

ORIGINAL

## Add-on therapy with the DPP-4 inhibitor sitagliptin improves glycemic control in insulin-treated Japanese patients with type 2 diabetes mellitus

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**Abstract.** The effect of add-on therapy with sitagliptin on glycemic control was prospectively investigated in patients with type 2 diabetes mellitus (T2DM) receiving insulin alone or insulin combined with oral antidiabetic drugs. Seventy-one patients were evaluated (38 men and 33 women aged 63.9±10.2 years). They were divided into three groups, which were 45 patients receiving premixed insulin twice daily, 15 patients receiving multiple daily insulin injections, and 11 patients receiving basal insulin with oral antidiabetic drugs (basal insulin therapy). Concomitant oral drugs included sulfonylureas,  $\alpha$ -glucosidase inhibitors and metformin. The hemoglobin A1c (HbA1c) of all patients improved significantly from 8.1±1.2% to 7.6±1.1% after 12 weeks of add-on therapy with sitagliptin ( $p<0.01$ ), and the insulin dosage was reduced from 27.3±15.8 U/day to 24.5±16.5 U/day ( $p<0.001$ ). Body weight did not change after the start of concomitant therapy and severe hypoglycemia was not observed. The baseline HbA1c and glycated albumin levels were identified as factors that predicted the response to add-on therapy with sitagliptin. These findings suggest that add-on therapy with sitagliptin can be expected to achieve improvement of poor glycemic control irrespective of a patient's demographic profile. Stratified analysis based on the insulin regimen revealed a stronger antidiabetic effect and a high efficacy of sitagliptin when it was added to basal insulin therapy. The results of this investigation confirmed that add-on therapy with sitagliptin to various insulin regimens could improve glycemic control without severe hypoglycemia and/or weight gain.

**Key words:** Dipeptidyl peptidase-4 inhibitor, Type 2 diabetes mellitus, Insulin therapy, Glycemic control, Hemoglobin A1c

**IN PATIENTS** with type 2 diabetes mellitus (T2DM), combining insulin therapy with conventional oral antidiabetic drugs has been reported to be more effective than using insulin alone [1-3]. The advantages of concomitant therapy are not only improvement of glycemic control, but also a reduction in the number of insulin injections and titration of the insulin dose. In addition, reduction of hypoglycemia risk, prevention of weight gain, and alleviation of psychological stress linked to the initiation of insulin therapy can be expected [4, 5].

The highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin has been reported to improve glycemic control under fasting and postprandial condi-

tions, as well as improving  $\beta$ -cell function [6]. The mechanism of its antihyperglycemic activity is related to enhancement of insulin secretion and inhibition of glucagon secretion in a blood glucose-dependent manner [7, 8]. In Japanese patients with T2DM, the efficacy of sitagliptin has been demonstrated as both monotherapy and in combination with various oral antidiabetic drugs [9-13].

Combined therapy with sitagliptin and insulin has also been shown to be effective in patients with T2DM [14, 15] and use of sitagliptin as add-on therapy was approved in Japan in September 2011. Because a variety of insulin regimens are used in the real-world manage-

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Abbreviations: HbA1c, glycated hemoglobin; GA, glycoalbumin; CPR, C-peptide reactivity; CPI, C-peptide reactivity index; DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NGSP, National Glycohemoglobin Standardization Program; T2DM, type 2 diabetes mellitus

ment diabetes, it was considered that the safety and efficacy of concomitant treatment with sitagliptin and insulin should be researched in a large patient population.

Accordingly, we conducted a prospective clinical study to assess the effect of add-on therapy with sitagliptin on glycemic control in T2DM patients who were receiving insulin monotherapy or insulin combined with other oral antidiabetic drugs.

## Subjects and Methods

### Subjects

The patients with T2DM who were recruited for this study were treated at Hyogo College of Medicine and Ikeda Hospital from September 2011 to March 2012 and fulfilled the following eligibility criteria. Inclusion criteria were 1) an age  $\geq 20$  years, 2) T2DM treated with insulin therapy (basal insulin therapy with oral antidiabetic drugs (basal insulin therapy), twice daily injection of premixed insulin, or multiple daily injections of insulin) for at least 6 months, and 3) a hemoglobin A1c (HbA1c)  $\geq 6.9\%$  (National Glycohemoglobin Standardization Program [NGSP] value). The exclusion criteria were 1) type 1 diabetes, 2) severe complications of diabetes, 3) severe hypoglycemia or recurrent asymptomatic hypoglycemia, 4) severe infection, 5) patients scheduled for surgery or those with serious trauma, 6) pregnant or nursing women and those who might be pregnant, and 7) other patients whom the investigator judged to be inappropriate for the study.

This study was conducted in accordance with the principles of the Declaration of Helsinki. All subjects were given an explanation of the details of this clinical study and written informed consent was obtained voluntarily from each subject.

