

# Short- and long-term effect of sitagliptin after near normalization of glycemic control with insulin in poorly controlled Japanese type 2 diabetic patients

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## Keywords

Dipeptidyl peptidase-4 inhibitor, Insulin therapy, Sitagliptin

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## ABSTRACT

**Aims/Introduction:** The aim of the present study was to examine the short- and long-term effect of sitagliptin on glucose tolerance after near normalization of glycemic control with insulin in poorly controlled type 2 diabetic patients.

**Materials and Methods:** We consecutively enrolled a total of 30 type 2 diabetic patients whose glycosylated hemoglobin levels (National Glycohemoglobin Standardization Program) were  $\geq 7.4\%$ , stopped all oral antidiabetic drugs and started insulin therapy. When fasting plasma glucose levels became  $<140$  mg/dL, we carried out the first oral glucose tolerance test (OGTT). After 1-week sitagliptin treatment (50 mg/day), the second OGTT was carried out. Furthermore, we evaluated the long-term efficacy of sitagliptin on glucose tolerance after near normalization of glycemic control with insulin.

**Results:** After 1-week sitagliptin treatment, the area under the curve of insulin was markedly increased, and the area under the curve of glucagon and glucose was markedly decreased. Duration of diabetes and insulin secretory capacity were correlated with the effect of sitagliptin. Furthermore, interestingly, near normalization of glycemic control with insulin therapy for 1–2 weeks brought out the long-term effectiveness of sitagliptin on glucose tolerance for 24 weeks, which was not observed with other antidiabetic drugs.

**Conclusions:** These findings suggest that near normalization of glycemic control with insulin improves the clinical response to sitagliptin in poorly controlled type 2 diabetic patients.

## INTRODUCTION

Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have often been used for type 2 diabetic patients. DPP-4 inhibitors are effective in glucose metabolism by preventing DPP-4 from deactivating glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide<sup>1–3</sup>. Sitagliptin is a potent and selective DPP-4 inhibitor for the treatment of patients with type 2 diabetes. Indeed, treatment with sitagliptin showed significant reduction in glycosylated hemoglobin (HbA1c) levels from baseline compared with placebo<sup>4–10</sup>.

We recently reported that under diabetic conditions, incretin receptor expression in mouse  $\beta$ -cells was downregulated,

which was recovered after amelioration of glycemic control with insulin<sup>11,12</sup>. Furthermore, it was reported that incretin receptor expression was downregulated in type 2 diabetic patients<sup>13</sup>, and that glucagon-like peptide-1-mediated insulin secretion was improved after amelioration of glycemic control with insulin in type 2 diabetic patients<sup>14,15</sup>. These results suggest that it would be better to use incretin-related medicine after amelioration of glycemic control in poorly controlled diabetic patients. However, there are a few reports evaluating the efficacy of DPP-4 inhibitor on glucose tolerance after amelioration of glycemic control. The aim of the present study was to evaluate the short- and long-term effect of sitagliptin on glucose tolerance after near normalization of glycemic control with insulin in poorly controlled type 2 diabetic

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patients, and to examine in which patients sitagliptin exerts more beneficial effects on glycemic control.

## MATERIALS AND METHODS

### Participants and Selection Criteria

Participants were recruited from inpatients who were admitted to Osaka University Hospital for treatment of type 2 diabetes from 1 April 2010 to 30 September 2011. Inclusion criteria were as follows: aged 20–80 years and poorly controlled diabetic patients (HbA1c  $\geq 7.4\%$ ). We excluded patients suffering from renal dysfunction (serum creatinine  $>1.2$  mg/dL), hepatic dysfunction, infection, connective tissue disease or malignancy. The present clinical study was approved by the institutional ethical committee. After a full explanation of this study, written informed consent was obtained from each participant.

