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Add-on Treatment with Mitiglinide Improves Residual Postprandial Hyperglycemia in Type 2 Diabetic Patients Receiving the Combination Therapy with Insulin Glargine and Sitagliptin

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The combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor and a long-acting insulin analogue is widely used in clinical practice. However, some patients fail to achieve lower postprandial hyperglycemia. Mitiglinide, a short-acting insulinotropic sulfonylurea receptor ligand, is effective for postprandial hyperglycemia. Recently, it has been reported that the combination therapy of mitiglinide with a DPP-4 inhibitor could improve glycemic control. However, the efficacy of those under long-acting insulin analogue therapy remains to be investigated. Thus, we conducted a prospective single-center study of eight Japanese patients with type 2 diabetes mellitus receiving mitiglinide added to the combination therapy of sitagliptin and insulin glargine, and evaluated its efficacy and safety by continuous glucose monitoring (CGM). Participants' (four men and four women) mean age was 70.3 ± 10.6 years. Their mean body mass index, HbA1c level, and urinary C-peptide level were 22.0 ± 2.8 kg/m^2, 9.2 ± 1.2%, and 50.0 ± 31.4 μg/day, respectively. CGM showed that as compared with the combination of only sitagliptin and insulin glargine, mitiglinide in combination with sitagliptin and insulin glargine significantly reduced glycemic fluctuation indices, total area for the range of 24-h glycemic fluctuations (p = 0.04), mean amplitude of glycemic excursions (p = 0.03), and the proportion of time in hyperglycemia (p = 0.02) without significant difference in the proportion of time in hypoglycemia (p = 0.18). Hence, we have demonstrated the efficacy and safety of the add-on treatment with mitiglinide in type 2 diabetic patients, receiving the combination therapy of sitagliptin and insulin glargine.

Keywords: basal-supported oral therapy; continuous glucose monitoring; glinide; mitiglinide; sitagliptin
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Introduction

The goal of diabetes therapy is to control hyperglycemia to nearly normal glucose levels and prevent the progression of micro- and macrovascular complications. Postprandial hyperglycemia has been demonstrated as an independent and significant factor for accelerating atherosclerosis (The DECODE Study Group 1999; Tominaga et al. 1999; Chiasson et al. 2002). Therefore, sufficient control of diurnal glycemic fluctuations is required in patients with type 2 diabetes mellitus (International Diabetes Federation Guideline Development Group 2014).

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has been widely used for type 2 diabetes mellitus therapy. It enhances the action of incretins that glucose-dependently promote insulin secretion, facilitating the correction of pre- and postprandial glucose levels. Basal-supported oral therapy (BOT) is also an effective option for glycemic control in type 2 diabetes mellitus and the combination of a DPP-4 inhibitor and a long-acting insulin analogue is now widely used in clinical practice. However, some patients receiving BOT might fail to achieve strict glycemic control because uncontrolled hyperglycemia still remains in postprandial period (Holman et al. 2007; Takahara et al. 2012).

Mitiglinide is a short-acting insulinotropic sulfonylurea receptor ligand that has been shown to improve postprandial hyperglycemia (Kaku et al. 2009). A recent study reported that the combination of mitiglinide and a DPP-4 inhibitor could improve glycemic control without increasing risk to safety (Kaku et al. 2014). However, the efficacy of the combination of a rapid-acting insulin secretagogue and a DPP-4 inhibitor under BOT has not been investigated in clinical practice. We conducted a prospective single-center study of eight Japanese patients with type 2 diabetes mellitus receiving mitiglinide added to a combination therapy of sitagliptin and once-daily insulin glargine. The aim of this study was to evaluate the efficacy and safety of the combination of mitiglinide and sitagliptin under BOT by

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continuous glucose monitoring (CGM).

