Efficacy and safety of sitagliptin monotherapy and combination therapy in Japanese type 2 diabetes patients

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ABSTRACT

Aims/Introduction: To determine the efficacy and safety of sitagliptin monotherapy and combination therapy in Japanese type 2 diabetes patients after 3 months' therapy.

Materials and Methods: A retrospective, observational study of 741 type 2 diabetes patients was carried out; 110 received sitagliptin monotherapy, and 631 received combination therapy with sitagliptin when other oral medications were insufficient. The primary outcome measure was glycated hemoglobin (HbA_{1c}) measured at 0, 4 and 12 weeks of sitagliptin therapy.

Results: In the monotherapy and combination therapy groups, HbA_{1c} decreased significantly after 12 weeks. Target HbA_{1c} (<7%) was achieved in 39.1% overall. On logistic regression analysis, baseline HbA_{1c} was the strongest contributing factor for achieving target HbA_{1c}; baseline body mass index and duration of diabetes were also significant factors. A total of 82 patients (11%) were unresponsive to sitagliptin. These patients' baseline body mass index was significantly higher and their baseline HbA_{1c} was significantly lower than those of patients who responded to sitagliptin. The most commonly co-administered drugs were sulfonylureas (508 patients). In these patients, the dose of sulfonylurea decreased with time. In 66 patients whose sulfonylurea dosage was reduced when sitagliptin was started, HbA_{1c} and bodyweight decreased significantly after 12 weeks. A total of 24 patients receiving sulfonylureas had mild hypoglycemia, but none discontinued sitagliptin.

Conclusions: Sitagliptin was effective and safe as both monotherapy and combination therapy in Japanese type 2 diabetes patients. When sulfonylureas were ineffective, sitagliptin improved glycemic control. In patients whose sulfonylurea dose was reduced at the start of sitagliptin, blood glucose improved and bodyweight decreased after 12 weeks. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00221.x, 2012)

KEY WORDS: Diabetes mellitus, Sitagliptin, Sulfonylurea

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors belong to a novel class of antidiabetic agents that increase the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[1–5]. Sitagliptin is the first DPP-4 inhibitor in Japan, where it has been available for approximately 2 years. The oral diabetes drugs that were available for clinical use before this were sulfonylureas, biguanides, thiazolidines, α-glucosidase inhibitors (αGI) and glinides. However, blood glucose cannot actually be well controlled in many type 2 diabetes patients with these drugs, and improved glycemic control in a greater number of diabetic patients is anticipated with sitagliptin, given its novel mechanism of action.

Japanese people have genetically low insulin secretory capacity[6–8], and sulfonylurea drugs are the most commonly used drug therapy for type 2 diabetes[9]. In monotherapy, sitagliptin is expected to be effective for a wide range of diabetes patients[10,11], as well as cases of secondary sulfonylurea failure, but there are currently no reported results on the efficacy and safety of sitagliptin in large numbers of patients in actual clinical practice. The study group of the diabetes committee has carried out several observational studies in Kanagawa, such as looking at the prevalence of diabetic complications (neuropathy[12] and nephropathy). Our committee carried out a retrospective,

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observational study of sitagliptin, which was given to type 2 diabetes patients in the community by the diabetes specialists of our committee. A large-scale analysis of the efficacy and safety of sitagliptin monotherapy and combination therapy for 12 weeks in actual clinical practice, in which the primary outcome was glycated hemoglobin (HbA_{1c}), is reported.