### Study Protocol, and Clinical and Biochemical Variables

At the time of admission, height, bodyweight, blood pressure, fasting plasma lipid, creatinine, blood urea nitrogen, glucose, C-peptide and HbA1c were measured using standard laboratory protocols. HbA1c in the present study was expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value; HbA1c (NGSP equivalent value) (%) = HbA1c (Japan Diabetes Society value) (%) + 0.4%<sup>16,17</sup>. After admission, we stopped all oral antidiabetic drugs and started insulin therapy under the diet therapy that is recommended by the Japan Diabetes Society (50–60% carbohydrate, not more than 25% fat by kilocalorie, and protein was 1.0–1.2 g/kg [body weight]). When we thought that insulin therapy would be beneficial for each diabetic patient, we explained the benefit of insulin therapy to each patient as follows: early induction of insulin therapy would exert beneficial effects on protection of  $\beta$ -cell function and DPP-IV inhibitors, as well as other antidiabetic drugs that would be more beneficial on glycemic control after removal of  $\beta$ -cell glucose toxicity. When we did not obtain the agreement about the introduction of insulin therapy, we started sitagliptin treatment without insulin. When we obtained the agreement, we used insulin for 1–2 weeks and then started treatment with sitagliptin or other antidiabetic drugs. The selection depended on the judgment of the physician in charge. The dose of basal and rapid insulin was adjusted as best as possible in order to obtain better glycemic control. When fasting plasma glucose (FPG) levels became  $<140$  mg/dL, we carried out the first oral glucose tolerance test (OGTT). One week after the start of sitagliptin (50 mg/day), the second OGTT was carried out (in this case, sitagliptin was taken 1 h before the test). Before and after the 1-week sitagliptin treatment, plasma glucose levels were measured before and 2 h after each meal and before sleep for 2 days.

### OGTT

After overnight fast, OGTT was carried out using 75-g oral glucose. Blood samples were collected before and 30, 60, 90, and 120 min after oral glucose load to determine plasma glucose,

insulin and glucagon levels. From these data, we calculated the area under the curve (AUC) of plasma glucose, insulin and glucagon levels. Insulinogenic index, C-peptide (CPR) Index and Secretary Units of Islets in Transplantation (SUIT) Index<sup>18</sup> were used to evaluate insulin secretory capacity. Homeostasis model assessment of insulin resistance (HOMA-IR) and the Matsuda Index were used to evaluate insulin resistance. The formula of these markers are as follows: SUIT Index =  $250 \times$  fasting CPR (ng/mL)/(FPG (mmol/L) – 3.43, CPR Index = fasting CPR (ng/mL)  $\times 100$  / FPG (mg/dL), HOMA-IR = fasting serum insulin ( $\mu$ U/mL)  $\times$  FPG (mg/dL) / 405. Insulin and CPR levels were measured using two-site sandwich immunoassay kits, and glucagon levels were measured by radioimmunoassay using a double-antibody method (SRL, Tokyo, Japan).

### Statistical Analysis

Data are given as mean  $\pm$  standard deviation. Differences among the groups were determined by unpaired Student's *t*-test or the  $\chi^2$ -test. Paired *t*-tests were used to compare the parameters before and after the observation period. In all statistical analyses,  $P < 0.05$  was considered statistically significant.

## RESULTS

### Baseline Characteristics of the Study Participants

A total of 30 Japanese type 2 diabetic patients (18 men and 12 women) met the criteria and participated in the study. Patients' characteristics in the present study were as follows: age  $57 \pm 11$  years, BMI  $26.3 \pm 4.2$  kg/m<sup>2</sup>, duration of diabetes  $8.5 \pm 6.9$  years, HbA1c (NGSP)  $8.9 \pm 1.9\%$ , FPG  $141 \pm 35$  mg/dL, systolic and diastolic blood pressure  $123 \pm 12$  and  $76 \pm 10$  mmHg, creatinine  $0.7 \pm 0.2$  mg/dL, estimated glomerular filtration rate  $80.0 \pm 16.6$  mL/min/1.73 m<sup>2</sup>, low-density lipoprotein cholesterol  $128 \pm 30$  mg/dL; high-density lipoprotein cholesterol  $47 \pm 10$  mg/dL, triglycerides  $153 \pm 49$  mg/dL (Table 1). Before admission, eight patients were treated with diet alone and 22 patients with some antidiabetic drugs.

