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Effects of 50 mg vildagliptin twice daily *vs*. 50 mg sitagliptin once daily on blood glucose fluctuations evaluated by long-term self-monitoring of blood glucose

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Abstract. To date, several clinical trials have compared differences in glucose fluctuation observed with dipeptidyl peptidase-4 inhibitor treatment in patients with type 2 diabetes mellitus. However, most patients were assessed for limited periods or during hospitalization. The aim of the present study was to evaluate the effects of switching from sitagliptin to vildagliptin, or vice versa, on 12-week glucose fluctuations using self-monitoring of blood glucose in the standard care setting. We conducted a multicenter, prospective, open-label controlled trial in Japanese patients with type 2 diabetes. Thirty-two patients were treated with vildagliptin (50 mg) twice daily or sitagliptin (50 mg) once daily and were allocated to one of two groups: vildagliptin treatment for 12 weeks before switching to sitagliptin for 12 weeks, or vice versa. Daily profiles of blood glucose were assessed several times during each treatment period, and the mean amplitude of glycemic excursions and M-value were calculated. Metabolic biomarkers such as hemoglobin A1c (HbA1c), glycated albumin, and 1,5-anhydroglucitol were also assessed. With vildagliptin treatment, mean amplitude of glycemic excursions was significantly improved compared with sitagliptin treatment (57.9 ± 22.2 *vs*. 68.9 ± 33.0 mg/dL; p=0.0045). M-value (p=0.019) and mean blood glucose (p=0.0021) were also lower with vildagliptin, as were HbA1c, glycated albumin, and 1,5-anhydroglucitol. There were no significant differences in other metabolic parameters evaluated. Reduction of daily blood glucose profile fluctuations by vildagliptin was superior to that of sitagliptin in Japanese patients with type 2 diabetes.

Key words: Blood glucose fluctuation, DPP-4 inhibitors, Type 2 diabetes mellitus

ONE MATTER to be resolved in patients with type 2 diabetes mellitus (T2DM) is prevention of cardiovascular disease (CVD); there is a markedly high incidence of CVD compared with those without diabetes [1]. Hyperglycemia and other metabolic risk factors have been reported to contribute to this risk elevation [2-4]. Although comprehensive care of risk factors for CVD includes glycemic control as well as treatment of hypertension, hyperlipidemia, and hyperuricemia, the rate of mortality remains higher in patients with diabetes [5]. Therefore, prevention and improvement of atherosclerosis are as important as maintaining favorable blood glucose conditions. Although several anti-diabetic chemical agents are administered based on patient diabetic status, hypoglycemic drugs that can suppress the risk of CVD are limited. For these reasons, anti-diabetic agents that exert anti-atherosclerotic effects would be beneficial. It has recently been reported that fluctuation in blood glucose levels is closely related to endothelial cell damage [6], which is the first stage of atherosclerosis. It is therefore important to control not only glycemic surrogate markers (including glycosylated hemoglobin A1c [HbA1c]) but also glycemic variability to prevent CVD. Although some hypoglycemic agents have been used to manage glycemic fluctuation, dipeptidyl peptidase-4 (DPP-4) inhibitors are frequently prescribed because of their glucose level-dependent hypoglycemic mechanism and safety profile. These drugs not only improve HbA1c and glycemic control, but also are expected to have anti-atherosclerotic and β-cell protective effects [7-9]. Although DPP-4 inhibitors

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differ in structure, metabolism, potency and half-life [10], differences in clinical outcomes have not yet been fully elucidated. Therefore, we compared differences in glucose fluctuation for two DPP-4 inhibitors, sitagliptin and vildagliptin, in long-term ambulatory care using self-monitoring of blood glucose (SMBG).

Materials and Methods

Study population

We enrolled 32 subjects with T2DM from Hokkaido University Hospital and two medical service units located in Hokkaido. We included patients aged over 20 years with T2DM receiving treatment with sitagliptin at 50 mg per day (the approved dose in Japan) or vildagliptin at 100 mg per day for more than 3 months and with a HbA1c in the range from 6.2% to 8.3%. Patients on insulin therapy or pregnant women were excluded. We also excluded patients who had inadequate blood pressure and plasma lipid controls, persistent elevation of serum transaminase levels (more than three times the upper limit of normal range), or severe renal dysfunction (estimated GFR <30 mL/min/1.73 m^2).

