Diabetol Int (2018) 9:56–65
https://doi.org/10.1007/s13340-017-0330-2

ORIGINAL ARTICLE

Efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus and comparison of hypoglycemic action of concomitant medications: a subanalysis of the JAMP study

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Received: 30 March 2017 / Accepted: 9 July 2017 / Published online: 28 July 2017

Abstract

Purpose To determine the efficacy and safety of sitagliptin when used with some therapeutic drugs to treat elderly patients.

Methods Sitagliptin (50 mg/day) was added to the pre-existing therapy for type 2 diabetes. Changes in the glycated hemoglobin (HbA1c) level after 3 months of treatment were compared with the baseline, and exploratory analysis was performed. These analyses were conducted as subanalyses of the JAMP study, which was an open-label observational study.

Results For patients who were ≥65 years of age, the change in HbA1c level from baseline ranged from −0.50 to −0.87% at 3 months after starting treatment. There was no significant difference in the change in HbA1c level between the patients treated with different concomitant drugs. No significant difference in HbA1c variations at 3 and 12 months from baseline was noted among the three age groups (≥75, 65–74, and <65 years). Multiple regression analysis was performed, and it revealed that patients with higher HbA1c levels at baseline were likely to show decreased HbA1c levels, while those with higher triglyceride (TG) levels were unlikely to show decreased HbA1c levels.

Conclusion Sitagliptin has the potential to both improve glycemic control and prevent hypoglycemia, and can be considered a potent alternative drug.

A complete list of the JAMP (Januvia Multicenter Prospective Trial in Type 2 Diabetes) Study Investigators is provided in the "Compliance with ethical standards" section.

Electronic supplementary material The online version of this article (doi:10.1007/s13340-017-0330-2) contains supplementary material, which is available to authorized users.

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Keywords DPP-4 inhibitor · Prospective observational study · Elderly patients · Sitagliptin · JAMP subanalysis · Type 2 diabetes mellitus

Introduction

The patient survey conducted in 2014 by the Ministry of Health, Labour, and Welfare of Japan showed that there were 3,166,000 patients with diabetes mellitus, which was the highest number reported thus far. The 2011 survey reported that there were 2,700,000 diabetes mellitus patients, meaning there was an increase of 466,000 between 2011 and 2014 [1]. Among people 70 years of age or older, one in four men (22.3%) and one in six women (17.0%) have diabetes mellitus [2], and this number is expected to increase in the future as Japanese society ages.

The problems associated with severe hypoglycemia in elderly people with diabetes mellitus must therefore be addressed [3]. Because patients who are 75 years of age or older often have impaired cognitive and physical function [4–8], their hypoglycemia symptoms can be overlooked, which may lead to a worsening of their condition [9]. Because renal function is also impaired in patients with diabetes mellitus, caution should be exercised, especially when administering multiple drugs simultaneously [6].

Dipeptidylpeptidase-4 (DPP-4) inhibitors, which are incretin-related drugs that include sitagliptin, are being used increasingly frequently. The hypoglycemic action of DPP-4 inhibitors involves the highly selective inhibition of DPP-4, an enzyme that inactivates incretin. Incretin is a gastrointestinal hormone that enhances insulin secretion. Because its mechanism of action is dependent on the blood glucose level, hypoglycemia is less likely to be induced. Outstanding efficacy and safety profiles of sitagliptin, the first DPP-4 inhibitor to be marketed, have been reported in many studies [10–12].

Sitagliptin has also been studied in relation to the treatment of elderly patients with diabetes, and Shankar et al. compared the additive effect of sitagliptin with that of sulfonylurea (SU) in elderly patients treated with diet therapy or metformin. Blood glucose control was similar in both the treatment groups, but fewer incidences of hypoglycemia or weight gain were noted in patients receiving sitagliptin compared with SU [13]. Another study compared the additive effect of sitagliptin or glimepiride in elderly patients, and none of the patients in the sitagliptin group experienced hypoglycemia; however, some patients in the glimepiride group experienced hypoglycemia [14]. Thus, sitagliptin can be used more safely than other drugs, but it also brings a risk of severe hypoglycemia when used with SU drugs in elderly patients, and dose adjustments for SU drugs must be given careful consideration [15, 16]. More data on the effects of the combined use of sitagliptin with medications other than SU drugs to treat elderly patients with diabetes are needed.