### Treatment

In patients who fulfilled the above eligibility criteria, add-on therapy with 50 mg of sitagliptin once daily after breakfast was provided for 12 weeks. Throughout the study period, emphasis was placed on avoiding episodes of hypoglycemia based on the glucose data obtained by self-measurement of blood glucose and the insulin dosage was adjusted to maintain a fasting blood glucose level  $<126$  mg/dL and a blood glucose level  $<140$  mg/dL at 2 hours after meals. Reduction of the insulin dosage was allowed if fasting blood glucose level was  $<80$  mg/dL and postprandial blood glucose was  $<100$  mg/dL. Even if these criteria were not met, the dosage could be

reduced if the attending doctor judged that there was a risk of hypoglycemia. During the study period, changing the dosages of conventional oral antidiabetic drugs was generally not allowed. However, if there was a risk of hypoglycemia in patients on concomitant sulfonylurea (SU) therapy, dose reduction or suspension of SU therapy was allowed.

As the study parameters, HbA1c (NGSP), glycated albumin (GA), body weight, insulin dosage, C-peptide reactivity (CPR), and the CPR index (CPI) were measured in all patients prior to starting combination therapy with sitagliptin (Week 0), as well as in Week 4, 8, and 12 after the initiation of combination therapy. Changes observed after administration of sitagliptin were compared among the patients with stratification based on concomitant oral antidiabetic drugs and insulin regimens. The incidence of severe hypoglycemia during the treatment period was also evaluated.

### Statistical analysis

In all patients, the changes of HbA1c and GA in Weeks 4, 8, and 12 *versus* Week 0 were evaluated by the two-way ANOVA followed by Dunnett's test. Changes of the body weight, CPI, absolute insulin dosage, and insulin dosage per kilogram of body weight kg in Week 12 *versus* Week 0 were evaluated by using the paired *t*-test or Wilcoxon signed-rank test. Comparisons based on the concomitant drugs used and on reduction/non-reduction of the insulin dosage were done with the unpaired *t*-test or the Mann-Whitney *U* test.

For stratified analysis based on the insulin regimen, comparison of demographic data among three groups was conducted by the chi-square test, Bartlett's test, or the Kruskal-Wallis test as appropriate. Comparison of the changes of HbA1c, GA, body weight, CPI, and insulin dosage was done with the Kruskal-Wallis test followed by the Steel-Dwass test.

Correlations between the changes of HbA1c and each demographic parameters were assessed by the Pearson product-moment correlation test. For all analyses,  $p < 0.05$  was taken to indicate statistical significance. For HbA1c (%), the NGSP value was calculated ( $\text{HbA1c (NGSP)} = 1.02 \times \text{HbA1c (JDS)} + 0.25\%$ ), based on the relationship between HbA1c (NGSP) values and HbA1c (JDS) (%) values measured with the Japanese standard and measurement method [16]. Data in the text and Tables are expressed as the mean  $\pm$  standard deviation (S.D.), while data in the Figures are shown as the mean  $\pm$  standard error (S.E.).

## Results

### 1. Overall results

#### 1-1. Patient characteristics

Baseline demographic and clinical characteristics of the 71 subjects (38 men and 33 women aged  $63.9 \pm 10.2$  years) at the initiation of the study are presented in Table 1. The most common insulin regimen was twice daily injections of premixed insulin. The most common class of antidiabetic drug being concomitantly used was SU in 42 patients (59.2%), followed by  $\alpha$ -glucosidase inhibitors ( $\alpha$ -GI) and metformin. Only 7 patients discontinued or reduced their antidiabetic drug therapy at the time of starting sitagliptin treatment (discontinued in 4 patients and dose reduction in 3 patients).

#### 1-2. Changes of HbA1c and GA

Changes of HbA1c and GA during concomitant treatment with sitagliptin for 12 weeks are presented in Fig. 1. In Weeks 8 and 12, HbA1c was significantly lower compared with that in Week 0 ( $p < 0.05$  and  $0.01$ , respectively). A significant decrease of GA occurred earlier than that of HbA1c and was observed from Week 4 ( $p < 0.01$ ). A significant reduction of GA compared with the Week 0 value was maintained throughout Weeks 8 and 12 ( $p < 0.01$ ).

#### 1-3. Changes of body weight

Body weight from Week 0 to Week 12 did not change ( $66.9 \pm 11.9$  vs.  $66.8 \pm 11.9$  kg) (Table 2).

