

# Obesity may attenuate the HbA1c-lowering effect of sitagliptin in Japanese type 2 diabetic patients

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## ABSTRACT

**Aims/Introduction:** The aim of the present study was to assess the independent predictors of the HbA1c-lowering effect of sitagliptin in Japanese type 2 diabetic patients.

**Materials and Methods:** Data were retrieved from the medical records of 151 type 2 diabetic patients who had been taking sitagliptin 25 or 50 mg once daily for inadequate glycemic control for at least 12 weeks, with or without other oral hypoglycemic agents. Spearman's rank correlation coefficients were calculated to investigate correlations between two independent continuous variables. Multiple stepwise regression analysis was used to identify independent predictors of reductions in HbA1c levels after 12 weeks of sitagliptin treatment ( $\Delta$ HbA1c).

**Results:** In all patients combined, Spearman's rank correlation coefficients showed that  $\Delta$ HbA1c was significantly correlated with baseline HbA1c alone ( $r = 0.371$ ,  $P < 0.0001$ ). However, multiple linear regression analysis among all patients using baseline variables revealed that the independent factors contributing to  $\Delta$ HbA1c, in order of importance, were method of prescribing ( $P < 0.0001$ ), baseline HbA1c ( $P < 0.0001$ ), body mass index (BMI;  $P = 0.004$ ), and duration of diabetes ( $P = 0.024$ ).

**Conclusions:** Our analysis may provide novel evidence that increased BMI contributes, in part, to attenuation of the HbA1c-lowering effect of sitagliptin in Japanese type 2 diabetic patients. Analysis of a larger population over a longer period of time is warranted to confirm these findings. (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00156.x, 2012)

**KEY WORDS:** Body mass index, HbA1c, Sitagliptin

## INTRODUCTION

Dipeptidyl peptidase (DPP)-4 inhibitors prevent the enzymatic degradation and inactivation of glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP), the major incretins involved in glucose homeostasis<sup>1</sup>. Sitagliptin is an oral, potent, highly selective once-daily DPP-4 inhibitor indicated for the treatment of type 2 diabetes mellitus<sup>2</sup>. Sitagliptin increases plasma concentrations of intact GLP-1 and GIP by two- to threefold in patients with type 2 diabetes mellitus, as well as in healthy volunteers<sup>3-6</sup>. In a recently published study, treatment with sitagliptin 100 mg q.d. for 12 weeks improved fasting and postprandial glycemic control and was generally well tolerated in Japanese patients with type 2 diabetes mellitus<sup>7</sup>. In October 2010, sitagliptin became the first DPP-4 inhibitor available in Japan. However, the factors predictive of the blood glucose-lowering effect of sitagliptin and the question as to whether there may be non-responders to sitagliptin have not yet been clearly determined. Therefore, in the present study, we used multiple stepwise linear regression analyses to identify independent predictors of reductions in HbA1c after 12 weeks sitagliptin treatment in Japanese patients with type 2 diabetes mellitus.

## MATERIALS AND METHODS

### Patients

Data were extracted from the medical records of Fukui-ken Saiseikai Hospital for 151 patients, aged between 20 and 85 years, who had been prescribed sitagliptin 25 or 50 mg once a day for at least 12 weeks for inadequate control of HbA1c (HbA1c  $\geq 6.9\%$ : NGSP equivalent value) and may or may not have been taking other oral hypoglycemic agents (OHAs). Patients were excluded from the study if they had a history of type 1 diabetes, insulin use, or any change in the use of other OHAs within the 12 weeks after starting sitagliptin, or if they exhibited poor drug compliance ( $<75\%$ ) based on information in their medical records.

### Parameters evaluated

Basic demographic data were collected for all patients from the medical records, including sex, age, height, weight, baseline HbA1c, duration of diabetes, estimated glomerular filtration rate (eGFR), complications such as retinopathy, hypertension (systolic blood pressure  $\geq 140$  and/or diastolic blood pressure  $\geq 90$  mmHg), dyslipidemia (total cholesterol  $\geq 220$ , high-density lipoprotein-cholesterol  $<40$  mg/dL, and/or triglycerides  $\geq 150$  mg/dL), and the use of OHAs. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared.