When treating patients with diabetes mellitus, glycemic control is often difficult to achieve with monotherapy and requires combinations of multiple drugs. However, there have been no comparative studies of antidiabetic drugs prescribed to elderly diabetic patients in which the patients were divided into as many as seven different pretreatment groups prior to the start of sitagliptin treatment.

We conducted the Januvia Multicenter Prospective Trial in Type 2 Diabetes (JAMP), which included patients with type 2 diabetes mellitus that was poorly controlled by at least 1 month of diet/exercise therapy or/and oral antidiabetic drug therapy. The patients were divided into seven pretreatment groups, and they received sitagliptin for 1 year [17]. As a subanalysis of the JAMP study, we compared the efficacy and safety of sitagliptin among the groups treated with different therapeutic drugs, and we also examined differences in its efficacy between different age groups.

Subjects and method

This open-label, central registration, multicenter, prospective observational study was conducted at the Tokyo Women's Medical University Hospital and at 69 collaborating institutions in Japan. Patients were enrolled from January 2011 to June 2013 and were followed up until June 2014. This study was approved by the ethics committee at the Tokyo Women's Medical University (UMIN000019154).

The study involved outpatients with type 2 diabetes mellitus who were 20 years of age or older and whose blood glucose levels were poorly controlled with diet/exercise therapy alone or with that therapy and the administration of antidiabetic drugs for a month or more.

In accordance with the Japan Diabetes Society guidelines that were available at the start of the study, a poorly controlled blood glucose level was defined as glycated hemoglobin (HbA1c) of $\geq$6.9% or a fasting blood glucose concentration of $\geq$130 mg/dL. At the start of the study in 2011, HbA1c values were expressed using the Japan Diabetes Society levels, which is the standard system in Japan, they but were changed to National Glycohemoglobin Standardization Program system values at the end of the study, in accordance with the Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus (Revision for International Harmonization), issued by The Japan Diabetes Society [18].

The patients were divided into the following seven groups based on the pretreatment received before sitagliptin administration: (1) diet/exercise therapy only; (2) low-dose glimepiride (0.5–1 mg); (3) medium-dose glimepiride (1.5–2 mg); (4) biguanide; (5) thiazolidine; (6) alpha-glucosidase inhibitor; and (7) combined therapy with two or more of the drugs described above.

Following the observation period, sitagliptin (50 mg once per day) was administered daily. After the third month of therapy, the dose was increased, changed, or the sitagliptin treatment was discontinued, and other antidiabetic drugs were prescribed on an as-needed basis. The patients were observed for 1 year under these study conditions (Fig. 1).

The primary endpoint was the change in HbA1c levels in elderly patients (≥65 years old). Data after 3 months was compared with the baseline and between each of the groups. The secondary endpoint was the change in HbA1c levels at 3 and 12 months from the baseline in elderly patients stratified by age (≥75, 65–74, and <65 years). The safety in patients who were ≥65 years of age was assessed by analyzing the laboratory test results and adverse events at 3 and 12 months from the baseline which were considered to be related to sitagliptin. Adverse events and hypoglycemia were diagnosed by the primary doctor or based on the patient's explanation of the symptoms.

In addition, multiple regression analysis was performed on the factors that affected the change in HbA1c level at 3 months from baseline.

The JMP software package version 12.1.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis processing. The measured values were compared within groups using a paired *t* test, variations between groups were compared using analysis of variance (ANOVA), and the patients' backgrounds were compared using the chi-squared test. The factors influencing the decrease in HbA1c levels were assessed using single and multiple regression analyses; parameters with $p < 0.20$ in the single regression analysis were assessed in the multiple regression analysis. The significance threshold in each two-sided test was $p < 0.05$. Continuous variables were presented as the mean ± standard deviation and the number of patients (%). Before participating in the study, all patients received a written explanation of the study and provided written informed consent.

Results

Of the 779 patients enrolled in this study, the safety and efficacy of the treatment were evaluated in 711 (369 were ≥75 years of age, 202 were 65–74 years of age, and 140 were <65 years of age) and 651 (130, 189, and 332, respectively) patients (see Fig. 2).

The characteristics of the patients stratified by age (≥75, 65–74, and < 65 years) are described in Table 1. The elderly patients had a smaller abdominal circumference and a longer duration of diabetes, and there were lower numbers of men, smokers, and alcohol drinkers compared with the younger patients.

