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ORIGINAL ARTICLE

Improved time in range and postprandial hyperglycemia with canagliflozin in combination with teneligliptin: Secondary analyses of the CALMER study

Kyu Yong Cho[1,2], Hiroshi Nomoto[1], Akinobu Nakamura[1], Shinichiro Kawata[1], Hajime Sugawara[3], Jun Takeuchi[4], So Nagai[5], Kazuno Omori[1], Kazuhisa Tsuchida[1], Aika Miya[1], Ikumi Shigesawa[1,5], Kenichi Tsuchida[6], Shingo Yanagiya[1], Hiraku Kameda[1], Hiroki Yokoyama[7], Shinji Taneda[6], Yoshio Kurihara[8], Shin Aoki[9], Naoki Nishimoto[10], Tatsuya Atsumi[1], Hideaki Miyoshi[1,11]*

[1]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, [3]Third Department of Internal Medicine, Hokkaido PWFAC Obihiro-Kosei General Hospital, Obihiro, Japan, [4]Sapporo Diabetes and Thyroid Clinic, Sapporo, Japan, [5]Division of Diabetes and Endocrinology, Department of Medicine, Sapporo Medical Center, NTT East Corporation, Sapporo, Japan, [6]Diabetes Center, Manda Memorial Hospital, Sapporo, Japan, [7]Department of Internal Medicine, Jiyugaoka Medical Clinic, Obihiro, Japan, [8]Kurihara Clinic, Sapporo, Japan, [9]Aoki Clinic, Sapporo, Japan, [10]Biostatistics Section, Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, and [11]Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

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***Correspondence**
Hideaki Miyoshi
Tel.: +81-11-706-8192
Fax: +81-11-706-8194
E-mail address: hmiyoshi@med.hokudai.ac.jp

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ABSTRACT

Aims/Introduction: We recently reported the beneficial effect of the combination of sodium–glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor on daily glycemic variability in patients with type 2 diabetes mellitus. Additional favorable effects of combination therapy were explored in this secondary analysis.

Materials and Methods: The CALMER study was a multicenter, open-label, prospective, randomized, parallel-group comparison trial for type 2 diabetes mellitus involving continuous glucose monitoring under meal tolerance tests. Patients were randomly assigned to switch from teneligliptin to canagliflozin (SWITCH group) or to add canagliflozin to teneligliptin (COMB group). The continuous glucose monitoring metrics, including time in target range, were investigated.

Results: All 99 participants (mean age 62.3 years; mean glycated hemoglobin 7.4%) completed the trial. The time in target range was increased in the COMB group (71.2–82.7%, $P < 0.001$). The extent of the reduction in time above target range was significantly larger in the COMB group compared with the SWITCH group (–14.8% vs –7.5%, $P < 0.01$). Area under the curve values for glucose at 120 min after all meal tolerance tests were significantly decreased in the COMB group compared with the SWITCH group ($P < 0.05$).

Conclusions: Sodium–glucose cotransporter 2 inhibitor combined with dipeptidyl peptidase-4 inhibitor improved the quality of glycemic variability and reduced postprandial hyperglycemia compared with each monotherapy.

INTRODUCTION

A goal for treatment of patients with type 2 diabetes mellitus is to prevent the development of diabetic complications by bringing their blood glucose level as close to normal as possible. Although glycated hemoglobin (HbA1c) has been recognized as a marker of diabetic complications for many years, it does not exactly reflect daily glycemic variability, postprandial hyperglycemia and hypoglycemia[1,2]. Previous studies showed that minimization of glucose variability reduced the frequency of cardiovascular events and dementia[3,4]. Postprandial hyperglycemia is also a well-known risk factor of the onset and progress of microvascular and macrovascular complications[5]. Continuous glucose monitoring (CGM) systems have been investigated, and are currently the most suitable devices for

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evaluating daily glycemic variability, postprandial hyperglycemia and asymptomatic hypoglycemia in clinical practice[6].