The primary efficacy analysis evaluated the change in HbA1c between baseline and Week 12 ( $\Delta$ HbA1c). In the present study,

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HbA1c was determined by high-performance liquid chromatography, with calibration using Japan Diabetes Society (JDS) Lot 2<sup>8</sup>. In the present study, according to the definition of the Japan Diabetes Society (JDS)<sup>9</sup>, the value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated using the formula  $\text{HbA1c (\%)} = \text{HbA1c (JDS) (\%)} + 0.4\%$ . The formula of Matsuo *et al.*<sup>10</sup> was used to calculate eGFR; this equation originated from the work of the Modification of Diet in Renal Disease (MDRD) study group<sup>11</sup>, has been adapted for Japanese individuals and is recommended by the Japanese Society of Nephrology:

$$\text{eGFR (mL/min per 1.73 m}^2\text{)} = 194 \times \text{SCr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739 \text{ (if female)}$$

where SCr is serum creatinine.

### Statistical analysis

Data are expressed as the mean  $\pm$  SD. The significance of differences between discrete variable data was analyzed by the Chi-squared test or Fisher's direct test, as appropriate. Differences between two variables were evaluated by two-tailed Student's paired or unpaired *t*-tests, as appropriate. Changes in HbA1c ( $\Delta\text{HbA1c}$ ) were calculated as (baseline HbA1c – HbA1c 12 weeks after starting sitagliptin). Because the relationship between BMI and  $\Delta\text{HbA1c}$ , as well as between age and  $\Delta\text{HbA1c}$ , was non-linear, correlations between two independent continuous variables were investigated using Spearman's rank

correlation coefficients. Patients were stratified into four groups for each of the following: baseline HbA1c, baseline BMI, duration of diabetes, and age. Differences between the subgroups for each parameter were analyzed by one-way ANOVA with Scheffé's multiple comparisons. Multiple stepwise regression analysis was used to identify independent predictors of  $\Delta\text{HbA1c}$ . All variables considered to be clinically meaningful were used as independent variables in the multivariate analysis, namely, sex, age, baseline BMI, baseline eGFR, method of prescribing, dose of sitagliptin, duration of diabetes, and baseline HbA1c. The *F*-value for the inclusion of the variables was set at 4.0. *P* < 0.05 was considered significant.

All statistical analyses were performed with StatView version 5.0 for Windows (SAS Institute, Cary, NC, USA). The study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki<sup>12</sup>. The study protocol was approved by the Ethics Committee of Fukui-ken Saiseikai Hospital.

### RESULTS

The baseline clinical characteristics of the study subjects are presented in Table 1. Patients were stratified into two groups depending on the dose of sitagliptin: 25 and 50 mg. The age of and duration of diabetes was significantly greater for patients in the 25-mg sitagliptin group (*n* = 91) compared with those in the 50-mg sitagliptin group (*n* = 60); Similarly, patients on 25 mg sitagliptin had a significantly greater rate of dyslipidemia

**Table 1** | Clinical characteristics of type 2 diabetic patients at baseline and after 12 weeks treatment with sitagliptin

	Sitagliptin			
	25 mg/day ( <i>n</i> = 91)		50 mg/day ( <i>n</i> = 60)	
	Baseline	Week 12	Baseline	Week 12
Sex (male/female)	57/34	–	45/15	–
Age (years)	67 $\pm$ 11	–	62 $\pm$ 10**	–
BMI (kg/m <sup>2</sup> )	24.3 $\pm$ 3.9	24.0 $\pm$ 3.7	25.3 $\pm$ 4.2	25.2 $\pm$ 4.4
HbA1c (%)	8.2 $\pm$ 1.1	7.6 $\pm$ 1.0	8.3 $\pm$ 1.3	7.6 $\pm$ 1.2
Duration of diabetes (years)	11.0 $\pm$ 6.4	–	8.7 $\pm$ 5.5*	–
eGFR (mL/min per 1.73 m <sup>2</sup> )	64.0 $\pm$ 17.0	63.6 $\pm$ 16.4	70.7 $\pm$ 13.5**	70.5 $\pm$ 13.6
Complications ( <i>n</i> )				
Retinopathy (SDR/PPDR/PDR)	11/3/7	–	4/4/1	–
Hypertension	57	–	34	–
Dyslipidemia	77	–	40**	–
Naïve/add-on/switch from $\alpha\text{GI}$	2/17/72	–	10/16/34	–
Additional OHA medication ( <i>n</i> )				
Sulfonylurea	78	–	49	–
Metformin	67	–	40	–
$\alpha\text{GI}$	72	–	34**	–
Glinide	1	–	1	–
Pioglitazone	10	–	9	–