The changes in the patients' HbA1c levels were assessed after they had been classified into three age groups (≥75, 65–74, and <65 years). There was no significant difference in the change in HbA1c level between the patients treated with different concomitant drugs, except for the alpha-glucosidase inhibitor groups, which contained ≤5 patients (Fig. 3a–c).

We found significant decreases ($p < 0.05$) in all three age groups at 3 months after the start of therapy, with the effect lasting until 12 months after starting therapy

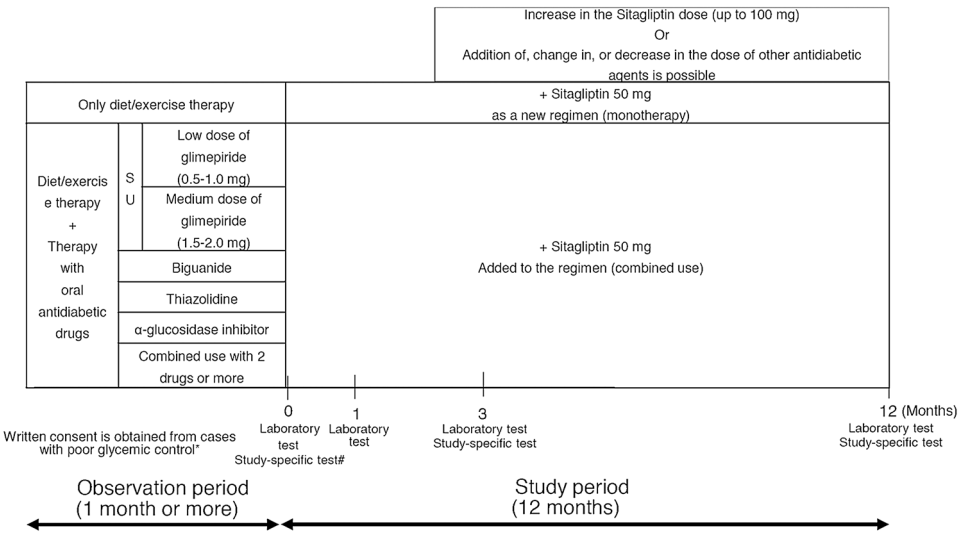

Fig. 1 Study design. *Criteria for poor glycemic control: HbA1c of ≥6.9% or fasting blood glucose of ≥130 mg/dL. #Study-specific test (arbitrary): GA, 1.5 AG, C-peptide, proinsulin/insulin ratio

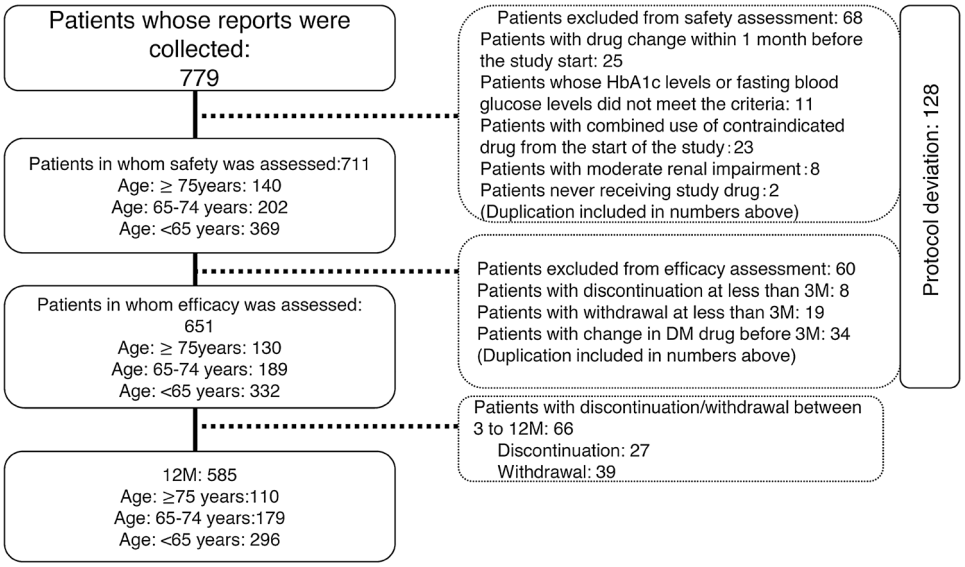

Fig. 2 Patient flow

Table 1 Comparison of patient characteristics between the elderly and non-elderly patients

