

# Efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus: A focus on hypoglycemia

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## Keywords

Hypoglycemia, Sitagliptin, Sulfonylurea

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## Clinical Trial Registry

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## ABSTRACT

**Aims/Introduction:** To investigate the efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus, with a focus on hypoglycemia.

**Materials and Methods:** Type 2 diabetes mellitus patients who started sitagliptin therapy and were followed for 52 weeks were enrolled in the Impact of Sitagliptin on Diabetes Mellitus in Japanese Elderly Patients study. The frequency of hypoglycemia and knowledge of hypoglycemia were analyzed using a questionnaire.

**Results:** In total, 5,130 patients (aged  $73.8 \pm 6.1$  years) were analyzed. A significant reduction in glycated hemoglobin ( $-0.7 \pm 1.1\%$ ,  $P < 0.001$ ) and glycoalbumin levels ( $-2.2 \pm 3.8\%$ ,  $P < 0.001$ ) was observed at week 52. The percentage of patients with hypoglycemia did not increase from the baseline (3.3%) to week 52 (2.8%) of sitagliptin administration. Hypoglycemia incidence was significantly higher for combination therapy with insulin (odds ratio 17.75,  $P < 0.001$ ) or sulfonylurea (odds ratio 2.22,  $P < 0.001$ ). The increase in sitagliptin dose for combination therapy with antidiabetic drug(s) increased the percentage of patients with hypoglycemia (5.6% in sitagliptin increased subgroup, 2.4% in sitagliptin maintained subgroup,  $P < 0.01$ ). The awareness of hypoglycemia symptoms and attitude to carry glucose as a countermeasure to prevent hypoglycemia increased during the study.

**Conclusions:** Sitagliptin did not increase the percentage of patients with hypoglycemia among elderly patients with type 2 diabetes mellitus. However, hypoglycemia occurred more frequently in add-on therapy to sulfonylurea or when the sitagliptin dose was increased in combination therapy, showing that sitagliptin should be used with caution.

## INTRODUCTION

The aging population in Japan is rapidly increasing, resulting in an aging society. A national survey in Japan reported that the prevalence of diabetes mellitus in Japan reached 10 million, and approximately two-thirds of patients were aged  $\geq 65$  years and approximately half of them were aged  $\geq 75$  years<sup>1</sup>. These findings show that most of the patients with diabetes mellitus in real-world clinical settings in Japan are elderly. Elderly patients with diabetes mellitus are more prone to hypoglycemia. Hypoglycemia is one of the biggest risk factors for frailty in elderly patients with diabetes mellitus<sup>2</sup>. It has been shown that severe hypoglycemia is a risk factor for cardiovascular events and cognitive impairment, which lower the quality of life of

patients and induce death<sup>3–6</sup>. Most of the patients transported by ambulance owing to severe hypoglycemia were elderly<sup>7</sup>, and this has become a serious social issue in Japan.

Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have become the most commonly used oral hypoglycemic agents in Japan<sup>7</sup>. A survey on hypoglycemia in elderly Japanese patients with type 2 diabetes mellitus carried out by the Japan Physicians Association showed that DPP-4 inhibitors were the most commonly prescribed oral antidiabetic drugs, followed by sulfonylurea (SU)<sup>8</sup>. Although DPP-4 inhibitors are known to have a lower risk of hypoglycemia in monotherapy, cases of severe drug-induced hypoglycemia were reported in dual therapy with SU<sup>9</sup>. ‘The Committee on Proper Usage of Incretin and Sulfonylurea Drugs’ recommended decreasing the dosage of SU when a DPP-4 inhibitor was administered as an add-on therapy to

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SU<sup>10</sup>. As SU is still widely prescribed to elderly patients in Japan, the present study investigated the efficacy and safety of sitagliptin, the first DPP-4 inhibitor approved for clinical use, in elderly patients with type 2 diabetes mellitus, with a focus on hypoglycemia.

## METHODS

### Study design

The Impact of Sitagliptin on Diabetes Mellitus in Japanese Elderly Patients (SMILE) study was designed as a multicenter, prospective, observational, single-arm study. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000009332), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors. The study protocol was approved by the ethics review board of each participating institution. This study was carried out according to the Declaration of Helsinki and current legal regulations in Japan. The processes of data collection and management were carried out by third-party entities for data without bias. All personal information was anonymized. Written informed consent was obtained from all participants after a full explanation of the present study.

