

# Efficacy and safety of sitagliptin in Japanese patients with type 2 diabetes switched from glinides

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## Keywords

Glinides, Sitagliptin, Type 2 diabetes

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## ABSTRACT

**Aims/Introduction:** The efficacy and safety of sitagliptin, a dipeptidyl peptidase (DPP)-4 inhibitor, were compared with those of glinides in Japanese patients with type 2 diabetes.

**Materials and Methods:** The participants were 82 patients with type 2 diabetes (glycated hemoglobin [HbA1c]  $\geq 6.0\%$  and  $< 10\%$ ) under treatment with glinides for glucose control. The participants were randomly assigned to a group ( $n = 44$ ) receiving continuous treatment with glinides and a group ( $n = 38$ ) switched to sitagliptin. Patients were followed for 12 weeks to evaluate glucose control. A meal tolerance test was carried out in weeks 0 and 12 to examine the pancreatic secretory response to postprandial hyperglycemia.

**Results:** The changes in HbA1c from week 0 to week 12 were  $-0.25$  and  $-0.05\%$  in the sitagliptin and glinide groups, respectively, with a significant improvement with sitagliptin. The differences in fasting plasma glucose (FPG), glycoalbumin and 1,5-anhydroglucitol between the two groups were 14.2 mg/dL, 0.7% and 1.7  $\mu\text{g/mL}$ , respectively, showing significant improvements with sitagliptin. In the meal tolerance test, glucose at 0 min was lower in the sitagliptin group; however, there were no differences in glucose elevation at 30 and 60 min compared with 0 min. Plasma insulin and glucagon secretion at week 12 were significantly lower than at baseline in the sitagliptin group. Adverse events including hypoglycemia did not differ between the groups.

**Conclusions:** FPG decreased and glucose control improved in patients who switched from glinides to sitagliptin. Sitagliptin decreased secretion of insulin and glucagon in a meal tolerance test compared with glinides, whereas the agents showed similar inhibition of postprandial hyperglycemia. This trial was registered with UMIN (UMIN-CTR no. 000003479).

## INTRODUCTION

Recently, incretins have been attracting attention in the treatment of diabetes<sup>1</sup>. Incretins are expected to improve glycemic control by mainly reducing the postprandial glucose level without causing hypoglycemia<sup>2–4</sup>. Dipeptidylpeptidase-4 (DPP-4) inhibitors increase the plasma level of endogenous incretins by

preventing their inactivation<sup>5,6</sup>, so DPP-4 inhibitors are gaining an important role in the current management of diabetes<sup>7</sup>.

Conventional antidiabetic agents used to treat postprandial hyperglycemia in patients in the early phase of diabetes include  $\alpha$ -glucosidase inhibitors ( $\alpha$ -GIs) and rapid-acting insulin secretagogues (prandial glucose regulators: glinides). Head-to-head comparisons have shown that DPP-4 inhibitors improve postprandial hyperglycemia relative to  $\alpha$ -GIs<sup>8,9</sup>, but a similar

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comparison of the effects of DPP-4 inhibitors and glinides on postprandial hyperglycemia has not been carried out. When administered preprandially, glinides transiently stimulate the adenosine triphosphate-sensitive potassium (KATP) channel in pancreatic  $\beta$ -cells along with the postprandial elevation of blood glucose, thereby promoting insulin secretion by these cells<sup>10</sup>. Sitagliptin is a highly selective DPP-4 inhibitor that has been shown to regulate postprandial hyperglycemia for 24 h with once daily administration<sup>11</sup>.

In December 2009, sitagliptin was approved for clinical use in Japan as monotherapy and as concomitant therapy with biguanides, sulfonyleureas (SUs) or thiazolidinediones. However, the combined use of sitagliptin with glinides has yet to be approved<sup>12,13</sup>. In the present study, we examined the efficacy and safety of switching patients with type 2 diabetes from glinides to sitagliptin, in comparison with continuous glinide treatment. Indicators of glycemic control and meal tolerance tests were used to compare the efficacy of these antidiabetic agents.

