

[Original]

Comparison of the Effects of Teneligliptin and Sitagliptin, Two Dipeptidyl Peptidase 4 Inhibitors with Different Half-Lives, on Glucose Fluctuation and Glucagon-Like Peptide-1 in Type 2 Diabetes Mellitus

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Abstract : Our purpose was to determine the effects of teneligliptin and sitagliptin, two dipeptidyl peptidase 4 inhibitors (DPP4-Is) with different half-lives, on glycemic variability and glucagon-like peptide-1 (GLP-1) levels in Japanese patients with type 2 diabetes mellitus (T2DM). The study subjects were 14 drug-naïve patients with T2DM who were allocated to either a 20 mg/day teneligliptin group (n = 7) or a 50 mg/day sitagliptin group (n = 7) for 7 days, then switched to the other treatment for another 7 days. Meal tolerance tests were performed at the time of no treatment, and after treatment with each DPP4-Is at supper. We evaluated the effects of each drug on glucose fluctuation using continuous glucose monitoring (CGM). There was no significant difference between the two groups in the primary endpoint (maximum glucose level after supper), nor in the secondary endpoint: area under the curve (AUC) for plasma glucose (≥ 140 mg/dL) after supper (18:00–24:00). Teneligliptin significantly improved the AUC for plasma glucose (≥ 140 mg/dL) after supper (20:00–24:00) ($P = 0.048$), and also significantly increased the GLP-1 level at 30 minutes after the meal load ($P = 0.030$). No serious adverse effects were noted in either group, apart from a few episodes of asymptomatic hypoglycemia. A daily dose of teneligliptin improved the AUC for plasma glucose at 20:00 to 24:00 (≥ 140 mg/dL) after the meal tolerance test, and also significantly increased the levels of activated GLP-1 after the test meal.

Keywords : glucagon like peptide-1, continuous glucose monitoring, dipeptidyl peptidase 4 inhibitors.

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Introduction

The results of large-scale clinical studies, such as the Japan diabetes complications study (JDACS) [1] and the Hisayama study [2], have shown that patients with type 2 diabetes mellitus (T2DM) are at a high risk of macroangiopathies. The diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe (DECODE) study concluded that postprandial hyperglycemia is a risk factor for death [3], whereas the action to control

cardiovascular risk in diabetes (ACCORD) trial [4] and the veterans affairs diabetes trial (VADT) [5] reported that hypoglycemia and weight gain are risk factors for macroangiopathy and mortality.

Dipeptidyl peptidase 4 inhibitors (DPP4-Is) enhance insulin secretion in a blood-glucose-dependent manner and suppress glucagon secretion by inhibiting DPP4 activity and elevating glucagon-like peptide 1 (GLP-1) levels, consequently lowering blood glucose levels [6]. When they are used alone, the inhibitors are less likely

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to cause hypoglycemia and suppress postprandial hyperglycemia without causing weight gain. DPP4-Is are classified into three subgroups (classes 1, 2 and 3) based on the presence of different binding sites. Both teneligliptin and sitagliptin belong to class 3 and bind to the section 1 (S1), section 2 (S2), and S2 extensive sites. It has been reported, however, that, compared with sitagliptin, teneligliptin seems to bind more potently to the S2 extensive site because of the three-dimensional conformation of teneligliptin, and that this property enhances its DPP4 inhibitory activity and DPP4 selectivity [7]. Moreover, teneligliptin suppresses the increase in triglyceride and free fatty acid levels after high-fat intake [8] and exerts an inhibitory effect on oxidative stress in rats [9]. These effects may be useful in preventing macroangiopathy. While large-scale clinical studies on incretin-related compounds concluded the noninferiority of DPP4-Is in the prevention of macroangiopathy relative to placebo [10–12], both the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial using liraglutide [13], a GLP-1 preparation, and the semaglutide unabated sustainability in treatment type 2 diabetes (SUSTAIN-6) trial, using semaglutide [14], concluded that the two agents significantly prevented cardiovascular-related deaths.