### Study population

The present study was carried out at 1,502 clinical sites in Japan, which mainly consisted of members of the Japan Physicians Association. Outpatients with type 2 diabetes mellitus were approached to participate in this study from December 2012 to November 2014. The inclusion criteria were as follows: (i) patients with type 2 diabetes mellitus; (ii) male and female patients aged  $\geq 65$  years and  $< 90$  years; (iii) patients with inadequate plasma glucose control by diet and exercise or with additional hypoglycemic agents; and (iv) patients who started sitagliptin therapy for the first time. The exclusion criteria were as follows: (i) patients with a history of hypersensitivity against sitagliptin; (ii) patients who had used incretin-related drugs in the past 3 months; (iii) patients with a history of serious ketosis, diabetic coma or precoma in the past 6 months; (iv) patients with serious infections, those who were scheduled for surgery or underwent a surgery, or those who suffered serious trauma; (v) patients with type 1 diabetes mellitus; (vi) patients who used glinides, which were not covered under insurance for use with sitagliptin; and (vii) patients who were considered unsuitable subjects by the attending physician. Regarding exclusion criterion (vi), although glinides were not covered under insurance for use with sitagliptin at the start of this study, they were covered during the study. Therefore, the study protocol was revised to include patients who used glinides.

### Study drug administration

Sitagliptin (12.5–100 mg) was administered once daily to patients who met the aforementioned criteria, depending on the patient's condition for 52 weeks. The dose of sitagliptin was

determined by the physician according to the package insert of sitagliptin. Dose change or additional administration of any other hypoglycemic agents was allowed during the study, according to the patients' condition.

### Observation

Observation was carried out for 52 weeks. Clinical data and biomarkers were collected at baseline (week 0) and week 52 after the start of sitagliptin therapy. Diabetic complications were diagnosed by the attending physicians according to the Treatment Guide for Diabetes 2010<sup>11</sup>. All adverse events were reported during the study. A questionnaire on hypoglycemia was given before and after sitagliptin therapy. The physician completed the questionnaire to describe the absence or presence of hypoglycemic symptoms in each participant during the past 1 month before the baseline or week 52 based on medical interview and medical records, which is defined as 'physician-recognized hypoglycemia' in the present study. In this study, hypoglycemia did not necessarily require the measurement of plasma glucose level, and the severity of hypoglycemia was not determined. The questionnaire for patients also contained the following items: (i) the presence or absence of symptoms; (ii) knowledge regarding hypoglycemia ('Do you know what hypoglycemia is?'); (iii) knowledge regarding hypoglycemia, such as treatment for hypoglycemia, symptoms, causes and susceptible time during the day; and (iv) whether the patient carried glucose or an equivalent item as a countermeasure for hypoglycemia.

### Study outcomes

The end-points of the present study were as follows: (i) the percentage of patients with hypoglycemia based on physician-recognized hypoglycemia; (ii) the relationship between the percentage of patients with hypoglycemia and characteristics of patients, use of concomitant antidiabetic drugs, complications, and glycemic control; (iii) the relationship between the percentage of patients with hypoglycemia and hypoglycemic symptoms; and (iv) the assessment of the knowledge and attitude of patients regarding hypoglycemia.

### Statistical analysis

The reported values were expressed as *n*, % or mean  $\pm$  standard deviation in the text. Statistical analyses were carried out using two-sided tests with 5% significance level. Two-sample *t*-test and analysis of variance (ANOVA) were applied to continuous variables for two-group comparisons and for comparing more than two groups, respectively. The  $\chi^2$ -test or Fisher's exact test were applied to nominal variables. In case a significant difference among groups was detected by ANOVA, multiple comparisons were carried out with multiple testing corrections by Tukey's method. In case a significant difference among groups was detected with the  $\chi^2$ -test or Fisher's exact test, multiple comparisons were carried out with Bonferroni correction. Logistic regression analysis was carried out to test the

relationship between the percentage of patients with hypoglycemia and the use of concomitant antidiabetic drugs; the former was set as the objective variable and the latter as the explanatory variable. Logistic regression analysis was further carried out to test the relationship between the percentage of patients with hypoglycemia and hypoglycemic symptoms, and the former was set as the objective variable and the latter as the explanatory variable. Multiple logistic regression analysis was carried out to test the relationship between the percentage of patients with hypoglycemia and risk factors. First, by using univariate logistic regression analysis, variables that had a *P*-value <0.1 were detected. By using these factors as explanatory variables, multiple logistic regression analysis was carried out.

## RESULTS

### Clinical characteristics

In total, 6,012 patients with type 2 diabetes mellitus were enrolled at 1,502 clinical sites during the study period. Among them, 882 patients were excluded from the analysis due to serious violations of the prespecified inclusion/exclusion criteria or protocol, duplicated registration, incomplete case report forms, withdrawal, or no visit after enrollment. Finally, 5,130 patients were included in the full analysis set. The characteristics of full analysis set patients were as follows: 51.7% men and 48.3% women, mean age  $73.8 \pm 6.1$  years, body mass index of  $24.2 \pm 3.6$  kg/m<sup>2</sup> and glycated hemoglobin (HbA1c) of  $7.5 \pm 1.2\%$ . The patients were divided into the following subgroups according to the criteria of the elderly in Japan: 65–74 years (young-old; 57.7%), 75–84 years (old-old; 36.3%) and  $\geq 85$  years (oldest-old; 6.0%). The major diabetic complications were as follows: diabetic retinopathy (11.3%), nephropathy (15.2%) and neuropathy (12.6%). SU was the most commonly prescribed drug (24.7%) at baseline, followed by metformin (14.9%). Even in the oldest-old subgroup (aged 85–89 years),