## MATERIALS AND METHODS

### Participants

The study participants were 82 outpatients aged 20–80 years with type 2 diabetes mellitus who met the diagnostic criteria of the Japan Diabetes Society (JDS). The study was carried out at three institutions from April 2010 to February 2011. All patients had been treated with mitiglinide at 30 mg/day or nateglinide at 270 mg/day for at least 3 months and had glycated hemoglobin (HbA1c)  $\geq 6.0\%$  and  $< 10.0\%$  at the start of the study. HbA1c values were JDS values converted into National Glycohemoglobin Standardization Program (NGSP) values<sup>14</sup>. Combination therapy with metformin or pioglitazone was allowed, but the oral antidiabetic agent had not been changed within the past 3 months. The major exclusion criteria were patients suspected of having type 1 diabetes or secondary diabetes, those within 6 months after diagnosis of diabetes (possible unstable glucose control), those with unstable glucose control ( $\geq 1.0\%$  difference in HbA1c between the maximum and minimum levels measured at least twice for 3 months before the start of the study), and those under treatment with insulin, SUs or  $\alpha$ -GIs (concomitant use with sitagliptin was not approved in Japan at the start of the study). Other exclusion criteria were renal impairment (eGFR  $\leq 50$  mL/min or serum creatinine  $> 1.5$  mg/dL in males and  $> 1.3$  mg/dL in females), advanced diabetic neuropathy possibly masking hypoglycemia, untreated proliferative retinopathy, severe liver damage (alanine transferase three times the normal value) and patients judged likely to have poor compliance by an investigator.

### Procedures

Participants gave informed consent, and were randomly assigned to the glinide and sitagliptin groups at their next visit, using block randomization of six participants/block with envelopes at each institution. Because of variation of HbA1c

between the two groups due to the relatively small number of participants, the subjects were stratified into subgroups with HbA1c  $< 6.9\%$  and  $\geq 6.9\%$ . Participants in the glinide group received continuous treatment with mitiglinide or nateglinide. In the sitagliptin group, glinides were discontinued and replaced with sitagliptin at a dose of 50 mg/day on the day after group assignment. The dosages of glinides and sitagliptin were not changed during the study period. Similarly, the dosages of concomitant metformin and pioglitazone were unchanged in patients receiving these drugs.

HbA1c, 1,5-anhydroglucitol (1,5-AG), glycoalbumin (GA), standard hematology, biochemistry laboratory values and body-weight were measured every 4 weeks during a 12-week observation period after group assignment. Compliance with diet and exercise therapy, and drugs and the incidence of hypoglycemia were examined using questionnaires.

A meal tolerance test was carried out at the start of the study (baseline) and in week 12. This test was carried out after administration of glinides just before a meal after overnight fasting at baseline, and after administration of glinides just before a meal (glinide group) or after administration of sitagliptin 2 h before a meal (sitagliptin group) in week 12. The standard meal included one drink of Calorie Mate<sup>®</sup> (Otsuka Pharmaceutical Co., Tokyo, Japan), one bar of Calorie Mate<sup>®</sup> and one pack of Calorie Mate<sup>®</sup> jelly (approximately 500 kcal; carbohydrate 60%, lipid 25%, and protein 15%) consumed within 15 min. Blood samples for measurement of glucose, insulin, C-peptide (CPR) and glucagon were collected immediately before the meal (0 min), and 30 and 60 min after the start of the meal in participants at rest in a sitting position. Blood sampling at 120 min after the start of the meal was not carried out because of limitations in the participating institutions.

### Efficacy End-points

The primary efficacy end-point was the change in HbA1c in week 12 from baseline. The sample size necessary to confirm the superiority of sitagliptin using the primary efficacy end-point was defined as follows. In placebo-controlled trials of sitagliptin and glinides in Japan, HbA1c decreased by approximately 1.0 and 0.7%, respectively, after 12 weeks; therefore, the difference in the change in HbA1c for the two agents was assumed to be 0.3%. If this difference is evaluated at a 5% significance level and a statistical power of 90% with the assumption of a standard deviation of 0.4%, 37 participants per group are required to ensure significance. Therefore, assuming a drop-out rate of 5% during the study, the targeted number of participants was 40 patients per group, or 80 patients in total.