The addition of a DPP-4 inhibitor (DPP-4i) or a sodium–glucose cotransporter 2 inhibitor (SGLT2i) to type 2 diabetes mellitus treatments was reported to show benefits in improving daily glycemic variability[7,8]. We recently reported, in the CALMER study, that DPP-4i–SGLT2i combination therapy had synergetic effects on reducing the mean amplitude of glycemic excursions, as the primary outcome, without increasing hypoglycemia[9]. Today, the concept of time ranges (TRs) has been well recognized in glycemic control[10]. Several previous studies showed time in target range (TIR) had a strong correlation with diabetic complications[11].

In the present study, we carried out secondary analyses of the CALMER study to investigate the merits of combination therapy with DPP-4i and SGLT2i by evaluating various CGM metrics other than mean amplitude of glycemic excursions, with a particular focus on TIR and postprandial hyperglycemia.

MATERIAL AND METHODS

Study overview

The present study comprised secondary analyses of the CALMER study, a multicenter (10 sites), open-label, prospective, randomized, parallel-group comparison trial using CGM and meal tolerance tests (MTTs) involving four consecutive meals (dinner, breakfast, lunch and dinner). All patients provided written informed consent before enrollment. The rationale and protocol of the CALMER study were described elsewhere[9], and the full list of inclusion and exclusion criteria is provided in Data S1. Briefly, eligible participants included patients with type 2 diabetes mellitus, aged 20–80 years, HbA1c of 6.5–9.0%, body mass index (BMI) of ≥23 kg/m^2, estimated glomerular filtration rate of ≥45 mL/min/1.73 m^2 and treatment with teneligliptin 20 mg/day for >12 weeks. All participants who met the criteria for enrollment were randomly assigned (1:1) to switch from teneligliptin 20 mg/day to canagliflozin 100 mg/day (SWITCH group) or to add canagliflozin 100 mg/day to teneligliptin 20 mg/day (COMB group), followed by 14 days of CGM. Allocation factors included age, BMI, HbA1c and estimated glomerular filtration rate. After performance of the first MTT while the patients were taking teneligliptin, the allocated medication was started in each group. After 7 days, the second identical MTT was carried out. For MTTs, we prepared the frozen food dish and several sides of packed rice (100, 130 and 200 g/meal) according to BMI. The total calorie intake was set to 30–35 kcal/the participant's ideal bodyweight (height [m]^2 × 22 kg)/day, and its carbohydrate ratio was approximately 50–65%. Participants were asked to maintain their lifestyle as similar as possible between the first and second MTTs. The CALMER study was registered with the University Hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN000029628), and protocol was approved by the institutional review board at Hokkaido University Hospital Clinical Research and Medical Innovation Center (017-0037), and it was carried out in accordance with the Declaration of Helsinki and its amendments.

In this analysis, we did not include the first dinner in the analyses, and thus used 24-h data including three consecutive meals (breakfast, lunch and dinner). The outcomes for the secondary efficacy end-points were designed before starting the original study. The changes in percentages of time per day in target glucose range (70–180 mg/dL; TIR), time per day below target range (<70 mg/dL; TBR), time per day above target range (≥180 mg/dL; TAR) and mean blood glucose (MBG) were investigated as core CGM metrics. The differences between pre-prandial and 120 min post-prandial glucose levels (Δ0–120) and the area under the curve values during 0–120 min (AUC 0–120) were analyzed for each meal during the MMTs.

Statistical analysis

Differences in the baseline characteristics between the two groups were evaluated by ANCOVA for continuous variables, and by a χ^2-test or Fisher's exact test for categorical variables. Correlations were evaluated by Spearman's rank-order correlation analysis. Logistic regression models were applied to identify factors independently associated with the rise of TIR in the COMB group, and a receiver operating characteristic curve analysis was used to define the cut-off values. Multiple regression analysis was used to determine predictors for the change in AUC (ΔAUC). The results within each group were compared by a paired-sample *t*-test or the Wilcoxon signed-rank test. Data were analyzed using JMP Pro v14.1.1 software (SAS Institute, Cary, NC, USA), and values of $P < 0.05$ were considered statistically significant.