Patients and Methods

Patients

This prospective, non-blinded, pilot study was approved by the Ethics Committee of Osaka Red Cross Hospital. All subjects were sufficiently informed about the aims of the study; they provided their informed consent for participation prior to the start of the study. We enrolled patients with type 2 diabetes mellitus who were hospitalized in Osaka Red Cross Hospital from December 2013 to August 2014, receiving intensive insulin therapy and planning to switch to BOT. We excluded patients with apparent liver or renal dysfunction, those with inflammatory status or those receiving daily steroids, and those deemed to be seriously ill. All of the participants received appropriate diet therapy consisting of breakfast at 07:00, lunch at 12:00, and dinner at 18:00 h. Also, all participants received an intensive insulin regimen using three times-daily ultra-rapid-acting insulin and once-daily insulin glargine; they should be having a glycemic condition in which the level of fasting blood glucose and 2 h after each meal were less than 130 and 220 mg/dL, respectively, by means of self-monitoring blood glucose. No patient received oral hypoglycemic agents during intensive insulin therapy after admission.

Procedures of CGM-based study

Once glycemic control was stabilized under intensive insulin therapy, the participants were monitored using the CGMS® System Gold™ or iPro™2 Digital Recorder (Medtronic, Northridge, CA, USA) for 6 consecutive days (Fig. 1). For CGM, glucose levels were measured every 5 min for 24 h with a sensor implanted subdermally to monitor tissue fluid (Mori et al. 2013). Ultra-rapid-acting insulin use was stopped on day 1, while the dosage and administration schedule of insulin glargine similar to that of the prior intensive insulin therapy regimen was continued during the CGM-based study. Only for cases that were considered to be at a high risk of severe hypoglycemia, the dosage of insulin glargine was decreased, and the patients received sitagliptin (100 mg once daily) before breakfast from day 1. On days 3 and 4, they additionally received oral mitiglinide (10 mg three times a day) immediately (within 5 min) before each meal. Blood samples before and 2 h after breakfast were drawn on days 2 and 4. In addition to plasma glucose and C-peptide, plasma glucagon concentrations were measured using a glucagon radioimmunoassay kit (SML; Euro-Diagnostica AB, Malmö, Sweden). From the CGM data obtained on days 2, 4, and 6, the following parameters were calculated, as previously reported (Yoshihara et al. 2006): 24-h mean glucose levels (± standard deviation); mean amplitude of glycemic excursions (MAGE); total range of 24-h glycemic fluctuations; and the proportions of time in hyperglycemia (> 180 mg/dL) and hypoglycemia (< 70 mg/dL).

Procedures of follow-up study

Hemoglobin A1c (HbA1c) levels and body weight were also evaluated 3 months after the CGM-based study.

Statistical analysis

Statistical analyses were performed using Statcel3 (OMS, Tokyo, Japan) and StatView 5.0 software (SAS Institute, Inc., Cary, NC, USA). All data were analyzed using the Wilcoxon signed-ranks test and are expressed as mean ± standard deviations (SD). A probability (p) value of < 0.05 was considered statistically significant.

Results

The baseline characteristics of the study population are shown in Table 1. The mean age of the eight patients (four men, four women) was 70.3 ± 10.6 years, while the mean body weight was 55.7 ± 11.2 kg and body mass index (BMI) was 22.0 ± 2.8 kg/m^2. On admission, the mean HbA1c and urinary C-peptide levels were 9.2 ± 1.2% and 50.0 ± 31.4 μg/day, respectively; the subjects required 0.48 ± 0.13 U/day/kg of total insulin with 0.16 ± 0.05 U/day/kg insulin glargine under intensive insulin therapy. The CGM-based study was initiated 8.1 ± 1.8 days after the start of intensive insulin therapy. During the CGM-based study, the dosage of insulin glargine decreased on day 3 in only one patient.

Fluctuations in 24-h glycemic profiles of the eight patients are shown in Fig. 2. Postprandial hyperglycemia observed after each meal was markedly improved on day 4.