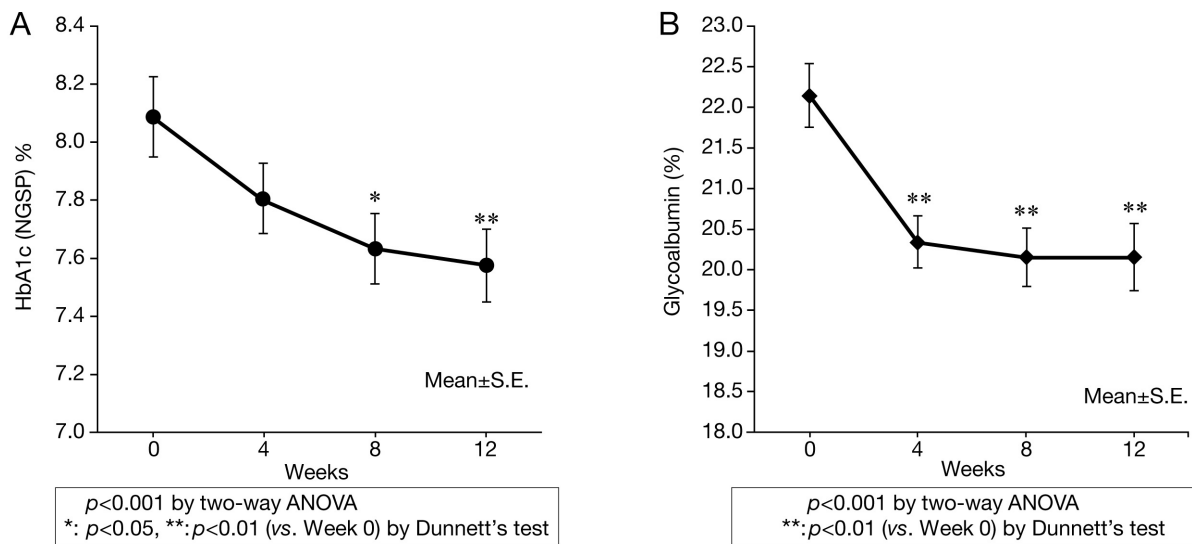
#### 1-4. Changes of CPI

CPI was significantly increased in Week 12 com-

**Table 1** Baseline demographic and clinical characteristics of the patients (n=71)

Age (years)	63.9±10.2
Sex, n (%)	
Male	38 (54)
Female	33 (46)
Body weight (kg)	66.8±11.9
Body mass index (kg/m <sup>2</sup> )	25.7±3.6
Duration of diabetes (years)	18.1±10.4
HbA1c, % (NGSP)	8.1±1.2
CPR index (CPI)	1.3±0.8
Duration of sulfonylurea therapy (years)	9.3±7.3
Insulin dose (U/day)	27.3±15.8
Insulin dose per body weight (U/day/kg)	0.4±0.21
Insulin therapy, n (%)	
Twice daily injections	45 (63.8)
Multiple daily injections	15 (21.1)
Basal insulin therapy	11 (15.5)
Oral antidiabetic drugs, n (%)	
None	12 (16.9)
Sulfonylureas	42 (59.2)
Glinides	5 (5.6)
Metformin	24 (33.8)
Thiazolidinediones	1 (1.4)
$\alpha$ -glucosidase inhibitors	28 (39.4)

Data are the mean  $\pm$  S.D. HbA1c, hemoglobin A1c.



**Fig. 1** Effect of add-on treatment with sitagliptin (50 mg/day) for 12 weeks on (A) HbA1c and (B) glycoalbumin in all patients

**Table 2** Parameters at baseline and in Week 12, as well as changes from baseline

	Baseline	Week 12	Change from baseline to Week 12	<i>p</i> value
Body weight (kg)	66.9±11.9	66.8±11.9	-0.1±1.0	0.604 <sup>a</sup>
CPR index	1.3±0.8	1.6±1.0	0.3±0.05	<0.001 <sup>b</sup>
Insulin dose (U/day)	27.3±15.8	24.5±16.5	-1.7±3.3	<0.001 <sup>a</sup>
Insulin dose per kilogram of body weight (U/day/kg)	0.40±0.21	0.38±0.22	-0.03±0.05	<0.001 <sup>a</sup>

Data are the mean ± S.D. <sup>a</sup>, Paired *t*-test; <sup>b</sup>, Wilcoxon signed-rank test

**Table 3** Correlations between baseline characteristics and the change of HbA1c after 12 weeks

	Correlation coefficient	<i>p</i> value
Age	0.088	0.463
Duration of diabetes mellitus	0.058	0.631
Body weight	0.042	0.726
Body mass index	-0.009	0.938
Duration of sulfonylurea therapy	0.042	0.938
Insulin dose	0.127	0.731
Insulin dose per kilogram of body weight	0.127	0.292
HbA1c	-0.431	0.0002
Glycoalbumin	-0.258	0.030
CPR index	0.152	0.207
Systolic blood pressure	0.033	0.787

Pearson's correlation analysis was employed. HbA1c, hemoglobin A1c.

pared with Week 0 (1.3±0.8 vs. 1.6±1.0, *p*<0.001) (Table 2).