Seven types of DPP4-Is are currently available in Japan as preparations for daily use. Although they differ in their characteristics, such as half-life and excretion pathway, it is clinically uncertain whether they have different effects on glycemic variability. There are only a few studies on the effects of a once-daily dose of DPP4-Is with different half-lives on GLP-1 secretion or that compare the 24-hour blood glucose profile based on continuous glucose monitoring (CGM). The present crossover controlled study using CGM was designed to determine the effects of teneligliptin and sitagliptin, two DPP4-Is with different half-lives (teneligliptin: 24.2 hours, sitagliptin: 11.4 hours), on glycemic variability and GLP-1 levels. For this purpose, we tested the effects of 1-week treatment with once-daily oral doses of teneligliptin and sitagliptin, two of the seven available DPP4-Is in Japan with different half-lives, in patients with T2DM.

Materials and Methods

Patients

The research participants were 14 drug-naïve patients with T2DM, aged over 20 years, who were hospitalized at the University of Occupational and Environmental Health, department of endocrinology, metabolism and diabetes and affiliated hospitals between January 2014 and January 2015. Patients using insulin and oral antihyperglycemic agents, those with severe liver dysfunction, those with moderate renal dysfunction (male: serum Cre ≥ 1.5 mg/dl, female: serum Cre ≥ 1.3 mg/dl), those with severe trauma and those with severe infection were excluded. Any change in other drugs was prohibited until the end of the study. The institutional review board of the University of Occupational and Environmental Health approved this study. This clinical trial was registered with the university hospital medical information network (UMIN) (No. UMIN 000022885). The study was explained to the participants in writing, and their written consent was obtained. All samples were obtained and processed appropriately according to the Declaration of Helsinki.

Study design

The study was designed as a randomized crossover study, and participants were allocated to either a 20 mg/day teneligliptin group or a 50 mg/day sitagliptin group (Fig. 1). Each participant wore a continuous glucose monitoring system (CGMS[®] System Gold[™], Medtronic Inc., Fridley, MN) from the night of two days after admission to the morning of the fifth day (no drugs), from the night of 9 days after admission to the morning of the twelfth day (first DPP4-I) and from the night of 16 days after admission to the morning of the nineteenth day (second DPP4-I). A meal tolerance test was performed at supper time on hospital day 4 (without treatment). Oral administration of the first DPP4-I was started after supper on hospital day 5 and continued for 7 days. Another meal tolerance test was performed at supper time on hospital day 11. Oral administration of the second DPP4-I was started after supper on hospital day 12 and continued for 7 days. One more meal tolerance test was performed at supper time on hospital day 18. Both teneligliptin and sitagliptin were administered 2 hours after supper, and

