ORIGINAL

Advance Publication
doi: 10.1507/endocrj. EJ13-0198

# Efficacy and safety of sitagliptin as add-on therapy on glycemic control and blood glucose fluctuation in Japanese type 2 diabetes subjects ongoing with multiple daily insulin injections therapy

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**Abstract**. To assess the efficacy and safety of adding sitagliptin, an oral dipeptidyl peptidase-4 inhibitor, in subjects with type 2 diabetes inadequately controlled with multiple daily insulin injections therapy (MDI). HbA1c, 1,5-anhydroglucitol (1,5-AG), body mass index (BMI), insulin doses, six-point self-measured plasma glucose (SMPG) profiles were assessed before, after 12 weeks, and after 24 weeks of MDI with 50 mg/day of sitagliptin in 40 subjects with type 2 diabetes. Safety endpoints included hypoglycemia and any adverse events. HbA1c significantly decreased during the first 12 weeks (−0.64 ± 0.60 %), and was sustained over 24 weeks (−0.69 ± 0.85 %). 1,5-AG increased significantly from 7.5 ± 4.5 μg/mL at baseline to 9.6 ± 5.5 μg/mL after 24 weeks. The bolus insulin dose at 12 weeks was decreased, and the mean plasma glucose, the SD of daily glucose, M-value, and the mean amplitude of glycemic excursions (MAGE) also decreased significantly as compared with baseline values. BMI and frequency of hypoglycemia were not changed significantly. Univariate linear regression analyses revealed that % change in HbA1c was significantly associated with BMI, and % changes in the indexes of glycemic instability (SD of daily glucose and MAGE) were significantly associated with age. In conclusion, adding sitagliptin to MDI significantly improved glycemic control and decreased the daily glucose fluctuation in subjects with type 2 diabetes inadequately, without weight gain or an increase in the incidence of hypoglycemia. This trial was registered with UMIN (no. UMIN000010157).

*Keywords*: Multiple daily insulin injections therapy (MDI), Sitagliptin, Hypoglycemia, Weight gain, Self-measured plasma glucose (SMPG)

**INSULIN** remains the most potent anti-hyperglycemic agent available for uncontrolled subjects with type 2 diabetes. Recent studies demonstrate that the addition of basal, prandial, premixed insulin or multiple daily insulin injections therapy (MDI) to existing anti-hyperglycemic regimens effectively lowers HbA1c [1]. Among these regimens, MDI regimen could potentially result in a smoother, less variable 24-h glucose profile with comparable HbA1c level to conventional insulin regimens, because MDI regimens more closely mimic the physiological requirements for insulin [2, 3]. A recent meta-analysis of 16 randomized control trials showed that the best rate of achievement of a HbA1c target of <7.0 % was observed with MDI regimens [4]. We also have demonstrated that intensive insulin therapy using MDI could delay the onset and/or progression of diabetic microvascular complications in subjects with type 2 diabetes in Kumamoto Study [5, 6].

Submitted May 11, 2013; Accepted Jul. 8, 2013 as EJ13-0198
Released online in J-STAGE as advance publication Aug. 3, 2013

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Abbreviations: MDI, multiple daily insulin injections therapy; 1,5-AG, 1,5-anhydroglucitol; BMI, body mass index; SMPG, self-measured plasma glucose; MPG, mean plasma glucose; MAGE, mean amplitude of glycemic excursions; CGM, continuous glucose monitoring.

In addition to the benefit above mentioned, it is also known that MDI therapy applied to uncontrolled subjects is associated with weight gain and severe hypoglycemia when applied to uncontrolled subjects, since more intensive therapy aimed at tighter glycemic control is usually associated with more weight gain and hypoglycemia when compared with less intensive treatment [1, 7-12]. Furthermore, in clinical practice, approximately 60 % of the subjects using MDI did not achieve HbA1c <7.0 % within 3-9 months of initiating MDI [13].

Notably, dipeptidyl peptidase-4 (DDP-4) inhibitors are less frequently associated with weight gain and/or hypoglycemia than other hypoglycemic agents except for metformin [14-18]. Sitagliptin is the most widely used because it is the first DPP-4 inhibitor approved in Japan and its efficacy and safety have been proven in Japanese clinical practice [15, 19]. It has been reported that the addition of DPP-4 inhibitors to the existing insulin therapy significantly improves the glycemic control of subjects of type 2 diabetes [19-27]. However, there has been only two prospective studies to investigate effects of sitagliptin on glycemic control in their subgroup analyses with small number of subjects (less than 15 subjects) receiving MDI [25, 27], and it remains unclear whether the combination of sitagliptin and MDI can improve blood glucose fluctuation without weight gain or an increase in the incidence of severe hypoglycemia.