### Short-Term Effect of Sitagliptin Treatment on Glucose Tolerance After Near Normalization of Glycemic Control with Insulin

After near normalization of glycemic control with insulin therapy, sitagliptin treatment was carried out for 1 week (Figure 1a). As shown in Figure 1b, although there was no difference in FPG between before and after 1-week sitagliptin treatment, post-challenge plasma glucose levels at all points (30, 60, 90, 120 min) were significantly reduced after sitagliptin treatment ( $208.1 \pm 26.4$  vs  $189.2 \pm 27.8$  mg/dL,  $P < 0.05$ ;  $275.6 \pm 35.5$  vs  $217.1 \pm 46.4$  mg/dL,  $P < 0.05$ ;  $306.1 \pm 38.5$  mg/dL vs  $222.4 \pm 52.4$  mg/dL,  $P < 0.05$ ;  $302.1 \pm 53.3$  mg/dL vs  $202.3 \pm 59.4$  mg/dL,  $P < 0.05$ , respectively). As the results, the AUC of plasma glucose was significantly reduced after sitagliptin treatment ( $491.2 \pm 56.8$  mg/dL vs  $387.7 \pm 61.3$  mg/dL,  $P < 0.001$ ). Also, as shown in Figure 1c, although there was no difference in fasting serum insulin levels 90 min and

**Table 1** | Baseline characteristic of the study participants treated with sitagliptin for 1 week after near normalization of glycemic control with insulin therapy

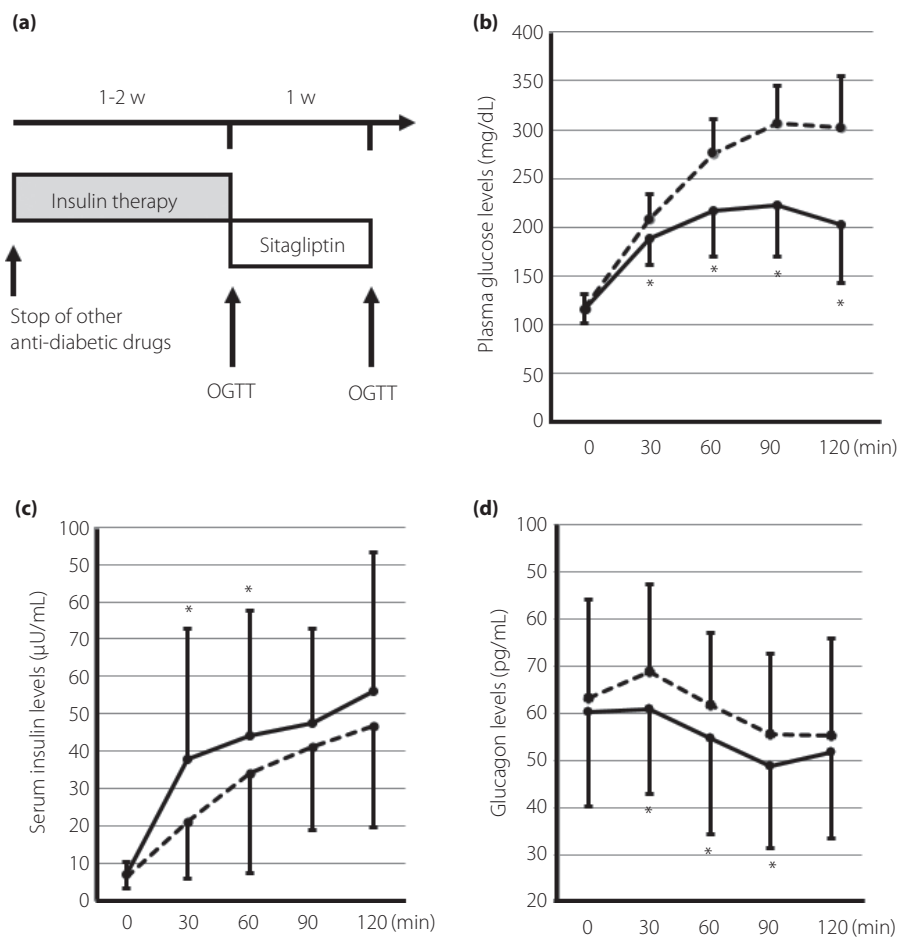
Sex (n)	Males 18, females 12
Age (years)	57 ± 11
BMI (kg/m <sup>2</sup> )	26.3 ± 4.2
Duration (years)	8.5 ± 7.1
HbA1c (%) (NGSP)	8.9 ± 1.9
FPG (mg/dL)	141 ± 35
Fasting CPR (ng/mL)	2.2 ± 0.9
Systolic BP (mmHg)	123 ± 12
Diastolic BP (mmHg)	76 ± 10
LDL cholesterol (mg/dL)	128 ± 30
HDL cholesterol (mg/dL)	47 ± 10
Triglycerides (mg/dL)	153 ± 49