#### 1-5. Changes of the insulin dosage

Between Weeks 0 and 12, the daily dose of insulin decreased significantly from 27.3±15.8 to 24.5±16.5 U/day (*p*<0.001), and the daily dose of insulin per body weight was also significantly reduced from 0.40±0.21 to 0.38±0.22 U/day/kg (*p*<0.001) (Table 2).

#### 1-6. Severe hypoglycemia

None of the 71 patients experienced an episode of hypoglycemia that required third party assistance or emergency treatment at hospital either before or after combination therapy with sitagliptin.

## 2. Stratified analysis by patient characteristics

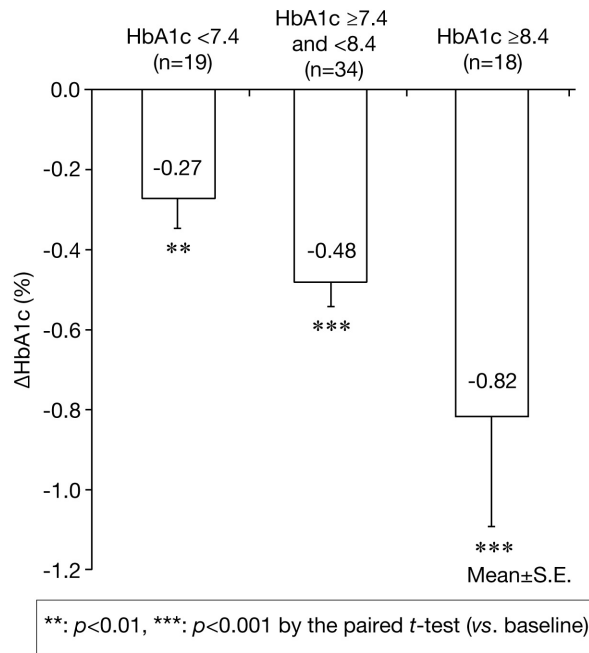
### 2-1. Evaluation of patients with successful combination therapy

In order to identify the patients for whom combination therapy of insulin with sitagliptin showed high

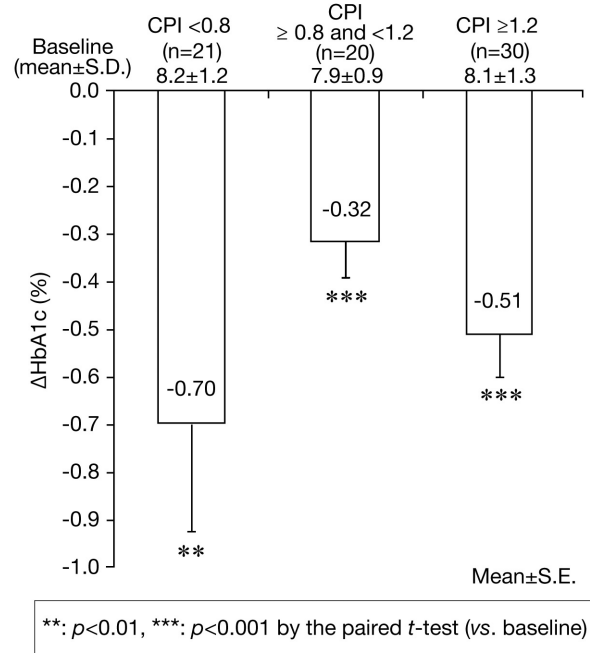
efficacy, correlations between the hypoglycemic effect (change of HbA1c from Week 0 to Week 12) and various baseline characteristics were evaluated (Table 3). The change of HbA1c showed an inverse correlation with baseline HbA1c (*r*=-0.431, *p*<0.001) and a weak correlation with baseline GA (*r*=-0.258, *p*=0.030). No correlations were observed with the other parameters.

### 2-2. Influence of HbA1c at the initiation of treatment

Since a correlation was found between the changes of HbA1c after 12 weeks of add-on therapy and baseline HbA1c, the patients were classified into three groups according to baseline HbA1c: 1) <7.4%, 2) ≥7.4% and <8.4%, and 3) ≥8.4%. Then the changes of HbA1c were compared among the groups (Fig. 2). There was a decrease of HbA1c by 0.27±0.31% (*p*=0.0010) in patients with a baseline HbA1c <7.4%, a decrease of 0.48±0.35% (*p*<0.001) in those with a baseline value between ≥7.4% and <8.4%, and a



**Fig. 2** Change of HbA1c from baseline to Week 12 for each HbA1c subgroup  
No significant differences were observed by Kruskal-Wallis test nor Steel-Dwass test (*post-hoc* multiple comparisons).



**Fig. 3** Change of HbA1c from baseline to Week 12 for each CPI subgroup  
No significant differences were observed by Kruskal-Wallis test nor Steel-Dwass test (*post-hoc* multiple comparisons).

decrease of  $0.82 \pm 1.17\%$  in those with a baseline value  $\geq 8.4\%$  ( $p < 0.001$ ). Thus, the largest and most significant decrease was observed in the patients with a baseline HbA1c  $\geq 8.4\%$ .