The present study is the first report that focusing on evaluating the efficacy and safety of sitagliptin on glucose control and blood glucose fluctuation in type 2 diabetes subjects ongoing with MDI.

## Materials and Methods

### *Subject and study design*

The study included 40 subjects with type 2 diabetes who visited our medical institutions as outpatients. The study was designed in accordance with the principles stated in the Declaration of Helsinki. All subjects gave written informed consent to the study. The study protocol was approved by the ethics committee of Kumamoto University (approval number 1611).

Eligible subjects were type 2 diabetes treated with MDI at dose of at least 10 units/day and for at least 12 months, aged ≥20 years, HbA1c level ≥6.9 %, and no improvement in HbA1c within 12 weeks. Subjects with type 1 diabetes, secondary diabetes, severe renal disease, severe hepatic disease, alcoholism, severe depression or severe psychological condition, malignancy or abnormal hemoglobinemia were excluded. Subjects who had received a blood transfusion within 4 months before the start of the study, and pregnant and nursing women were also excluded. Subjects who were taking medications, aside from antidiabetic medications, known to affect glycemic control, such as glucocorticoids were also excluded. Antidiabetic agents containing insulin, antihypertensive agents, statins or fibrates were not newly administered or their doses were not increased or changed from 16 weeks before the start until the end of the study. In subjects, sitagliptin was added at 50 mg once daily without changing the insulin dosage. Investigators were allowed to decrease a subject's insulin dose according to their clinical judgment only in the event of hypoglycemic episode. The subjects were asked not to alter their lifestyle, including diet, exercise, and habits during the study.

### *Study measurements*

#### Efficacy

The values of HbA1c, 1,5-anhydroglucitol (1,5-AG), BMI, insulin doses, six-point self-measured plasma glucose (SMPG) profiles at baseline were compared with those after 12 weeks and 24 weeks of treatment. Subjects were asked to complete 1-day six-point glucose profile (pre-breakfast, 2 h post-breakfast, pre-lunch, 2 h post-lunch, pre-dinner, and 2 h post-dinner) at baseline, after 12 weeks and after 24 weeks. Subjects used SMPG meter, Medisafe-Mini (Terumo Corporation, Tokyo, Japan), which is based on the optoelectric colorimetry method. Six-point glucose measurements were analyzed to calculate the mean plasma glucose (MPG), the SD of daily glucose, M-value of Schlichtkrull [28], and the mean amplitude of glycemic excursions (MAGE) [29], as indexes of glycemic instability.

#### Safety

Safety endpoints included the incidence of hypoglycemic episodes and incidence of adverse events, and clinical laboratory assessments. Hypoglycemia was reported as any symptomatic event with cognitive and/or adrenergic signs with or without confirmation of plasma glucose. Severe hypoglycemia was defined as any symptomatic event requiring assistance by another person. The frequency of hypoglycemic episodes from 12 weeks before the addition of sitagliptin was compared with that from start to 12 weeks post treatment period.

HbA1c was measured by high-performance liquid chromatography. 1,5-AG levels were measured by

enzymatic, colorimetric assay (Lana 1,5AG auto liquid; Nippon Kayaku Co., Ltd., Tokyo, Japan) in a private laboratory (BML, Inc., Tokyo, Japan).

***Statistical analysis***

Data are expressed as means ± standard deviation. Changes in clinical parameters following sitagliptin administration were evaluated by paired *t* tests or Wilcoxon signed-rank test. To identify predictors of reductions of HbA1c following sitagliptin addition, Pearson's correlation coefficient analysis was used to evaluate univariate correlations between the reductions in HbA1c and individual baseline characteristics. Similarly, univariate correlations between the improvements in the indexes of glycemic instability (1,5-AG, SD of daily glucose, M-value and MAGE) and individual baseline characteristics were determined. *P*-values of less than 0.05 were considered to be statistical significant. Data analysis was performed using SPSS software version 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

***Subjects characteristics***

The characteristics of the subjects at baseline are shown in Table 1. All 40 subjects completed the trial. Thirty subjects had completed six-point SMPG at baseline, after 12 weeks, and 24 weeks of treatment.