The secondary end-points were the changes in GA, 1,5-AG and fasting plasma glucose (FPG) in week 12 from baseline. The insulinogenic index, homeostatic model assessment of  $\beta$ -cell function (HOMA- $\beta$ ), HOMA of insulin resistance (HOMA-IR) and secretory units of islets in transplantation (SUIT) index<sup>17</sup> were used as other end-points, and glucose,

insulin, CPR and glucagon were evaluated in meal tolerance tests. All blood samples were measured by SRL Inc. (Tokyo, Japan). Proinsulin and glucagon were measured by RIA (Linco Research, Inc., St. Charles, MO, USA) and the RIA 2 antibody method (Millipore Corp., Billerica, MA, USA), respectively.

### Data Analysis

Analysis of efficacy was carried out in the per protocol set. In the primary efficacy analysis, the decrease in HbA1c from baseline to week 12 was used to evaluate the superiority of sitagliptin compared with glinides. Patients with data at baseline and in week 12 were included in the analysis set. In statistical analysis, the least square mean (LS mean) and 95% confidence interval (CI) were estimated using analysis of covariance (ANCOVA) with HbA1c at baseline as a covariate. If the margin of the 95% CI was <0%, sitagliptin was considered to be superior to glinides. Using ANCOVA with other values at baseline as covariates, the LS mean and 95% CI of other efficacy end-points were similarly calculated. For changes in HbA1c and other parameters, intragroup comparison was carried out using a paired *t*-test. Safety and tolerability were evaluated by comparison of the incidences of hypoglycemia and adverse events between the two groups using a Fisher's exact test.

### Ethics and Good Clinical Practice

Written informed consent was obtained from all participants. The present study was carried out in accordance with the Declaration of Helsinki. The protocol and explanatory documents for patients were approved by the institutional review boards of the respective institutions.

### RESULTS

The 82 patients were randomly assigned to the sitagliptin ( $n = 38$ ) and glinide ( $n = 44$ ) groups. All participants completed the 12-week study. In one participant in the glinide group, a blood sample for all measurements, except plasma glucose, could not be collected in the 12-week meal tolerance test; therefore, data for plasma glucose alone were used in the meal tolerance test for this participant. There were no significant differences in sex ratio, age, body mass index, duration of diabetes, FPG, HbA1c and 1,5-AG between the two groups at baseline (Table 1). Fasting plasma insulin, CPR, proinsulin and glucagon in the early morning also did not differ significantly between the groups. There was no significant difference in the frequency of administration of metformin or pioglitazone or in complications of diabetic retinopathy and diabetic nephropathy (grade 3 or higher).

### Efficacy

The change in LS mean HbA1c, the primary efficacy end-point, from baseline to week 12 was  $-0.05\%$  in the glinide group and  $-0.25\%$  in the sitagliptin group (Table 1). The upper limit of the 95% CI of the difference between the two groups was  $-0.04\%$  (i.e., <0%), showing that sitagliptin was superior to glinides in decreasing HbA1c. In intragroup comparison, HbA1c significantly decreased from baseline by  $-0.14$ ,

**Table 1** | Demographic data and baseline characteristics

Parameter	Sitagliptin group $n = 38$	Glinide group $n = 44$
Age (years)	66.0 ± 9.2	62.3 ± 11.4
Males, $n$ (%)	20 (53)	22 (50)
Body mass index (kg/m <sup>2</sup> )	24.3 ± 3.7	24.8 ± 4.6
HbA1c (%)	7.3 ± 0.6 (6.2–8.9)	7.4 ± 0.8 (6.0–9.5)
Fasting plasma glucose (mg/dL)	134.6 ± 23.1	142.2 ± 29.1
1,5-Anhydroglucitol (µg/mL)	11.7 ± 6.8	9.3 ± 6.8
Glycoalbumin (%)	18.8 ± 2.9	19.4 ± 4.0
Duration of type 2 diabetes (years)	10.2 ± 5.8	8.8 ± 5.7
Use of antidiabetic agents, $n$ (%)		
Mitiglinide	36 (95)	37 (84)
Nateglinide	2 (5)	7 (16)
Metformin	8 (21)	12 (27)
Pioglitazone	6 (16)	8 (18)

HbA1c, glycated hemoglobin.