SU was prescribed to 21.6% of the patients. The mean dose of SU at baseline was  $1.5 \pm 1.7$  mg/day of glimepiride, if other SU drugs were converted to glimepiride at a dose of glimepiride 1 mg for gliclazide 40 mg or glibenclamide 0.625 mg. The use of alpha-glucosidase inhibitor ( $\alpha$ -GI), pioglitazone, glinide and insulin was 13.0, 7.7, 1.1 and 9.0%, respectively, at baseline, and no significant difference was observed among the different age subgroups. The percentage of full analysis set patients untreated with antidiabetic drugs at baseline was 52.7%.

### Effect of sitagliptin on clinical laboratory values

HbA1c and glycoalbumin values at baseline were  $7.5 \pm 1.2\%$  and  $20.3 \pm 5.0\%$ , respectively. The changes in HbA1c and glycoalbumin from baseline to week 52 of sitagliptin administration were  $-0.7 \pm 1.1\%$  and  $-2.2 \pm 3.8\%$ , respectively (both  $P < 0.001$ ; Table 1). A similar improvement in HbA1c and glycoalbumin was observed in all age subgroups. The bodyweight, body mass index, systolic blood pressure, diastolic blood pressure and hepatic function biomarkers (alanine transaminase and gamma-glutamyl transpeptidase) also showed significant reduction from baseline to week 52 (all  $P < 0.001$ ).

### Relationship between hypoglycemia and use of antidiabetic drugs

Table 2 presents the percentage of patients with hypoglycemia before baseline and at week 52 in patients treated or untreated with antidiabetic drugs. The percentage of patients with hypoglycemia among those treated with insulin, metformin,  $\alpha$ -GI and SU was 18.1, 5.2, 3.5 and 3.1%, respectively, and it was higher than that in patients untreated with any antidiabetic drugs (all  $P < 0.001$ ) at baseline. No significant change in the percentage of patients with hypoglycemia was observed from baseline to week 52 in any subgroups of patients treated with other antidiabetic drugs. However, it significantly decreased

**Table 1** | Changes in clinical laboratory values from baseline

	Baseline	Change at week 52 from baseline	<i>P</i> -value
HbA1c (%)	$7.5 \pm 1.2$	$-0.7 \pm 1.1$	<0.001
GA (%)	$20.3 \pm 5.0$	$-2.2 \pm 3.8$	<0.001
FPG (mg/dL)	$141.2 \pm 43.6$	$-17.7 \pm 35.3$	<0.001
PPG (mg/dL)	$187.7 \pm 73.2$	$-32.6 \pm 70.9$	<0.001
Bodyweight (kg)	$59.8 \pm 11.2$	$-0.3 \pm 2.5$	<0.001
BMI (kg/m <sup>2</sup> )	$24.2 \pm 3.6$	$-0.1 \pm 1.0$	<0.001
SBP (mmHg)	$133.8 \pm 16.2$	$-2.0 \pm 15.4$	<0.001
DBP (mmHg)	$73.5 \pm 10.5$	$-1.3 \pm 10.1$	<0.001
AST (IU/L)	$25.3 \pm 13.6$	$-0.3 \pm 11.1$	0.095
ALT (IU/L)	$23.6 \pm 17.2$	$-1.7 \pm 15.4$	<0.001
$\gamma$ GTP (mg/dL)	$41.5 \pm 63.1$	$-3.9 \pm 34.8$	<0.001
Urine Alb/Cre ratio (mg/g Cr)	$69.1 \pm 292.5$	$4.6 \pm 226.4$	0.61

Data are shown as mean  $\pm$  standard deviation. Dose of sitagliptin (*n*) at baseline: 12.5 mg (15 patients), 25 mg (943 patients), 50 mg (4,107 patients) and 100 mg (65 patients).  $\gamma$ GTP, gamma-glutamyl transpeptidase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GA, glycoalbumin; PPG, postprandial plasma glucose; SBP, systolic blood pressure; Urine Alb/Cre ratio, urine albumin/creatinine ratio.

from baseline (1.4%) to week 52 (0.5%) among patients untreated with any antidiabetic drugs ( $P = 0.0079$ ).

The effect of antidiabetic drugs on the percentage of patients with hypoglycemia receiving sitagliptin treatment was further investigated with logistic regression analysis (Table 3). Insulin therapy had the greatest effect on the percentage of patients with hypoglycemia at baseline (odds ratio [OR] 11.59,  $P < 0.001$ ), followed by metformin (OR 1.55,  $P = 0.036$ ); however, no statistically significant effect was detected in treatment with SU, glinide,  $\alpha$ -GI and pioglitazone. After 52-week treatment with sitagliptin, combination therapy with insulin and sitagliptin had the greatest effect (OR 17.75,  $P < 0.001$ ). Combination therapy with SU and sitagliptin also had a significant effect (OR 2.22,  $P < 0.001$ ), whereas combination therapy with sitagliptin and glinide,  $\alpha$ -GI, metformin, and pioglitazone had no significant effect on the percentage of patients with hypoglycemia.