RESULTS

A total of 99 patients were randomly assigned either to the SWITCH group ($n = 48$) or to the COMB group ($n = 51$), and all participants completed the study. The baseline characteristics of the study participants have already been reported[9]. Briefly, 61.6% of patients were men, the mean age was 62.3 years, mean BMI was 26.3 kg/m^2, mean HbA1c was 7.4% (57.0 mmol/mol) and 49 patients used sulfonylurea or insulin.

As shown in Table 1, MBG and TAR were significantly decreased in both groups, and the extents of the reductions were significantly larger in the COMB group compared with the SWITCH group (MBG: COMB, −22.3 mg/dL [143.9 ± 28.7 to 121.6 ± 26.1 mg/dL] vs SWITCH, −10.6 mg/dL [148.1 ± 27.0 to 137.5 ± 23.0 mg/dL], $P < 0.01$; TAR: COMB, −14.8% (26.5–11.6%) vs SWITCH, −7.5% (26.8–19.3%), $P < 0.01$). Meanwhile, TIR and TBR were significantly increased in both groups, but the extents of the increases did not differ significantly between the two groups (TIR: COMB, +11.5% [71.2–82.7%] vs SWITCH, +5.8% [72.5–78.3%], $P = 0.09$; TBR: COMB, +3.3% [2.4–5.7%] vs SWITCH, +1.7% [0.8–2.5%], $P = 0.13$). TRs <54 mg/dL (%) were rare and comparable between the groups (COMB 0.1–0.4% vs SWITCH 0.0–

Table 1 | Comparisons of mean blood glucose and time range in the switched from teneligliptin to canagliflozin and added canagliflozin to teneligliptin groups

	SWITCH (n = 48)		COMB (n = 51)		P
	First MTT	Second MTT	First MTT	Second MTT	
MBG (mg/dL)	148.1 ± 27.0	137.5 ± 23.0	143.9 ± 28.7	121.6 ± 26.1**	<0.01
TAR (%)	26.8	19.3***	26.5	11.6***	<0.01
TIR (%)	72.5	78.3**	71.2	82.7***	0.09
TIR >70% achievement (%)	62.5	77.1*	58.0	79.2***	0.20
TBR (%)	0.8	2.5*	2.4	5.7*	0.13

Values are presented as the mean ± standard deviation. The P-values were calculated for the mean changes from first meal tolerance test (MTT; baseline) to second MTT (after allocation) between the switched from teneligliptin to canagliflozin (SWITCH) group and the added canagliflozin to teneligliptin (COMB) group (ANCOVA, χ^2-test or Fisher's exact test). *P < 0.05, **P < 0.01, ***P < 0.001 between first MTT and second MTT (paired-sample t-test, χ^2-test or Fisher's exact test). MBG, mean blood glucose; TAR, time above target range; TBR time below target range; TIR, time in target range; TR, time range.

Table 2 | Logistic regression analysis for baseline parameters to identify independent factors associated with time in target range of increase in the added canagliflozin to teneligliptin group

	Simple logistic regression	P	Multiple logistic regression	P
Age	0.98 (0.94–1.03)	0.48	1.03 (0.95–1.11)	0.43
BMI	1.07 (0.92–1.25)	0.39	1.14 (0.88–1.48)	0.32
FPG	1.03 (1.01–1.05)	<0.01	1.02 (0.99–1.05)	0.29
MBG	1.08 (1.05–1.12)	<0.01	1.10 (1.05–1.17)	<0.01
MAGE	1.02 (1.00–1.03)	0.01	1.00 (0.98–1.03)	0.66
HbA1c	3.81 (1.39–10.42)	0.02	1.23 (0.24–6.24)	0.80
CPR	1.68 (0.95–2.96)	0.06	2.13 (0.81–5.64)	0.13
eGFR	1.01 (0.98–1.05)	0.36	1.06 (0.99–1.12)	0.16

Values are presented as odds ratio (95% confidence interval). BMI, body mass index; CPR, C-peptide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; MAGE, mean amplitude of glycemic excursions; MBG, mean blood glucose.

