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BRIEF ARTICLE

Sitagliptin counteracts seasonal fluctuation of glycemic control

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Abstract

AIM: To assess the effect of sitagliptin therapy on seasonal fluctuation of glycemic control in Japanese type 2 diabetic patients.

METHODS: Participating patients (age: 29-80 years) had been treated with conventional oral antidiabetic agents and/or diet and exercise therapy for over 6 mo. From December 2009, 35 patients were additionally prescribed oral sitagliptin starting from 50 mg once daily, while 19 patients taking α-glucosidase inhibitors were switched to sitagliptin. Twenty-four patients who refused sitagliptin formed the control group. Changes of mean monthly hemoglobin A_{1c} (HbA_{1c}) during the "winter holiday season" were compared between groups using Student's *t*-test (2008-2009 *vs* 2009-2010). Statistical significance was accepted at $P < 0.05$. Multivariate analysis was performed to assess whether sitagliptin use was associated with deterioration or improvement of glycemic control.

RESULTS: Both add-on sitagliptin and switching from α-glucosidase inhibitors to sitagliptin prevented the seasonal deterioration of glycemic control and tended to improve HbA_{1c}. Multivariate analysis revealed that both adding and switching to sitagliptin were negatively correlated with deterioration of glycemic control. In 44 patients who continued sitagliptin therapy for another year, elevation of HbA_{1c} was suppressed without adverse effects.

CONCLUSION: Sitagliptin is a suitable oral agent for preventing deterioration of glycemic control during the winter holiday season.

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Key words: Type 2 diabetes mellitus; Dipeptidyl-peptidase 4 inhibitors; Sitagliptin; Seasonal variation; Hemoglobin A_{1c}

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INTRODUCTION

In Japan, glycemic control typically deteriorates during the New Year winter holiday season[1-3], since diabetic patients (like other Japanese) celebrate with a high calorie diet and alcohol. In 2009, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin was approved as the first

incretin enhancer for use in Japan[4-11]. Although it has been suggested that seasonal fluctuations of hemoglobin A1c (HbA1c) are noted in patients with type 2 diabetes, no reports have been published concerning the efficacy of antidiabetic agents for such fluctuations. Because the hypoglycemic effect of sitagliptin (a DPP-4 inhibitor) becomes stronger with an increase of the blood glucose level, it has the potential to inhibit seasonal HbA1c fluctuations[12-14]. To evaluate the effect of sitagliptin on seasonal fluctuation of glycemic control, we studied patients with relatively good blood glycemic control over 2 years while on treatment with conventional oral antidiabetic agents and/or diet and exercise.

Table 1 Baseline characteristics

	Add-on group (n = 35)	Switching group (n = 19)	Control group (n = 24)	P value
Age (yr)	64.66 ± 10.63	55.84 ± 12.96	63.04 ± 8.85	0.171
Gender				
Male	28	15	18	0.897
Female	7	4	6	
Disease duration (yr)	11.98 ± 9.66	10.00 ± 11.22	8.31 ± 8.25	0.797
Body mass index (kg/m^2)	24.28 ± 3.49	23.94 ± 3.69	25.20 ± 3.27	0.536
Using sulfonylureas	16	12	13	0.463

MATERIALS AND METHODS

Patients with type 2 diabetes aged 29-80 years were enrolled. Type 2 diabetes was diagnosed from clinical criteria according to the Japan Diabetes Society guidelines. They were all patients periodically attending our hospital. They were prescribed adequate diet/exercise therapy by specialists and nutritionists and received other appropriate treatment depending on their condition. There were no differences of baseline treatment between the sitagliptin and control groups. Exclusion criteria were type 1 diabetes, treatment with insulin or steroids, and poor glycemic control (HbA1c ≥ 10%). Each patient provided informed consent for monthly blood tests and the study was approved by the ethics committee of our institution. Patients receiving DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists were also excluded.