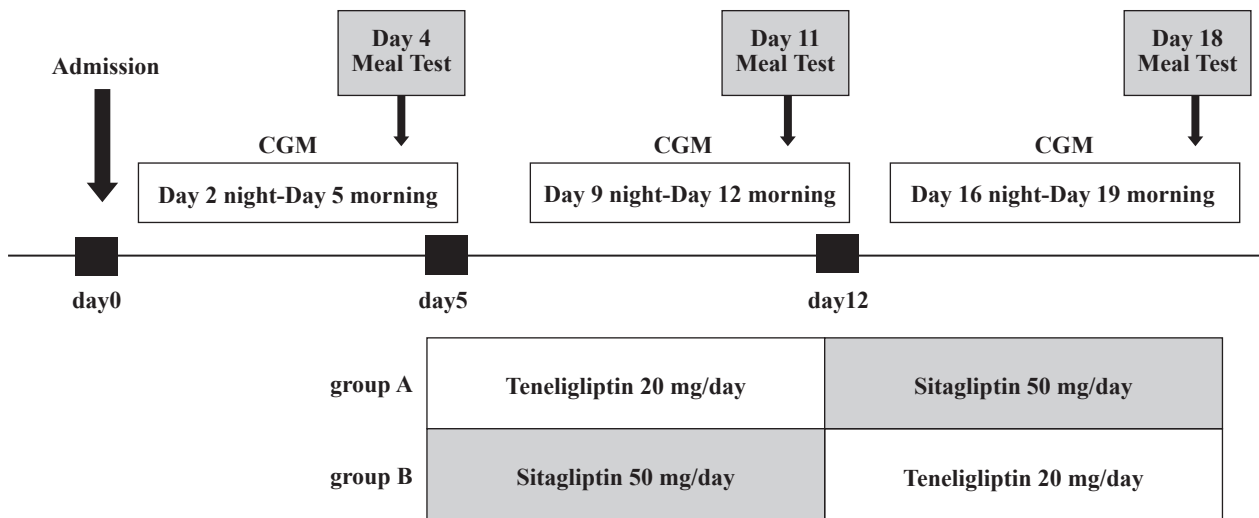


Fig. 1. Design of the study to compare the effect of tenueligliptin and sitagliptin. The study design was a randomized cross-over study, and participants were allocated to either group A or B. Patients were treated with either tenueligliptin (20 mg/day) or sitagliptin (50 mg/day). Each participant wore a continuous glucose monitoring (CGM) device from the night of day 2 for 3 days as no drug. Next, the participant wore a CGM device from the night of day 9 for 3 days as first dipeptidyl peptidase 4 inhibitor (DPP4-I). Similarly, the participant wore a CGM device from the night of day 16 for 3 days as second DPP4-I. Thus, each patient underwent 3-day CGM three times, followed by assessment of glucose level. Also, each patient underwent meal tests at day 4 (no drug), day 11 (first DPP4-I) and day 18 (second DPP4-I).

analysis was conducted on the CGM data obtained on hospital days 4, 11, and 18, after the meal tolerance tests had been performed. The tests were performed 6 hours after lunch by administering a standard test meal (25 kcal/ideal body weight, 22% fat, 60% carbohydrate, and 18% protein) at 18:00. Blood glucose and insulin levels were measured at 0, 30, 60, and 120 minutes after the test meal, while activated GLP-1 levels were measured at 0 and 30 minutes.

The primary endpoint was a difference in maximum glucose levels after supper in the two groups. The secondary endpoints were differences in the two groups in the area under the curve (AUC) for plasma glucose (≥ 140 mg/dL) after supper 18:00-24:00, AUC for plasma glucose (≥ 140 mg/dL) after supper 20:00-24:00, GLP-1 levels at 30 minutes after load, and immunoreactive insulin (IRI) levels at 2h after the load.

Laboratory tests

Active GLP-1 was measured by EGLP-35K (Millipore, Billerica, MA). IRI was measured using a chemiluminescence enzyme immunoassay (CLEIA, SRL Co, Tokyo). Plasma glucose (PG) level was measured by the glucose oxidase method. hemoglobin A1c (HbA1c)

was measured by high-performance liquid chromatography (HPLC) using Tosoh HLC-723 G8 (Tosoh Co., Kyoto, Japan). HbA1c (%) was estimated as the national glycohemoglobin standardization program (NGSP) equivalent value, which was calculated as HbA1c (NGSP) (%) = HbA1c (JDS) (%) + 0.4%, considering the relationship of HbA1c (NGSP) values to HbA1c (JDS) (%) values measured by the Japanese standard and measurement method. The homeostasis model assessment for insulin resistance (HOMA-IR), which represents insulin resistance, was calculated (formula: $\text{HOMA-IR} = \text{fasting glucose level} \times \text{fasting insulin level} \div 405$). Blood samples were collected during fasting, and urinary C-peptide immunoreactivity (u-CPR) levels were measured in 24-h urine samples. All samples were stored at -80°C until measurement.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD). The Wilcoxon test was used for the parameters between sitagliptin and tenueligliptin. The level of significance was set as $P < 0.05$. All statistical analyses were conducted using the statistical package for social science version 21.0 (SPSS Inc., Chicago, IL).