Study protocol

This was a multicenter, open-label, prospective, controlled trial. The protocol for the present study is illustrated in Fig. 1. All individuals started to measure their fasting blood glucose levels at least three times each week using an SMBG system following enrollment, and performed 7-point SMBG measurements (before and 2 hours after each meal, and at bedtime) once every 1 or 2 weeks for 12 weeks. After the 12-week period, DPP-4 inhibitors were switched (sitagliptin 50 mg once daily to vildagliptin 50 mg twice daily, and vice versa) and treatment proceeded for an additional 12 weeks. SMBG samples were obtained from the finger and measured using a One Touch Ultra blood glucose meter (Johnson & Johnson, New Brunswick, NJ, USA). The accuracy for this system has been reported and produced coefficients of variation of <5%, with a measurable range from 20 to 600 mg/dL [11]. Serum biomarkers, including fasting plasma glucose, HbA1c, glycated albumin, and 1,5-anhydroglucitol (1,5AG), were assessed at 0, 12, and 24 weeks. The primary endpoint of the study was the extent of change in the mean amplitude of glycemic excursions (MAGE) over 12 weeks. MAGE assessed by SMBG was calculated as described previously [12]. Briefly, MAGE was calculated for each subject by taking the arithmetic mean of the SMBG values increased or decreased (from nadirs to peaks or vice versa) when both ascending and descending segments exceeded the value of one standard deviation of the SMBG values for the same 24-hour period. Secondary endpoints were M-values of blood glucose fluctuation, mean blood glucose levels of SMBG, changes in metabolic parameters, and surrogate markers of β-cell function. M-values were the average of the M × (SMBG/SMBG) values, and M × (SMBG/SMBG) = 10 × $[\log (BG/120)]^3$. Hypoglycemia was defined as blood glucose levels less than 70 mg/dL. All patients were encouraged to

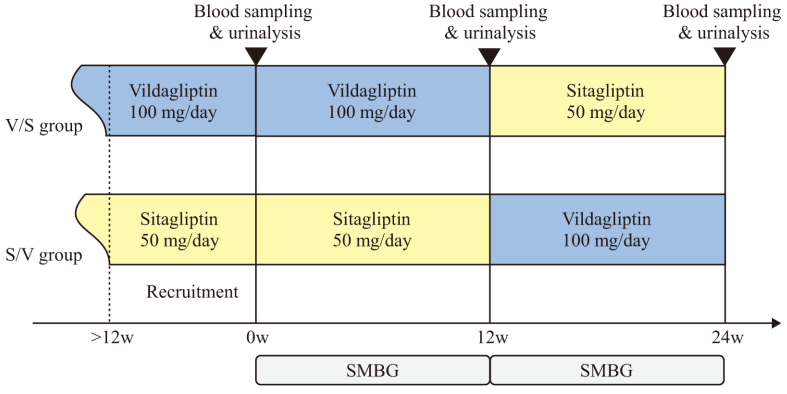


Fig. 1 Study protocol

Patients were allocated to one of two groups that received vildagliptin for 12 weeks before switching to sitagliptin for 12 weeks, or vice versa. Self-monitoring of blood glucose (SMBG) measurement systems were distributed to all patients and seven-point SMBG measurements (daily profile of blood glucose levels before and 2 hours after each meal, and at bedtime) were performed during the trial. Seven-point SMBG data were collected more than once each week over the 24-week study period. V/S, vildagliptin to sitagliptin; S/V, sitagliptin to vildagliptin.

continue diet and exercise therapy during the study and were advised not to change their levels of daily activity. Changes in anti-hyperglycemic agents, except for DPP-4 inhibitor switching at 12 weeks, were not allowed during the study period. For biochemical analysis, low-density lipoprotein (LDL)-cholesterol levels were calculated using the Friedewald formula. Plasma immunoreactive insulin (IRI), C-peptide immunoreactivity (CPR), and interleukin 6 (IL-6) were measured by chemiluminescent enzyme immunoassay. Proinsulin and glucagon, oxidized LDL, and tumor necrosis factor-alpha (TNF-α) were assessed by double-antibody radioimmunoassay and enzyme-linked immunosorbent assay, respectively (SRL, Inc, Tokyo, Japan).