Unless indicated otherwise, data are shown as the mean  $\pm$  SD. \**P* < 0.05, \*\**P* < 0.01 compared with the 25 mg/day sitagliptin group.

BMI, body mass index; eGFR, estimated glomerular filtration rate; SDR, simple diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy;  $\alpha\text{GI}$ ,  $\alpha$ -glucosidase inhibitor; OHA, oral hypoglycemic agent.

and were prescribed  $\alpha$ -glucosidase inhibitors ( $\alpha$ GI) at a significantly higher rate than patients in the 50 mg sitagliptin group. However, eGFR significantly lower in patients on 25 mg compared with 50 mg sitagliptin. There were not significant differences for any of the other characteristics between the two groups.

After 12 weeks treatment, each dose of sitagliptin had resulted in a significant ( $P < 0.001$ ) reduction in HbA1c ( $-0.61 \pm 0.74\%$ ) from baseline. There was no significant change in BMI at Week 12 compared with baseline (Table 1).

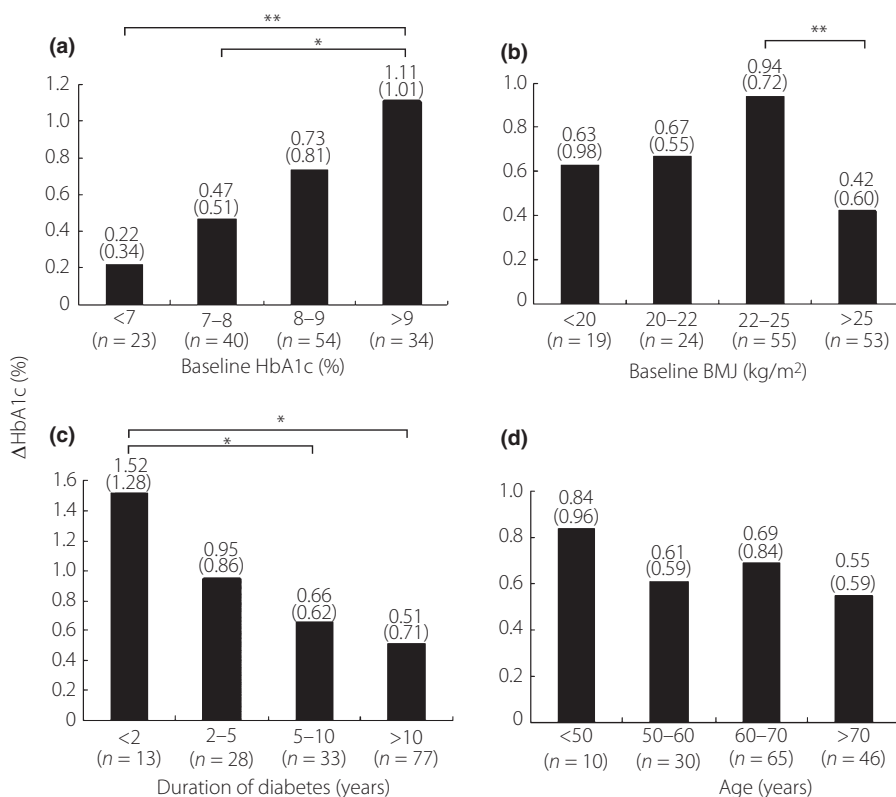
For all patients, Spearman's rank correlation coefficients indicated that  $\Delta$ HbA1c was significantly correlated with baseline HbA1c alone ( $r = 0.371$ ,  $P < 0.0001$ ); the difference in  $\Delta$ HbA1c between the 25- and 50-mg sitagliptin groups did not differ significantly (0.59% vs 0.64%, respectively;  $P = 0.72$ ). Figure 1 shows differences in  $\Delta$ HbA1c in the four subgroups for baseline HbA1c, BMI, duration of diabetes, and age. As can be seen from Figure 1, the  $\Delta$ HbA1c was significantly greater in patients with baseline HbA1c  $>9$  compared with patients with baseline HbA1c  $<7\%$  or 7–8% ( $P = 0.003$  and  $P = 0.01$ , respectively). In addition, the  $\Delta$ HbA1c was significantly greater in patients with a duration of diabetes  $<2$  years compared with those with diabetes for 5–10 or  $>10$  years ( $P = 0.03$  and  $P = 0.02$ , respectively). However,  $\Delta$ HbA1c was significantly lower in patients with a