Table 1. Patient characteristics

Parameter	Mean \pm SD or Number (range)	
Sex (male: female)	14	(8 : 6)
Age (years)	63.9 \pm 16.3	(28 - 81)
Duration of diabetes (years)	2.4 \pm 2.8	(1 - 10)
Body weight (kg)	71.4 \pm 12.8	(54.0 - 93.0)
BMI (kg/m ²)	26.4 \pm 4.5	(19.8 - 33.8)
Diabetic neuropathy (%)	57	
Diabetic retinopathy (%)	0	
Diabetic nephropathy (%)	14	
HbA1c (%)	7.8 \pm 1.0	(6.6 - 10.5)
Fasting plasma glucose (mg/dl)	144.6 \pm 55.5	(82 - 214)
Insulin (μ U/ml)	9.0 \pm 5.4	(4.1 - 21.0)
HOMA-IR	2.9 \pm 1.8	(1.2 - 7.1)
u-CPR (μ g/day)	102.5 \pm 55.5	(37.3 - 210.6)

SD: standard deviation, range: minimum-maximum, BMI: body mass index, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model assessment insulin resistance, u-CPR: urinary C-peptide immunoreactivity

Results

Patient characteristics

Table 1 shows the demographic details of the study subjects. Of the 14 participants, 8 were males and 6 were females. The mean age of the participants was 63.9 ± 16.3 years. The subjects were mildly obese, with mean body mass index (BMI) of 26.4 ± 4.5 kg/m² and abdominal circumference (AC) of 94.7 ± 8.8 cm. Blood glucose was generally poorly controlled on admission, with mean HbA1c level at $7.8 \pm 1.0\%$. Insulin resistance was noted in most of the patients, with a group mean HOMA-IR of 2.9 ± 1.8 and u-CPR level of 102 ± 56 μ g/day. The level of low-density lipoprotein cholesterol (LDL-C) was 125 ± 27 mg/dl, high-density lipoprotein cholesterol (HDL-C) 41.7 ± 8.7 mg/dl and triglyceride 147 ± 47 mg/dl.

CGM data

The mean CGM data of all the patients are shown in Fig. 2, and the analyzed CGM data are shown in Table 2. There was no significant difference between the two groups in the primary endpoint, the maximum glucose level after supper. There were no significant differences in the secondary endpoints, either; including AUC

for plasma glucose (≥ 140 mg/dl) after supper (18:00–24:00), 24 h mean glucose level, standard deviation (SD) over 24 h, 0:00 to 19:00 mean glucose level, 24 h maximum glucose level, 24 h minimum glucose level, and differences between preprandial and highest postprandial glucose level after supper and at time from start of supper to the highest postprandial glucose level (Table 2 and Fig. 3.A). However, the AUC for plasma glucose (≥ 140 mg/dl) after supper (20:00–24:00) was significantly improved by the teneligliptin ($P=0.048$) (Table 2 and Fig. 3.B).

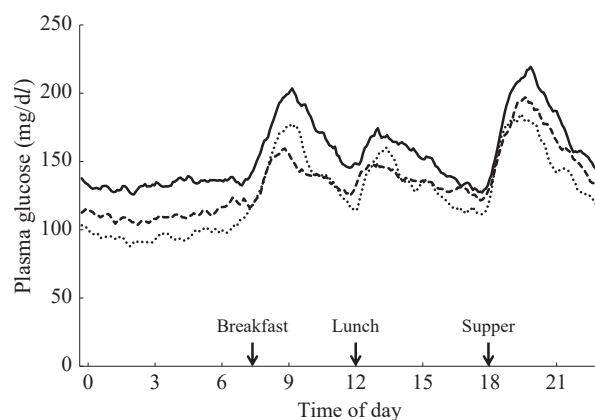


Fig. 2. The mean values of continuous plasma glucose levels detected by continuous glucose monitoring (CGM) in all the participants who were treated with either teneligliptin or sitagliptin. —: No drug, ···: Teneligliptin, - -: Sitagliptin.