Sitagliptin was released in December 2009 as the first DPP-4 inhibitor to be approved in Japan. Because this clinical study was started simultaneously with its release, patients who had already received DPP-4 inhibitor therapy were not enrolled. There is a rule in Japan that patients receiving a new drug should be examined every 2 wk for 1 year after release of the drug, so subjects were assigned to the sitagliptin and control groups solely based on whether they could attend hospital at fortnightly intervals or not. Because basal treatment was identical and there were no differences of other baseline characteristics between the two groups, the subjects were considered to be comparable. Laboratory data from 2008-2009 before the start of this study were used for baseline values. From December 2009, 35 patients were additionally prescribed oral sitagliptin starting from 50 mg once daily (add-on group), while 19 patients taking α-glucosidase inhibitors were switched to sitagliptin (switching group). Twenty-four patients who refused sitagliptin formed the control group. Throughout the 2 year observation period, the doses of oral diabetic agents other than sitagliptin were not changed. To test baseline characteristics, analysis of variance was employed for age, disease duration and body mass index, while the χ^2 test was performed for sex and use of sulfonylureas. Changes of mean monthly HbA1c during the "winter holiday season" were compared between groups using Student's t-test (2008-2009 *vs* 2009-2010) and statistical significance was accepted at $P < 0.05$. Multivariate analysis was performed to assess whether sitagliptin use was associated with deterioration or improvement of glycemic control.

RESULTS

There were no significant differences of baseline characteristics among the three groups (Table 1). When this study was started, the 54 subjects had already been treated for at least 1 year at our hospital and had a good relationship with their physicians. There were no differences of patient education between the sitagliptin group attending hospital every 2 wk and the control group attending every 4 wk because compliance with diet/exercise therapy was adequate in both groups. Since the subjects were assigned to the treated and control groups solely based on their ability to attend the hospital, there was no bias of baseline characteristics between the two groups, making it appropriate to compare the two groups in this study. From December 2008 to February 2009, the mean change of HbA1c was + 0.19% (6.51% ± 0.13% *vs* 6.72% ± 0.14%, $P < 0.001$) in the add-on group and + 0.23% (6.40% ± 0.13% *vs* 6.63% ± 0.16%, $P = 0.002$) in the control group (Figure 1). Thus, both groups showed an increase while on conventional antidiabetic therapy. From December 2009 to February 2010, the mean change of HbA1c was -0.08% (6.60% ± 0.14% *vs* 6.52% ± 0.15%, $P = 0.19$) in the add-on group and 0.22% (6.33% ± 0.12% *vs* 6.55% ± 0.14%, $P = 0.005$) in the control group. Seasonal deterioration of HbA1c was prevented in the add-on group (0.19% *vs* -0.08%). In the switching group, the mean change of HbA1c from December 2008 to February 2009 was 0.33% (6.55% ± 0.23% to 6.88% ± 0.25%, $P < 0.001$), while the mean change from December 2009 to February 2010 was 0.13% (6.48% ± 0.19% to 6.61% ± 0.18%, $P = 0.013$). Thus, deterioration of HbA1c was less marked (0.33% *vs* 0.13%). There were no changes of body weight in any group.

Multivariate analysis showed that both adding sitagliptin and switching to sitagliptin were negatively correlated with deterioration of glycemic control (defined as an increase of HbA1c by > 0.1%) after adjustment for age, gender, duration of antidiabetic therapy and body