**Table 1** Demographic and baseline characteristics of the study subjects

| Characteristics | Value |
|---|---|
| Males / Females | 26 / 14 |
| Age (years) | 62.5 ± 13.6 |
| BMI (kg/m$^2$) | 26.2 ± 5.4 |
| SBP (mmHg) | 135 ± 20 |
| DBP (mmHg) | 74 ± 14 |
| Creatinine (mg/dL) | 0.78 ± 0.23 |
| HbA1c (%) | 8.0 ± 1.1 |
| 1,5-AG (μg/mL) | 7.5 ± 4.5 |
| Duration of diabetes (years) | 15.3 ± 8.5 |
| Duration of MDI (years) | 5.3 ± 4.2 |
| Insulin, *n* (%) | |
| Bolus insulin | |
| Aspart | 25 (62.5) |
| Lispro | 13 (32.5) |
| Regular | 2 (5.0) |
| Basal insulin | |
| Detemir | 21 (52.5) |
| Glargine | 17 (42.5) |
| NPH | 2 (5.0) |
| Antidiabetic agents, *n* (%) | |
| α-glucosidase inhibitor | 5 (12.5) |
| Voglibose | 2 (5.0) |
| Migritol | 3 (7.5) |
| Biguanide | 11 (27.5) |
| Thiazolidinedione | 1 (2.5) |

Data are means ± SD or *n*.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; MDI, multiple daily insulin injections; NPH, neutral protamine hagedorn

***Clinical efficacy***

The changes from baseline in HbA1c and 1,5-AG during the 24 weeks of treatment are shown in Fig. 1. HbA1c significantly decreased from 8.0 ± 1.1 % at baseline to 7.4 ± 1.1 % at 12 weeks ($p<0.01$) and 7.3 ± 1.3 % at 24 weeks ($p<0.01$). At 24 weeks, 42.5 % of the study subjects achieved HbA1c <7.0 %. At the same time, 1,5-AG significantly increased from 7.5 ± 4.5 μg/mL at baseline to 9.0 ± 5.2 μg/mL at 12 weeks ($p<0.01$) and 9.6 ± 5.5 μg/mL at 24 weeks ($p<0.01$).

The six-point SMPG profiles are shown in Fig. 2. The glucose levels before each meal and at 2-h after each meal were significantly lower after 12 weeks than those at baseline, and those before dinner and at 2-h after each meal were significantly lower after 24 weeks than those at baseline. In particular, postprandial 2-h glucose levels were dramatically improved at 24 weeks (post-breakfast; −36.2 ± 46.2 mg/dL, $p<0.001$, post-lunch; −40.7 ± 49.6 mg/dL, $p<0.001$, post-dinner; −38.5 ± 46.1 mg/dL, $p<0.001$) as compared with baseline.

The mean basal insulin dose was not changed significantly, while the mean bolus insulin dose was slightly but significantly decreased from 0.346 ± 0.131 unit/kg/day to 0.330 ± 0.132 unit/kg/day at 12 weeks and to 0.322 ± 0.138 unit/kg/day units at 24 weeks ($p<0.05$, Table 2). As a result, a statistically significant decrease in total daily insulin dose was also observed both at 12 and 24 weeks ($p<0.05$, Table 2).

Despite the fact that the bolus insulin dose was decreased, the MPG, SD of the daily glucose level, and M-value significantly decreased after starting sitagliptin ($p<0.05$, Table 3). A statistically significant reduction in MAGE was also observed. The statistical significance was disappeared at 24 weeks, however, the trend in MAGE reduction was still observed at 24 weeks.