The mean insulin dose was  $22.0 \pm 17.0$  U/day ( $n = 463$ ) at baseline and  $22.1 \pm 14.9$  U/day ( $n = 395$ ) at week 52 of sitagliptin therapy, and no significant change was detected from baseline to week 52. Stratified analysis based on the

presence or absence of hypoglycemia showed no significant difference in the mean insulin dose between patients with hypoglycemia ( $23.5 \pm 15.1$  U/day,  $n = 73$ ) and those without hypoglycemia ( $21.8 \pm 14.1$  U/day,  $n = 330$ ) at baseline. The mean insulin dose in patients with hypoglycemia ( $27.0 \pm 15.8$  U/day,  $n = 61$ ) was significantly higher than that in patients without hypoglycemia ( $20.8 \pm 14.3$  U/day,  $n = 293$ ) at week 52 of combination therapy with insulin and sitagliptin ( $P = 0.003$ ).

Most of the insulin users were also treated with other oral hypoglycemic agents. Among patients treated with the combination therapy of sitagliptin and insulin at week 52, no other oral hypoglycemic agents had a significant effect on the percentage of patients with hypoglycemia. Among patients untreated with insulin, combination therapy with sitagliptin and SU had a significant effect on the percentage of patients with hypoglycemia (OR 4.01,  $P < 0.001$ ), followed by combination with pioglitazone (OR 2.18,  $P = 0.043$ ; Table 3). Combination therapy with sitagliptin and glinide showed a trend towards an increase in hypoglycemia (OR 4.14,  $P = 0.07$ ).

**Table 2** | Percentage of patients with hypoglycemia at baseline and week 52 of sitagliptin treatment among patients treated or untreated with other antidiabetic drugs

Antidiabetic drug	Baseline			Week 52			P-value (0 week vs 52 weeks)
	Percentage of patients with hypoglycemia (%)	<i>n</i>	P-value (vs untreated)	Percentage of patients with hypoglycemia (%)	<i>n</i>	P-value (vs untreated)	
Sulfonylurea	3.1	35/1140	<0.001	4	42/1153	<0.001	0.25
Glinide	3.8	2/52	0.17	3.9	3/76	0.013	1
$\alpha$ -GI	3.5	21/601	<0.001	3.3	18/542	<0.001	0.86
Metformin	5.2	36/697	<0.001	3.5	24/188	<0.001	0.12
Pioglitazone	2.5	9/356	0.1	3.5	11/312	<0.001	0.46
Insulin	18.1	73/404	<0.001	17.2	61/344	<0.001	0.76
Untreated	1.4	32/2339	–	0.5	10/1841	–	0.0079

Data are shown as % and *n*.  $\alpha$ -GI, alpha-glucosidase inhibitor.

**Table 3** | Effect of antidiabetic drugs on the percentage of patients with hypoglycemia at baseline and week 52 of sitagliptin treatment

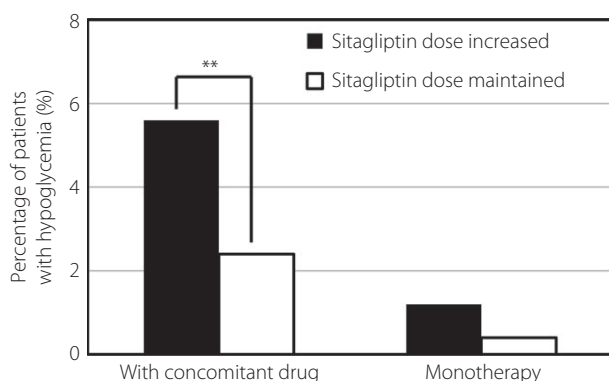
Antidiabetic drug	Baseline		Week 52					
	FAS ( <i>n</i> = 4,514)		FAS ( <i>n</i> = 3,876)		With insulin ( <i>n</i> = 354)		Without insulin ( <i>n</i> = 3,522)	
	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value
Sulfonylurea	0.98	0.92	2.22	<0.001	1.10	0.79	4.01	<0.001
Glinide	1.66	0.51	2.05	0.26	0.83	0.86	4.14	0.07
$\alpha$ -GI	0.68	0.13	0.74	0.28	0.72	0.35	0.73	0.49
Metformin	1.55	0.036	1.10	0.71	1.18	0.64	0.93	0.84
Pioglitazone	0.73	0.37	1.59	0.18	0.54	0.42	2.18	0.043
Insulin	11.59	<0.001	17.75	<0.001	–	–	–	–

Data are shown as odds ratio.  $\alpha$ -GI, alpha-glucosidase inhibitor; FAS, full analysis set.