BMI, body mass index; BP, blood pressure; CPR, C-peptide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

120 min after glucose load between before and after 1-week sitagliptin treatment, serum insulin levels 30 min and 60 min after glucose load were significantly increased after sitagliptin treatment ( $21.6 \pm 15.3$  vs  $37.6 \pm 35.0$   $\mu\text{U/mL}$ ,  $P < 0.05$ ), ( $34.7 \pm 26.8$  vs  $44.2 \pm 33.4$   $\mu\text{U/mL}$ ,  $P < 0.05$ , respectively; before vs after sitagliptin treatment). As the results, the AUC of insulin was significantly increased ( $61.0 \pm 37.5$  vs  $81.8 \pm 49.8$   $\mu\text{U/mL}$ ,  $P < 0.01$ ).

Next, we examined the effect of sitagliptin on insulin secretory capacity and insulin sensitivity. Insulinogenic index, CPR index and SUIIT index, all of which are markers for insulin secretory capacity, were significantly increased after 1-week sitagliptin treatment ( $0.17 \pm 0.18$  vs  $0.41 \pm 0.44$ ,  $P < 0.01$ ;  $1.5 \pm 0.7$  vs  $1.7 \pm 0.7$ ,  $P < 0.01$ ;  $48.4 \pm 23.8$  vs  $58.0 \pm 26.9$ ,  $P < 0.01$ , respectively), although there was no difference in HOMA-IR and Matsuda Index, both of which are markers for insulin sensitivity ( $1.8 \pm 1.0$  vs  $2.0 \pm 1.0$ ,  $5.4 \pm 3.4$  vs  $5.1 \pm 2.7$ , respectively).

In addition, as shown in Figure 1d, although there was no difference in fasting glucagon levels and glucagon levels



**Figure 1** | The short-term effect of sitagliptin on glucose tolerance after near normalization of glycemic control with insulin. (a) After near normalization of glycemic control with insulin, sitagliptin treatment was carried out for 1 week. Oral glucose tolerance test (OGTT) was carried out before and after sitagliptin treatment. (b) Plasma glucose levels, (c) serum insulin levels and (d) glucagon levels were examined before, and 30 min, 60 min and 120 min after glucose load. \* $P < 0.05$ .

120 min after glucose load between before and after 1-week sitagliptin treatment, glucagon levels 30 min, 60 min and 90 min after glucose load were significantly decreased after sitagliptin treatment ( $68.6 \pm 18.6$  vs  $60.9 \pm 18.0$  pg/mL,  $P < 0.05$ ;  $61.7 \pm 15.2$  vs  $54.4 \pm 20.2$  pg/mL,  $P < 0.05$ ;  $55.4 \pm 17.1$  vs  $48.6 \pm 17.2$  pg/mL,  $P < 0.05$ ; before vs after sitagliptin treatment). As the results, the AUC of glucagon was significantly decreased ( $61.0 \pm 37.5$  vs  $81.8 \pm 49.8$  pg/mL,  $P < 0.01$ ).

Taken together, after near normalization of glycemic control with insulin, sitagliptin exerted marked beneficial effects on insulin secretion and glycemic control.