MATERIALS AND METHODS

The survey participants were type 2 diabetes patients receiving outpatient treatment at 28 hospitals or clinics specializing in diabetes belonging to the Diabetes Committee of the Kanagawa Physicians Association from December 2009 to August 2010. Oral consent for participation in the present study was obtained from type 2 diabetes patients who were using diet and exercise therapy, and from patients with insufficient glycemic control despite the use of hypoglycemic agents. Sitagliptin monotherapy or sitagliptin in addition to other drugs was then given, starting at a dose of 25 mg or 50 mg. If good glycemic control was not obtained after this, the sitagliptin dose could be increased to 100 mg. The total number of registered patients was 741 (Figure 1). The monotherapy group (n = 110) enrolled drug-naive patients who were given sitagliptin when glycemic control was inadequate on diet and exercise therapy, and the combination therapy group (n = 631) enrolled patients who were given sitagliptin in addition to the previously prescribed medications when other oral medications were insufficient. In order to evaluate the efficacy of sitagliptin without the effects of discontinuation of conventional drugs, those in whom one or more conventional antidiabetes drugs were discontinued at the start of sitagliptin were not enrolled. The present study was an observational study that aimed to evaluate the efficacy and adverse events of sitagliptin, and approval was obtained from the Ethics Review Board of the Kanagawa Physicians Association.

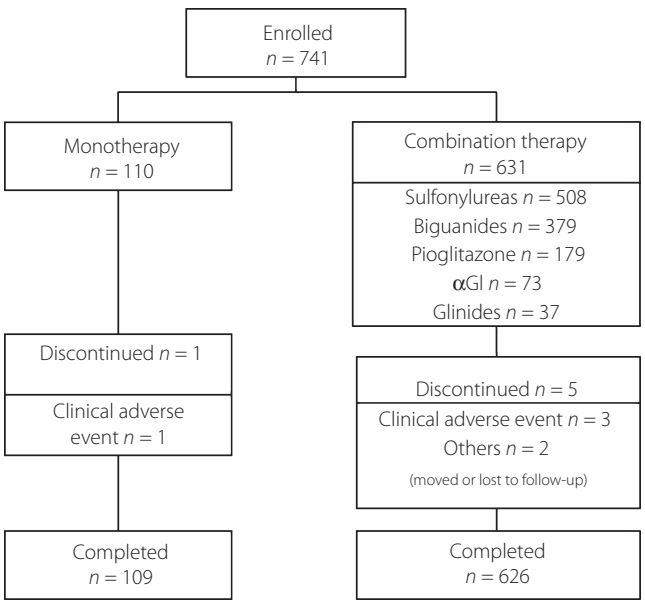

Figure 1 | Disposition of enrolled patients. αGI, α-glucosidase inhibitors.

Outcome Measures

The patients' baseline characteristics were as follows: monotherapy group, n = 110 (64 men, 46 women), mean age 63.4 ± 11.8 years, duration of diabetes 8.2 ± 6.4 years and body mass index (BMI) 23.84 ± 4.36 kg/m^2; and combination therapy group n = 631 (360 men, 271 women), mean age 63.4 ± 11.2 years, duration of diabetes 12.8 ± 8.2 years and BMI 24.85 ± 4.35 kg/m^2. In these combined 741 patients (424 men, 317 women, mean age 63.4 ± 11.3 years, duration of diabetes 12.1 ± 8.1 years, BMI 24.70 ± 4.37 kg/m^2), HbA_{1c}, the primary outcome measure, was measured at the start, and after 4 and 12 weeks of sitagliptin therapy. Bodyweight was also measured at the start and after 12 weeks. HbA_{1c}, expressed in National Glycohemoglobin Standardization Program (NGSP) units-equivalent value[13], was measured by high-performance liquid chromatography.

Co-administered drugs in the combination therapy group were analyzed (Figure 1), and the numbers of patients taking sulfonylureas, biguanides, pioglitazone, αGI and glinides were 508, 379, 179, 73 and 37, respectively. Of 508 patients (297 men, 211 women, mean age 64.3 ± 10.7 years, duration of diabetes 13.8 ± 8.2 years, BMI 24.50 ± 4.30 kg/m^2) using sulfonylureas, the dose of sulfonylurea was reduced at the start of sitagliptin in 66 patients and not reduced in 442 patients. In both the reduced and non-reduced sulfonylurea dose groups, HbA_{1c} was analyzed at baseline and after 4 and 12 weeks, and bodyweight was analyzed at baseline and after 12 weeks.