$-0.22$  and  $-0.25\%$  in weeks 4, 8 and 12, respectively, in the sitagliptin group, but showed no change in the glinide group. For the secondary efficacy end-points, the decreases in the LS means of GA and FPG from baseline to week 12 in the sitagliptin group were superior to those in the glinide group, and the increase in the LS mean for 1,5-AG from baseline to week 12 was higher in the sitagliptin group. These results show that there was greater improvement of all four indicators of glucose control in the sitagliptin group compared with the glinide group.

### Changes in Pancreatic $\beta$ -Cell Function

In evaluation of pancreatic  $\beta$ -cell function, there were no significant differences in the changes in fasting plasma CPR, CPR index and proinsulin/insulin ratio from baseline to week 12 between the groups. The changes in HOMA- $\beta$  and SUI index showed a tendency for improvement in the sitagliptin group (Table 2).

### Meal Tolerance Test

The results of meal tolerance tests are shown in Figure 1. The 1-h postprandial plasma glucose levels in week 12 were  $216.8 \pm 53.5$  and  $206.9 \pm 47.4$  mg/dL in the glinide and sitagliptin groups, respectively, with no significant difference between the two groups. Glucose, insulin, and glucagon were similar at baseline and in week 12 in the glinide group. In contrast, in the sitagliptin group, plasma glucose at 0 min in week 12 was significantly lower than that at baseline. Glucose levels at 30 and 60 min in week 12 were also lower than those in week 0, but these differences were not significant. Insulin

**Table 2** | Glycemic and insulin-related end-points at baseline and in week 12

	<i>n</i>	Week 0 (baseline) mean (SD)	Week 12 mean (SD)	LS mean (95% CI) change from baseline	Difference in LS mean (95% CI) change
HbA1c (%)					
Sitagliptin	38	7.27 (0.64)	7.02 (0.61)	-0.25 (-0.37, -0.13)	-0.21 (-0.37, -0.04)
Glinide	44	7.39 (0.81)	7.34 (0.87)	-0.05 (-0.16, 0.07)	
Fasting plasma glucose (mg/dL)					
Sitagliptin	38	134.6 (23.1)	127.1 (20.7)	-8.3 (-13.2, -3.3)	-14.2 (-21.0, -7.4)
Glinide	44	142.2 (29.1)	147.5 (30.2)	5.9 (1.3, 10.5)	
1,5-Anhydroglucitol ( $\mu$ g/mL)					
Sitagliptin	38	11.7 (6.8)	12.4 (6.6)	0.8 (-0.1, 1.7)	1.68 (0.47, 2.88)
Glinide	42	9.3 (6.7)	8.5 (6.9)	-0.9 (-1.68, -0.0)	
Glycoalbumin (%)					
Sitagliptin	38	18.8 (2.9)	18.9 (2.8)	0.1 (-0.4, 0.7)	-0.7 (-1.4, -0.0)
Glinide	43	19.4 (4.0)	20.2 (4.2)	0.9 (0.4, 1.4)	
Fasting serum insulin ( $\mu$ U/mL)					
Sitagliptin	38	6.8 (4.0)	7.0 (6.5)	0.2 (-1.0, 1.3)	0.1 (-1.6, 1.7)
Glinide	43	8.3 (5.7)	8.3 (5.8)	0.1 (-1.0, 1.2)	
Fasting serum proinsulin (pmol/L)					
Sitagliptin	38	16.7 (12.3)	19.1 (30.6)	2.4 (-2.0, 6.9)	0.6 (-5.6, 6.7)
Glinide	43	16.6 (9.3)	18.4 (10.9)	1.8 (-2.4, 6.1)	
Proinsulin/insulin ratio					
Sitagliptin	38	2.8 (1.5)	2.7 (1.3)	-0.0 (-0.41, 0.36)	-0.2 (-0.8, 0.3)
Glinide	43	2.5 (1.2)	2.7 (1.8)	0.2 (-0.2, 0.6)	
Fasting serum C-peptide (ng/mL)					
Sitagliptin	38	1.8 (0.6)	1.9 (0.9)	0.1 (-0.1, 0.3)	0.0 (-0.2, 0.2)
Glinide	43	1.8 (0.7)	1.9 (0.8)	0.1 (-0.5, 0.3)	
Fasting serum glucagon (pg/mL)					
Sitagliptin	38	67.9 (21.3)	66.8 (24.4)	-0.8 (-6.8, 5.2)	-7.7 (-15.9, 0.6)
Glinide	43	64.3 (15.3)	71.4 (23.2)	6.9 (1.2, 12.5)	
HOMA- $\beta$					
Sitagliptin	38	35.5 (20.0)	45.4 (46.6)	9.0 (-0.8, 18.5)	12.6 (-1.0, 26.1)
Glinide	43	42.9 (34.8)	38.5 (26.9)	-3.6 (-12.8, 5.7)	
HOMA-IR					
Sitagliptin	38	2.3 (1.5)	2.3 (2.3)	-0.1 (-0.5, 0.4)	0.3 (-0.4, 0.9)
Glinide	43	2.9 (2.1)	3.1 (2.2)	0.2 (-0.3, 0.6)	
SUIT index					
Sitagliptin	38	40.2 (16.7)	55.0 (58.0)	14.9 (2.3, 27.6)	16.6 (0.7, 34.0)
Glinide	43	38.8 (20.1)	37.2 (17.6)	-1.7 (-13.6, 10.2)	
Bodyweight (kg)					
Sitagliptin	38	62.2 (11.2)	61.7 (11.0)	-0.5 (-0.9, -0.1)	-0.7 (-1.3, -0.1)
Glinide	42	64.6 (16.7)	64.8 (16.9)	0.2 (-0.2, 0.6)	