Table 4 shows the correlations between individual baseline characteristics and the % change in HbA1c {calculated as (post-treatment value – baseline value)×100 /

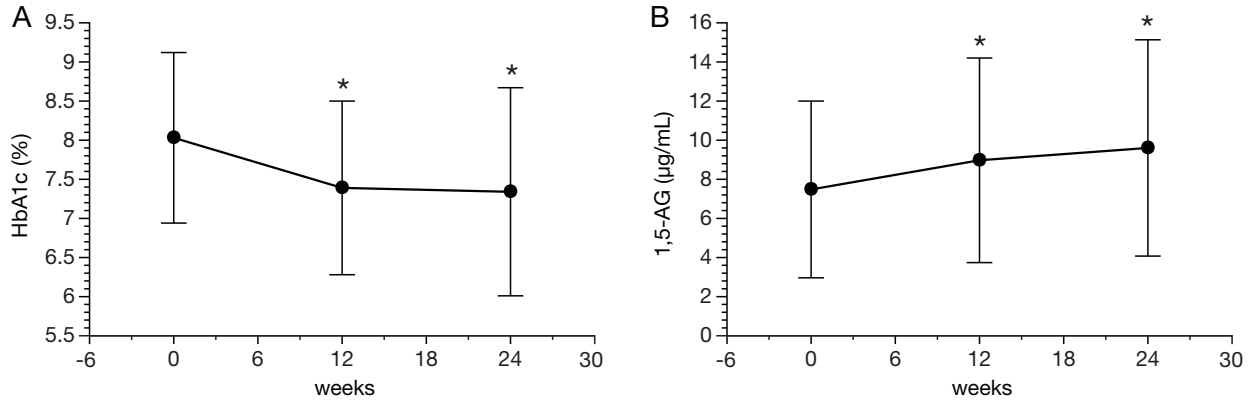


**Fig. 1** Time course of HbA1c (A) and 1,5-AG (B) during the 24 weeks of treatment. Data are means ± SD. *$p$ <0.01 vs. baseline.

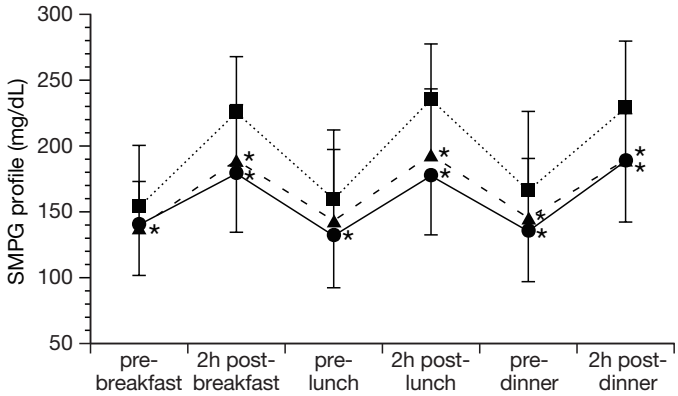


**Fig. 2** The 6-point plasma glucose profiles at baseline (squares, dotted line), 12 weeks (circles, solid line) and 24 weeks (triangles, broken line) after adding sitagliptin. Data are means ± SD. *$p$ <0.05 vs. baseline.

**Table 2** Bolus, basal and total insulin dose in a 24-week study

| | baseline | after 12 weeks | after 24 weeks |
|---|---|---|---|
| Bolus insulin dose (unit/kg/day) | 0.346 ± 0.131 | 0.330 ± 0.132* | 0.322 ± 0.138* |
| Breakfast (unit/kg/day) | 0.130 ± 0.063 | 0.123 ± 0.063* | 0.120 ± 0.065* |
| Lunch (unit/kg/day) | 0.113 ± 0.057 | 0.108 ± 0.058* | 0.104 ± 0.059* |
| Dinner (unit/kg/day) | 0.104 ± 0.041 | 0.100 ± 0.038* | 0.100 ± 0.042* |
| Basal insulin dose (unit/kg/day) | 0.194 ± 0.125 | 0.189 ± 0.130 | 0.187 ± 0.133 |
| Total insulin dose (unit/kg/day) | 0.540 ± 0.215 | 0.520 ± 0.221* | 0.509 ± 0.231* |

Data are means ± SD. *$p$ < 0.05 vs. baseline.