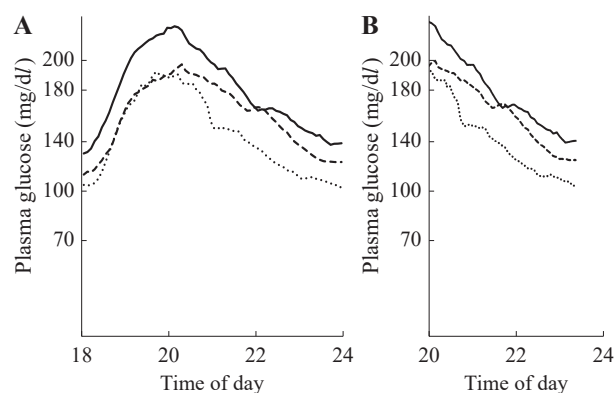


Fig. 3. Area under the curve (AUC) for plasma glucose (≥ 140 mg/dl) at meal test detected by continuous glucose monitoring (CGM) in all the participants who were treated with either teneligliptin or sitagliptin. —: No drug, ···: Teneligliptin, - -: Sitagliptin.

Table 2. Continuous glucose monitoring (CGM) data in the two treatment groups

Parameter	Sitagliptin	Teneligliptin	<i>P</i> value	No drug
	Mean \pm SD	Mean \pm SD		Mean \pm SD
24 h mean glucose level (mg/dl)	135.4 \pm 26.5	126.4 \pm 20.0*	0.510	156.9 \pm 31.5
SD over 24 h (mg/dl)	30.6 \pm 12.5	33.9 \pm 16.8	0.600	32.1 \pm 13.2
0:00 to 19:00 mean glucose level (mg/dl)	111.1 \pm 27.2**	96.3 \pm 26.0**	0.331	133.5 \pm 29.0
24 h maximum glucose level (mg/dl)	216.9 \pm 52.4	210.9 \pm 55.6	0.382	245.4 \pm 49.3
24 h minimum glucose level (mg/dl)	89.3 \pm 18.3*	81.9 \pm 17.5**	0.285	107.1 \pm 28.5
Maximum glucose level after supper (mg/dl)	210.8 \pm 43.3*	202.7 \pm 39.4**	0.257	235.9 \pm 52.7
Differences between preprandial and highest postprandial glucose level after supper (mg/dl)	95.5 \pm 44.1	93.4 \pm 52.0	0.730	106.4 \pm 52.3
Time from start of supper to the highest postprandial glucose level (minutes)	128.9 \pm 64.0	111.4 \pm 39.0	0.470	107.9 \pm 35.9
AUC for plasma glucose (≥ 140 mg/dl) after supper 18:00-24:00 (mg \cdot h/dl)	156.9 \pm 130.0*	109.9 \pm 114.9**	0.074	238.3 \pm 182.0
AUC for plasma glucose (≥ 140 mg/dl) after supper 20:00-24:00 (mg \cdot h/dl)	107.3 \pm 96.6	66.0 \pm 85.4**	0.048	150.7 \pm 148.0

SD: standard deviation, *P* values are for difference between sitagliptin and teneligliptin groups, by Wilcoxon test, *: $P < 0.05$: sitagliptin or teneligliptin versus no drug group, **: $P < 0.01$: sitagliptin or teneligliptin group versus no drug group, by Wilcoxon test, AUC: area under the curve

Table 3. Results of the meal loading test

Parameter	Sitagliptin	Teneligliptin	<i>P</i> value	No drug
	Mean \pm SD	Mean \pm SD		Mean \pm SD
AUC for IRI within 2 h ($\mu\text{U} \cdot \text{h}/\text{mL}$)	46.7 \pm 31.5	45.3 \pm 28.0	0.110	51.2 \pm 38.3
IRI level at 2h after load ($\mu\text{U}/\text{mL}$)	36.1 \pm 25.6	29.9 \pm 20.2	0.140	35.1 \pm 29.5
AUC for GLP-1 within 30 minutes (pmol \cdot h/l)	2.2 \pm 0.8**	2.6 \pm 1.1**	0.280	1.4 \pm 0.6
GLP-1 level at pre load (pmol/l)	3.3 \pm 1.9**	3.4 \pm 2.3**	0.930	1.9 \pm 1.4
GLP-1 level at 30 minutes after load (pmol/l)	5.5 \pm 2.1**	6.8 \pm 3.0**	0.030	3.7 \pm 1.7

SD: standard deviation, *P* values are for differences between sitagliptin and teneligliptin groups, by Wilcoxon test, **: $P < 0.01$: sitagliptin or teneligliptin group versus no drug group, by Wilcoxon test, AUC: area under the curve, IRI: immunoreactive insulin, GLP-1: glucagon-like peptide-1

Meal loading test

Treatment with teneligliptin resulted in a significant increase in GLP-1 level at 30 minutes after the meal load (Table 3). Apart from this difference between the two DPP4-Is, there were no significant differences in all other tested secondary endpoints, including IRI level at 2 h after the load, AUC for IRI within 2 h, GLP-1 level at pre load, and AUC for GLP-1 within 30 minutes (Table 3).