0.0%, P = 0.21). The use of insulin/sulphonylurea/glinide in the COMB group did not affect the difference in TBR (using [n = 17] 6.4%; not using [n = 34] 5.0%, n = 0.66). Among the baseline parameters in the COMB group, baseline MBG was an independent predictor for the increase in TIR based on multivariate logistic regression analysis (odds ratio 1.10, 95% confidence interval 1.05–1.17, P < 0.01; Table 2). Using a receiver operating characteristic analysis, the MBG cut-off value for the increase in TIR was 145.4 mg/dL (AUC 0.93, sensitivity 73.5%, specificity 100.0%), implying that when the baseline MBG value was higher than this, the combination of a DPP-4 inhibitor and an SGLT2 inhibitor increased TIR.

When the postprandial hyperglycemia at individual meals was considered separately (Figure 1), the AUC 0–120 values for all meals were significantly decreased in the second MTT compared with the first MTT in the COMB group (breakfast 401.1 ± 100.4 to 326.4 ± 82.6 mg/dL h, P < 0.001; lunch 325.3 ± 92.6 to 278.0 ± 65.3 mg/dL h, P < 0.001; dinner 329.4 ± 91.4 to 285.8 ± 90.9 mg/dL h, P < 0.001), whereas the AUC 0–120 value at breakfast only was decreased in the SWITCH group (384.5 ± 91.2 to 344.1 ± 91.4 mg/dL h, P < 0.01). The decrease in the COMB group was greatly superior to that in the SWITCH group (P < 0.05; Table 3, Figure 2). When postprandial hyperglycemia was analyzed using the Δ0–120 values, similar tendencies to the AUC 0–120 values were seen in both groups, although the improvement in Δ0–120 values did not reach statistical significance for lunch in the COMB group (Table 4).

DISCUSSION

The present analyses showed beneficial effects of the combination of teneligliptin and canagliflozin on two distinctive features: TRs and postprandial glycemic excursions. TRs are currently used for assessment of glycemic control in patients with diabetes, with TIR >70% and TAR <25% recommended as an international consensus in 2019[10,11]. In the present study, the combination therapy increased the mean TIR to 82.7% (+11.5%) and the achievement rate of TIR >70% was increased from 58.0 to 79.2% by adding canagliflozin to teneligliptin. Increases in TIR contribute to a decline in diabetic complications, at least for some classical microvascular complications and atherosclerosis[12–15], because TIR is determined by not only the average glycemic control, but also the extent and magnitude of hyperglycemia[16]. Furthermore, 10% improvement in TIR