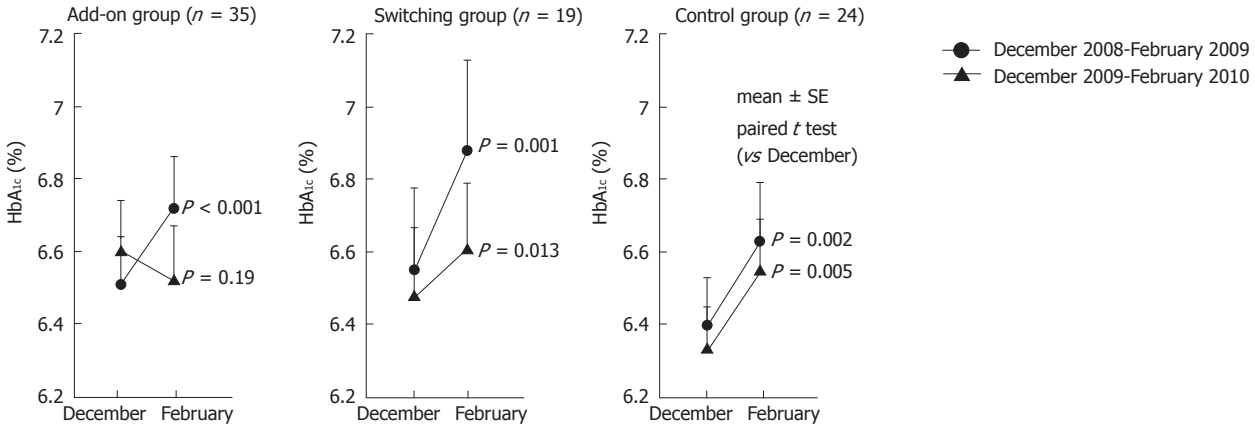

Figure 1 Changes of mean hemoglobin A1c during the winter holiday season. Circles are from December 2008 to February 2009 and triangles are from December 2009 to February 2010. Data are the mean ± SE. HbA1c: Hemoglobin A1c.

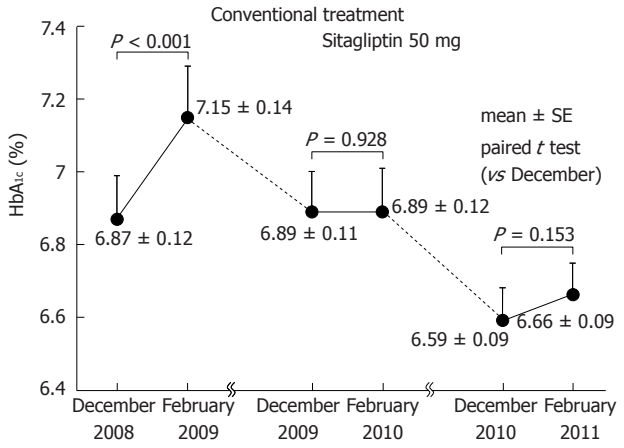

Figure 2 Changes of mean hemoglobin A1c in 44 patients during one year before and after initiation of sitagliptin therapy. Data are the mean ± SE. HbA1c: Hemoglobin A1c.

mass index [odds ratio (OR): 0.07, 95% confidence interval (CI): 0.02-0.31, and $P = 0.007$ for adding sitagliptin; OR: 0.20, 95% CI: 0.04-0.94, and $P = 0.041$ for switching to sitagliptin]. Sitagliptin treatment was also significantly correlated with a decrease of HbA1c by > 0.1% (OR: 9.85, 95% CI: 2.75-35.1, and $P < 0.001$ for adding; OR: 4.71, 95% CI: 1.11-19.8, and $P = 0.034$ for switching).

We also followed 44 patients who continued to receive sitagliptin for another year without any changes in dosages of concomitant drugs for another year (Figure 2). As occurred during the first year of sitagliptin treatment, elevation of HbA1c in February was suppressed in the second year. No adverse events or changes of weight were observed.

DISCUSSION

In Japanese patients, the effect of overeating around New Year is usually reflected by elevation of monthly HbA1c values between December and February. Although we focused on type 2 diabetic patients with good glycemic control for 2 years, HbA1c levels still increased significantly during the winter holiday season, suggesting that conventional oral antidiabetic therapy cannot prevent seasonal deterioration of glycemic control. However, the present study showed that add-on therapy with sitagliptin prevented seasonal deterioration of glycemic control and tended to improve HbA1c despite the increased calorie intake and decrease of physical activity during the New Year holiday period.