Adverse Effects

The CGM data showed a single (7.2%) hypoglycemic episode with blood glucose level of 64 mg/dl before medical intervention, two episodes (14.3%) during treatment with teneligliptin (blood glucose: 42 and 47 mg/dl), and a single episode (7.2%) during treat-

ment with sitagliptin (blood glucose: 63 mg/dl). None of these episodes, however, was associated with any hypoglycemic symptoms. No adverse reactions to either drug, such as gastrointestinal symptoms or hepatic dysfunction, were observed.

Discussion

In this pilot study, the meal tolerance test performed in the evening on the seventh day of treatment with oral DPP4-Is showed no significant differences in either peak blood glucose level after supper or AUC for plasma glucose levels at 18:00 to 24:00 (≥ 140 mg/dl), although the AUC for PG at 20:00 to 24:00 (≥ 140 mg/dl) improved significantly after treatment with teneligliptin. Moreover, activated GLP-1 level at 30 minutes

after the meal test was significantly higher than that after treatment with teneligliptin. Compared with other DPP4-Is, teneligliptin is reported to have a more potent DPP4 inhibitory activity, approximately five times higher than that of sitagliptin, based on 50% inhibitory concentration [15], and it remains effective for a long period of time because of its long half-life of 24.2 ± 5.0 hours. In the present study, because DPP4-Is were orally administered 2 hours after supper (at 20:00) on the day before the meal tolerance test, it is conceivable that the difference in activated GLP-1 levels (based on the different half-lives of sitagliptin and teneligliptin) contributed to the difference in AUC for PG at 20:00 to 24:00 (≥ 140 mg/dl).

Sakamoto *et al* [16] summarized the results of the Jikei-Vildagliptin and sitagliptin with CGM to Real Blood Glucose Control in Type 2 Diabetes (J-VICTORIA) Study, which compared the effects of DPP4-Is using CGM data. The crossover design study compared a once-daily dose of 50 mg sitagliptin with a twice-daily dose of 50 mg vildagliptin. The main finding was that vildagliptin significantly improved 24-hour mean blood glucose levels, nighttime mean blood glucose levels, and peak blood glucose levels after supper. The observed improvements were interpreted as follows: administration of 50 mg sitagliptin suppressed the DPP4 activity for 24 hours by $\leq 70\%$ [17], whereas twice-daily administration of 50 mg vildagliptin suppressed the activity by $\geq 80\%$ [18]; and vildagliptin was administered twice a day, i.e., morning and evening. In comparison, our study is the first controlled study using CGM in patients treated with DPP4-Is once a day.

In another study on the effects of teneligliptin on the improvement of glycemic control over a 24-hour period, Eto *et al* reported that administration of 20 mg teneligliptin for 4 weeks increased activated GLP-1 levels for 24 hours compared with placebo [19]. The AUC at 0 to 2 hours after each meal also showed a teneligliptin-induced suppression of glucagon levels and falls in PG levels in addition to an increase in activated GLP-1 levels, although no differences were observed in insulin levels. The present study showed similar results. Although no significant difference in the 0:00 to 19:00 mean glucose level was observed between the DPP4-Is (Table 2), nighttime blood glucose

levels tended to be lower after treatment with teneligliptin, as shown in Fig. 2. This trend is probably due to the suppression of glucagon levels induced by high activated GLP-1 levels during the night. The CGM data in the present study also showed a single hypoglycemic episode (blood glucose levels of ≤ 70 mg/dl) before medical intervention, two episodes during treatment with teneligliptin, and a single episode during treatment with sitagliptin, although none of these episodes were associated with any subjective symptoms, and hypoglycemia was mild. It should be added that all the episodes of asymptomatic hypoglycemia detected before medical intervention and during treatment with teneligliptin occurred in the same patient. Because this patient had a u-CPR rate of 100 to 150 μ g/day at baseline, and since all episodes of hypoglycemia developed 3 to 5 hours after supper, the findings were assumed to be caused by postprandial reactive hypoglycemia due to insulin resistance.