### Characteristics of Responders and Non-Responders to Sitagliptin

To examine in which patients sitagliptin exerts more beneficial effect, we divided the participants into two groups: the responder group (average FPG  $<130$  mg/dL and PPG  $<180$  mg/dL) and non-responder group. Of the 30 patients, 23 were responders. As shown in Table 2, there was no difference in age, BMI, HbA1c, FPG and fasting CPR between the two groups. Interestingly, duration of diabetes was significantly shorter in the responder group ( $6.8 \pm 6.2$  vs  $13.0 \pm 7.6$  years,  $P < 0.05$ ), and dose of insulin used for amelioration of glycemic control tended to be smaller in the responder group ( $14.6 \pm 7.5$  vs  $21.1 \pm 10.4$  U/day; responder vs non-responder), although it did not reach a statistical significance. SUIT, a marker for  $\beta$ -cell insulin secretory capacity, also tended to be larger in the

**Table 2** | Characteristics in responders and non-responders to sitagliptin in poorly controlled type 2 diabetic patients

	Responders	Non-responders	P
On admission			
Age (years)	$56.8 \pm 11.7$	$58.1 \pm 11.4$	NS
BMI ( $\text{kg}/\text{m}^2$ )	$26.2 \pm 4.1$	$26.5 \pm 4.8$	NS
Duration (years)	$6.8 \pm 6.2$	$13.0 \pm 7.6$	$<0.05$
HbA1c (%) (NGSP)	$9.3 \pm 1.9$	$8.3 \pm 1.7$	NS
FPG (mg/dL)	$145.2 \pm 36.2$	$129.8 \pm 32.8$	NS
Fasting CPR (ng/mL)	$2.4 \pm 0.9$	$1.9 \pm 0.8$	NS
After insulin therapy			
Amounts of insulin (units/day)	$14.6 \pm 7.5$	$21.1 \pm 10.4$	0.084
Insulinogenic Index	$0.19 \pm 0.20$	$0.12 \pm 0.07$	NS
CPR Index	$1.6 \pm 0.7$	$1.2 \pm 0.5$	NS
SUIT	$53.3 \pm 25.1$	$38.0 \pm 18.0$	0.083
HOMA-IR	$1.8 \pm 1.0$	$1.9 \pm 1.1$	NS
Matsuda Index	$5.5 \pm 3.9$	$5.0 \pm 2.1$	NS
AUC (glucose)	$480.0 \pm 57.1$	$517.2 \pm 49.7$	NS
AUC (insulin)	$66.4 \pm 43.0$	$48.4 \pm 15.3$	NS
AUC (glucagon)	$125 \pm 35.0$	$114 \pm 18.4$	NS

AUC, area under the curve; BMI, body mass index; BP, blood pressure; CPR, C-peptide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; SUIT, Secretory Units of Islets in Transplantation.

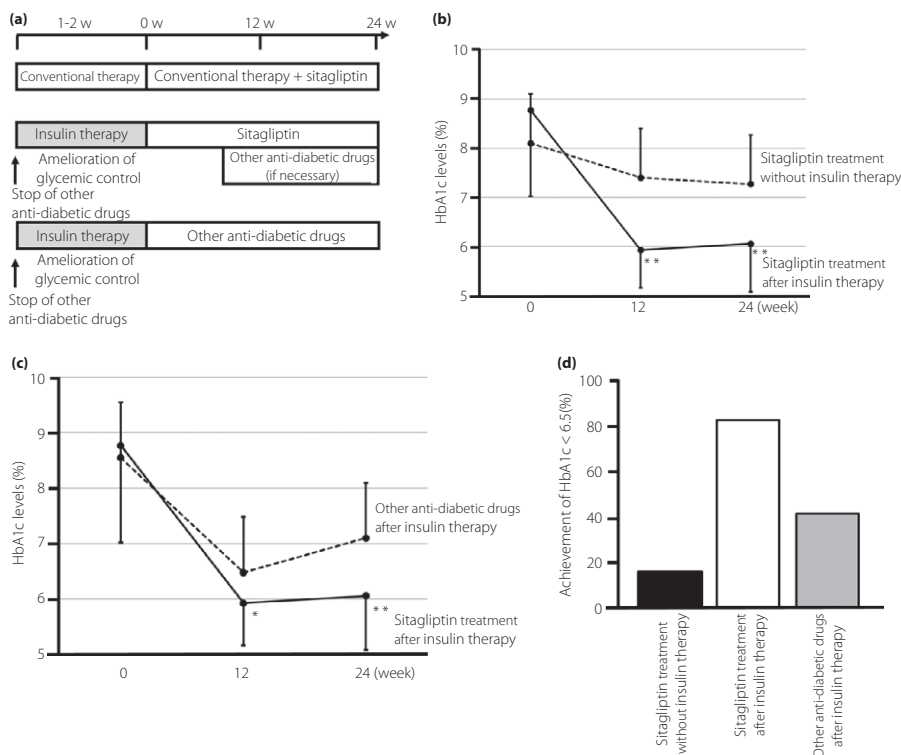
responder group ( $53.3 \pm 25.1$  vs  $38.0 \pm 18.0$ ). There was no difference in insulin sensitivity markers, such as HOMA-IR and Matsuda Index, and in the AUC of glucose, insulin and glucagon. Taken together, sitagliptin exerts more beneficial effect in patients whose duration of diabetes is shorter and whose  $\beta$ -cell function is preserved.