### 2-3. Influence of CPI

Baseline CPI was used to clarify the patients into three groups: 1) CPI <0.8, 2) CPI  $\geq 0.8$  and <1.2, and 3) CPI  $\geq 1.2$ . Then the changes of HbA1c were compared between these groups (Fig. 3). In the patients with a CPI <0.8, CPI  $\geq 0.8$  and <1.2, and CPI  $\geq 1.2$ , there was a decrease of HbA1c by  $0.70 \pm 1.03\%$ ,  $0.32 \pm 0.34\%$ , and  $0.51 \pm 0.49\%$ , respectively. A significant decrease was observed in Week 12 *versus* Week 0 in all three groups. There were no significant differences in the changes of HbA1c among the three groups.

### 2-4. Influence of oral antidiabetic drugs

Changes of HbA1c and GA were examined in the patients treated with different oral antidiabetic drugs. When insulin monotherapy was compared with combination therapy using oral antidiabetic drugs, the baseline (Week 0) HbA1c was significantly higher in patients who received combination therapy (insulin monotherapy:  $7.4 \pm 0.7\%$  vs. combination therapy:  $8.2 \pm 1.2\%$ ,  $p = 0.0143$ ). However, there was no significant difference with respect to the change of HbA1c

between the two groups. When patients using three concomitant antidiabetic drugs (SU, metformin, and  $\alpha$ -GI) were compared, there were no significant differences of HbA1c and GA in Week 0, and the change of these parameters also showed no differences. The change of GA was largest for patients receiving concomitant treatment with  $\alpha$ -GI ( $-2.35 \pm 1.50\%$ ). When the changes of HbA1c and GA were compared between patients with or without SU, metformin and  $\alpha$ -GI, no significant differences were observed between those with and without each concomitant drug. However, changes of HbA1c and GA were greater for patients using  $\alpha$ -GI than for those without  $\alpha$ -GI (HbA1c: decrease of  $0.59 \pm 0.38\%$  vs.  $0.46 \pm 0.81\%$ ; GA: decrease of  $2.35 \pm 1.50\%$  vs.  $1.75 \pm 2.22\%$ ).

## 3. Stratified analysis by insulin regimen

### 3-1. Profile of the three groups

The insulin regimens included twice daily injection of premixed insulin in 45 patients (63%: twice daily group), multiple daily injections of insulin in 15 patients (21%: multiple group), and basal insulin therapy in 11 patients (16%: basal insulin therapy group). The demographic profile of each group is presented in Table 4. When three groups were compared, average

**Table 4** Baseline demographic and clinical characteristics of the three insulin subgroups (n=71)

	Twice daily injections (n=45)	Multiple daily injections (n=15)	Basal insulin therapy (n=11)	<i>p</i> value
Age (years)	65.1±10.0	62.9±9.0	61.3±13.8	0.2807 <sup>a</sup>
Sex, n (%)				
Male	20	10	8	0.1247 <sup>b</sup>
Female	25	5	3	
Body weight (kg)	66.3±13.0	71.6±10.8	62.3±6.0	0.0293 <sup>a</sup>
Body mass index (kg/m <sup>2</sup> )	25.4±3.5	27.7±3.6	23.6±3.2	0.7211 <sup>a</sup>
Duration of diabetes (years)	18.3±10.9	17.2±10.6	18.2±8.7	0.6889 <sup>a</sup>
HbA1c (NGSP), %	8.1±1.3	8.2±0.9	8.0±1.0	0.3148 <sup>a</sup>
Glycoalbumin (g/dL)	22.1±3.7	22.1±2.3	22.6±2.8	0.1083 <sup>a</sup>
CPR index (CPI)	1.4±0.9	1.2±0.8	1.1±0.5	0.4261 <sup>c</sup>
Systolic blood pressure (mmHg)	139.3±15.9	136.9±16.6	138.2±17.1	0.9497 <sup>a</sup>
Diastolic blood pressure (mmHg)	80.7±13.1	76.9±12.9	81.0±7.3	0.1159 <sup>a</sup>
Duration of sulfonylurea therapy (years)	9.3±7.8	7.0±7.0	12.5±4.2	0.0973 <sup>a</sup>
Insulin dose (U/day)	26.4±13.0	38.7±20.6	15.4±7.0	0.0026 <sup>a</sup>
Insulin dose per kilogram of body weight (U/day/kg)	0.4±0.2	0.5±0.3	0.2±0.1	0.0058 <sup>a</sup>
Oral antidiabetic drugs, n (%)				
None	8 (18)	4 (27)	0	0.1939 <sup>b</sup>
Sulfonylureas	28 (62)	4 (27)	10 (91)	0.0035 <sup>b</sup>
Glinides	5 (11)	0	0	0.2114 <sup>b</sup>
Metformin	15 (33)	6 (40)	3 (27)	0.7900 <sup>b</sup>
Thiazolidinediones	0	0	1 (9)	0.0629 <sup>b</sup>
α-glucosidase inhibitors	18 (40)	3 (20)	7 (64)	0.0790 <sup>b</sup>