Statistical analysis

The sample size was determined using the assumption that vildagliptin would improve MAGE by at least 25 mg/dL (SD = 22.6) compared with sitagliptin, based on a previous study that directly compared differences in MAGE between 100 mg sitagliptin per day and vildagliptin at 100 mg per day [13]. It was determined that 26 patients were needed to detect a significant difference with 80% power and statistical significance of 5%. To account for the potential loss of subjects, the sample size was set at 40 patients (20 per group). Results are expressed as means ± standard deviations (SD) or medians and 25–75% quartile. We employed the paired *t*-test or Wilcoxon signed test. The Kolmogorov–Smirnov test for normality was used to determine the appropriate statistical test for the continuous variables. A p-value <0.05 was considered statistically significant. Data were analyzed using Ekuseru-Toukei 2012 software (Social Survey Research Information, Tokyo, Japan).

Ethics statement

The present study was reviewed and approved by the institutional review board of Hokkaido University and written consent was obtained from all participants. The study has been registered in the UMIN Clinical Trials Registry System under the identifier UMIN 000005627.

Results

Patients' enrollment and baseline characteristics

In total, 32 patients (16 men and 16 women) were enrolled, completed the initial examination, and commenced SMBG measurement. All of the patients completed the study and SMBG measurements were well tolerated. The average age of patients was 59.8 ± 10.3 years, and mean HbA1c levels were 7.3 ± 0.6%. Baseline characteristics of participants are shown in Table 1. All participants had used sitagliptin or vildagliptin for more than 3 months at the time of enrollment (n =18, sitagliptin; n = 14, vildagliptin). The duration of DPP-4 inhibitor treatment before study enrollment was not significantly different (Table 1). Treatment with other anti-diabetic agents including sulfonylurea, metformin, thiazolidine, and alpha-glucosidase inhibitors was maintained, and concomitant medications were not changed throughout the study period.

Table 1 Baseline patient characteristics (n=32)

Characteristics	Values (V/S group, n=14)	Values (S/V group, n=18)
Age (years)	59.4 ± 12.1	60.2 ± 9.0
Gender (male/female)	6/8	10/8
Body mass index (kg/m^2)	24.9 ± 2.1	25.0 ± 4.8
Diabetes duration (year)	9.4 ± 6.4	14.8 ± 7.5
HbA1c (%)	7.2 ± 0.5	7.0 ± 0.7
Glycated albumin (%)	18.3 ± 1.8	18.3 ± 3.9
1,5-anhydroglucitol (μg/mL)	7.8 ± 4.5	10.5 ± 6.2
AST (IU/L)	21.5 (20.0-31.3)	23.0 (19.3-29.0)
ALT (IU/L)	24.0 (18.3-36.5)	22.5 (17.3-37.0)
GGT (IU/L)	30.5 (24.3-55.3)	26.0 (19.3-35.0)
eGFR (mL/min/1.73m^2)	68.9 ± 16.8	80.0 ± 17.7
Treatment of diabetes		
None (diet/exercise only)	4	0
Sulfonylurea	7	13
Metformin	10	13
Thiazolidine	1	2
Alpha-glucosidase inhibitor	0	1
Glinide	0	0
Insulin	0	0
Pretreatment duration of DPP-4 inhibitors (months)	6.0 (3.0-12.0)	7.0 (5.8-11.8)
Treatment of comorbidity		
ARB/ACE inhibitor	6	11
Statin	8	9
Complications		
Hypertension	7	11
Dyslipidemia	12	15
Diabetic retinopathy	1	2
Diabetic nephropathy	3	6
Diabetic neuropathy	8	9

Data are mean ± SD, Median (25-75%) or n. HbA1c, hemoglobin A1c; GGT, γ-glutamyltransferase; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme; V/S, vildagliptin to sitagliptin; S/V, sitagliptin to vildagliptin.