BMI  $>25$  kg/m<sup>2</sup> compared with those with a BMI of 22–25 kg/m<sup>2</sup> ( $P = 0.001$ ). There were no significant differences in  $\Delta$ HbA1c between the four age subgroups (Figure 1).

To explore the independent determinants of  $\Delta$ HbA1c, multiple stepwise linear regression analyses were performed using  $\Delta$ HbA1c as a dependent variable and sex, age, baseline BMI, baseline eGFR, method of prescription (naïve or add-on vs switch from an  $\alpha$ GI), dose of sitagliptin (25 vs 50 mg), duration of diabetes, and baseline HbA1c as independent variables. This analysis indicated that, among all patients, the factors contributing to  $\Delta$ HbA1c, in order of importance (Table 2), were: method of prescription ( $P < 0.0001$ ), baseline HbA1c ( $P < 0.0001$ ), baseline BMI ( $P = 0.004$ ), and duration of diabetes ( $P = 0.024$ ). The coefficients for all variables were significant ( $P = 0.0238$  to  $<0.0001$ ) in the resulting regression equation:

$$\begin{aligned} \Delta\text{HbA1c (\%)} = & -(0.357 \times \text{prescription; naïve or add-on} \\ & = 0; \text{switch from } \alpha\text{GI} = 1) + (0.343 \times \text{baseline HbA1c}) \\ & - (0.230 \times \text{BMI}) - (0.195 \times \text{duration of diabetes}) + 0.5. \end{aligned}$$

All four variables together explained 33.1% of the total variance in  $\Delta$ HbA1c (Table 2).



**Figure 1** | Changes in HbA1c from baseline to after 12 weeks therapy with sitagliptin ( $\Delta$ HbA1c), stratified according to (a) baseline HbA1c, (b) baseline body mass index (BMI), (c) duration of diabetes, and (d) age. Data are shown as mean values, with the mean (SD) values specified above each. \* $P < 0.05$ , \*\* $P < 0.01$  (one-way ANOVA with Scheffé's multiple comparison test).

**Table 2** | Independent predictors of  $\Delta$ HbA1c identified by multiple stepwise linear regression analysis

	Beta coefficient	r <sup>2</sup>	P-value
$\Delta$ HbA1c (%)			
Prescribing method	-0.357	0.169	<0.0001
Baseline HbA1c	0.343	0.092	<0.0001
Baseline BMI	-0.230	0.034	0.004
Duration of diabetes	-0.195	0.036	0.024
Baseline eGFR			0.063
Total r <sup>2</sup>		0.331	

Values show independent contributions to r<sup>2</sup> for each predictor in the model.

The dependent variable was  $\Delta$ HbA1c (%). The independent variables were: sex, age, baseline body mass index (BMI), baseline estimated glomerular filtration rate (eGFR; in mL/min per 1.73 m<sup>2</sup>), method of prescribing, dose of sitagliptin, duration of diabetes (years), and baseline HbA1c.

Sex, age, eGFR, and dose of sitagliptin were not retained in the model because they were not significant predictors of  $\Delta$ HbA1c.

Method of prescribing: naïve or add-on = 0; switch from  $\alpha$ -glucosidase inhibitor = 1.

Dose of sitagliptin: 25 mg = 0; 50 mg = 1

Sex: female = 0; male = 1.