Data are the mean ± S.D. <sup>a</sup>, Bartlett's test; <sup>b</sup>, chi-square test; <sup>c</sup>, Kruskal-Wallis test; HbA1c, hemoglobin A1c

body weight ( $p=0.0293$ ), daily average insulin dose ( $p=0.0026$ ), and daily average insulin dose per kilogram of body weight ( $p=0.0058$ ) were significantly higher in the multiple group. There was no significant difference of HbA1c among the three groups in Week 0 (Table 4).

### 3-2. Changes of HbA1c and GA

From Week 0 to Week 12, HbA1c decreased by  $0.51\pm0.75\%$  in the twice daily group, by  $0.28\pm0.49\%$  in the multiple group, and by  $0.83\pm0.44\%$  in the basal insulin therapy group. All groups showed significant improvement compared with Week 0. The change was largest in the basal insulin therapy group and was statistically different from that in the twice daily group or the multiple group ( $p<0.05$ ) (Fig. 4). Changes of GA were also largest in the basal insulin therapy group and there was a significant difference from the multiple

group ( $p<0.05$ ).

### 3-3. Changes of body weight

No significant differences were observed in the changes of body weight from Week 0 to Week 12 (Table 5).

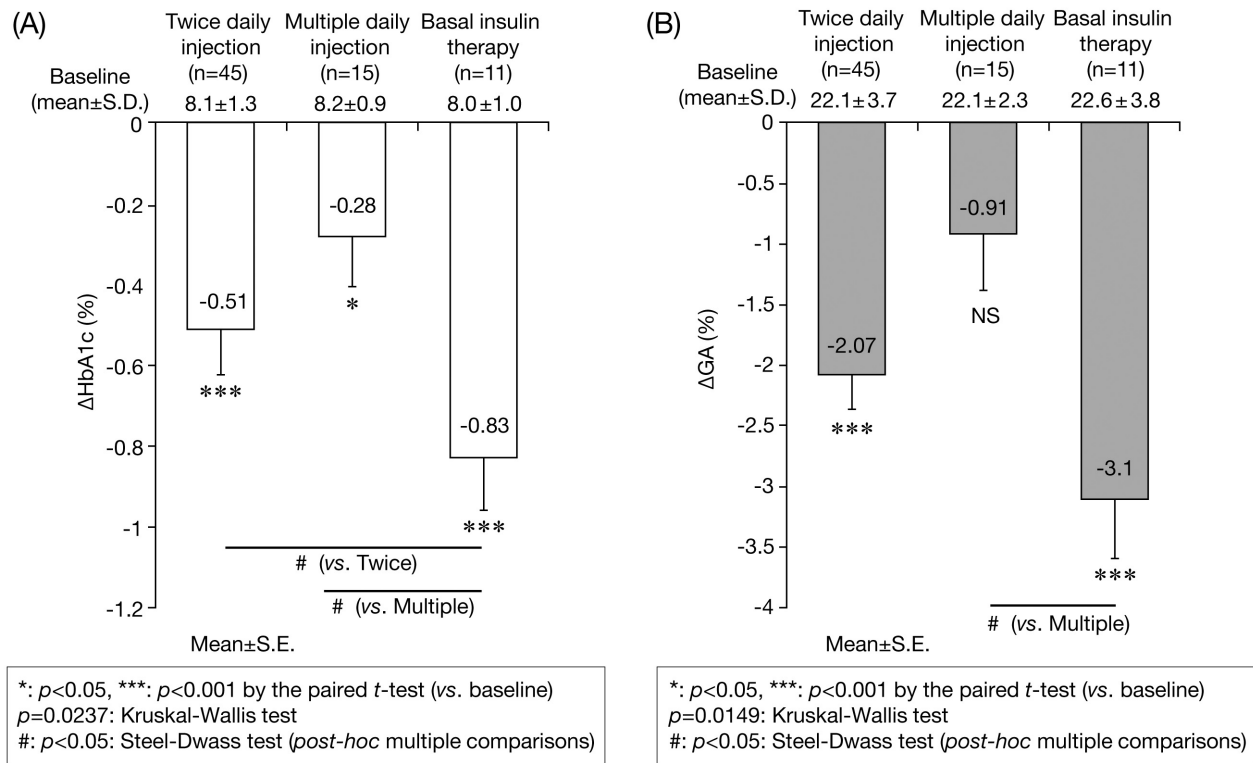
### 3-4. Changes of CPI

There was a significant increase of CPI in the basal insulin therapy and twice daily groups from Week 0 to Week 12, but there was no significant change in the multiple group (Table 5).