CI, confidence interval; HbA1c, glycated hemoglobin; HOMA- $\beta$ , homeostatic model assessment of  $\beta$ -cell function; HOMA-IR, homeostatic model assessment of insulin resistance; LS, least square; SD, standard deviation; SUIT, secretory units of islets in transplantation index.

and glucagon at 30 and 60 min were significantly lower at week 12 than at baseline in the sitagliptin group (Figure 1).

### Safety and Tolerability

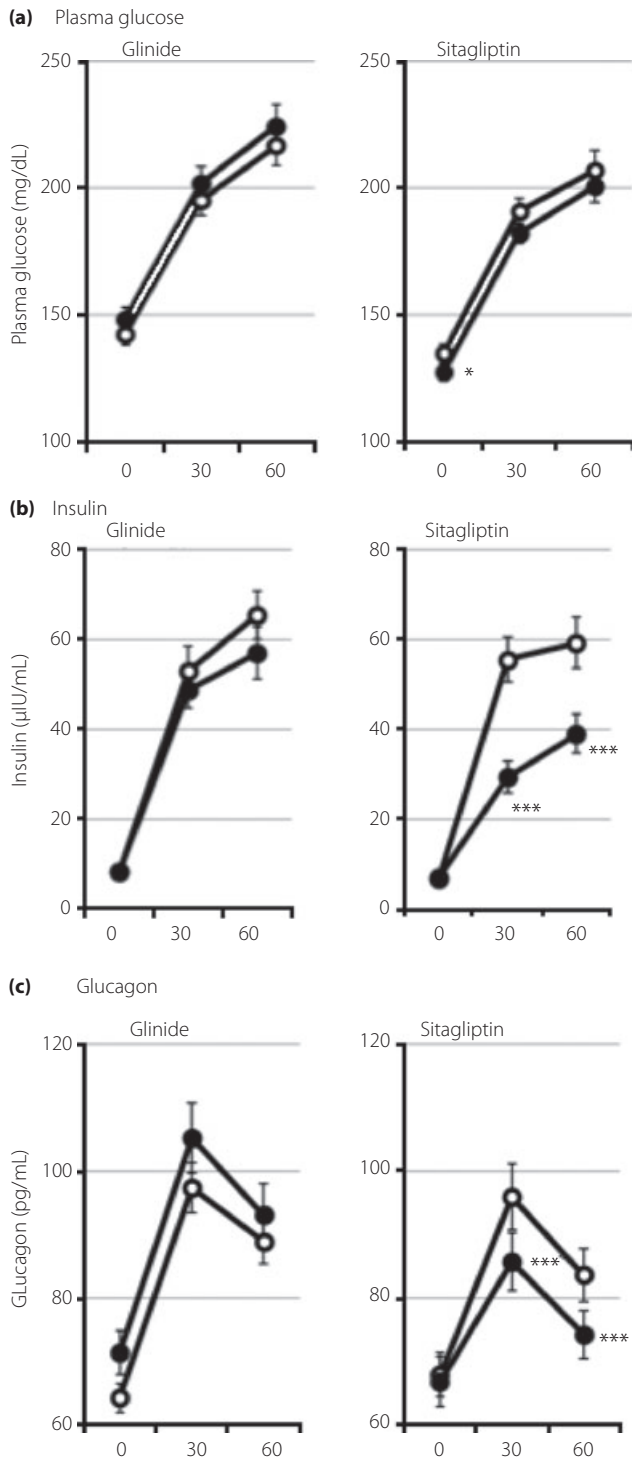
Almost all participants in both groups had >90% compliance based on a questionnaire. Hypoglycemia occurred in one participant in the sitagliptin group, and in seven in the glinide group. However, there was no significant difference in the incidence, and the severity was slight or moderate with no severe hypoglycemia. There were no other severe adverse events. In

