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CLINICAL TRIAL

Impact of endogenous insulin secretion on the improvement of glucose variability in Japanese patients with type 2 diabetes treated with canagliflozin plus teneligliptin

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ABSTRACT

Aims/Introduction: To identify the effect of combination therapy with a dipeptidyl peptidase-4 inhibitor and a sodium–glucose cotransporter 2 inhibitor compared with switching from a dipeptidyl peptidase-4 inhibitor to a sodium–glucose cotransporter 2 inhibitor on improving the glucose variability in patients with or without impaired endogenous insulin secretion.

Materials and Methods: A secondary analysis regarding the relationship between endogenous insulin secretion and the change in mean amplitude of glycemic excursions (ΔMAGE) was carried out in a multicenter, prospective, randomized, parallel-group comparison trial that enrolled patients with type 2 diabetes who had been taking teneligliptin and were treated by switching to canagliflozin (SWITCH) or adding canagliflozin (COMB). Participants were categorized into the following four subgroups: SWITCH or COMB and high or low fasting C-peptide (CPR) divided at baseline by the median.

Results: ΔMAGE in the COMB group was greatly improved independent of a high or low CPR (−29.2 ± 28.3 vs −20.0 ± 24.6, respectively; $P = 0.60$). However, ΔMAGE was not ameliorated in the low CPR SWITCH group, and the ΔMAGE was significantly smaller than that in the high CPR COMB group ($P < 0.01$).

Conclusions: COMB would be a better protocol rather than switching teneligliptin to canagliflozin to improve daily glucose variability in patients with impaired endogenous insulin secretion.

INTRODUCTION

Unstable glucose variability (GV) is related to the risk of hypo- and hyperglycemia and diabetes-related complications[1–3]. Thus, particular attention should be paid to the effect of each hypoglycemic agent on reducing the GV. We have previously shown that impaired endogenous insulin secretion in type 2 diabetes could affect the instability of GV using continuous glucose monitoring (CGM), and the coefficient of variation (CV),

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which is an index of GV, increased especially in patients with low fasting C-peptide (CPR)[4]. Thus, we hypothesized that the improvement in GV that was caused by hypoglycemic agents was lower in patients with impaired endogenous insulin secretion, depending on the agents that were used.

In the present study, we carried out secondary analyses 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 (CALMER study)[5] to investigate the effect of combination therapy with dipeptidyl peptidase-4 (DPP-4) inhibitor and sodium–glucose cotransporter 2 (SGLT2) inhibitor in comparison with switching from DPP-4 inhibitor to SGLT2 inhibitor on improving the GV in patients with or without impaired endogenous insulin secretion.

MATERIALS AND METHODS

Study population and design

The present study comprised a secondary analysis of the CALMER study, a multicenter (10 sites), randomized, open-label, parallel-group comparison, prospective trial using a meal tolerance test (MTT)[5]. Briefly, Japanese outpatients aged 20–80 years with type 2 diabetes, glycated hemoglobin level ranging from 47.5 mmol/mol to 74.9 mmol/mol (6.5–9.0%), whose body mass index (BMI) ≥23 kg/m^2 and estimated glomerular filtration rate ≥ 45 mL/min/1.73 m^2, were included in the study if they had been receiving teneligliptin 20 mg/day for ≥12 weeks. Patients were allocated randomly to switch from teneligliptin (20 mg/day) to canagliflozin (100 mg/day; SWITCH group) or to add on canagliflozin (100 mg/day) to teneligliptin (COMB group). Allocation factors included age, glycated hemoglobin, BMI and estimated glomerular filtration rate.

Biochemical analyses and data collection

Fasting blood samples were collected, and the first MTT involving four consecutive meals (dinner, breakfast, lunch and dinner) was carried out while the participants were taking teneligliptin. Thereafter, the allocated medication was started in each group. After 7 days, the second identical MTT was carried out. Two MTTs were carried out by each patient at their respective homes. The total amount of calories in each meal was determined based on the patient's ideal bodyweight (height [m]^2 × 22 kg). Their daily glycemic levels were tracked for the 14 consecutive days using CGM (Freestyle Libre Pro®, Abbott Laboratories, Chicago, IL, USA). The mean amplitude of glycemic excursions (MAGE)[6] and the 24-h mean blood glucose level were estimated using CGM data. The attending physicians confirmed the patients' drug adherence using a questionnaire, and they also confirmed that all patients had taken their medications as directed. As described in the original report, the primary end-point was the change in MAGE[5]. The outcomes for the secondary efficacy end-points were designed before starting the original study. The study was registered with the University Hospital Medical Information Network (UMIN) Center registration number UMIN000029628. The study protocol was accepted by the institutional review board at Hokkaido University Hospital Clinical Research and Medical Innovation Center. It was carried out in accordance with the Declaration of Helsinki. Signed informed consent was obtained from all the participants.