### 3-5. Changes of the insulin dose

There was a significant decrease of the insulin dose and daily average insulin dose per body weight from Week 0 to Week 12 in both the twice daily group and the multiple group, while there was no such change in the basal insulin therapy group (Table 5).





**Fig. 4** Changes of (A) HbA1c and (B) GA after 12 weeks of sitagliptin therapy in relation to the baseline insulin regimen

**Table 5** Changes of factors from baseline to week 12 in the three insulin subgroups

	Baseline	Week 12	Change from baseline	$p$ value (vs. baseline) <sup>a</sup>	$p$ value
Body weight (kg)					
Twice daily injections	66.4±12.9	66.4±13.3	0.03±1.16	0.9188	
Multiple daily injections	71.7±10.9	71.5±10.5	-0.23±0.83	0.3077	N.S. <sup>b</sup>
Basal insulin therapy	62.3±6.0	62.1±5.7	-0.18±0.8	0.4832	N.S. <sup>c</sup>
CPR index (CPI)					
Twice daily injections	1.4±0.9	1.7±0.9	0.39±0.65	0.0044	
Multiple daily injections	1.2±0.8	1.5±1.3	0.27±0.59	0.1102	N.S. <sup>b</sup>
Basal insulin therapy	1.1±0.5	1.4±0.3	0.34±0.37	0.0179	N.S. <sup>c</sup>
Insulin dose (U/day)					
Twice daily injections	26.4±13.0	24.8±14.4	-1.5±3.3	0.0032	
Multiple daily injections	38.7±20.6	35.7±21.8	-2.9±4.0	0.0129	N.S. <sup>b</sup>
Basal insulin therapy	15.4±7.0	14.5±6.7	-0.9±2.1	0.1762	N.S. <sup>c</sup>
Insulin dose per weight (U/day/kg)					
Twice daily injections	0.39±0.17	0.37±0.19	-0.02±0.05	0.0016	
Multiple daily injections	0.54±0.28	0.50±0.30	-0.04±0.05	0.0156	N.S. <sup>b</sup>
Basal insulin therapy	0.25±0.12	0.24±0.11	-0.01±0.03	0.2046	N.S. <sup>c</sup>

Data are the mean ± S.D. <sup>a</sup>, Paired  $t$ -test; <sup>b</sup>, Kruskal-Wallis test; <sup>c</sup>, Steel-Dwass test; N.S., not significant

## Discussion

When concomitant therapy with sitagliptin and insulin was previously investigated in Japanese patients with T2DM, 18 weeks of add-on sitagliptin therapy significantly improved HbA1c, fasting blood glucose, and post-prandial blood glucose compared with placebo, and was also well-tolerated [15]. In the present study, 12 weeks of concomitant sitagliptin therapy with other oral antidiabetic drugs led to significant improvement of glycemic control without severe hypoglycemia. Further, add-on therapy with sitagliptin achieved a significant increase of CPI in patients on insulin treatment. These findings suggest that concomitant use of sitagliptin enhances endogenous insulin secretion, thereby improving glycemic control. The present study also demonstrated significant improvement of GA in Week 4. In general, GA reflects changes of glycemic control during the preceding 1-2 weeks and is readily influenced by the improvement of postprandial blood glucose [17]. Accordingly, the results of this study suggested that concomitant sitagliptin therapy could improve postprandial glucose, probably both by glucose-dependent increase of insulin secretion and glucagon suppression with sitagliptin [18]. In addition, there was no weight gain along with better glycemic control, possibly because sitagliptin treatment augments GLP-1 levels [6].

The study protocol did not allow changes to the doses of oral antidiabetic drugs that were already being used concomitantly, but the dose of insulin could be titrated. As a result, concomitant sitagliptin therapy resulted in a significant decrease of the insulin dose, which provided a new insight into the effects of concomitant therapy with a DPP-4 inhibitor.

In order to characterize the patients who showed a better response, we investigated the correlations between HbA1c in Week 12 and demographic factors. Patients with higher baseline HbA1c and GA levels showed greater improvement of HbA1c. However, improvement of glycemic control was not correlated with the age, body weight (body mass index), duration of diabetes, duration of SU treatment, insulin dose, or CPI. In previous clinical studies of sitagliptin monotherapy and concomitant therapy with various oral antidiabetic drugs, no demographic factor other than baseline HbA1c has been found to influence glycemic control, and the results of the present investigation were consistent with those reports [8-13].