Blood glucose fluctuations

The 12-week values for MAGE, which reflect daily fluctuations in blood glucose and was the primary endpoint of this study, are shown in Table 2 and the Supplementary Fig. 1. The frequency of SMBG measurements was not different in both groups during each treatment period (Table 2). Vildagliptin treatment was associated with significantly lower MAGE than sitagliptin (p=0.0045). Moreover, M-value (p=0.019) and mean blood glucose (p=0.0021) were also significantly improved with vildagliptin treatment. Seven-point SMBG measurements revealed that vildagliptin treatment was associated with significantly lower postprandial blood glucose levels than sitagliptin, but only for measurements taken after dinner (p<0.001) (Fig. 2). However, a significantly high frequency of hypoglycemia was observed during the vildagliptin treatment period (Table 2). There were no obvious correlations observed between the degree of change in MAGE and other baseline characteristics (Table 3).

Glycemic control and metabolic parameters

Vildagliptin treatment also significantly improved all of the measured surrogate biomarkers related to blood glucose conditions (HbA1c, p=0.015; glycated albumin, p=0.010; and 1,5AG, p=0.018) compared with sitagliptin. There were no significant differences in atherosclerotic and other biochemical parameters, such as lipid profiles and inflammatory markers, observed between the drugs (Table 4). We also demonstrated that effects on β-cell function, as assessed by the proinsulin/insulin ratio and C-peptide index, were not significantly different between these agents.

Table 2 Parameters of glucose fluctuations and hypoglycemia over 12 weeks in patients treated with vildagliptin (100 mg daily) or sitagliptin (50 mg daily) (n=32)

	Vildagliptin	Sitagliptin	p-value
MAGE (mg/dL)	57.9 ± 22.2	68.9 ± 33.0	0.0045
M-value	20.6 (11.1–33.1)	29.3 (20.6–48.5)	0.0019 *
Mean glucose level (mg/dL)	151.0 ± 31.6	157.5 ± 28.7	0.0021
Total SMBG measurements (times/patients)	99.3 ± 39.0	101.5 ± 43.4	0.70
Hypoglycemia (times/patients)	1.82 ± 3.23	0.84 ± 1.85	0.013 *

Data are mean ± SD or median (25–75%CI). Paired t-test or Wilcoxon signed-rank test. * By Wilcoxon signed-rank test. MAGE, mean amplitude of glycemic excursions; SMBG, self-monitoring of blood glucose.

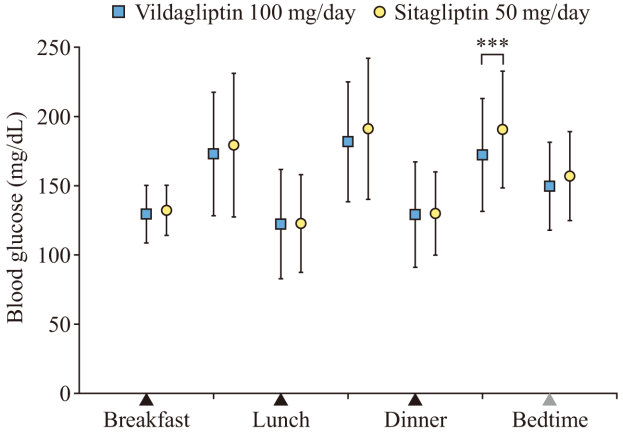


Fig. 2 Glucose levels over 12 weeks of treatment with vildagliptin or sitagliptin in 32 patients

Several time points of seven-point self-monitoring of blood glucose were captured during the study periods. Vildagliptin treatment was associated with significantly lower postprandial blood glucose levels than sitagliptin, but only for measurements taken after dinner. Data are mean ± SD. Paired t-test. *** p < 0.001.