Statistical analysis

All participants were categorized into two groups including SWITCH or COMB, as described earlier. To define whether endogenous insulin secretion modified the effect in canagliflozin and/or teneligliptin in this analysis, participants were stratified by a baseline median fasting CPR of 1.9 ng/mL. All participants were then categorized into four subgroups, including SWITCH with low CPR (<1.9), COMB with low CPR (<1.9), SWITCH with high CPR (1.9 ≥) or COMB with high CPR (1.9≥). Biochemical and anthropometric characteristics were compared among the four subgroups using a one-way analysis of variance, the Kruskal–Wallis test or the χ^2-test as appropriate. MAGE, which was used as the metric for GV during the first and second MTT, was compared for each subgroup. The change in MAGE between the first and second MTT (ΔMAGE) was compared in the four subgroups. These data were analyzed using an analysis of covariance, followed by Tukey's honest significant difference test for multiple post-hoc comparisons. Tests were two-sided, and $P < 0.05$ was considered to be significant. Data analyses were carried out using JMP Pro 14.0.0 (SAS Inc., Cary, NC, USA).

RESULTS

Participant characteristics

All 95 participants (36 women) completed the study and were categorized into four groups: SWITCH with low CPR (n = 25), COMB with low CPR (n = 22), SWITCH with high CPR (n = 22) or COMB with high CPR (n = 26; Figure S1). The overall and subgroup characteristics are shown in Table 1. BMI, insulinotropic agent use (sulphonyl urea/glinide) and fasting plasma glucose (FPG) were different among the four subgroups. Hypoglycemic agents were continued at a constant dose while the patients participated in the study. However, the dose of basal insulin in one patient in the COMB with low CPR group was reduced because of non-severe hypoglycemia. Supplementary sugar was required in one patient in the COMB with low CPR group because of non-severe hypoglycemia. No severe adverse events, such as severe hypoglycemia, were reported.

Changes in characteristics from the first to second meal tolerance test

Figure 1 shows the changes in MAGE from the first MTT to the second MTT among the four subgroups. MAGE at the second MTT was significantly reduced compared with that at the first MTT in the COMB with low CPR, SWITCH with high CPR and COMB with high CPR groups. However, there was

Table 1 | Patient characteristics overall and in the four subgroups

	Total patients	SWITCH with low CPR	COMB with low CPR	SWITCH with high CPR	COMB with high CPR	*P*-value
n	95	25	22	22	26	
Age (years)	65.0 (56.0–69.0)	67.0 (59.0–69.5)	65.0 (54.5–68.8)	59.0 (53.8–67.0)	65.5 (56.8–71.0)	0.26
No. women, *n* (%)	36 (37.9)	10 (40.0)	7 (31.8)	10 (45.5)	9 (34.6)	0.79
BMI (kg/m^2)	26.1 (23.3–28.1)	24.1 (22.7–26.7)	25.0 (23.0–26.2)	28.4 (25.8–31.0)	26.9 (24.8–29.0)	<0.05
Diabetes treatment, *n* (%)						
Biguanide	63 (66.3)	18 (72.0)	15 (68.2)	14 (63.6)	16 (61.5)	0.87
Insulinotropic agent	33 (34.7)	16 (64.0)	7 (31.8)	1 (4.6)	9 (34.6)	<0.05
Pioglitazone	4 (4.2)	1 (4.0)	1 (4.6)	0 (0)	2 (7.7)	0.62
α-Glucosidase inhibitor	5 (5.3)	3 (12.0)	2 (9.1)	0 (0)	0 (0)	0.13
Insulin use	13 (13.7)	4 (16.0)	6 (27.3)	2 (9.1)	1 (3.9)	0.11
FPG (mg/dL)	148.6 ± 27.7	138.6 ± 23.7	143.1 ± 29.0	161.9 ± 33.1	151.6 ± 20.9	<0.05
HbA1c (%)	7.3 ± 0.5	7.2 ± 0.4	7.3 ± 0.5	7.3 ± 0.5	7.4 ± 0.7	0.71
HbA1c (mmol/mol)	56.5 ± 6.0	55.3 ± 4.9	55.9 ± 5.9	56.7 ± 5.5	57.9 ± 7.4	0.71
Fasting CPR (ng/mL)	1.9 (1.3–2.6)	1.3 (1.1–1.7)	1.2 (1.0–1.6)	2.9 (2.2–3.6)	2.4 (2.2–2.8)	<0.05