To identify factors contributing to the achievement of HbA_{1c} <7.0% and factors contributing to responsiveness to sitagliptin treatment after administration of sitagliptin for 12 weeks, logistic regression analyses were carried out for age at baseline, sex, duration of diabetes, baseline BMI, baseline HbA_{1c} and whether HbA_{1c} <7.0% was reached after 12 weeks or whether HbA_{1c} after12 weeks was decreased from the baseline value. Unresponsiveness to sitagliptin treatment was defined as HbA_{1c} after 12 weeks equal to or higher than baseline HbA_{1c}.

Statistical Analysis

All analyses were carried out using SPSS version 19 for Windows (SPSS, Chicago, IL, USA). For bodyweight, data were analyzed by paired t-tests. For HbA_{1c}, data were analyzed by one-way ANOVA. Statistical analysis comparing the baseline characteristics of the responsive and unresponsive groups was carried out using the Mann–Whitney U-test. Data are presented as means ± SD. A P-value < 0.05 was considered significant.

RESULTS

The analysis included 741 patients, 110 patients who received sitagliptin monotherapy and 631 patients who received combination therapy. Most patients in the combination therapy group had either two co-administered drugs (33.9%) or one

co-administered drug (33.6%), followed by three (15.5%) and four co-administered drugs (2.2%). The most common co-administered drugs were sulfonylureas (80.5% of the combination therapy group). More than half (60.1%) also used biguanides, followed by pioglitazone (28.4%), αGI (11.6%) and glinides (5.9%). In the monotherapy and combination therapy groups, HbA_{1c} was 7.88 ± 1.54% and 8.07 ± 1.06%, respectively, at the start of sitagliptin, decreasing significantly to 7.59 ± 1.20% ($P < 0.01$ vs baseline) and 7.71 ± 0.97% ($P < 0.01$ vs baseline) after 4 weeks and 7.09 ± 0.71% ($P < 0.01$ vs baseline or 4 weeks) and 7.31 ± 0.88% ($P < 0.01$ vs baseline or 4 weeks) after 12 weeks (Table 1). The decrease in HbA_{1c} from baseline to 12 weeks (ΔHbA_{1c} 0–12 weeks) was 0.79 ± 1.33% points and 0.76 ± 0.77% points, respectively. The results of an analysis that was stratified on the basis of the baseline HbA_{1c} showed that ΔHbA_{1c} 0–12 weeks was 1.45 ± 1.21% points in the ≥8.5% group, 0.65 ± 0.52% points in the ≥7.5% to <8.5% group, and 0.34 ± 0.44% points in the <7.5% group. ΔHbA_{1c} 0–12 weeks was larger in patients with higher baseline HbA_{1c} (Figure 2a).

In all patients, the monotherapy group and the combination therapy group, the blood glucose treatment target of HbA_{1c} <7% was achieved at rates of 39.1, 44.5 and 38.2%, respectively. In all groups, the achievement rate was higher with lower baseline HbA_{1c} (Figure 2b). A logistic regression analysis of all patients was carried out to identify factors that affect the achievement of HbA_{1c} <7%. The results showed that the strongest factor was HbA_{1c} at the start of sitagliptin therapy, whereas baseline BMI and duration of diabetes were also significant (higher rates of patients with lower basal BMI or with shorter duration of diabetes are expected to achieve the target; Table 2). No correlation was seen for age, sex or whether the therapy was monotherapy or combination therapy.