### Long-Term Effect of Sitagliptin Treatment on Glucose Tolerance After Near Normalization of Glycemic Control with Insulin

To examine the long-term effect of sitagliptin treatment after near normalization of glycemic control with insulin, we examined HbA1c levels 12 and 24 weeks after the start of sitagliptin treatment (Figure 2a). As shown in Table 3, there was no significant difference in ratio of male, age, BMI, duration of diabetes and HbA1c levels between the patients without and after near normalization with insulin therapy. As shown in Figure 2b, in patients who started sitagliptin without insulin therapy, HbA1c levels before the start of sitagliptin, and 12 and 24 weeks after the start of sitagliptin were  $8.10 \pm 1.14$ ,  $7.40 \pm 1.09$ , and  $7.27 \pm 1.07\%$ , respectively. In patients who started sitagliptin after near normalization with insulin therapy, HbA1c levels before the start of sitagliptin, and 12 and 24 weeks after the start of sitagliptin were  $8.77 \pm 1.75$ ,  $5.93 \pm 0.77$ , and  $6.06 \pm 0.98\%$ , respectively. Interestingly, there was a significant difference in HbA1c levels 12 and 24 weeks after the start of sitagliptin treatment between without and after near normalization with insulin therapy ( $7.40 \pm 1.09$  vs  $5.93 \pm 0.77\%$ ,  $P < 0.01$  and  $7.27 \pm 1.07$  vs  $6.06 \pm 0.98\%$ ,  $P < 0.01$ , respectively). These results suggest that near normalization of blood glucose levels with insulin therapy could bring out the long-term effectiveness of sitagliptin on glucose tolerance in poorly controlled diabetic patients.

Next, we examined whether such phenomena are observed with other antidiabetic drugs after near normalization of glycemic control with insulin. As shown in Table 3, there was no significant difference in ratio of male, age, BMI, duration of diabetes and HbA1c levels between the patients treated with sitagliptin and other antidiabetic drugs after near normalization of blood glucose levels with insulin. As shown in Figure 2c, in patients who started other antidiabetic drugs after near normalization of blood glucose levels with insulin, HbA1c levels before, and 12 and 24 weeks after the start of sitagliptin were  $8.55 \pm 1.11$ ,  $6.48 \pm 0.75$ , and  $7.10 \pm 1.29\%$ , respectively. Interestingly, after near normalization of blood glucose levels with insulin, there was a significant difference in HbA1c levels at 12 and 24 weeks between the sitagliptin group and the other antidiabetic drug group ( $5.93 \pm 0.77$  vs  $6.48 \pm 0.75\%$ ,  $P < 0.05$  and  $6.06 \pm 0.98$  vs  $7.10 \pm 1.29\%$ ,  $P < 0.01$ , respectively). These results suggest that near normalization of blood glucose levels with insulin would be very important, especially when we use DPP-IV inhibitor rather than other antidiabetic drugs.