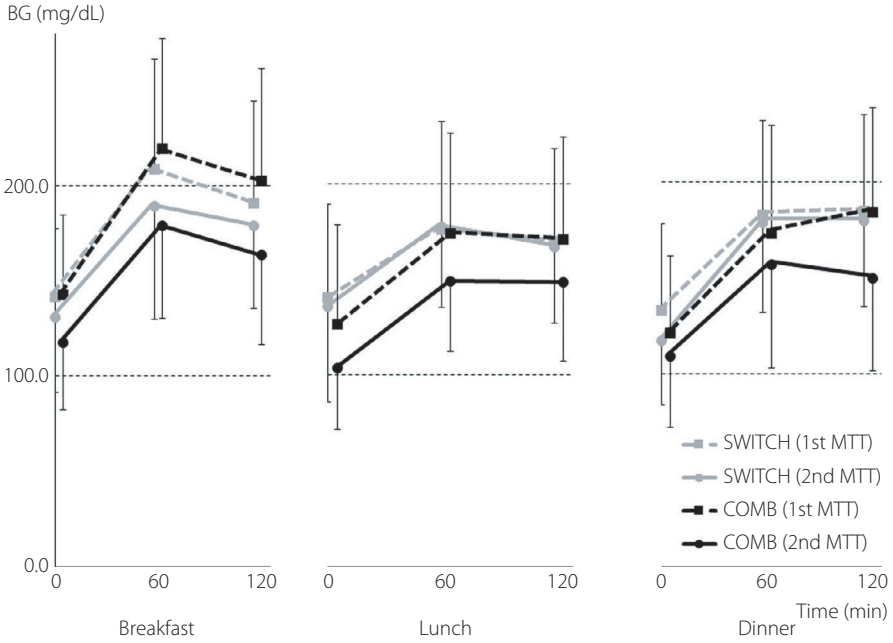

Figure 1 | Blood glucose concentrations during meal tolerance tests (MTTs). Dashed lines indicate the data at the first MTT while taking teneligliptin. Solid lines indicate the data at the second MTT. Grey lines indicate the group that switched from teneligliptin to canagliflozin (SWITCH). Black lines indicate the group that added canagliflozin to teneligliptin (COMB). BG, blood glucose.

Table 3 | Comparisons of the area under the curve values for glucose at 120 min after meal tolerance tests between the groups

	First MTT	Second MTT	*P*
Breakfast			
SWITCH (mg/dL h)	384.5 ± 91.2	344.1 ± 91.4**	<0.05
COMB (mg/dL h)	401.1 ± 100.4	326.4 ± 82.6***	
Lunch			
SWITCH (mg/dL h)	334.6 ± 97.9	320.5 ± 72.5	<0.05
COMB (mg/dL h)	325.3 ± 92.6	278.0 ± 65.3***	
Dinner			
SWITCH (mg/dL h)	337.4 ± 99.1	331.1 ± 75.9	<0.05
COMB (mg/dL h)	329.4 ± 91.4	285.8 ± 90.9***	

Values are presented as the mean ± standard deviation. The *P*-values were calculated for the differences in area under the curve values between the switched from teneligliptin to canagliflozin (SWITCH) group and the added canagliflozin to teneligliptin (COMB) group (ANCOVA). **$P < 0.01$, ***$P < 0.001$ during first meal tolerance test (MTT) and second MTT (paired-sample *t*-test).

was identified as a useful indicator for preventing diabetic complications[15,17]. TIR was increased by >10% in the COMB group, meaning that the combination therapy could be one of the promising therapies for comprehensive control of diabetic complications. We showed in a logistic regression analysis that MBG was a key characteristic predicting the improvement of TIR in the combination therapy (Table 2). It indicates that adding SGLT2i to DPP-4i in type 2 diabetes mellitus patients with a higher level of baseline MBG might lead to greater effects on increasing TIR. The combination therapy could be a crucial strategy for patients with type 2 diabetes mellitus who are at high risk of diabetic complications.

For strict glycemic control, appropriate reduction of insulin or sulfonylurea should be always considered[18]. The combination therapy slightly, but significantly, increased TBR (2.4–5.7%) in the COMB group, although the group difference was not significant and the TRs <54 mg/dL were not increased. Because glycemic variability is a significant and independent determinant of hypoglycemia in patients with type 2 diabetes mellitus on insulin therapy[19], once the dose of insulin or sulfonylurea has been adjusted appropriately, TBR should be rather decreased by the combination therapy through an improvement in glycemic variability[9]. Previous studies showed that CGM values were lower than self-monitoring blood glucose values in the low glucose range[20], and that capillary and venous glucose concentrations can differ under dynamic conditions[21]. Therefore, CGM data might not be highly accurate and the possibility of such inaccuracies should be considered, especially in the low glucose region.