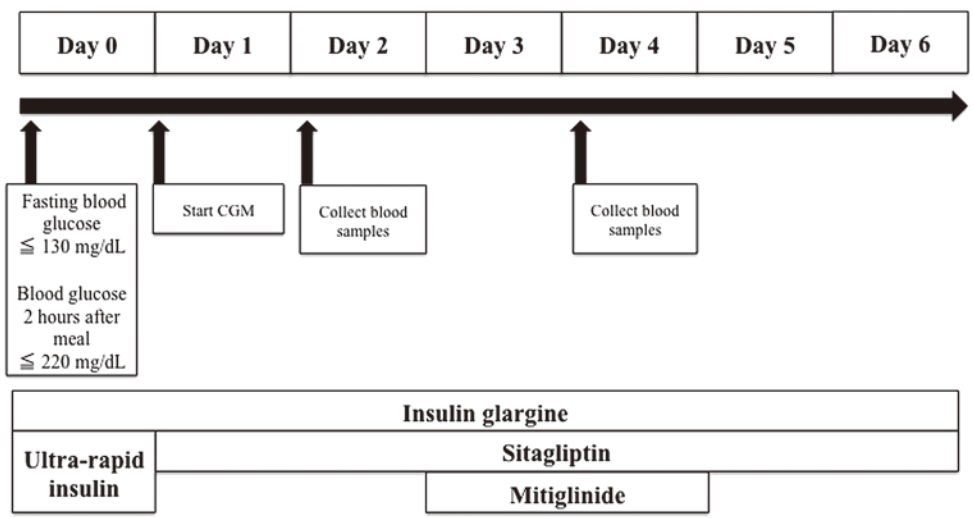

Fig. 1. Procedures of CGM-based study.

Table 1. Clinical characteristics on admission.

Age (year)	70.3 ± 10.6
Sex: male/female	4/4
Body weight (kg)	55.7 ± 11.2
Body mass index (kg/m^2)	22.0 ± 2.8
Diabetic duration (year)	15.9 ± 10.0
Hemoglobin A1c (%)	9.2 ± 1.2
Estimated glomerular filtration rate (mL/min/1.73 m^2)	74.6 ± 14.6
Fasting plasma glucose (mg/dL)	156.3 ± 45.8
Fasting serum C-peptide (ng/mL)	1.04 ± 0.65
Fasting C-peptide index	1.12 ± 1.46
Urinary C-peptide (μg/day)	50.0 ± 31.4
Intensive insulin therapy duration (day)	8.1 ± 1.8
Total insulin per body weight (units/day/kg)	0.48 ± 0.13
Insulin glargine per body weight (units/day/kg)	0.16 ± 0.05
Prior oral hypoglycemic agents	
Insulin (%)	25%
Sulphonylureas (%)	37.5%
Dipeptidyl peptidase-4 inhibitors (%)	25%
Thiazolidinediones (%)	12.5%
Biguanides (%)	25%
Rapid-acting insulin secretagogues (%)	12.5%