Individual differences in the glucose-lowering effects of sitagliptin were observed in the present study, and 82 patients (11%) were unresponsive to 12 weeks' treatment with this drug. The characteristics of the two groups (659 patients who responded and 82 patients who did not respond to sitagliptin) are shown in Table 3. The baseline BMI was significantly higher ($P < 0.05$) and the baseline HbA_{1c} was significantly lower ($P < 0.01$) in unresponsive patients than in patients who responded to sitagliptin. A logistic regression analysis was also carried out to identify factors contributing to responsiveness to sitagliptin. The results show that baseline HbA_{1c} (odds ratio [OR] 2.24, 95%

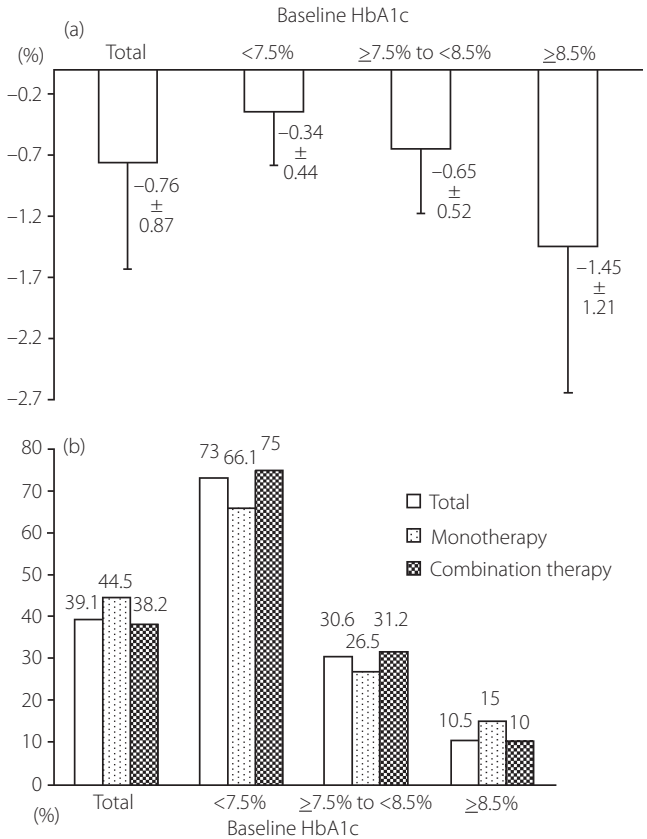

Figure 2 | The results of analyses stratified by baseline glycated hemoglobin (HbA_{1c}) are shown. (a) Change in HbA_{1c} between 0 and 12 weeks; (b) Proportion of patients with HbA_{1c} <7.0% at 12 weeks.

Table 1 | Time course of glycated hemoglobin levels in patients in the monotherapy and combination therapy groups

	HbA_{1c} (%)			ΔHbA_{1c} (0–12 weeks)
	Baseline	4 weeks	12 weeks	
Total (n = 741)	8.04 ± 1.14	7.69 ± 1.01*	7.28 ± 0.86*,**	0.76 ± 0.87
Monotherapy (n = 110)	7.88 ± 1.54	7.59 ± 1.20*	7.09 ± 0.71*,**	0.79 ± 1.33
Combination therapy (n = 631)	8.07 ± 1.06	7.71 ± 0.97*	7.31 ± 0.88*,**	0.76 ± 0.77

ANOVA: vs baseline *$P < 0.01$, vs 4 weeks **$P < 0.01$. HbA_{1c}, glycated hemoglobin.

Table 2 | Factors affecting the proportion of patients with glycated hemoglobin <7.0% at 12 weeks

Independent variables	Partial regression coefficient	Standardized partial regression coefficient	Odds ratio	95% CI	P
Baseline HbA_{1c}	−1.5001	−1.6982	0.223	0.165–0.302	0.000
Duration of diabetes	−0.0358	−0.2947	0.965	0.942–0.988	0.003
Baseline BMI	−0.0665	−0.2776	0.936	0.893–0.981	0.006
Age					0.067
Sex					0.780
Monotherapy or combination therapy					0.198

BMI, body mass index; HbA_{1c}, glycated hemoglobin.