**Table 3** MPG, SD of daily glucose, M-value of Schlichtkrull and MAGE in a 24-week study

| | baseline | after 12 weeks | after 24 weeks |
|---|---|---|---|
| MPG (mg/dL) | 193 ± 36 | 158 ± 33* | 165 ± 35* |
| SD of daily glucose (mg/dL) | 49 ± 20 | 37 ± 17* | 38 ± 14* |
| M-value of Schlichtkrull | 21.4 ± 13.6 | 9.9 ± 8.6* | 11.9 ± 11.2* |
| MAGE (mg/dL) | 81.7 ± 36.4 | 65.7 ± 29.6* | 71.1 ± 26.0 |

Data are means ± SD. *$p$ < 0.05 vs. baseline.
MPG, mean plasma glucose; MAGE, mean amplitude of glycemic excursions

**Table 4** Correlations between individual baseline characteristics and % change in HbA1c or % change in indexes of glycemic instability at 12 weeks

| | | *r* | *p*-value |
|---|---|---|---|
| % change in HbA1c | BMI | 0.343 | 0.03 |
| % change in SD of daily glucose | age | -0.388 | 0.03 |
| % change in MAGE | age | -0.379 | 0.04 |

MAGE, mean amplitude of glycemic excursions; BMI, body mass index

baseline value} or % changes in the indexes of glycemic instability determined at 12 weeks by linear regression analysis. The result revealed that baseline BMI was significantly and positively correlated with the % change in HbA1c. On the other hand, significant negative correlations were noted between age and % change in SD of daily glucose, and between age and % change in MAGE. There was a trend in positive correlation between age and 1,5-AG, however, did not reach at statistically meaningful significance ($r$=0.318, $p$=0.07). No significant correlation was found between baseline characteristics and % change in M-value.

***Safety***

Hypoglycemia was experienced by 40 % of subjects in this study, but there was no severe hypoglycemic event. The frequency of hypoglycemic episodes (event per person-year) did not change (from 12 weeks before the addition of sitagliptin to the start of this study; 5.11 ± 8.46 events per patient-year, and from the start of this study to after 12 weeks; 6.19 ± 10.73 events per patient-year). BMI did not change during 24 weeks (at baseline; 26.2 ± 5.4 kg/m$^2$, at 12 weeks; 26.2 ± 5.4 kg/m$^2$, at 24 weeks; 26.1 ± 5.5 kg/m$^2$).

The percentage of subjects reporting adverse events (AEs) that were judged by the investigator to be possibly related to study medication was 27.5 %. The most commonly reported specific AEs related to sitagliptin were constipation (17.5 %), abdominal distension (12.5 %), nausea (10.0 %). The majority of adverse events were mild in intensity and there was no withdrawal because of AEs. There were no significant changes in other measured biochemical parameters (data not shown).

## Discussion

The addition of sitagliptin to MDI resulted in a significant improvement of HbA1c without weight gain or an increase in the incidence of hypoglycemia in subjects with type 2 diabetes inadequately controlled. Katsuno *et al*. also published the effect of DPP-4 inhibitor add-on to insulin-treated subjects with type 2 diabetes recently, and the improvement of HbA1c was significantly larger in the basal insulin therapy than in the twice daily insulin therapy or MDI [27]. MDI subgroup of their study showed that sitagliptin add-on therapy also significantly reduced HbA1c change from baseline by 0.28 % after 12 weeks treatment without changing body weight, although baseline demographic and clinical characteristics of MDI subgroup was different and the number of subjects was smaller compared with our study. On the other hand, in the present study, the addition of sitagliptin decreased HbA1c by 0.7 %, which is almost comparable to that in basal insulin therapy subgroup of their study. Our present results with larger number of subjects further expand their findings, i.e., sitagliptin add-on to MDI therapy demonstrates much greater HbA1c reduction without affecting body weight gain.

The beneficial effect of sitagliptin was mostly a lowering of the postprandial glucose in this study [30, 31], while some authors have reported that the addition of sitagliptin to long-acting insulin or biphasic insulin preparations markedly reduced not only postprandial glucose levels but also preprandial glucose levels [22, 26]. Our result was consistent with these reports, that is, combination therapy significantly decreased both pre- and postprandial glucose levels.

Differences in the glucose-lowering efficacy of DPP-4 inhibitors between Japanese and non-Japanese [32] or between Asians and non-Asians [33] were investigated by meta-analyses, and these analyses indicated that DPP-4 inhibitors are more effective for glycemic control in Asian (Japanese) subjects than in non-Asian (non-Japanese) subjects. Although there is no report in which effects of add-on therapies to insulin with DPP-4 inhibitors were examined between Asian (Japanese) subjects and non-Asian (non-Japanese) subjects at present, taken together with our present results and the fact that DPP-4 inhibitors are more efficacious in Asian subjects, the combination therapy with insulin and DPP-4 inhibitors is expected to improve glycemic control in Asian type 2 diabetes subjects, including Japanese, better than in non-Asian type 2 diabetes subjects.