The stratified analysis of SU dose showed that SU dose had no significant effect on the percentage of patients with hypoglycemia in combination therapy with sitagliptin. The percentage of patients with hypoglycemia was 6.4% (16/250), 2.3% (10/437), 4.3% (9/211) and 4.5% (7/155) among those treated with glimepiride at doses <1.0, 1.0–1.5, 1.0–3.0 and >3.0 mg, respectively, at week 52 ( $P = 0.58$ ), when the dose of other SU drugs was converted to that of glimepiride. The effect of sitagliptin dose on the percentage of patients with hypoglycemia was analyzed. The dose of sitagliptin had no significant effect on the percentage of patients with hypoglycemia. The percentage of patients with hypoglycemia was 20.0% (2/10), 6.7% (17/253), 4.3% (71/1658) and 7.0% (8/144) among patients treated with sitagliptin at doses of 12.5, 25, 50 and 100 mg, respectively, at week 52 ( $P = 0.73$ ). However, the dose of sitagliptin was increased in some patients during the study. In patients receiving sitagliptin monotherapy, no significant difference was detected in the percentage of patients with hypoglycemia between the subgroups in which sitagliptin dose was increased (1.2%) or maintained (0.4%) during the study ( $P = 0.31$ ; Fig. 1). In contrast, in patients treated with sitagliptin and other concomitant antidiabetic drug(s), the percentage of patients with hypoglycemia was significantly higher in the subgroup in which sitagliptin dose was increased (5.6%) than in the subgroup in which sitagliptin dose was maintained (2.4%;  $P < 0.01$ ).

#### Relationship between hypoglycemia and glycemic control

The mean HbA1c at baseline in patients who had or did not have hypoglycemia before baseline was  $7.6 \pm 1.1\%$  ( $n = 151$ ) and  $7.5 \pm 1.2\%$  ( $n = 4,653$ ), respectively. No significant difference in mean HbA1c was detected between the two subgroups ( $P = 0.32$ ). At week 52 of sitagliptin therapy, the mean HbA1c in patients with or without hypoglycemia was  $7.2 \pm 0.8\%$



**Figure 1** | Effect of sitagliptin dose on the percentage of patients with hypoglycemia. Hypoglycemia was defined as hypoglycemia recognized by the physician during the past 1 month. The percentage of patients with hypoglycemia among patients treated with sitagliptin and other concomitant antidiabetic drugs or among patients treated with sitagliptin monotherapy is shown. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

( $n = 101$ ) and  $6.7 \pm 0.8\%$  ( $n = 3,508$ ), respectively. HbA1c improved in both subgroups from baseline to week 52, but the mean HbA1c was significantly lower in patients without hypoglycemia than in patients with hypoglycemia ( $P < 0.001$ ).

The recent guideline for diabetes treatment in the elderly issued by the Japan Diabetes Society<sup>12</sup> indicated the glycemic control target. In patients with diabetes mellitus who use insulin or SU, HbA1c should be  $\geq 6.5\%$  in the elderly aged 65–74 years, and  $\geq 7.0\%$  in elderly aged  $\geq 75$  years. Among the patients who used insulin or SU in the present study, 136 patients aged 65–74 years had HbA1c  $< 6.5\%$ , and 245 patients aged  $\geq 75$  years had HbA1c  $< 7.0\%$  at week 52 of sitagliptin therapy. The percentage of patients with hypoglycemia among patients who used insulin or SU was 0 and 4.1%, respectively (Table 4). The percentage of patients with hypoglycemia was not higher among patients whose HbA1c was lower than the lower limits indicated in the guidelines.

#### Relationship between hypoglycemia and other risk factors

Figure 2 shows the relationship between the percentage of patients with hypoglycemia and diabetic complications at baseline. The percentage of patients with hypoglycemia was higher among patients with diabetic retinopathy, nephropathy or neuropathy than among patients without these complications (all  $P < 0.001$ ). A similar trend was also detected at week 52 of sitagliptin therapy. The relationship between the percentage of patients with hypoglycemia and risk factors was further investigated by multiple logistic regression analysis. The duration of diabetes ( $\geq 20$  years; OR 2.488,  $P = 0.0028$ ) and use of insulin (OR 10.935,  $P < 0.0001$ ) had significant effects on the percentage of patients with hypoglycemia, and diabetic nephropathy (OR 1.578,  $P = 0.0658$ ) and use of SU (OR 1.559,  $P = 0.0697$ ) showed significant trends (Table 5).

#### Relationship between hypoglycemia and hypoglycemic symptoms

Table 6 summarizes the frequent hypoglycemic symptoms in patients with hypoglycemia. At baseline, cold sweat was the most common symptom (OR 15.22,  $P < 0.001$ ), followed by intense hunger (OR 7.45,  $P < 0.001$ ), tremulousness (OR 3.04,  $P < 0.001$ ), and feeling languid (OR 1.86,  $P = 0.007$ ). Similar trends in the incidence of hypoglycemic symptoms were observed at week 52 of sitagliptin therapy, although slight changes were seen in the order of hypoglycemic symptoms.