Values are expressed as the mean ± SD, median (interquartile range), or number (%) of patients in each category. BMI, body mass index; COMB, the group that added canagliflozin (100 mg/day) to teneligliptin (20 mg/day); CPR, C-peptide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SD, standard deviation; SWITCH, the group that switched from teneligliptin (20 mg/day) to canagliflozin (100 mg/day).

no change in MAGE at the second MTT in the SWITCH with low CPR group (Table S1). ΔMAGE in the COMB with high CPR group was significantly greater than that in the SWITCH with low CPR group (−29.2 ± 28.3 vs −2.5 ± 28.8; $P < 0.01$; Figure 1). FPG in blood samples and the 24-h mean blood glucose level that was estimated using CGM also showed similar changes (Tables S2, S3). Although bodyweight at the second MTT was significantly lower than that at the first MTT in each subgroup, the mean changes in bodyweight from the first to the second MTT were not different among the four groups (Supplemental Table S4). In addition, a stratified analysis on the basis of the median BMI was carried out to determine the degree to which BMI modified the association. There was no change in MAGE from the first to the second MTT in the SWITCH with low BMI group (Supplemental Table S5). To exclude the possibility of a correlation between CPR and BMI, multicollinearity was assessed between CPR and BMI using the variance inflation factor. We found no indication of multicollinearity between these variables (data not shown). Therefore, the effect of SWITCH might be related to both endogenous insulin secretion and BMI. We also carried out a stratified analysis on the basis of the mean FPG. There was no change in the MAGE between the first and second MTT in the SWITCH with low FPG and SWITCH with high FPG groups (data not shown). This result suggested that the degree of FPG does not affect the improvement of glucose variability in the SWITCH. We carried out a stratified analysis on the basis of whether the patient received an insulinotropic agent to determine if insulinotropic agent use modified the association. There was no change in MAGE between the first and second MTT in the SWITCH with or without insulinotropic agent groups (data not shown). There results suggested that insulinotropic agent use did not significantly affect canagliflozin's performance.

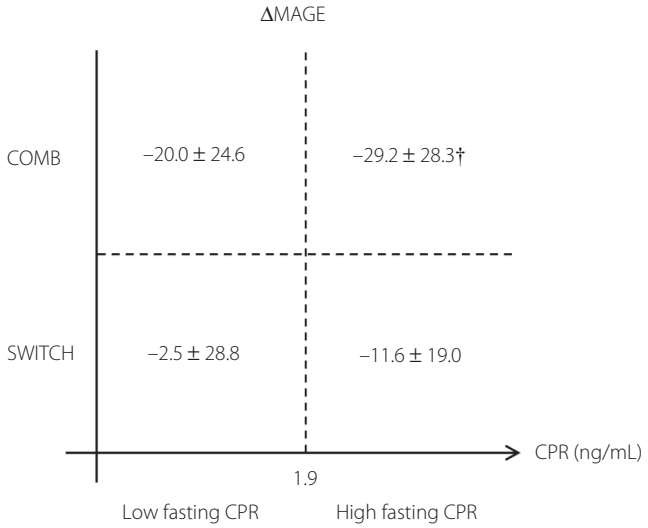

Figure 1 | Changes in mean amplitude of glycemic excursions (ΔMAGE) from the first to second meal tolerance test among four subgroups. Values are expressed as the mean ± standard deviation of patients in each category. †$P < 0.01$ versus SWITCH with low C-peptide (CPR) subgroup. COMB, the group that added canagliflozin (100 mg/day) to teneligliptin (20 mg/day); SWITCH, the group that switched from teneligliptin (20 mg/day) to canagliflozin (100 mg/day).

DISCUSSION

The present study verified that switching to canagliflozin had less effect on MAGE in patients with low fasting CPR who were treated with teneligliptin. However, the combination of canagliflozin and teneligliptin reduced MAGE in patients with high or low fasting CPR. These results support our hypothesis that GV improvement by hypoglycemic agents is reduced in patients with impaired endogenous insulin secretion, depending

on the agents. Our results also suggested that fasting CPR levels can help to identify the optimal agent choice for patients with type 2 diabetes.