In 44 patients who continued sitagliptin therapy for an additional year, elevation of HbA1c was also suppressed in the second year, demonstrating the characteristics of incretin therapy, which exerts a stronger hypoglycemic effect when blood glucose levels are high. Our results suggest that sitagliptin, which has been reported to suppress diurnal variation of blood glucose levels, may also suppress seasonal variation and is a suitable oral agent for preventing deterioration of glycemic control during the winter holiday season in Japanese patients with type 2 diabetes.

Although this was a relatively small study, the results are considered to be reliable because: (1) all of the patients who visited our hospital during a one month period (December) were enrolled, except for those who met the exclusion criteria; and (2) patients assigned to the control group were selected solely on the basis that they could not attend the hospital fortnightly and all participating patients received similar basal treatment (including diet).

According to Takao *et al*[15] who investigated glycemic control over 10 years in Japanese type 2 diabetic patients, there was a correlation between the change of blood glucose and progression of diabetic retinopathy. In addition, Wadén *et al*[16] reported that HbA1c variability could not only predict incident microalbuminuria and progression of renal disease, but also cardiovascular events in type 1 diabetes patients. Bouchi *et al*[17] recently reported that there is a relationship between blood glucose changes and cardiovascular events in Japanese patients with type 2 diabetes. Thus, the importance of good glycemic control has continued to attract attention. There is a possibility that cardiovascular events can be prevented by regulating blood glucose excursion. Because previous reports

concerning cardiovascular events in Japanese type 2 diabetic patients have not clarified this issue, whether blood glucose excursion is related to cardiovascular events remains to be determined[18]. HbA_{1c} elevation during the winter holiday season was also attenuated by switching from α-glucosidase inhibitors to sitagliptin (HbA_{1c} increased by 0.33% before switching *vs* 0.13% after switching). This 0.2% difference of HbA_{1c} over 2 mo between α-glucosidase inhibitor therapy and sitagliptin is clinically important.

It is too early to draw definite conclusions from our study without placebo control. Further investigations are needed to confirm whether better glycemic control by using sitagliptin with or without other oral hypoglycemic agents can improve pre-existing atheroma and thus prevent major cardiovascular events[19-26].

COMMENTS

Background

Epidemiological studies have suggested that seasonal fluctuations of hemoglobin A_{1c} (HbA_{1c}) are noted in patients with type 2 diabetes, but no reports have been published concerning the efficacy of antidiabetic agents for such HbA_{1c} fluctuations.

Research frontiers

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was the first incretin enhancer approved in Japan (in 2009). This drug causes few side effects when regulating blood glucose levels but the effect of sitagliptin therapy on seasonal fluctuation of glycemic control in Japanese type 2 diabetic patients is unknown.

Innovations and breakthroughs

This is the first study to demonstrate that add-on therapy with sitagliptin can prevent seasonal deterioration of glycemic control and even improve HbA_{1c} levels despite the increased calorie intake and decrease of physical activity during the New Year holiday period.

Applications

In Japan, glycemic control typically deteriorates during the New Year winter holiday season, since Japanese people (including diabetic patients) celebrate with a high calorie diet and alcohol. By understanding and utilizing the response to sitagliptin demonstrated in the present study, treatment can be tailored to better manage the seasonal deterioration of glycemic control, which is unfavorable for patients with type 2 diabetes.

Terminology

DPP-4 inhibitors, of which sitagliptin was the first to be released in Japan, inhibit the enzyme DPP-4 and are used to treat type 2 diabetes. Inhibition of DPP-4 enhances the activity of incretins that play an important role in regulating insulin secretion and blood glucose.

Peer review

This is an interesting study that suggests the beneficial effects of sitagliptin during the winter holiday period in Japanese diabetic patients. The authors report that HbA_{1c} was significantly reduced during the holiday period in diabetic patients switching to sitagliptin or using it as add-on therapy compared with control patients.

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