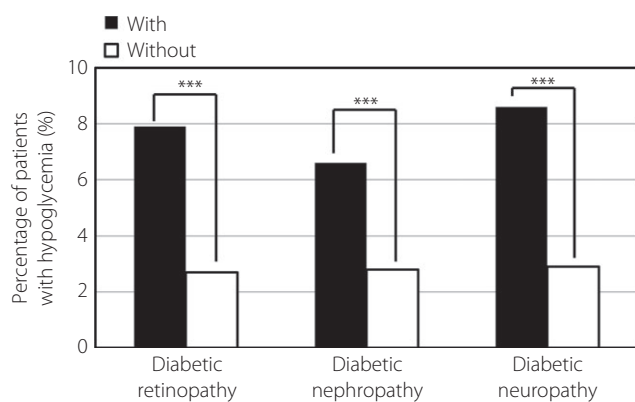
#### Assessment of knowledge and attitude of patients regarding hypoglycemia

At baseline, 70.8% of patients aged 65–74 years answered that they had knowledge of hypoglycemia, but awareness of hypoglycemia was lower in the elderly subgroups (Fig. 3a). Figure 3b shows the content of knowledge of hypoglycemia in patients who answered that they had knowledge of hypoglycemia at baseline. The most common knowledge in any age subgroup was the treatment for hypoglycemia, followed by

**Table 4** | Percentage of patients with hypoglycemia between glycated hemoglobin subgroups in patients treated with insulin or sulfonylurea

Age (years)	Week	HbA1c	Percentage of patients with hypoglycemia (%)	<i>n</i>	<i>P</i> -value
65–74	52	<6.5%	0	0/136	<0.001
		≥6.5%	9.0	55/608	
≥75	52	<7.0%	4.1	10/245	0.11
		≥7.0%	7.4	20/269	

Data are shown as *n* and %. HbA1c, glycated hemoglobin.

**Figure 2** | Effect of diabetic complications on the percentage of patients with hypoglycemia. Hypoglycemia was defined as hypoglycemia recognized by the physician during the past 1 month.

\**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.

symptoms. The awareness of susceptible time during the day or cause of hypoglycemia tended to be low in all age subgroups. The awareness increased from the baseline to week 52 of sitagliptin therapy in all age subgroups.

As a countermeasure to prevent hypoglycemia, 71.2% of insulin users always carried or intended to carry glucose at baseline (Fig. 4a). Whereas just 37.8% of SU users prepared glucose at baseline, this ratio increased to 45.0% from baseline to week 52. The ratio of carrying glucose increased from baseline (28.4%) to week 52 (38.9%) in the 65–74 years subgroup, but it did not change in the elderly subgroups during the study (Fig. 4b).

## DISCUSSION

In the present study, we aimed to investigate the efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus, with a focus on hypoglycemia. The add-on therapy of sitagliptin with any antidiabetic drugs, including insulin, did not show a significant increase in the percentage of patients with hypoglycemia. Although SU had no significant effect on the percentage of patients with hypoglycemia at baseline, the combination therapy of sitagliptin and SU for 52 weeks showed a significant impact on the percentage of patients with hypoglycemia. In addition, when sitagliptin dose was increased in combination therapy, the percentage of patients with

**Table 5** | Multiple logistic regression analysis to determine the risk factors for hypoglycemia

Variables	Odds ratio	<i>P</i> -value
BMI (kg/m <sup>2</sup> )	0.969	0.3147
SBP (mmHg)	0.985	0.0702
DBP (mmHg)	0.995	0.7022
HbA1c (NGSP, %)	1.036	0.7002
Duration of diabetes		
≥5 years, <10 years	1.477	0.7683
≥10 years, <20 years	1.008	0.1002
≥20 years	2.488	0.0028
Diabetic complications		
Retinopathy	1.41	0.1969
Nephropathy	1.578	0.0658
Neuropathy	1.025	0.9281
Sulfonylurea	1.559	0.0697
Insulin	10.935	<0.0001

Data are shown as odds ratio. BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program; SBP, systolic blood pressure.