addition, the Diabetes Treatment Satisfaction Questionnaire (Japanese version) was carried out after completion of the study, and this showed that the sitagliptin group had a higher level of satisfaction with treatment than the glinide group (data not shown).

### DISCUSSION

Sitagliptin is a DPP-4 inhibitor that was first approved for clinical use in Japan, and has been shown to improve HbA1c, postprandial hyperglycemia and FPG at a dose of 50 mg once a





**Figure 1** | Postprandial responses to a standard meal (mean ± standard error). Baseline (open circles), week 12 (filled circles); sitagliptin  $n = 38$ ; glinides  $n = 44$  for plasma glucose,  $n = 43$  for all other parameters. \* $P < 0.05$ , \*\*\* $P < 0.001$  vs baseline (paired  $t$ -test)

day<sup>8,13</sup>. Concomitant use of sitagliptin with oral antidiabetic agents including biguanide, thiazolidinediones, SUs and  $\alpha$ -GIs has also been approved in Japan. Glinides have also been

shown to improve HbA1c and postprandial hyperglycemia by t.i.d. administration immediately before a meal (usual doses in Japan: 30 mg/day for mitiglinide and 270 mg/day for nateglinide)<sup>10</sup>, but combined use of a glinide with sitagliptin has not been approved to date. Switching treatment in this way might be preferable to improve patient adherence.

The current study was carried out to evaluate the efficacy of sitagliptin in clinical practice using glinides as an active control drug. Patients with type 2 diabetes mellitus under treatment with glinides for glucose control were randomly assigned to groups in which treatment was switched to sitagliptin or continued with glinides. A 12-week prospective and comparative study of efficacy and safety was then carried out. HbA1c at baseline immediately after group assignment (i.e., when patients were still receiving glinides) did not differ significantly between the sitagliptin ( $7.3 \pm 0.6\%$ ) and glinide ( $7.4 \pm 0.8\%$ ) groups. However, in week 12, HbA1c showed a significant decrease of 0.25% from baseline in the sitagliptin group, but no significant decrease in the glinide group, although a small decrease of 0.05% was obtained. The difference in the decrease of HbA1c between the groups did not reach the expected level of 0.3%; however, HbA1c in the sitagliptin group was significantly decreased by 0.21% in comparison with that in the glinide group. Similarly, GA and 1,5-AG were significantly improved in the sitagliptin group compared with the glinide group.