The combination therapy showed marked improvement of postprandial hyperglycemia in the present study. Previous studies showed that postprandial hyperglycemia was associated with an increased risk of death[22,23], and was an independent factor for arteriosclerosis and cardiovascular events[24]. Postprandial hyperglycemia induced oxidative stress[25], decreased vasodilator response[26] and damaged endothelial cells[27]. We previously

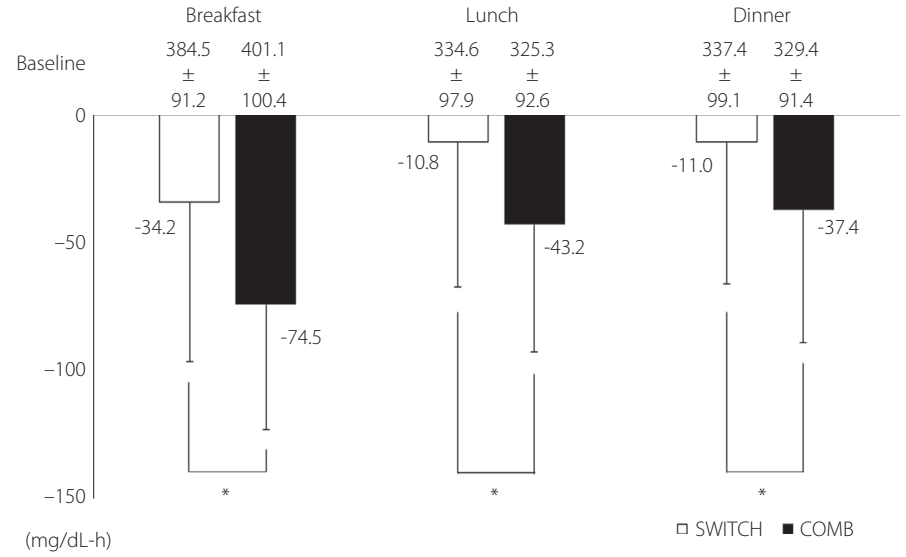

Figure 2 | Changes in the area under the curve values for glucose at 120 min after meal tolerance tests. Data are shown as the mean ± standard deviation. White bars indicate the group that switched from teneligliptin to canagliflozin (SWITCH). Black bars indicate the group that added canagliflozin to teneligliptin (COMB). *$P < 0.05$, significant difference between the two groups.

described several possible mechanisms for the synergistic effects of the combination therapy on reducing glycemic variability[9], including complementary effects on pancreatic α- and β-cell functions[28,29], and decreasing soluble DPP-4[30]. These mechanisms would be likewise included in the decrease of postprandial blood glucose elevation by the combination therapy.

The improvement in lowering post-prandial hyperglycemia was especially highlighted at breakfast. The glucose-lowering effect of incretin is diminished in the hyperglycemic state and can be improved by lowering the plasma glucose level[31]. SGLT2i effectively decreases the fasting plasma glucose level, thereby restoring the DPP-4i effect, especially after breakfast in the combination therapy. However, the post-prandial hyperglycemia (AUC 0–120) at breakfast was also significantly lowered in the SWITCH group. Therefore, other additional mechanisms might be involved in its improvement. Canagliflozin has a different characteristic from other SGLT2i. It inhibits SGLT2 in the kidney, as the other SGLT2is do, but also partially inhibits SGLT1 in the intestinal tract and pancreatic α-cells[32,33]. The combination therapy of canagliflozin and DPP-4i increased plasma GLP-1 levels and improved glucose excursions in diabetic fatty rats[32]. In a randomized controlled trial, canagliflozin provided smaller postprandial plasma glucose excursions than dapagliflozin[34]. Furthermore, in likely support for the hypothesis of partial SGLT1 inhibition in the intestinal tract with canagliflozin, no significant differences were found for the success of glycemic control in the Diversity-CVR study, which compared dapagliflozin with DPP-4i[35].