Our present study was the first to report the relationship between endogenous insulin secretion and the extent of MAGE amelioration in patients with type 2 diabetes who were switched to canagliflozin or had canagliflozin added. As already reported in a cross-over study with patients taking luseogliflozin[7] and a randomized trial with dapagliflozin[8], SGLT2 inhibitors caused a downward shift in the glucose profile based on the urinary glucose excretion, whereas SGLT2 inhibitor monotherapy or the combination of SGLT2 inhibitor and insulin was less effective in reducing MAGE. Our current study showed that switching from teneligliptin to canagliflozin reduced 24-h mean blood glucose, but did not show any additional improvement in MAGE in patients with low fasting CPR, as previously reported[7,8]. However, this switching therapy was effective in both 24-h mean blood glucose and MAGE in patients with high fasting CPR. In a randomized controlled trial in patients who were administered tofogliflozin[9], postprandial blood glucose decreased and insulin secretion after meals increased significantly in patients with higher fasting insulin values. This previous result supports the present results that the improvement in GV that was caused by SGLT2 inhibitors was decreased in patients with impaired endogenous insulin secretion. Although SGLT2 inhibitors are known to lead to an immediate improvement in insulin sensitivity and pancreatic β-cell dysfunction[10], endogenous insulin secretion ability was not restored to the same extent in patients whose insulin secretion was already impaired.

Next, the efficacy of the combination of DPP-4 and SGLT2 inhibitors on GV has been previously reported. Add-on teneligliptin to canagliflozin was related to greater reductions in fasting and postprandial glucose[11], and this combination improved GV[5]. This result suggests that the combination of canagliflozin and teneligliptin might increase active glucagon-like peptide-1 levels because of the combined effects of canagliflozin on glucagon-like peptide-1 secretion and teneligliptin on DPP-4 inhibition[12]. Additionally, teneligliptin suppressed glucagon secretion, and concurrent use of canagliflozin did not enhance glucagon secretion[13], although SGLT2 inhibitors were previously shown to increase plasma glucagon level in patients with type 2 diabetes[14]. This combination effect might be enhanced by the reduction in glucotoxicity by SGLT2 inhibitors in patients with type 2 diabetes with both impaired and preserved endogenous insulin secretion. These results suggest that the combination of DPP-4 and SGLT2 inhibitors is a better protocol than switching from DPP-4 inhibitors to SGLT2 inhibitors to further improve GV in patients with type 2 diabetes and impaired endogenous insulin secretion.

It was reported that their calorie intake tended to increase after administration of SGLT2 inhibitors to patients with type 2 diabetes[15]. A strength of the present study was that MTT involved four consecutive meals (dinner, breakfast, lunch and dinner). The caloric content of the MTT was determined from the ideal weight of each participant; no other food, alcohol or beverages, except water, were allowed during the MTT. However, the present study was limited by the differences in the patients' characteristics among the groups at baseline. Prospective studies in patients with matching baseline characteristics other than endogenous insulin secretion are required to confirm these results. Additionally, the present findings might not be applicable to lean patients because of the criteria that excluded lean patients. Although we discussed the effect of the combination of canagliflozin and teneligliptin on active glucagon-like peptide-1 action and glucagon secretion, neither of these levels was measured. This randomized controlled trial had an open-label design, which might have introduced some biases.

The combination of canagliflozin and teneligliptin was a better choice than switching from teneligliptin to canagliflozin to improve GV in patients with impaired endogenous insulin secretion. Fasting CPR levels could help to identify the optimal drug choice for patients with diabetes.

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DISCLOSURE

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SUPPORTING INFORMATION

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

Figure S1 | Flow chart of patients throughout the study.

Table S1 | Changes in mean amplitude of glycemic excursions from the first to the second meal tolerance test among the four subgroups.

Table S2 | Changes in fasting plasma glucose from the first to the second meal tolerance test among the four subgroups.

Table S3 | Changes in 24-h mean blood glucose from the first to the second meal tolerance test among the four subgroups.

Table S4 | Changes in bodyweight from the first to the second meal tolerance test among four subgroups.

Table S5 | Changes in mean amplitude of glycemic excursions from the first to the second meal tolerance test among the four subgroups divided by mean body mass index.