In a meal tolerance test, there were no significant differences in the glucose levels at 0, 30 and 60 min at baseline, and those in week 12 in the glinide group. In the sitagliptin group, glucose at 0 min (FPG) was significantly lower in week 12 compared with baseline ( $-8.4$  mg/dL). Glucose was also lower at 30 and 60 min in week 12 compared with baseline, but without a significant difference, and the changes from glucose at 0 min were similar to those in the glinide group. These results suggest that HbA1c in the sitagliptin group improved because FPG was improved more than that in the glinide group, whereas the effect on postprandial glucose was similar in the two groups. That is, glinides selectively decrease postprandial hyperglycemia and do not affect FPG, whereas sitagliptin decreases both postprandial hyperglycemia and FPG.

In evaluation of the response of pancreatic secretion in the meal tolerance test, changes in insulin and glucagon at baseline and in week 12 were similar in the glinide group. In contrast, in the sitagliptin group, insulin at 30 and 60 min was significantly lower than that at baseline, and glucagon also decreased significantly. These results suggest that improvement of postprandial hyperglycemia by sitagliptin contributes to inhibition of insulin hypersecretion and glucagon secretion. In patients with type 2 diabetes, glucagon secretion in hyperglycemia is usually less suppressed. DPP-4 inhibitors, including sitagliptin, stimulate insulin secretion glucose-dependently and inhibit glucagon secretion, with resultant improvement of hyperglycemia<sup>9,16–18</sup>. It has been shown that inhibition of glucagon secretion contributes to the glucose-lowering effect of glucogen-like peptide 1 (GLP-1) in patients with type 2 diabetes, as does

stimulation of insulin secretion<sup>19</sup>. The results of the present study suggest that replacement of glinides with sitagliptin suppresses postprandial hyperglycemia without excessive stimulation of insulin secretion, leading to a reduced burden on pancreatic  $\beta$ -cells.

Incretins, such as GLP-1, recover the function of pancreatic  $\beta$ -cells. Thus, GLP-1 receptor agonists and DPP-4 inhibitors, which are related to the action of incretins, can improve the pancreatic insulinogenic index<sup>20–22</sup>. However, in the present study, the changes in the fasting plasma CPR, CPR index, HOMA- $\beta$ , SUI index, proinsulin/insulin ratio and insulinogenic index showed no significant differences between the sitagliptin and glinide groups, although HOMA- $\beta$  and the SUI index showed greater improvement in the sitagliptin group compared with the glinide group. DPP-4 inhibitors and GLP-1 receptor agonists are also thought to have similar effects on bodyweight<sup>23</sup>, but in the current study the decrease in bodyweight of 0.5 kg in week 12 in the sitagliptin group was significantly greater than that in the glinide group. However, the study period of 12 weeks might have been too short to evaluate the effect of sitagliptin on pancreatic  $\beta$ -cells and bodyweight. A long-term follow-up study is required to examine these effects of sitagliptin.

The present study had several limitations. First, it was a relatively small-scale open-label trial. Second, there was only one-way switching of therapy; that is, it was not a cross-over study. Finally, we only carried out testing at 1 h after the standard meal, primarily because it was not easy to obtain consent from the patients to wait for as long as 2 h for testing (in fact, there is often no place for patients to wait in the daily clinical setting). Accordingly, we did not obtain area under the curve (AUC) data for 2 h. Although we still considered it possible to discuss the postprandial kinetics of glucose and insulin, it should be noted that the present study does not provide a sufficient comparison of meal load tests between sitagliptin and other existing DPP-4 inhibitors or glinides.

In conclusion, we investigated the efficacy and safety of switching from glinide therapy to the DPP-4 inhibitor, sitagliptin, in patients who were considered to require further improvement of glycemic control. The present results show that short-term glycemic control was improved by replacement of glinides with oral sitagliptin in patients showing an insufficient response, and that suppression of glucagon and insulin secretion reduced the burden on pancreatic  $\beta$ -cells. No severe adverse events were found, and there were no problems with tolerance associated with the switch in therapy. Therefore, replacement of glinides with DPP-4 inhibitors might be of value for the oral treatment of type 2 diabetes.

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