	≥75 years ($n = 130$)		65–74 years ($n = 189$)		<65 years ($n = 332$)		p
	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	
Age	130	80.0 ± 4.7	189	69.2 ± 2.9	332	54.5 ± 7.4	0.000*
Height	127	156.2 ± 9.6	187	161.0 ± 8.6	328	166.2 ± 8.8	0.000*
Waist circumference	80	85.7 ± 10.5	120	87.3 ± 9.6	193	89.9 ± 12.0	0.009*
Duration of diabetes	111	121.4 ± 94.6	181	114.1 ± 78.4	308	95.4 ± 74.4	0.003*
Sex (male)	67	51.5	117	61.9	250	75.3	0.000*
Smoking	13	10.3	34	18.6	96	29.8	0.000*
Alcohol consumption	39	31.7	82	45.1%	180	56.1	0.000*
Retinopathy	8	6.2	8	4.2	32	9.6	0.064
Arteriosclerosis obliterans	6	4.6	21	11.1	28	8.4	0.122
Stroke	0	0.0	1	0.6	0	0.0	0.288
Myocardial infarction	7	5.4	5	2.6	6	1.8	0.108
Angina pectoris	8	6.2	8	4.2	11	3.3	0.387
Cardiac failure	5	3.8	2	1.1	4	1.2	0.102
Atrial fibrillation	4	3.1	5	2.6	7	2.1	0.817
Diet/exercise therapy	49	37.7	48	25.4	92	27.7	0.044*
Low dose of glimepiride	18	13.8	25	13.2	29	8.7	0.153
Medium dose of glimepiride	9	6.9	21	11.1	20	6.0	0.104
BG	9	6.9	25	13.2	65	19.6	0.002*
TZD	7	5.4	12	6.3	19	5.7	0.929
α-GI	5	3.8	3	1.6	10	3.0	0.446
Multidrug therapy	33	25.4	55	29.1	97	29.2	0.692
Antihypertensive drug	81	62.3	106	56.1	144	43.4	0.000*
Antihyperlipidemic drug	62	47.7	94	49.7	156	47.0	0.832
Antihyperuricemic drug	6	4.6	9	4.8	16	4.8	0.996
Antithrombogenic drug	22	16.9	44	23.3	52	15.7	0.088