A recent study has shown an association between hypoglycemic events and risk of cardiovascular events [34]. Monnier *et al*. reported that glucose fluctuations during postprandial periods and during glucose swings exhibited a more specific triggering effect on oxida-

tive stress than chronic sustained hyperglycemia [35]. Glucose variability may be an important risk factor for cardiovascular disease [36]. In the present study, MPG, SD of the daily glucose, and MAGE decreased by the addition of sitagliptin, although their bolus insulin dosage significantly decreased. Furthermore, the frequency of hypoglycemia after sitagliptin addition was not changed significantly as compared with those before sitagliptin addition. Our results demonstrated that the combined therapy with MDI and sitagliptin decreased HbA1c and achieved better control of glucose excursion. Thus, present results suggest that the addition of sitagliptin to MDI is useful and safety method for treatment to the patients with type 2 diabetes complicated with cardiovascular disease, in particular, older subjects with type 2 diabetes are known to have a higher rate of cardiovascular disease [37].

One of advantages to the sitagliptin addition strategy is the absence of weight gain observed during the 24 weeks study in the present study. The subjects of the present study were overweight, as is common in individuals with type 2 diabetes. An undesired side effect of certain antidiabetic agents is increased body weight [38], although this is typically associated with improved glycemic control [39]. Especially, the initiation of insulin therapy is often accompanied by weight gain. However, BMI did not change significantly during 24 weeks. This result supports the use of sitagliptin in patients with concerns for weight gain.

In the present study, the mean bolus insulin dose and the mean total insulin dose were significantly decreased at both 12 and 24 weeks. However, the mean HbA1c did not achieve lower than 7.0% and this reduction of insulin dose might induce the attenuation of HbA1c lowering effect by this combination therapy. Furthermore, because investigators decreased a subject's insulin dose according to their clinical judgment only in the event of hypoglycemic episode without using insulin titration algorithm, it was possible that method of insulin titration influenced the frequency of hypoglycemia episodes and weight gain. However, 42.5 % of the study subjects achieved HbA1c <7.0% and adding sitagliptin to MDI came closer to the accepted HbA1c thresholds.

It is revealed that lower BMI was significantly correlated to greater HbA1c reduction, and this result was consistent with previous reports [40-42]. We also found that higher age was significantly correlated to greater SD of daily glucose and MAGE reductions. On the other hand, no significant correlations were shown between age and % change in 1,5-AG, and between age and % change in M-value. However, the trend in positive correlation between age and 1,5-AG was observed ($r$=0.318, $p$=0.07). The precise reason for these relationships is not clear, and clarification of these relationships will require multivariate analysis in a large number of subjects in future studies. However, these findings in the current study suggest that BMI and age are predictive factors of the reduction of HbA1c and the improvements of the indexes of glycemic instability response, respectively, to sitagliptin addition in the subjects with type 2 diabetes on therapy with MDI. Recently, Rizzo *et al.* reported that MAGE reduction by DPP-4 inhibitors was associated with the reduction of glucagon by DPP-4 inhibitors in type 2 diabetic patients [43]. Previous studies established that older subjects with type 2 diabetes tend to have predominant postprandial hyperglycemia [44] and higher plasma glucagon levels than younger people [45]. Although glucagon levels were not evaluated in the present study, our results demonstrate that the reductions in the indexes of glycemic instability (SD of daily glucose and MAGE) were significantly correlated with age, therefore, these older subjects may achieve the most benefit from sitagliptin addition.

This study has several limitations and issues to be considered. First, the number of subjects enrolled was still relatively small and there was no control group in the current study. Second, since the glucose profile was examined for only 1-day six-point glucose profile at baseline, after 12 weeks and 24 weeks by SMPG and not by continuous glucose monitoring (CGM) during 24 weeks of treatment, the reliability and reproducibility of our data were not so well evaluated compared with the use of CGM. Third, contents of meals in the day of SMPG at baseline, 12-week and 24-week may be different because we did not use a test meal. Therefore, a large-scale prospective evaluation in outpatients should be performed to confirm the present results.

In conclusion, adding sitagliptin to MDI significantly improved glycemic control and decreased daily glucose excursion without weight gain or an increase in the incidence of hypoglycemia in Japanese subjects with type 2 diabetes inadequately controlled with MDI.

## Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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