The negative findings of the present study included no significant differences between before and after treatment with DPP4-Is in the standard deviation over 24 hours, 24-hour maximum glucose levels, or differences between preprandial and highest postprandial glucose levels after supper. Since adipose tissue is an important site for the expression of DPP4, previous studies in obese individuals found high serum levels of soluble DPP4/cluster of differentiation 26 [20] and strong positive correlation between serum soluble DPP4 levels and body mass index (BMI)/homeostasis model assessment-insulin resistance (HOMA-IR); the latter was also confirmed in studies of healthy individuals [21]. Meta-analyses of clinical studies using DPP4-Is have shown that reduction in HbA1c level is greater as BMI is lower [22] and as patients are older [23]. The present study was conducted in obese (mean BMI, 26.4 kg/m²; mean abdominal circumference, 94.7 cm), insulin resistant (mean HOMA-IR, 2.9; mean u-CPR, 102.5 μ g/day) patients with a mean age of 63.9 years. Future studies of older patients with milder insulin resistance who appear to respond to DPP4-Is might show more clear differences in the effects of the two drugs.

The limitations of the present crossover study are the small sample size of 14 patients and the lack of measurement of glucagon levels after supper and during the night.

In conclusion, the present study demonstrated the difference of once-daily doses of DPP4-Is of different half-lives, and that once-daily teneligliptin improved the AUC for plasma glucose at 20:00 to 24:00 (≥ 140 mg/dl) after the meal tolerance test and also significantly increased the levels of activated GLP-1 after the test meal.

Acknowledgments

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Conflicts of Interest

Y Okada and Y Tanaka have received consultancy fees from MSD, Ono Pharmaceutical Corporation and Mitsubishi Tanabe Pharmaceutical Corporation. The other authors declare no conflict of interest.

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2型糖尿病患者における半減期の異なる2種類のdipeptidyl peptidase 4阻害薬テネリグリプチンとシタグリプチンの血糖変動およびGLP-1に対する効果の比較検討

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要 旨：今回我々は、日本人2型糖尿病患者において、半減期の異なる dipeptidyl peptidase 4 (DPP4) 阻害薬であるテネリグリプチンとシタグリプチンによる血糖変動と glucagon like peptide-1 (GLP-1) 分泌に対する効果に関して検討した。14名の薬剤未使用2型糖尿病患者をテネリグリプチン 20 mg 先行群(7名)もしくはシタグリプチン 50 mg 先行群(7名)へ無作為に割り付けクロスオーバーで7日間ずつ内服した。食事負荷試験は夕食時に薬剤なし、それぞれのDPP4阻害薬内服下で施行した。各薬剤の血糖変動に対する効果は、continuous glucose monitoring (CGM) を用いて評価した。主要評価項目である夕食後最大血糖値は2群間で有意差は認めなかった。副次評価項目である夕食後18:00-24:00における血糖値 140 mg/dl 以上の area under the curve (AUC) は2群間で有意差は認めなかったが、夕食後20:00-24:00における血糖値 140 mg/dl 以上の AUC はテネリグリプチンの方が有意にコントロール良好であった ($P=0.048$)。また食事負荷30分後の GLP-1 はテネリグリプチンの方が有意に高値であった ($P=0.030$)。数例で無症候性の低血糖を認めたが、両薬剤とも重大な有害事象は認めなかった。1日1回内服のテネリグリプチンは、食事負荷試験において20:00-24:00における血糖値 140 mg/dl 以上の AUC を改善させ、活性型 GLP-1 を増加することが明らかとなった。

キーワード：グルカゴン様ペプチド-1, 持続血糖モニタリング, ジペプチジルペプチダーゼ 4 阻害薬。