* $p < 0.05$

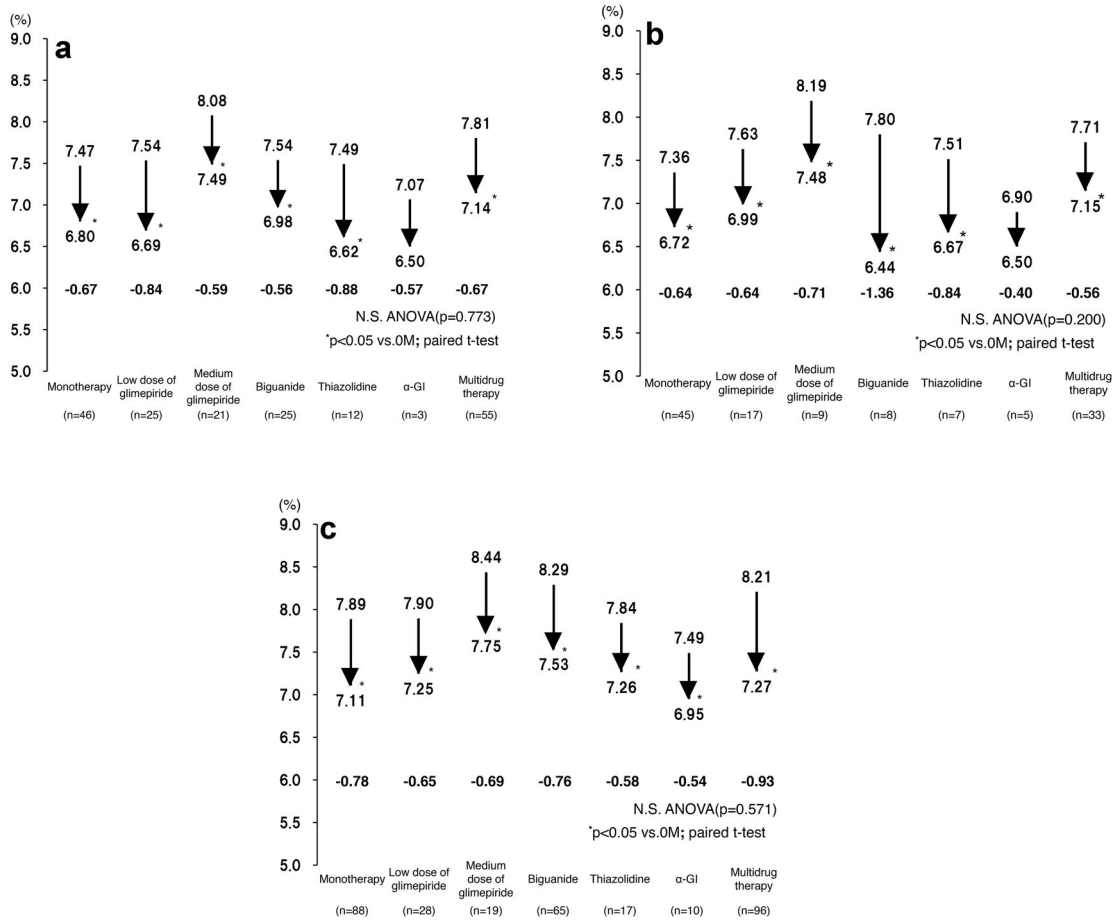

Fig. 3 **a** ΔHbA1c level at 3 months after the start of therapy according to concomitant drug type (age ≥ 75 years). **b** ΔHbA1c level at 3 months after the start of therapy according to concomitant drug type (age 65–74 years). **c** ΔHbA1c level at 3 months after the start of therapy according to concomitant drug type (age < 65 years)

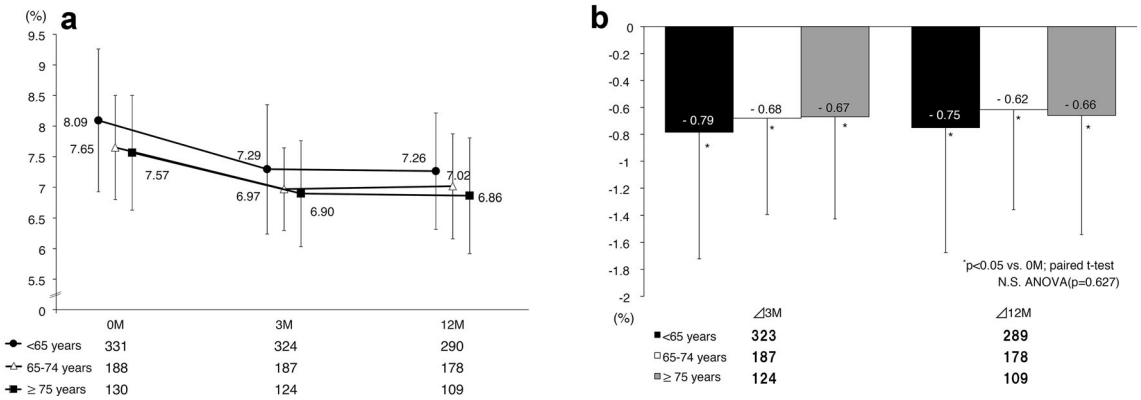

Fig. 4 **a** HbA1c level; **b** changes in HbA1c

(Fig. 4a). No significant differences in HbA1c variations at 3 and 12 months from baseline were noted among the three age groups (Fig. 4b).

The factors influencing the changes in the HbA1c levels were analyzed in patients who were ≥65 years old. The factors with $p > 0.20$ in the single regression analysis included smoking, TG levels, concomitant use of agents to correct insulin resistance, and antihypertensive drugs. Multiple regression analysis using the above factors was performed, and it revealed that patients with higher HbA1c

Table 2 Analysis of factors affecting HbA1c variations at 3 months after the start of therapy (age ≥ 65 years)