Table 3 Relationship between changes in MAGE by vildagliptin compared with sitagliptin and other baseline parameters (n=32)

Variables	r	p-value for the Spearman's rank-correction
Age (years)	0.1084	0.55
Diabetes duration (years)	0.0062	0.96
Body mass index (kg/m^2)	0.2327	0.20
HbA1c (%)	−0.0303	0.87
1,5-anhydroglucitol (μg/mL)	0.2101	0.25
FPG (mg/dL) *	0.0313	0.87
Fasting IRI (μU/mL)	0.2719	0.13
Fasting CPR (ng/mL)	0.1756	0.34
Glucagon (pg/mL) **	0.0265	0.89
eGFR (mL/min/1.73m^2)	0.0092	0.96

* Data were obtained from 31 patients. ** Data were obtained from 30 patients. HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity; eGFR, estimated glomerular filtration rate.

Table 4 Post-treatment changes in metabolic parameters in patients treated with vildagliptin (100 mg daily) or sitagliptin (50 mg daily) (*n*=32)

	Vildagliptin	Sitagliptin	*p*-value
HbA1c (%)	7.0 (6.7-7.4)	7.2 (6.9-7.6)	0.015 §
Glycated albumin (%) *	17.7 ± 3.0	18.3 ± 3.0	0.010
1,5-anhydroglucitol (μg/mL) *	7.7 (5.4-13.6)	7.5 (4.3-11.2)	0.018 §
FPG (mg/dL) **	139.8 ± 28.2	135.0 ± 35.2	0.45
Fasting IRI (μU/mL) *	6.4 (3.2-9.4)	4.9 (2.9-8.9)	0.33 §
Fasting CPR (ng/mL) *	1.70 (0.95-2.85)	1.89 (0.97-2.35)	0.26 §
Proinsulin *	15.3 (11.1-21.2)	16.0 (12.0-25.9)	0.16 §
Proinsulin/IRI *	41.6 ± 23.7	46.0 ± 19.9	0.22
C-peptide index ***	1.1 (0.8-1.4)	1.1 (0.8-1.6)	0.73 §
Glucagon (pg/mL) ***	75.5 (64.8-107.5)	81.0 (64.8-115.5)	0.89 §
UACR (mg/g.Cre)	13.0 (8.4-39.5)	10.6 (6.5-20.1)	0.17 §
Body mass index (kg/m^2)	24.7 (22.3-25.9)	24.6 (22.3-25.8)	0.29 §
Systolic BP (mmHg)	127.3 ± 8.9	128.2 ± 10.9	0.62
Diastolic BP (mmHg)	75.5 (64.8-80.0)	76.0 (65.0-80.0)	0.81 §
HDL-C (mg/dL)	56.5 ± 12.7	54.0 ± 14.1	0.073
Triglyceride (mg/dL) **	124.0 ± 58.3	131.1 ± 65.2	0.38
LDL-C (mg/dL) **	102.6 ± 24.0	100.7 ± 26.4	0.56
Oxidized LDL-C (U/L) ****	120.0 (86.0-172.0)	111.0 (95.0-168.0)	0.88 §
Free fatty acid (μEq/L)	422.5 ± 168.6	436.5 ± 132.4	0.75
IL-6 (pg/mL) *	9.3 (2.1-396.5)	8.8 (2.1-202.5)	0.071 §
TNF-α (pg/mL) *	20.8 (1.1-45.0)	10.6 (1.2-27.1)	0.064 §

* Data were obtained from 27 patients. ** Data were obtained from 31 patients. *** Data were obtained from 26 patients. **** Data were obtained from 25 patients. Data are mean ± SD or median (25–75%CI). Paired *t*-test or Wilcoxon signed-rank test. § By Wilcoxon signed-rank test. HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity; UACR, urine albumin to creatinine ratio; BP, Blood pressure; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha. Paired *t*-test.