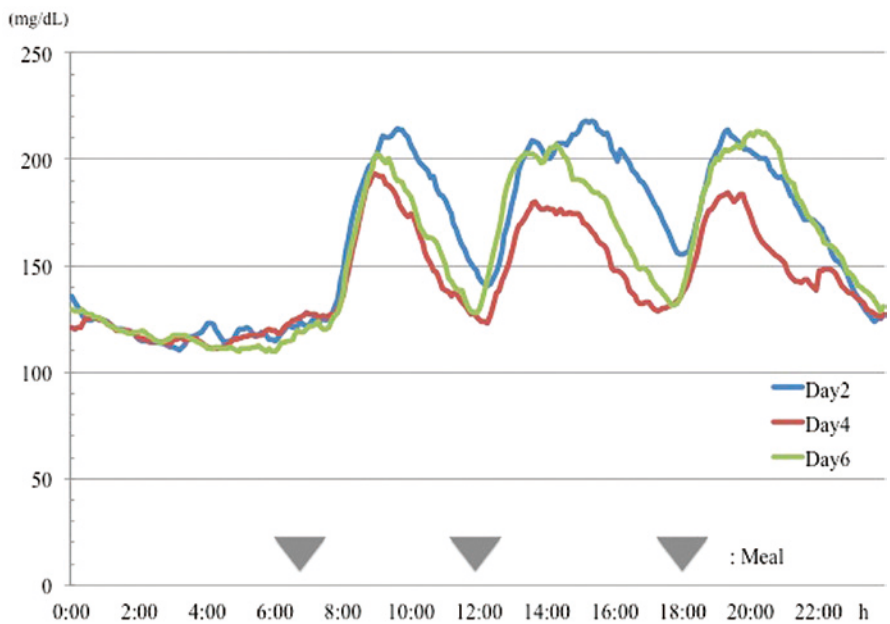

Fig. 2. The 24-hour glycemic fluctuations on CGM in the eight patients.
Postprandial hyperglycemia observed after each meal was markedly improved on day 4.
Days 2 and 6, sitagliptin (100 mg); Day 4, sitagliptin (100 mg) + mitiglinide (10 mg) three times a day.

Glycemic fluctuation analysis in the patients (Fig. 3, Table 2) also showed that the combination of mitiglinide and sitagliptin (Day 4) significantly reduced the range of 24-h glycemic fluctuations (p = 0.01 vs. Day 2; p = 0.04 vs. Day 6), MAGE (p = 0.03 vs. day 6) and the proportion of time in hyperglycemia (> 180 mg/dL) (p = 0.02 vs. Day 2; p = 0.02 vs. Day 6) as compared with those reduced on using sitagliptin alone. The combination of mitiglinide and sitagliptin also tended to reduce the mean glucose and SD values of 288 glucose measurements although the reduction was not statistically significant. On the other hand, there were no significant differences in the proportion of time in hypoglycemia (< 70 mg/dL) between the combination of mitiglinide and sitagliptin and sitagliptin alone (p = 0.65,

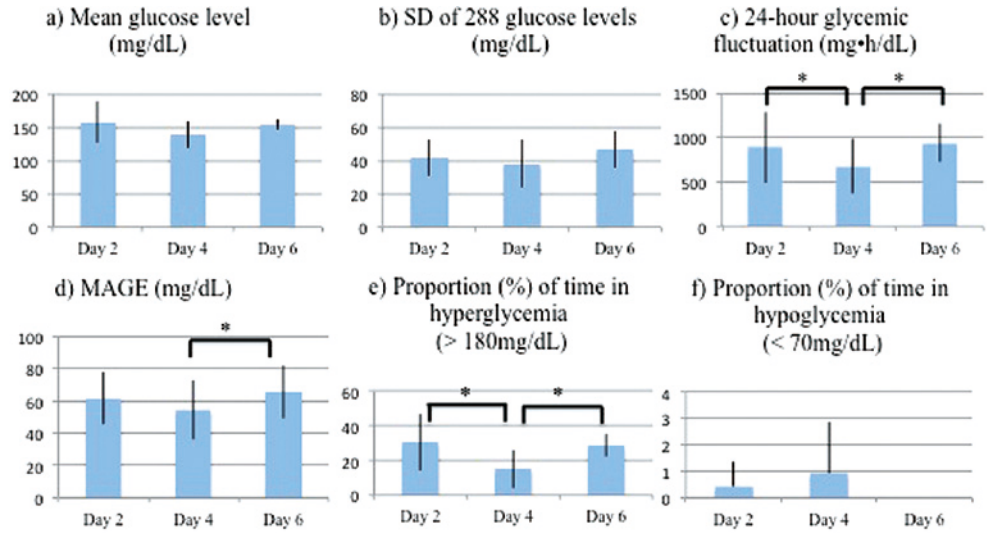

Fig. 3. Changes in the indices for 24-hour glycemic fluctuations during the CGM-base study.
The CGM data shown are (a) 24-h mean glucose level, (b) SD of 288 glucose levels, (c) 24-h glycemic fluctuations, (d) MAGE, (e) the proportion of time in hyperglycemia (> 180 mg/dL), and (f) the proportion of time in hypoglycemia (< 70 mg/dL) of each day during the CGM-based study. As compared to those with sitagliptin alone (Days 2 and 6), the combination of mitiglinide and sitagliptin (Day 4) significantly reduced the range of 24-h glycemic fluctuations, MAGE and the proportion of time in hyperglycemia but did not increase the proportion of time in hypoglycemia. *$p < 0.05$.
SD, standard deviations; MAGE, mean amplitude of glycemic excursion.

