria	3 (6.3)	3 (5.9)	
Atherosclerotic vascular disease, n (%)			
Coronary	4 (8.3)	3 (5.9)	0.63
Cerebrovascular	2 (4.2)	2 (3.9)	0.95
Peripheral	0 (0.0)	1 (2.0)	0.25
Hypertension, n (%)	24 (50.0)	26 (51.0)	0.92
Dyslipidaemia, n (%)	32 (66.7)	34 (66.7)	1.00
Fatty liver, n (%)	9 (18.8)	10 (19.6)	0.91
Treatment for diabetes mellitus. Oral antidiabetic drug therapy, n (%)			
Biguanide	33 (68.8)	34 (66.7)	0.82
Sulphonylurea/glinide	20 (41.7)	14 (27.5)	0.14
Pioglitazone	2 (4.2)	2 (3.9)	0.95
α-Glucosidase inhibitor	3 (6.3)	2 (4.0)	0.60
Insulin, n (%)	5 (10.4)	10 (19.6)	0.20
ACE inhibitor/ARB, n (%)	22 (45.8)	25 (49.0)	0.75
CCB, n (%)	12 (25.0)	14 (27.5)	0.78
β-Blocker, n (%)	2 (4.2)	1 (2.0)	0.52
Diuretic, n (%)	2 (6.3)	4 (7.8)	0.76
Statin, n (%)	25 (52.1)	29 (56.9)	0.63
Fibrate, n (%)	2 (4.2)	3 (5.9)	0.70
Ezetimibe, n (%)	2 (4.2)	3 (5.9)	0.70
EPA/DHA ethyl esters, n (%)	2 (4.2)	3 (5.9)	0.70

Notes: Values are presented as mean ± SD unless otherwise indicated.
P value: SWITCH vs COMB groups.
*COMB group had two missing data points.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase-4; EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid; SGLT2, sodium-glucose co-transporter-2.

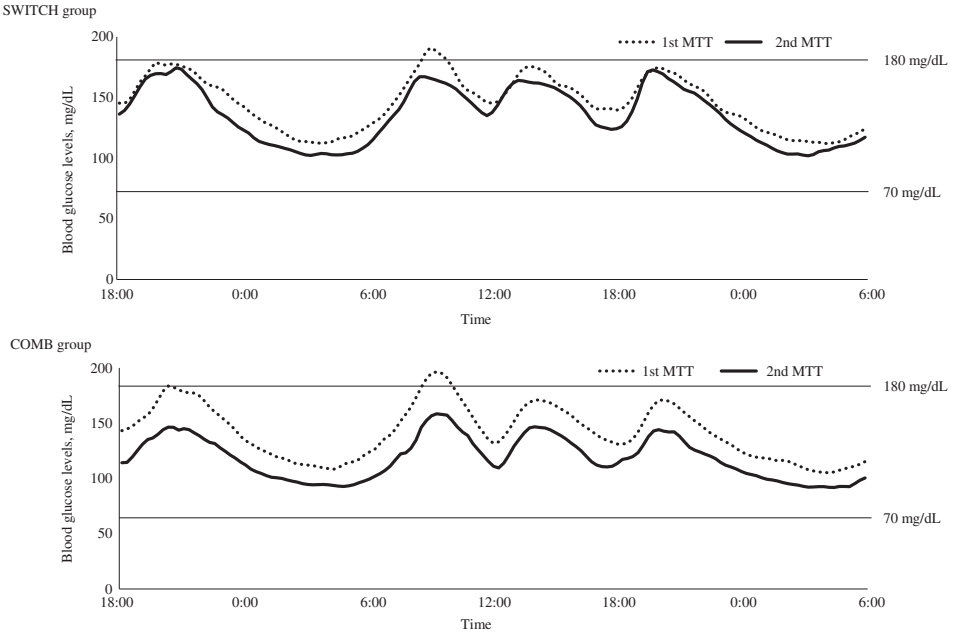

FIGURE 1 Comparison of blood glucose fluctuations from continuous glucose monitoring in the group that switched to 100 mg/d of canagliflozin (SWITCH group) and the group who added 100 mg/d of canagliflozin (COMB group). BG, blood glucose; MTT, meal tolerance test

Mean blood glucose decreased significantly in both groups, and the extent of the reduction was significantly larger in the COMB group compared with the SWITCH group (COMB 142.3 ± 28.7 to 119.5 ± 25.1 mg/dL vs SWITCH 146.4 ± 25.5 to 135.5 ± 22.4 mg/dL; $P < 0.01$). The improvement in mean blood glucose reached significance by switching to or adding canagliflozin, a finding which was different from the MAGE or M-value results. The rate of blood glucose <70 mg/dL showed a trend toward increasing in both groups during the trial, but these changes did not reach significance. However, the rate of blood glucose >180 mg/dL showed a trend toward a decrease in both groups, and it was significantly decreased in the COMB group compared with the SWITCH group ($P < 0.01$; Table S1).