Furthermore, in this analysis, pre-prandial hyperglycemia was improved, as well as post-prandial hyperglycemia, in the COMB group. It is well known that alpha-glucosidase inhibitors[36] and glinide[37] acting directly on postprandial hyperglycemia also improved pre-prandial hyperglycemia. DPP-4 inhibitors that improved postprandial hyperglycemia on glycemic responsiveness also improve the next pre-prandial glucose level[38]. It is important to ensure control of postprandial hyperglycemia and not carry it over to the next pre-prandial. The strong interaction of the combination therapy in the COMB group had a positive effect on both pre-prandial glucose levels and postprandial glucose, and improved glycemic variability.

There were several limitations to the present study. First, the trial had an open-label design, which might have contributed to bias. Second, the study duration for the analysis was short. Because fat mass reduction would be sustained for more than a few months after starting SGLT2i[39], the results for CGM metrics might be clearer after long-term use of SGLT2i. However, SGLT2i can rapidly relieve glucose toxicity, and its glycemic effects should be seen relatively earlier than those of other oral hypoglycemic agents[40]. Furthermore, previous studies showed that CGM during the most recent 14 days was strongly correlated with long-term mean glucose, time in TRs and hyperglycemia metrics[41,42]. Therefore, we decided on a shorter observation period to reduce the influence of various other external factors on blood glucose fluctuations, and maintain higher quality of the data in a randomized control style using MTTs.

In conclusion, SGLT2i combined with DPP-4i improved the quality of glycemic variability and reduced post-prandial hyperglycemia compared with each monotherapy.

Table 4 | Blood glucose concentrations for each meal during meal tolerance tests

Time (min)	First MTT				Second MTT				*P*	*P*
	0	60	120	Δ0–120	0	60	120	Δ0–120	(Δ0–120)	
Breakfast										
SWITCH	141.6 ± 35.7	208.5 ± 58.0	190.6 ± 53.7	49.0 ± 54.7	130.6 ± 39.3*	189.3 ± 59.7*	178.8 ± 43.4	48.2 ± 47.6	0.93	<0.05
COMB	142.7 ± 42.1	219.2 ± 58.0	202.7 ± 58.4	60.0 ± 56.5	117.7 ± 35.7***	178.8 ± 48.4***	163.5 ± 46.8***	45.8 ± 46.4	<0.05	
Lunch										
SWITCH	140.5 ± 49.2	176.2 ± 56.7	170.2 ± 48.4	29.7 ± 50.8	136.0 ± 50.3	178.0 ± 42.4	167.1 ± 40.0	31.6 ± 58.4	0.89	0.71
COMB	127.0 ± 51.5	174.2 ± 52.5	171.3 ± 53.4	44.3 ± 63.2	104.0 ± 32.2***##	149.1 ± 36.5**##	148.5 ± 40.9**#	44.4 ± 42.3	0.69	
Dinner										
SWITCH	133.0 ± 45.2	182.7 ± 48.8	184.4 ± 50.4	51.3 ± 49.7	117.4 ± 33.7*	178.8 ± 46.7	179.3 ± 44.3	61.9 ± 47.7	0.38	< 0.01
COMB	121.2 ± 39.9	173.2 ± 55.8	184.1 ± 54.3	62.7 ± 53.7	109.4 ± 37.0	156.7 ± 53.4*##	149.9 ± 48.1***,###	40.4 ± 49.6	< 0.01	

Values are presented as the mean ± standard deviation. The *P*(Δ0–120)-values were calculated for the changes from 0 to 120 min (Δ0–120) during first meal tolerance test (MTT; baseline) and second MTT in each group (paired-sample *t*-test). The *P*-values were calculated for the difference in Δ0–120 between the switched from teneligliptin to canagliflozin (SWITCH) group and the added canagliflozin to teneligliptin (COMB) group (ANCOVA). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ during the first MTT and second MTT (paired-sample *t*-test). #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$ at the corresponding time between the SWITCH group and the COMB group (ANCOVA).

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SUPPORTING INFORMATION

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

Data S1 | Criteria for inclusion and exclusion.