Variables	Univariate analysis					Multivariate analysis				
	Partial regression coefficient	Standard partial regression coefficient	Lower limit	Upper limit	*p* value*	Partial regression coefficient	Standard partial regression coefficient	Lower limit	Upper limit	*p* value*
Age	−0.001	−0.007	−0.014	0.012	0.907					
Sex (male)	−0.048	−0.033	−0.213	0.117	0.567					
Duration of diabetes	0.000	0.012	−0.001	0.001	0.837					
HbA1c	−0.476	−0.572	−0.552	−0.399	0.000*	−0.481	−0.581	−0.561	−0.401	0.000*
Systolic blood pressure	0.001	0.016	−0.005	0.006	0.777					
Smoking	−0.153	−0.077	−0.376	0.071	0.180	−0.080	−0.042	−0.266	0.105	0.393
Alcohol consumption	0.078	0.052	−0.093	0.249	0.370					
Group with diet/ exercise therapy	0.033	0.020	−0.147	0.212	0.721					
Group with SU (excluding multidrug therapy)	−0.036	−0.021	−0.229	0.158	0.717					
Insulin resistance improving drug (excluding multidrug therapy)	−0.143	−0.073	−0.361	0.074	0.196	−0.173	−0.093	−0.349	0.004	0.055
BMI	−0.014	−0.063	−0.038	0.011	0.273					
Waist circumference	−0.003	−0.040	−0.013	0.007	0.573					
Triglyceride	0.001	0.095	0.000	0.002	0.104	0.001	0.128	0.000	0.002	0.010*
LDL-C	−0.001	−0.026	−0.004	0.002	0.661					
eGFR	−0.001	−0.030	−0.006	0.004	0.614					
Antihypertensive drug	0.108	0.073	−0.057	0.274	0.198	−0.056	−0.038	−0.196	0.085	0.437
Antihyperlipidemic drug	0.036	0.025	−0.126	0.199	0.660					

Factors with $p < 0.2$ in the single regression analysis were extracted, and multiple regression analysis was performed using these factors

Patients with higher baseline HbA1c levels were likely to show large decreases in HbA1c levels, while patients with higher triglyceride levels were unlikely to do so

* $p < 0.05$

levels at baseline were likely to show decreased HbA1c levels, while those with higher TG levels were unlikely to show decreased HbA1c levels (Table 2).

Variations in the laboratory results for patients who were ≥65 years old were measured at 3 and 12 months from baseline. We found no significant variations in the pulse rate, body weight, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urine albumin-to-creatinine ratio, or platelet count. Significant variations were found in the systolic and diastolic blood pressure, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), γ-glutamyltransferase (γ-GTP), and estimated glomerular filtration rate (eGFR), although these variations were not large (Table 3).

In addition, among the 319 patients who were ≥65 years old and in whom the treatment safety was assessed, hypoglycemia was noted in only one patient receiving sitagliptin monotherapy. Another adverse event that was considered to have a causal relationship with sitagliptin was anemia, which was found in just one patient receiving sitagliptin monotherapy.

Discussion

The study compared the additive effect of sitagliptin in reducing HbA1c in patients who were classified into three age groups (≥75, 65–74, and <65 years) and were divided into seven groups based on the pretreatment drug. We observed a significant reduction in HbA1c levels in all age groups and all seven pretreatment groups except for the alpha-glucosidase inhibitor groups, which had ≤5 patients, but there was no difference compared with each pretreatment group.