3.3 | Safety

There were no severe adverse events, such as a recurrent infection, severe hypoglycaemia, dehydration, ketoacidosis, or a cardiovascular event. Although several adverse events were reported in both the groups (Table S3), none of them were serious and all resolved with appropriate treatment. Thus, no patients discontinued the trial.

4 | DISCUSSION

This is the first randomized controlled trial using CGM and MTTs to show that the combination of DPP-4 and SGLT2 inhibitor therapy is promising for reducing glycaemic variability in people with T2DM compared with SGLT2 inhibitor monotherapy. Reducing glycaemic variability could possibly contribute to reducing diabetic complications. The highlight of the trial was the outstanding combined effect of DPP-4 and SGLT2 inhibitors, which decreased the daily blood glucose fluctuation. The combination therapy was expected to have a synergistic effect on reducing glycaemic variability. Several mechanisms for improving glycaemic variability and postprandial hyperglycaemia can be proposed. First, an increase in circulating glucagon levels after treatment with SGLT2 inhibitors, which occurs because of the compensatory effect against urinary glucose disposal, can be reduced by adding a DPP-4 inhibitor via complementary effects on α- and β-cell function.[7] Second, a further increase in the DPP-4 inhibitor effect could occur by adding a SGLT2 inhibitor. One week of treatment with SGLT2 inhibitors in diabetic mice increased expression levels of the glucagon-like peptide-1 receptor and key β-cell factors, which are critical for β-cell function.[8] Additionally, SGLT2 inhibitor treatment enhanced β-cell proliferation by reducing oxidative stress in the islet cells.[9] Third, the additive effect could occur via the restoration of liver dysfunction by treatment with SGLT2 inhibitors.[10] Attenuation of the glucose-lowering effect of DPP-4 inhibitors in obese patients can be partially explained by the higher circulating level of a hepatokine, soluble DPP-4/CD26.[11] The reduction in the high liver enzyme levels after treatment with SGLT2 inhibitors was associated with a decrease in serum soluble DPP-4,[12] suggesting that reducing serum soluble DPP-4 levels by SGLT2 inhibitors can restore the glucose-lowering effect of DPP-4 inhibitors.

The present study had three important limitations. First, this randomized controlled trial had an open-label design, which might have led to bias. Second, glucagon was not measured in this trial, although we checked insulin secretion levels using C-peptide. Glucagon is an important contributing factor to the improvement of glycaemic control and fluctuation in the combination group, as stated above. Unfortunately, there were no standardized measurement methods for serum glucagon when we started this trial.[13] Third, the study duration for the major analysis was only 4 to 5 weeks, and CGM was only used for 2 weeks. Because fat mass reduction would be sustained for more than a few months after starting an SGLT2 inhibitor,[14] the results for glycaemic control or variability may be better with long-term use of SGLT2 inhibitors. However, SGLT2 inhibitors can rapidly relieve glucose toxicity and improve insulin sensitivity,[15] and their glycaemic effects should be seen relatively earlier compared with other oral hypoglycaemic agents.

Our findings showed that SGLT2 inhibitors combined with DPP-4 inhibitors strongly reduced glucose fluctuation in people with T2DM without increasing hypoglycaemia compared with SGLT2 inhibitor monotherapy.

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CONFLICT OF INTEREST

Nakamura A, Manda N, Kurihara Y, Atsumi T, and Miyoshi H have received honoraria for lectures and received research funding from some organizations as described below. The other authors declare no conflict of interest. Nakamura A has received research funding from Mitsubishi Tanabe Pharma Co., Ono Pharmaceutical Co., Ltd. Manda N has received honoraria for lectures from Ono Pharmaceutical Co., Ltd. Kurihara Y has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Mitsubishi Tanabe Pharma Co., MSD K.K., Ono Pharmaceutical Co., Ltd., Sanofi, Shionogi & Co., Ltd., Taisho Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. Atsumi T has received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co., Bristol-Myers Squibb Co., UCB Japan Co. Ltd., Eli Lilly Japan K.K., and has received research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Alexion Inc. Miyoshi H has received honoraria for lectures from Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., MSD K.K., Novartis Pharma, Novo Nordisk Pharma, Kowa Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., and Sanofi, and has received research funding from Astellas Pharma Inc., Daiichi Sankyo Co., Sumitomo Dainippon Pharma Co. Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Novo Nordisk Pharma, Kowa Pharmaceutical Co., Ltd., Abbott Japan Co., Nippon Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Co., Ltd.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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