CPR index (CPI) is a marker of  $\beta$ -cell function, and it was not correlated with changes of HbA1c caused by add-on therapy with sitagliptin. Based on this observation, we conducted a stratified analysis of baseline CPI and changes of HbA1c. Even in patients with a baseline CPI  $<0.8$ , which is considered to indicate insulin dependence [19], improvement of glycemic control was comparable to that in patients with a CPI between  $\geq 0.8$  and  $<1.2$  or those with a CPI  $\geq 1.2$ . Although detailed analysis of insulin secretory capacity would be necessary needed to confirm these results, this study demonstrated that add-on therapy with sitagliptin can even improve glycemic control in patients with reduced insulin secretion receiving insulin therapy. Glucagon-like peptide-1 (GLP-1) lowers glucose both by enhancing insulin secretion and suppressing glucagon secretion, and the contribution of these two factors is reported to be almost equivalent [20]. Since sitagliptin is a DPP-4 inhibitor that suppresses glucagon secretion as well as enhancing insulin secretion [6, 7], the improvement of glycemic control in our patients with reduced insulin secretion was considered to be at least partly due to suppression of glucagon.

When the influence of concomitant oral antidiabetic drugs was assessed, patients who were being treated with SU, metformin, and  $\alpha$ -GI all showed improvement of glycemic control when sitagliptin was added to these therapies. The improvement of glycemic control was comparable to that in patients on insulin monotherapy. In the previous clinical studies of concomitant therapy with insulin and sitagliptin, the effect of add-on sitagliptin has been investigated in patients receiving insulin monotherapy or insulin in combination with metformin [14, 15]. In the present study, insulin was administered concomitantly with various oral antidiabetic drugs and we were able to confirm the improvement of glycemic control by sitagliptin in patients using several different drugs. Because of small patient numbers, no significant difference was observed between patients with or without  $\alpha$ -GI, although the changes of HbA1c and GA were larger in those with  $\alpha$ -GI. Because  $\alpha$ -GI inhibit degradation of disaccharides in the upper small intestine and promote absorption of monosaccharides in the lower intestine, these drugs potentially enhance the secretion of GLP-1 [21]. In addition, concomitant treatment with  $\alpha$ -GI and sitagliptin has been reported to further increase the plasma level of GLP-1 *versus* monotherapy with either agent [22]. Although the present study did not show a statistically significant difference, it



was suggested that better glycemic control could be achieved when sitagliptin is added to treatment with insulin and  $\alpha$ -GI.

When concomitant administration of insulin and sitagliptin was previously studied in Japanese patients with T2DM, the main insulin regimen was twice daily injection of premixed insulin (30Mix or 25Mix), and patients receiving multiple injections of rapid-acting insulin were excluded [15]. In the present study, twice daily injection of premixed insulin accounted for 63% of patients and was also the most common regimen, with multiple injections of insulin in 21% and basal insulin therapy in 15%. Accordingly, we conducted a stratified analysis based on the insulin regimen. The basal insulin therapy group, twice daily group, and multiple group showed no significant differences of baseline HbA1c. However, the improvement of HbA1c was significantly larger in the basal insulin therapy group than in the twice daily or multiple groups, and the change of GA was also significantly larger in the basal insulin therapy group than in the multiple group. These results suggest that adding sitagliptin to basal insulin therapy is most effective. This may be due to the fact that basal insulin therapy is intended to improve glycemic control while fasting by supplementing basal insulin secretion [23]. Therefore, there were many basal insulin therapy patients whose postprandial glycemic control was inadequate and add-on therapy with sitagliptin resulted in the improvement of postprandial hyperglycemia, leading to greater overall improvement of glycemic control. Another reason that the basal insulin therapy group demonstrated greater improvement of HbA1c and GA compared with the twice daily group and the multiple injections group may have been the significant reduction of the insulin dosage in the latter two groups. On the other hand, especially in the multiple injection group, postprandial hyperglycemia would

tend to be corrected by injection of rapid-acting insulin in many patients. The improvement of postprandial glycemic control would be smaller than with basal insulin therapy, hence the decreases of HbA1c and GA were smaller compared with the other treatment regimens. However, in patients from the multiple injection group whose insulin dosage was reduced, the dose of rapid-acting insulin was cut either in the morning or at lunch time. Therefore, concomitant use of sitagliptin with multiple insulin injections may be beneficial to avoid the risk of hypoglycemia before lunch and dinner.

In conclusion, it was confirmed that add-on therapy with sitagliptin was not associated with severe hypoglycemia or weight gain, while glycemic control was improved, inpatients receiving various insulin regimens. Although we investigated various possible factors predicting the hypoglycemic effect, we would not identify any such factors apart from baseline HbA1c and GA levels. In other words, irrespective of the history, body habitus, insulin dose, and insulin secretory capacity, this concomitant therapy is likely to be effective in patients with poor glycemic control. Stratified analysis based on the insulin regimen suggested that add-on therapy with sitagliptin is most effective when combined with basal insulin therapy. Since this was a single-arm observational study, further randomized controlled trials will be necessary to validate the results. In addition, due to the limited size of the basal insulin therapy group, it is difficult to draw conclusions. Accordingly, further investigation on a larger scale is warranted in the future.

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