Discussion

Incretin agents, including DPP-4 inhibitors, reduce glucose fluctuations by increasing glucose-dependent insulin secretion and inhibiting glucagon release [14]. These agents also play an important role in avoiding hypoglycemia by diminishing insulin secretion and preventing glucagon secretion under normo- to hypoglycemic conditions [15]. A previous study of the efficacy of DPP-4 inhibitors in addition to metformin treatment in T2DM showed that DPP-4 inhibitors significantly reduced glucose variability [16]. Moreover, a crossover study comparing 100 mg/day vildagliptin and 2 mg/day glimepiride in addition to metformin in patients with T2DM showed that vildagliptin was associated with relatively lower glucose fluctuations than glimepiride [17]. Although DPP-4 inhibitors were found to flatten glucose fluctuation from these clinical evidences, the differences among the different DPP-4 inhibitors were not fully elucidated.

In the present study, we aimed to clarify the differences in glucose fluctuations in real-world conditions following treatment with two frequently used DPP-4 inhibitors, vildagliptin and sitagliptin. Both MAGE and M-value data suggested that vildagliptin had a significantly more potent effect on glucose fluctuations compared with sitagliptin. SMBG data showed that vildagliptin significantly suppressed postprandial glucose levels after dinner, although no differences were observed at other time points. This reduction may be accounted for by the pharmacological differences in DPP-4 activity exhibited by these drugs over 24 h. Vildagliptin (50 mg, twice daily) suppressed >80% of DPP-4 activity over the 24-h period, whereas a single dose of sitagliptin (50 mg, once daily) was reported to inhibit >80% of DPP-4 activity for almost 14 h [18, 19]. Furthermore, a previous meta-analysis reported that even 100 mg sitagliptin was slightly inferior to 100 mg vildagliptin in the weighted average inhibition of DPP-4 [20]. Regarding differences between

the DPP-4 inhibitor effects on MAGE in Caucasian and Asian patients with T2DM, several studies have been published with inconsistent results. Some trials showed that 100 mg/day vildagliptin was significantly more effective in decreasing MAGE than 50 or 100 mg/day sitagliptin [13, 18, 19], although our previous study comparing 100 mg/day vildagliptin and 100 mg/day sitagliptin in insulin-treated T2DM patients did not support these findings [21]. These studies evaluated continuous glucose monitoring (CGM) and glucose fluctuations over several days, and most were conducted during hospitalization or out patients who were served nutrient-controlled meals. The novelty of our study was that all SMBG data were collected in the ambulatory care setting. Under these conditions, patients did not have a fixed daily calorific balance, and both snack intake and meal timing were flexible; therefore, our data better reflect real-world conditions. Moreover, we obtained seven-point SMBG data over a relatively long study period, whereas CGM assessments are performed only for several days, meaning that variation in CGM data because of daily activity may be partially suppressed. Our study indicates that 100 mg/day vildagliptin may be more beneficial than 50 mg sitagliptin under controlled, non-uniform conditions.

We also showed that vildagliptin significantly improved mean blood glucose levels (SMBG), postprandial hyperglycemia after dinner, HbA1c, glycated albumin, and 1,5AG compared with sitagliptin treatment without affecting any other metabolic biomarkers or β-cell function; however, the frequency of hypoglycemia increased. A previous CGM study comparing 100 mg vildagliptin *versus* 100 mg sitagliptin with metformin reported that both agents equally improved 24-h glucose variability and postprandial hyperglycemia, although a significant reduction of overall hyperglycemia and pre-prandial hyperglycemia was observed only following treatment with vildagliptin but not sitagliptin [16]. These results seemed to be partially inconsistent with our study. One of the reasons may be that this study described postprandial hyperglycemia using integration of AUC of each postprandial glucose measure; however, we compared SMBG data after each meal. A recent comparison study that assessed the efficacy of HbA1c reduction with 50 mg or 100 mg sitagliptin *versus* 100 mg vildagliptin in a Japanese T2DM population also showed that vildagliptin at 50 mg twice daily was significantly associated with greater HbA1c reduction than sitagliptin at 50 mg or 100 mg once daily [22]. Furthermore, in another study where 50 mg sitagliptin was switched to 100 mg sitagliptin or 100 mg vildagliptin, 100 mg vildagliptin (but not 100 mg sitagliptin) was shown to significantly lower HbA1c levels [21]. In terms of the effects on anti-inflammatory and lipid profiling, incretin drugs including DPP-4 inhibitors have been shown to possess favorable roles by mediation of several pathways: attenuation of TNF-α mediated induction of PAI-1 expression [23]; prevention of reactive oxygen species-induced cell senescence in endothelial cell lines [24]; and increasing serum adiponectin levels [25]. Moreover, many basic studies have demonstrated a protective effect of DPP-4 inhibitors on pancreatic β-cells, including reduction of apoptosis [9, 26], for which one of the possible protective pathways is the antioxidant response [27]. Although both sitagliptin and vildagliptin were similarly expected to exert these effects and vildagliptin treatment significantly improved glucose fluctuations, we could not find obvious differences between these agents in the present study. This might be partially explained by the high incidence of hypoglycemia observed during the vildagliptin treatment periods.