Table 2. Changes in the indices for 24-hour glycemic fluctuations.

	Day 2	Day 4	*P* (Day 2 vs. 4)	Day 6	*P* (Day 4 vs. 6)
Mean glucose level (mg/dL)	157.6 ± 30.7	139.4 ± 20.3	0.07	154.4 ± 7.8	0.07
SD of 288 glucose levels (mg/dL)	41.9 ± 11.1	38.1 ± 14.3	0.40	46.3 ± 11.0	0.09
24-hour glycemic fluctuation (mg·h/dL)	888.3 ± 398.5	674.3 ± 303.6	0.01	934.1 ± 213.3	0.04
MAGE (mg/dL)	61.8 ± 16.2	54.7 ± 18.5	0.12	65.6 ± 16.6	0.03
Hyperglycemia (> 180 mg/dL)	30.4 ± 16.6	15.0 ± 10.9	0.02	29.1 ± 6.7	0.02
Hypoglycemia (< 70 mg/dL)	0.4 ± 1.0	0.9 ± 2.0	0.65	0 ± 0	0.18

SD, standard deviations; MAGE, mean amplitude of glycemic excursion.

Table 3. Analysis of fasting and postprandial blood samples.

	Sitagliptin	Mitiglinide + Sitagliptin	*P* (< 0.05)
Fasting plasma glucose (mg/dL)	126.4 ± 20.2	121.1 ± 12.8	0.26
Postprandial plasma glucose (mg/dL)	224.8 ± 54.1	187.1 ± 47.8	0.02
Fasting plasma C-peptide (ng/mL)	0.93 ± 0.41	1.04 ± 0.61	0.27
Postprandial plasma C-peptide (ng/mL)	2.81 ± 1.32	3.95 ± 1.95	0.05
Fasting CPI	0.75 ± 0.36	1.02 ± 0.83	0.26
Postprandial CPI	1.14 ± 0.47	2.18 ± 1.07	0.01
Fasting plasma glucagon (pg/mL)	164.5 ± 29.4	159.8 ± 25.3	0.89
Postprandial plasma glucagon (pg/mL)	178.6 ± 43.1	169.5 ± 23.4	0.40

CPI, C-peptide index.

Day 4 vs. Day 2; $p = 0.18$, Day 4 vs. Day 6). Analysis of fasting and postprandial blood samples (Table 3) revealed that the combination of mitiglinide and sitagliptin significantly improved postprandial plasma glucose levels ($pp = 0.02$), although there were no significant changes in fasting plasma glucose levels ($p = 0.26$). The combination therapy significantly increased postprandial plasma C-peptide levels and C-peptide index (CPI) as compared with those increased on treatment with sitagliptin only ($p = 0.05$ and 0.01, respectively), whereas there were no significant dif-

ferences in fasting CPI ($p = 0.26$), fasting plasma glucagon ($p = 0.89$), or postprandial plasma glucagon ($p = 0.40$).

The participants continued to receive the same combination BOT regimen after the CGM-based study. Evaluations at 3 months after the CGM-based study showed that HbA1c levels were significantly improved (7.1 ± 0.7 vs. 9.2 ± 1.2%, $p = 0.03$), while there was no significant increase in body weight (57.6 ± 0.7 vs. 55.7 ± 11.2 kg, $p = 0.53$).

Discussion

BOT has been widely accepted as a versatile option for glycemic control in type 2 diabetes mellitus. While the usefulness of rapid-acting insulin secretagogues plus insulin combination therapy has been previously reported (Yoshihara et al. 2006; Kumashiro et al. 2007), the usefulness of the combination of DPP-4 inhibitors and long-acting insulin analogue remains inconclusive. Some studies have demonstrated efficient postprandial glucose-lowering effects of the combination therapy of a rapid-acting insulin secretagogue and a DPP-4 inhibitor (Jung et al. 2013; Kaku et al. 2014). However, BOT with DPP-4 inhibitors might result in unsatisfactory control of glycemic fluctuations (Mori et al. 2013). Actually, as shown in Fig. 2, the highest postprandial glucose concentrations were > 200 mg/dL under the highest dose of the combination of sitagliptin and insulin glargine in our study.