Table 3 | Characteristics of the patients in the responsive and unresponsive groups to sitagliptin therapy

	Responsive group	Unresponsive group	*P*
n	659	82	
Age (years)	63.3 ± 11.4	64.4 ± 10.9	NS
Sex (male/female)	381/278	43/39	NS
Duration of diabetes (years)	10.9 ± 8.6	10.7 ± 7.5	NS
Baseline HbA_{1c} (%)	7.71 ± 1.16	7.10 ± 0.78	<0.01
Baseline BMI (kg/m^2)	24.59 ± 4.25	25.52 ± 4.18	<0.05

BMI, body mass index; HbA_{1c}, glycated hemoglobin; NS, not significant.

Table 4 | Mean doses of sulfonylureas for total patients and those whose doses of sulfonylurea were reduced at the start of sitagliptin

	Before addition of sitagliptin	0 weeks	12 weeks
Total patients			
Glimepiride (*n* = 324)	2.57 ± 1.57	←	2.23 ± 1.42
Glibenclamide (*n* = 121)	4.88 ± 2.26	←	3.77 ± 1.98
Gliclazide (*n* = 63)	44.69 ± 29.42	←	38.52 ± 23.18
Patients whose doses of sulfonylurea were reduced at the start of sitagliptin			
Glimepiride (*n* = 49)	2.95 ± 1.56	1.68 ± 1.01	1.65 ± 0.98
Glibenclamide (*n* = 13)	6.54 ± 1.84	3.65 ± 1.66	3.65 ± 1.80
Gliclazide (*n* = 4)	70.00 ± 17.32	35.00 ± 8.66	30.00 ± 10.00

Data are presented as daily doses (mg/day). ←, values unchanged from before addition of sitagliptin.

confidence interval [CI] 1.57–3.20, $P < 0.01$) and baseline BMI (OR 0.91, 95% CI 0.86–0.97, $P < 0.05$) were significant factors.

Sulfonylurea dosage was analyzed in the 508 combination therapy group patients, and the dosage trends for each sulfonylurea drug are shown in Table 4. It was found that the dose decreased with time, even during the treatment course of up to 12 weeks. Administration of sulfonylurea drugs was discontinued in 18 patients during the 12 weeks (glimepiride 12 patients, glibenclamide 4 patients and gliclazide 2 patients). It was found that the sulfonylurea dose was reduced at the start of sitagliptin therapy in 66 patients (13.0%). Both the 66 patients in the reduced dose group and the other 442 patients in the non-reduced dose group showed significantly lower HbA_{1c} levels, from 7.97 ± 0.77% to 8.11 ± 1.08% at baseline to 7.31 ± 0.76% ($P < 0.01$) and 7.38 ± 0.92% ($P < 0.01$) at 12 weeks, respectively. The respective ΔHbA_{1c} 0–12 weeks values were 0.65 ± 0.67% points and 0.73 ± 0.77% points. Bodyweight over the course of therapy was examined in both groups. No significant difference in bodyweight was seen between baseline and 12 weeks in the non-reduced dose group, but a significant difference ($P < 0.05$) was seen between bodyweight at baseline (62.15 ± 15.00 kg) and after 12 weeks (61.75 ± 14.86 kg) in the reduced dose group (Table 5).

Table 5 | Bodyweight (baseline, 12 weeks and change from baseline)

	n	Bodyweight (kg)		
		0 weeks	12 weeks	*P* (12 weeks vs 0 weeks)
Patients with sulfonylurea dose reduction	66	62.15 ± 15.00	61.75 ± 14.86	<0.05
Patients without sulfonylurea dose reduction	442	63.59 ± 12.89	63.75 ± 13.07	NS
Total	508	63.43 ± 13.22	63.48 ± 13.35	NS

NS, not significant.