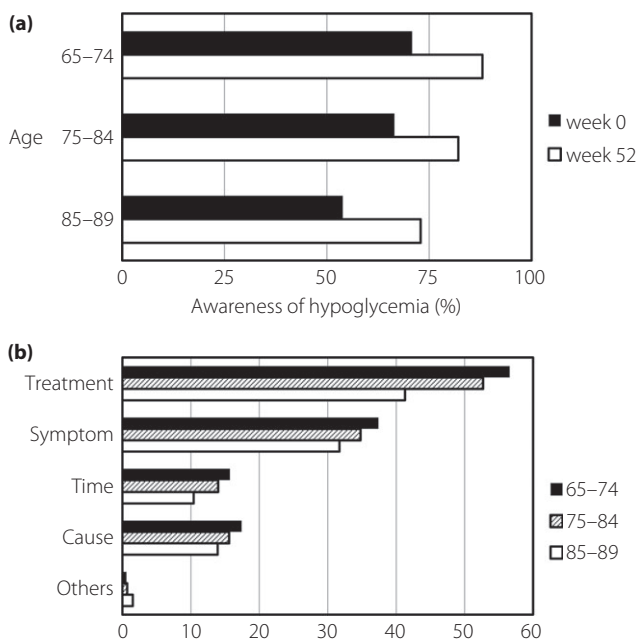
hypoglycemia increased. These findings showed that sitagliptin should be used with caution.

In case of add-on therapy to SU, sitagliptin should be administered with much caution to patients with hypoglycemia. Our previous study showed that SU is still prescribed to >30% of elderly patients with type 2 diabetes mellitus<sup>8</sup>. We also showed that SU was most commonly prescribed to elderly patients (24.7%), even to the oldest-old subgroup (85–89 years; 21.6%). The dose of SU should be <2 mg/day of glimepiride in combination therapy with sitagliptin, as announced previously<sup>10</sup>. In the present study, the mean dose of SU was 1.5 ± 1.7 mg/day of glimepiride both at baseline and week 52 of sitagliptin administration. The dose of SU had no significant effect on hypoglycemia, when the dose of other SU drugs was converted to that of glimepiride. These results suggested that sitagliptin should be used in combination with SU with caution in regard to hypoglycemia, even if the dose of SU is low. Although dose reduction in SU has been recommended, when DPP-4 inhibitor is administered as an add-on therapy to SU<sup>10</sup>, the dose of SU was not modified after the start of sitagliptin administration in the present study. This might have contributed to the increase in OR for hypoglycemia in this study.

**Table 6** | Hypoglycemic symptoms in patients with hypoglycemia

Week	Hypoglycemic symptoms	Type of symptoms	Odds ratio	P-value
0 (n = 4,514)	Cold sweat	Sympathetic nerve	15.22	<0.001
	Intense hunger	Parasympathetic nerve	7.45	<0.001
	Tremulousness	Sympathetic nerve	3.04	<0.001
	Feeling languid	Central nerve	1.86	0.007
52 (n = 3,876)	Cold sweat	Sympathetic nerve	17.70	<0.001
	Tremulousness	Sympathetic nerve	6.71	<0.001
	Intense hunger	Parasympathetic nerve	5.49	<0.001
	Lightheadedness	Central nerve	2.40	0.012
	Palpitation	Sympathetic nerve	2.41	0.022

Data are shown as odds ratio.



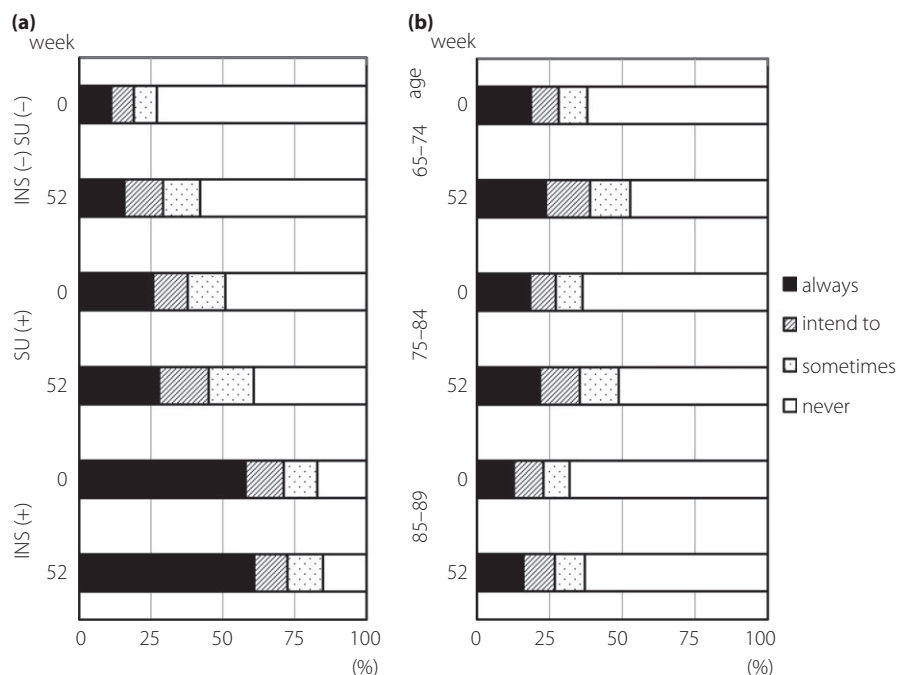
**Figure 3** | Knowledge of hypoglycemia. (a) Awareness of hypoglycemia in different age subgroups. (b) Content of knowledge of hypoglycemia.