Table 3 Variations in laboratory results for patients ≥ 65 years old

	0 months	3 months	12 months	Change at 3 months	Change at 12 months
SBP	132.1 ± 15.4 ($n = 316$)	129.6 ± 14.6 ($n = 311$)	131.1 ± 14 ($n = 284$)	−2.6 ± 16.1 ($n = 311$)*	−0.4 ± 16.1 ($n = 283$)
DBP	73.4 ± 10.4 ($n = 316$)	72.1 ± 9.9 ($n = 311$)	73.2 ± 10.7 ($n = 284$)	−1.4 ± 10.1 ($n = 311$)*	−0.3 ± 10.1 ($n = 283$)
Pulse rate	75.3 ± 11.6 ($n = 259$)	74.8 ± 11.1 ($n = 252$)	75.7 ± 11.9 ($n = 229$)	−0.5 ± 9.8 ($n = 247$)	0.7 ± 10.1 ($n = 226$)
Body weight	61.1 ± 10.9 ($n = 310$)	61.3 ± 10.9 ($n = 293$)	61.2 ± 10.6 ($n = 271$)	−0.1 ± 1.7 ($n = 292$)	−0.3 ± 2.4 ($n = 270$)
BMI	24.1 ± 3.4 ($n = 307$)	24.2 ± 3.4 ($n = 290$)	24.1 ± 3.4 ($n = 270$)	0 ± 0.7 ($n = 289$)	−0.1 ± 1 ($n = 269$)
HbA1c	7.62 ± 0.89 ($n = 318$)	6.94 ± 0.75 ($n = 311$)	6.96 ± 0.89 ($n = 287$)	−0.68 ± 0.73 ($n = 311$)*	−0.63 ± 0.8 ($n = 287$)*
TG	136.5 ± 89.6 ($n = 297$)	129.8 ± 74.5 ($n = 289$)	125.6 ± 64.8 ($n = 269$)	−7 ± 80 ($n = 280$)	−10 ± 81.9 ($n = 260$)*
HDL-C	55.9 ± 14.7 ($n = 288$)	54.3 ± 15 ($n = 282$)	54.2 ± 15.4 ($n = 265$)	−1.4 ± 8.1 ($n = 274$)*	−1.4 ± 7.9 ($n = 256$)*
LDL-C	110.2 ± 28.2 ($n = 294$)	106.8 ± 26.5 ($n = 283$)	109.7 ± 29.2 ($n = 267$)	−2.6 ± 19.1 ($n = 273$)*	−0.3 ± 23.5 ($n = 256$)
AST	24.4 ± 10.4 ($n = 297$)	24.3 ± 10.7 ($n = 287$)	24.5 ± 10.5 ($n = 267$)	0 ± 7.6 ($n = 278$)	0.4 ± 9 ($n = 258$)
ALT	23.7 ± 14.8 ($n = 297$)	22.6 ± 14.7 ($n = 286$)	23 ± 15.5 ($n = 266$)	−1.1 ± 9.8 ($n = 277$)	−0.5 ± 11.8 ($n = 257$)
γ-GTP	41.5 ± 57.7 ($n = 293$)	38 ± 46.1 ($n = 283$)	39.3 ± 47.1 ($n = 267$)	−3 ± 21.5 ($n = 272$)*	−2.8 ± 31.8 ($n = 255$)
UACR	55.9 ± 168.6 ($n = 137$)	51.9 ± 137.1 ($n = 125$)	99.2 ± 383.4 ($n = 147$)	−19.7 ± 117.2 ($n = 108$)	38.1 ± 249.1 ($n = 115$)
eGFR	72.4 ± 16.5 ($n = 269$)	69.5 ± 15.8 ($n = 260$)	68.5 ± 15.5 ($n = 270$)	−2.7 ± 8.1 ($n = 253$)*	−3.8 ± 9.5 ($n = 262$)*
Platelets	21.1 ± 5.7 ($n = 284$)	20.9 ± 5.2 ($n = 275$)	21.2 ± 5.8 ($n = 258$)	−0.3 ± 3.1 ($n = 266$)	0.1 ± 3.4 ($n = 249$)

* $p < 0.05$

Our results suggest that monotherapy with sitagliptin in patients during the early stages can lead to improvements in glycemic control. Additional administration of sitagliptin in patients who are already being treated for diabetes mellitus and who have poor glycemic control can also have a significant hypoglycemic effect regardless of the kind of drug that is used concomitantly. Results of comparing the patients classified into three age groups (≥75, 65–74, and <65 years) indicated that there was no significant difference in efficacy between the age groups, which suggests that sitagliptin can improve blood glucose levels in patients of any age.

The safety assessment showed that among the 319 patients who were ≥65 years old, only one patient (0.3%) receiving monotherapy with sitagliptin was suspected of having hypoglycemia. Barzilia et al. compared treatments with sitagliptin and placebo for 24 weeks in 206 elderly patients who were ≥65 years old, and reported no hypoglycemia in the group receiving sitagliptin; thus, sitagliptin demonstrated no safety concerns [19]. The results of our study are consistent with those of previous studies that demonstrated the safety of sitagliptin. Thus, sitagliptin is unlikely to cause hypoglycemia in elderly patients with diabetes mellitus.

A high dose of SU drugs incurs a risk of hypoglycemia. However, sitagliptin acts in a blood glucose level-dependent manner, and is unlikely to cause hypoglycemia. A previous study involving elderly patients reported that, despite increasing the dose of sitagliptin to 100 mg, the incidence of hypoglycemia was lower in the sitagliptin group compared with patients who were not taking sitagliptin [20]. Our study also confirmed that there was no increase in the incidence of hypoglycemia among the 31 patients whose sitagliptin dose was increased to 100 mg. Thus, sitagliptin was considered to be safe even at high doses (Table S1 in the Electronic supplementary material, ESM).