Adverse events were generally mild to moderate. Hypoglycemia occurred in 24 patients using sulfonylureas (glimepiride 16 patients, glibenclamide 8 patients and gliclazide 0 patients). All cases were mild, and the dose of sulfonylurea drugs was decreased after the occurrence of hypoglycemia in 20 patients, but there were no cases in which the administration of sitagliptin was discontinued. Gastrointestinal adverse events included constipation ($n = 3$) and abdominal bloating ($n = 1$); dizziness ($n = 4$), eczema ($n = 1$) and edema ($n = 1$) were also reported. Four patients dropped out because of adverse events: constipation ($n = 1$), eczema ($n = 1$) and dizziness ($n = 2$). In these patients, all symptoms improved after sitagliptin was discontinued.

DISCUSSION

DPP-4 inhibitors have a novel mechanism of action, and their efficacy and safety in monotherapy or combination therapy with conventional oral diabetes drugs have not yet been reported in large numbers of patients in actual clinical settings. In the present observational study of Japanese type 2 diabetes patients receiving sitagliptin, a very large number of patients (741 patients) was enrolled. The analyses included 110 monotherapy patients and 631 combination therapy patients at 3 months after the start of sitagliptin. It was found that, in the combination therapy group, sitagliptin was used together with a wide range of 1–4 other drugs. Sulfonylurea drugs were the most common co-administered drugs, used in approximately 80% of cases. In recent results for type 2 diabetes patients being treated by diabetes specialists in Japan, sulfonylurea was used in more than 60% of patients treated with oral drugs[9]. The accumulated results for co-administered drugs in the present study are thought to reflect this state of oral drug use in Japan. In the current patient group, HbA_{1c} decreased significantly in both the sitagliptin monotherapy and combination therapy groups after administration for 12 weeks, whereas ΔHbA_{1c} 0–12 weeks was 0.79 ± 1.33% points and 0.76 ± 0.77% points, respectively. The improvement in blood glucose was about the same in the two groups. The glycemic control target is a HbA_{1c} of <7% to prevent diabetic complications, and with the administration of sitagliptin, this target was achieved in 39.1% of all 741 patients after administration for

12 weeks. In a meta-analysis of sitagliptin, the HbA_{1c} <7% achievement rate was reported to be approximately 40%[14], similar to the results in the present study. In actual clinical practice, glycemic control is attempted with various drug combinations depending on the patient's condition and other factors, and sitagliptin was shown to be efficacious even in these various combinations.

The effect of sitagliptin is also known to vary greatly among individuals. In the present study, therefore, with the aim of identifying factors that contribute to achieving the target of HbA_{1c} <7%, a regression analysis was carried out in which the dependent variable was whether the target HbA_{1c} of <7% had been reached at 12 weeks, and the explanatory variables were patient background and baseline HbA_{1c}. Three factors were found to have significant effects: (i) baseline HbA_{1c}; (ii) baseline BMI; and (iii) duration of diabetes. Similar to earlier reports, it was also found that patients with a low baseline HbA_{1c} were more likely to reach the target HbA_{1c}[14]. However, this is the first report to show that patients with low baseline BMI and patients with short duration of diabetes have a higher rate of achieving the target HbA_{1c}. The two factors of baseline BMI and duration of diabetes were much weaker than baseline HbA_{1c}, but they were identified as significant factors. Because these two factors have been shown to affect the hypoglycemic action of sitagliptin[15,16], the hypoglycemic characteristics of sitagliptin might also affect the target achievement rate. The characteristics of the glucose-lowering effects of sitagliptin were also examined in the patients who were responsive and those who were unresponsive to sitagliptin treatment. Overall, 11% of patients were unresponsive to sitagliptin, and the baseline BMI was significantly higher and the baseline HbA_{1c} was significantly lower in the unresponsive group than in the responsive group. The subsequent logistic regression analysis showed that these two factors, baseline BMI and HbA_{1c}, were significantly related to responsiveness to sitagliptin therapy. Although the regulation of incretin systems and the actions of DPP-4 inhibitors have been under intensive investigation[17–22], they are not fully understood. Therefore, the mechanisms by which baseline BMI and duration of diabetes contribute to the efficacy of DPP-4 inhibitors are still unknown. Interestingly, given that it has been reported that people with low BMI secrete a large amount of GLP-1, at least some of the contribution of BMI to the efficacy of DPP-4 inhibitors can be explained by differences in GLP-1 secretion[17,18].