The dose of sitagliptin should be increased with caution, because increasing the sitagliptin dose increased the percentage of patients with hypoglycemia in combination therapy with other antidiabetic drugs. In the present study, insulin had the highest OR for hypoglycemia both at baseline and at week 52, and the OR for hypoglycemia further increased at week 52 of sitagliptin treatment. In contrast, previous randomized controlled trials in Korea<sup>13</sup> and Japan<sup>14</sup> reported that the addition of sitagliptin to insulin decreased the frequency of hypoglycemia. Because sitagliptin shows an effect to suppress the amplitude of glucose excursion<sup>15</sup>, it might prevent hypoglycemia on infusion of external insulin. Although previous trials showed that the daily dose of insulin decreased after the administration of sitagliptin<sup>13,14</sup>, the insulin dose did not

change in the present study. This might contribute to the increase of the OR for hypoglycemia after the administration of sitagliptin. Indeed, the insulin dose for patients with hypoglycemia was significantly higher than that for patients without hypoglycemia. The suppression of glucose excursion amplitude by sitagliptin administration to drug-naïve patients at baseline might contribute to the decrease in the percentage of patients with hypoglycemia.

The treatment guidelines for diabetes issued by the Japan Diabetes Society<sup>12</sup>, announced after the present study, indicated the targets of glycemic control, including the lower limits, to avoid severe hypoglycemia when insulin or SU is used, based on the age and frailty of elderly patients. A recent survey of treatment-related severe hypoglycemia by the Japan Diabetes Society<sup>16</sup> showed that 93.9% of causal agents of severe hypoglycemia were insulin and SUs, and the median HbA1c value at onset of severe hypoglycemia was 6.8% in patients with type 2 diabetes mellitus. Although HbA1c in patients treated with insulin or SU in the present study was lower than the recommended lower limits in the current guidelines, the percentage of patients with hypoglycemia did not increase in the subgroups and the patients were safely controlled (Table 5). However, dose reduction or withdrawal of insulin and SU should be considered in such patients in future according to the current guidelines. The percentage of patients with hypoglycemia was higher in patients with any diabetic complications than in patients without complications. Impairment of renal function is a known risk factor for hypoglycemia<sup>6</sup>. We could not assess the relationship between the frequency of hypoglycemia and renal function, because we did not measure estimated glomerular filtration rate in the present study. However, multiple logistic regression analysis showed that the duration of diabetes ( $\geq 20$  years) had a significant effect on hypoglycemia, and diabetic nephropathy showed a trend toward higher OR, although it was not statistically significant. These findings suggest that further caution is required in regard to hypoglycemia in patients with diabetic nephropathy.

Although the awareness of hypoglycemia tended to be lower in the elderly subgroups, it tended to increase from baseline to



**Figure 4** | Attitude to carry glucose as a countermeasure to prevent hypoglycemia. (a) Attitude of patients who were treated with/without insulin (INS) and sulfonylurea (SU). (b) Attitude of patients in different age subgroups.

week 52 of the administration of sitagliptin in all age subgroups. The attitude of patients to carry glucose was improved in the 65–74 years subgroup. This might be because the awareness and recognition of hypoglycemia in patients were improved through the questionnaire and medical interview with the attending physicians. The improvement of attitude was less in the elderly subgroups, probably because elderly patients tend to have a stronger status quo bias and a change in attitude is more difficult. These findings suggest that tenacious, repeated and easy-to-understand indications are required for elderly patients in clinical practice.

There were certain limitations to the present study. First, this was an observational, single-arm study without a placebo or control group. Second, more than half of the participating patients in this study were treated with antidiabetic drugs. Third, the definition of hypoglycemia in this study was based on hypoglycemic symptoms and not on plasma glucose measurement, because the majority of the patients who were treated with oral hypoglycemic agents or even some of the patients treated with insulin did not carry out self-monitoring of blood glucose. Fourth, we did not measure creatinine levels in this study; therefore, the relationship between the frequency of hypoglycemia and glomerular filtration rate could not be analyzed. Fifth, we did not distinguish the types of institutions, such as rural versus urban area, hospital versus clinic or diabetes specialist versus non-specialist. However, the majority of the institutions that participated were clinics or small-scale hospitals. Sixth, the relationship between the frequency of

hypoglycemia and renal function was not assessed, because we did not measure the estimated glomerular filtration rate in the present study.

Sitagliptin, a DPP-4 inhibitor, did not increase the percentage of patients with hypoglycemia among elderly patients with type 2 diabetes mellitus. However, hypoglycemia occurred more frequently with add-on therapy to SU or when the sitagliptin dose was increased in the combination therapy, showing that sitagliptin should be used with caution.

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#### DISCLOSURE

MF received lecturer's fees from Ono Pharmaceutical Co., Ltd. and Mitsubishi Tanabe Pharma Corporation. The other authors declare no conflict of interest.

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