Elderly people often have multiple comorbidities and physical function is likely to worsen in this age group [21]. Therefore, severe hypoglycemia can be easily induced. Severe hypoglycemia impairs cognitive function and is associated with a risk of cardiovascular events [22]. Based on this background, the glycemic control target for elderly patients with diabetes was prepared by the Joint Committee of the Japan Diabetes Society and the Japan Geriatrics Society in 2015 to improve therapeutic outcomes [23]. The committee emphasized that the glycemic control target should be defined individually after careful consideration of the patient's medical history and factors affecting their health status, such as age, cognitive and physical function, comorbid conditions, risk of severe hypoglycemia, and life expectancy. It also stressed that, if severe hypoglycemia is a concern, a safer treatment must be performed by setting a lower target. Based on this background, sitagliptin was administered only once per day, thus allowing good compliance with a lower risk of hypoglycemia, even in elderly patients.

Although significant decreases in some results were seen in the various laboratory tests performed after the administration of sitagliptin, the variations in the values were small, and therefore no problems with clinical safety are expected. The overall eGFR significantly decreased, and while some patients with a high baseline eGFR showed only a slight decrease, other patients with a low baseline eGFR did not show a further decrease (Table S2 in ESM). As other studies have also reported, patients taking sitagliptin showed neither weight gain [24, 25] nor deterioration in any major laboratory findings after long-term administration [26], and sitagliptin seems to be a safe drug choice.

Our study showed that the hypoglycemic action of sitagliptin continued until 12 months after starting therapy. Although the observation period of our study was 12 months, Ching-Jung et al. reported that the blood glucose-improving effect of sitagliptin in elderly patients with a mean age of 71.3 ± 11.7 years lasted from 6 to 48 months, with no adverse events of hypoglycemia [27]. Sitagliptin may also allow stable glycemic control for a long time in elderly patients.

The multivariable analysis of the factors influencing HbA1c variations in elderly patients suggested that higher HbA1c levels before therapy are associated with greater improvement, while high TG levels suppress improvements in HbA1c levels. Some reports indicate that insulin resistance associated with aging causes abnormalities in glucose and lipid metabolism [28–32], and the same mechanism was considered to have contributed to the results of our study. Although sitagliptin is expected to be effective in many clinical contexts, patients with high TG levels should be treated after careful consideration of the glycemic control effect.

Limitations

There are several limitations to this study. Firstly, the JAMP study was an open-label observational study. Secondly, at the start of this study, drugs such as glinides, insulin, and sodium-glucose cotransporter 2 (SGLT2) inhibitors were not approved for insurance coverage. Thus, no data were available on the combined use of sitagliptin and these drugs, making it impossible to examine their effects in this study.

Conclusion

We studied patients with long-term diabetes who had already been treated with antidiabetic agents and were prescribed sitagliptin in addition to other agents when poor glycemic control was noted. This situation more closely reflects actual clinical practice than studies such as a Japanese dose-ranging study of sitagliptin [33]. Patients receiving sitagliptin achieved good outcomes in these studies, including in situations where its use was combined with other antidiabetic drugs.

Our results have demonstrated that concomitant antidiabetic drugs do not affect the glycemic control effect in elderly patients. No increase in the incidence of hypoglycemia was observed, even after the dose of sitagliptin was increased to 100 mg. Thus, sitagliptin has the potential to both improve glycemic control and prevent hypoglycemia, and it can be considered a potent alternative drug.

Acknowledgements We would like to express our sincere gratitude to Mr. Shogo Shishikura (MSD K.K.) (Teikyo University Graduate School of Public Health, MPH) for scientific advice, including references, when revising the manuscript. We would also like to thank Nouvelle Place Inc. for conducting the data analyses.

Compliance with ethical standards

Funding This study was funded by the Japan Diabetes Foundation.

Conflict of interest Hiroshi Sakura received honoraria from Mitsubishi Tanabe Pharma Corporation and a research grant from Ono Pharmaceutical Co., Ltd. The other authors declare that they have no conflict of interest.

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Ethical approval and consent to participate All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The ethics committee at the Tokyo Women's Medical University approved the study (approval number: 2064) on 11 January 2011. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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