In addition, as target HbA1c levels (NGSP) are 6.9% in general, we examined the achievement of HbA1c  $<6.9\%$  24 weeks



**Figure 2** | Long-term effect of sitagliptin on glucose tolerance after near normalization of glycemic control with insulin. (a) After conventional therapy or after near normalization of glycemic control with insulin, treatment with sitagliptin or other antidiabetic drugs was carried out for 24 weeks. (b) Glycated hemoglobin (HbA1c) levels were examined 12 and 24 weeks after sitagliptin treatment without and after near normalization of glycemic control with insulin therapy. (c) HbA1c levels were examined 12 and 24 weeks after treatment of sitagliptin or other antidiabetic drugs after near normalization with insulin therapy. (d) Achievement of HbA1c <6.9% was evaluated 24 weeks after treatment of sitagliptin or other antidiabetic drugs after near normalization with insulin therapy. \* $P < 0.05$ , \*\* $P < 0.01$ .

**Table 3** | Baseline characteristics of the study participants treated with sitagliptin for 24 weeks without and after insulin therapy

	Sitagliptin without insulin therapy (n = 41)	Sitagliptin after insulin therapy (n = 23)	Other anti-diabetic drugs after insulin therapy (n = 29)	P
Sex (n)	Males 31, females 10	Males 14, females 9	Males 18, females 11	NS
Age (years)	60 ± 9	58 ± 12	60 ± 10	NS
BMI (kg/m <sup>2</sup> )	25.3 ± 4.0	26.7 ± 3.8	25.9 ± 3.7	NS
Duration (years)	10.4 ± 4.8	8.2 ± 7.2	8.1 ± 6.0	NS
HbA1c (%)	8.5 ± 1.1	9.2 ± 1.7	9.0 ± 1.0	NS

BMI, body mass index; HbA1c, glycated hemoglobin, NS, not significant.

after treatment with sitagliptin or other antidiabetic drugs without or after insulin therapy. As shown in Figure 2d, the achievement in the patients with sitagliptin treatment without insulin therapy was as low as 17.1%. In contrast, the achievement in the patients with sitagliptin after near normalization with insulin therapy was as high as 82.6%, which was markedly

higher compared with those without insulin therapy (17.1%). In addition, interestingly, the achievement in the patients with other antidiabetic drugs after near normalization with insulin therapy was not very high (41.4%), which was markedly lower compared with those with sitagliptin after insulin therapy (82.6%). Taken together, near normalization of glycemic control with short-term insulin therapy for 1–2 weeks could bring out the long-term effectiveness of sitagliptin on glucose tolerance for 24 weeks, which was not observed with other antidiabetic drugs.

**DISCUSSION**

After amelioration of glycemic control with insulin therapy in poorly controlled type 2 diabetic patients, only 1-week sitagliptin treatment exerted marked beneficial effects on glucose tolerance. The AUC of insulin was significantly increased, and the AUC of glucagon and glucose were significantly decreased. These findings suggest that near normalization of the blood glucose levels with insulin therapy improves the clinical response to sitagliptin in poorly controlled type 2 diabetic patients. We recently reported that under diabetic conditions, incretin receptor expression in mouse β-cells was downregulated, which was recovered after amelioration of glycemic control with insulin<sup>11,12</sup>. Therefore, although not examined in the pres-



ent study, it is possible that incretin receptor expression was recovered after near normalization of blood glucose levels with insulin therapy, and thereby sitagliptin exerted more beneficial effect in such diabetic patients.

In addition, there were responders and non-responders to sitagliptin treatment. Duration of diabetes was shorter, and  $\beta$ -cell insulin secretory capacity was preserved in the responder group compared with the non-responder group. It is likely that duration of diabetes and residue  $\beta$ -cell function are clinically useful indicators to estimate the efficacy of sitagliptin therapy. In addition, we assume that it would be better to recover  $\beta$ -cell function with some treatment (e.g., insulin therapy) before administration of sitagliptin when  $\beta$ -cell function, such as insulin secretory capacity, is deteriorated in type 2 diabetic patients.

Furthermore, the data of the present study suggest that near normalization of glycemic control with short-term insulin therapy for 1–2 weeks could bring out the long-term effectiveness of sitagliptin on glucose tolerance for 24 weeks. We believe that this point is very important from the clinical point of view in order to understand how we could effectively use DPP-IV inhibitors in clinical medicine. It is noted, however, that the present study was carried out with a limited number of patients, and that we cannot deny the possibility that there was some selection bias in this study. Therefore, a further randomized study with a larger number of patients would be necessary to strengthen our hypothesis.

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