Recent clinical studies have shown that control of both hypoglycemia and postprandial hyperglycemia is important for inhibiting the development of CVD [28, 29]. It is critical that diabetic therapy not only achieves the ideal HbA1c level, but also controls glucose fluctuations to prevent the development of vascular complications. Therefore, 50 mg twice daily of vildagliptin may be more beneficial than 50 mg of sitagliptin in the Japanese population in flattening glucose fluctuations; however, we have to take care of underlying hypoglycemia.

The major limitations of the present study were the small sample size and lack of double blinding. In addition, the sample size was calculated from a previous study using 100 mg per day sitagliptin. Moreover, the study was conducted in a standard clinical practice setting and did not use CGM assessment. To resolve these potential issues, we employed multiple seven-point SMBG measurements during the study period.

In conclusion, vildagliptin (50 mg twice daily) showed significant and potent effects compared with sitagliptin (50 mg once daily) both on daily blood glucose variability and improvement of the glycemic surrogate markers HbA1c, glycated albumin, and 1,5AG in Japanese T2DM patients.

Role of Contributors

HN and KK contributed to the data analysis and wrote the manuscript. HN, KK, HM, HK, SN, and TK contributed to patient enrollment. HM, AN, and TA contributed to the discussion, and reviewed and edited the manuscript. HM designed and performed the research and wrote the manuscript. HM is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Conflicts of Interest

HM has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Dainippon Pharma Co., Eli Lilly, Kissei, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma, and Sanofi, and has received research funding from Astellas Pharma Inc., AstraZeneca, Eli Lilly, Mitsubishi Tanabe Pharma Co.

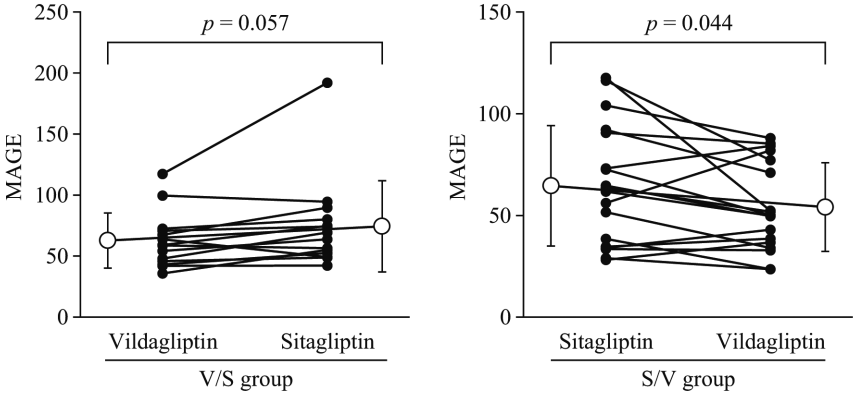
AN has received honoraria for lectures from Sanofi.

SN has received fees for promotional materials from Eli Lilly and AstraZeneca.

TK has received honoraria for lectures from AstraZeneca, MSD and Ono Pharmaceutical Co., Ltd.

TA has received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd, Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd, Pfizer Inc., and AbbVie Inc., and has received research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, and Otsuka Pharmaceutical Co., Ltd.

HN, KK, HK and KYC have no conflicts of interest to declare.



Supplementary Fig. 1 Comparison of individual changes of MAGE before and after changing from vildagliptin to sitagliptin or vice versa.

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