Japanese people have genetically low insulin secretion[6–8], and sulfonylurea drugs are the most commonly used drugs for the treatment of type 2 diabetes in Japan. As the glycemic control of many such patients has not reached the target level, there is much interest in the efficacy of sulfonylurea drugs combined with sitagliptin. The results of the present study show that significant glycemic control improvement was achieved in patients whose glycemic control was inadequate even with therapy centered on sulfonylurea drugs. In addition, an analysis of the trends in sulfonylurea dosage showed that the sulfonylurea dose was greatly decreased compared with before the administration of sitagliptin. Thus, it was shown that good glycemic control could be achieved with lower sulfonylurea doses by administering sitagliptin. These results suggest that β-cell function is actually well activated with combined use of sulfonylurea drugs and DPP-4 inhibitors, although the effect of sitagliptin to lower glucagon[4] might also contribute to the reduced sulfonylurea doses. It is coming to be understood that incretin not only promotes the insulin release reaction in β-cells[5,23], but it also stimulates the insulin secretion response through multiple actions[24], such as promoting adenosine triphosphate generation in mitochondria[25], and both sulfonylurea and incretin act on exchange protein directly activated by cyclic adenosine monophosphate 2A in β-cells[26,27]. Therefore, incretin and sulfonylurea are supposed to stimulate insulin secretion in coordinated and synergistic manners, and the present results appear to reflect these stimulatory effects of incretin and sulfonylureas on pancreatic β-cells.

Of particular note is that bodyweight was also significantly, even in the short observation period of 12 weeks when the sulfonylurea dose was decreased at the start of sitagliptin therapy. It was shown in the present study that, by reducing the dose of sulfonylurea drugs, with which bodyweight is known to increase over time[28,29], and adding DPP-4 inhibitors, which have been shown to be neutral with regard to bodyweight[14], bodyweight decreased in actual treatment cases. As weight gain is an undesirable effect of sulfonylurea therapy, weight loss is thought to be a positive characteristic of the combined use of sulfonylurea drugs and sitagliptin.

In an investigation of the safety of combination therapy with sitagliptin and sulfonylurea drugs, the most common adverse event was hypoglycemia, although it was mild in all cases. The dose of sulfonylurea drugs was decreased after the occurrence of hypoglycemia in 20 patients, but there were no cases in which the administration of sitagliptin was discontinued.

The present paper has presented the results of an analysis of a very large number of patients receiving sitagliptin monotherapy and combination therapy in actual clinical settings. However, because this was an observational study without control, the results of the present study could include some limitations, such as bias in selecting patients. In addition, because the observational period of the present study was 12 weeks, longer-term investigation about the durability of the efficacy and about the safety of sitagliptin treatment will be required, which is now being carried out.

The analysis showed that sitagliptin is widely used in actual treatment, and its efficacy in both monotherapy and combination therapy was shown. In particular, with the addition of sitagliptin in cases when an insufficient effect is obtained with sulfonylurea drug therapy, we can expect not only improved glycemic control, but also a reduction in sulfonylurea dose and decreased bodyweight. This is thought to be a desirable characteristic of DPP-4 inhibitor combination therapy, and it will be important to take advantage of this characteristic in diabetes therapy. These results showing the efficacy and safety of sitagliptin will surely be of value to clinical practitioners.

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