Poor control of glycemic fluctuations has been thought to be an independent factor, and to be one of the main mechanisms of diabetes-induced macrovascular complications (The DECODE Study Group 1999; Tominaga et al. 1999; Chiasson et al. 2002). Many studies have focused on postprandial hyperglycemia as a therapeutic target. The guideline for the management of postmeal glucose by the International Diabetes Federation states that the target for postmeal glucose at 1-2 h after a meal is 160 mg/dL (International Diabetes Federation Guideline Development Group 2014), and the American Diabetes Association (2014) also recommended that the postprandial glucose level should be < 180 mg/dL.

On this point, it has been recently reported that the combination of mitiglinide and a DPP-4 inhibitor could improve glycemic control without jeopardizing safety (Kaku et al. 2009, 2014). Jung et al. (2013) reported that the addition of mitiglinide to sitagliptin substantially reduced postprandial glucose and accelerated earlier insulin secretion relative to mitiglinide or sitagliptin alone.

Therefore, in this study, we focused on the effect of mitiglinide added to BOT. Our CGM data demonstrated that the combination therapy of mitiglinide and sitagliptin with insulin glargine could significantly improve postprandial hyperglycemia and daily glycemic fluctuations without affecting fasting glucose levels or significantly increasing hypoglycemia (Figs. 2 and 3, Table 2). The significant improvements in the range of 24-h glycemic fluctuations, MAGE, and the proportion of time in hyperglycemia on Day 4 as compared with those on Day 6 and also with those on Day 2 ruled out the possibility of time-dependent effects on glycemic control; these improvements also supported the postprandial glucose-lowering efficacy of mitiglinide added to the combination of sitagliptin and insulin glargine.

Our blood sample analysis suggested that the improvement of postprandial hyperglycemia was because of an additional rapid insulin secretion effect of mitiglinide added to sitagliptin. These findings were compatible with those of previous studies without insulin therapy (Kaku et al. 2009, 2014; Jung et al. 2013). On the other hand, glucagon did not contribute to glycemic control in this study because there were no significant changes in glucagon concentration after treatment with sitagliptin or by the combination treatment, although another study reported that rapid-acting insulin secretagogues inhibited DPP-4 activity (Duffy et al. 2007), which was in accordance with the findings of a previous report (Jung et al. 2013).

In addition, our 3-month follow-up evaluations after the CGM-based study showed certain tolerability of the combination therapy of mitiglinide with sitagliptin and insulin glargine that may be a the result of the convenience, pain relief, and patient satisfaction obtained from this regimen, as previously shown in a study of mitiglinide and insulin glargine therapy (Kumashiro et al. 2007).

Finally, there were some limitations to this study that should be addressed. Primarily, this was a preliminary small-scale single-center study, and our follow-up period was only 3 months. Therefore, further studies are needed to examine the efficacy of long-term combination therapy in larger cohort of subjects with type 2 diabetes mellitus.

In conclusion, the findings of this study has demonstrated the efficacy and safety of add-on mitiglinide in Japanese patients with type 2 diabetes mellitus, receiving a combination therapy of sitagliptin and insulin glargine using CGM. This add-on therapy could be a useful therapeutic option with the aim of lowering both fasting and postprandial hyperglycemia.

Authors' Contribution

Takaaki Murakami collected the data and wrote the paper, Takuo Nambu collected the data and contributed to statistic analysis, Tomoko Kato, Yuki Matsuda, Shin Yonemitsu, Seiji Muro and Shogo Oki collected the data and contributed to making the therapeutic decisions.

Conflict of Interest

The authors declare no conflict of interest.

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