## DISCUSSION

Several predictors of reductions in HbA1c with sitagliptin in diabetic patients have been reported. Some studies<sup>13,14</sup> report that 25 mg sitagliptin produces significantly smaller reductions in HbA1c after 12 weeks treatment than does 50 mg sitagliptin. Similarly, our analysis showed that the reductions in HbA1c after 12 weeks treatment tended to be greater for patients on 50 mg sitagliptin compared with those on 25 mg sitagliptin (0.64% vs 0.59%, respectively), although the difference failed to reach statistical significance ( $P = 0.70$ ) and disappeared entirely on multiple linear regression analysis ( $P = 0.94$ ).

Conversely, previous short-term studies<sup>13,15,16</sup> and a pooled analysis of completed Phase III studies with sitagliptin 100 mg monotherapy<sup>17</sup> have all reported greater HbA1c reduction with sitagliptin in patients with higher (compared with lower) baseline HbA1c levels. Furthermore, Raz *et al.*<sup>15</sup> reported that patients with a baseline duration of diabetes at or below the median ( $\leq 3.0$  years) exhibited a greater reduction in HbA1c with sitagliptin than did patients with a baseline duration of diabetes  $> 3.0$  years. Consistent with these reports, multiple linear regression analysis in the present study revealed that baseline HbA1c levels ( $P < 0.0001$ ) and duration of diabetes ( $P = 0.024$ ) were independent predictors of  $\Delta$ HbA1c among all patients. Incidentally, Matthews *et al.*<sup>18</sup>, in a randomized active comparator study of type 2 diabetic patients whose disease was inadequately controlled by metformin monotherapy, recently reported that older age was a predictor of the sustainability of the effect of vildagliptin, another DPP4-inhibitor.

In contrast with the aforementioned predictors of drug effect, several previous reports<sup>13,15-17</sup> have demonstrated no significant

correlations between reductions in HbA1c with sitagliptin and baseline BMI. However, these results all stemmed from univariate analyses, not multivariate analyses; thus, the results are not necessarily valid because the aforementioned predictors, other than baseline BMI, naturally confound the reduction in HbA1c with this drug. In fact, our multivariate analyses demonstrated a definite significant correlation ( $P = 0.004$ ) between  $\Delta$ HbA1c and baseline BMI, whereas univariate analysis revealed no such significant correlation between these two variables ( $\rho = -0.133$ ,  $P = 0.165$ ). Incidentally, in the subgroup analyses,  $\Delta$ HbA1c in patients with BMI  $> 25$  kg/m<sup>2</sup> (a common definition of obesity in Japan) was significantly lower than that in patients with a BMI in the range 22–25 kg/m<sup>2</sup> ( $P = 0.001$ ).

Provided that this association really exists, the reason why increased BMI is associated with a smaller degree of HbA1c reduction with sitagliptin has yet to be elucidated. In some studies<sup>19-22</sup>, GLP-1 levels in response to oral carbohydrate or a meal have been reduced in obese patients; this may have contributed to the decline in HbA1c reduction with this drug with increasing BMI, although which feature of the obese state is causally related to the inhibition of GLP-1 release remains unknown. Circulating free fatty acids have been suggested to inhibit GLP-1 release and stimulate GIP secretion<sup>20</sup>. However, Verdich *et al.*<sup>22</sup> and Toft-Nielsen *et al.*<sup>23</sup> did not find a correlation between plasma free fatty acid levels and GLP-1 response.

Another explanation is that sitagliptin essentially belongs to a class of insulin secretagogues and not to a class of insulin sensitizers, like the glitazones or biguanides, even though it does have some limited favorable effects on insulin resistance<sup>13,16,24</sup>. Therefore, with the addition of this drug alone, it may be more difficult to overcome increasing insulin resistance complicated by high BMI.

Furthermore, obese patients may not adhere to their diet therapy as well as lean patients; this may contribute, in part, to the poorer reduction in the HbA1c in the former group, although we have no objective data to support this.

One major limitation of the present study is its retrospective design and the limited number of patients studied. Almost all the patients received add-on therapy or switched from an  $\alpha$ GI to sitagliptin; the number of drug-naïve patients was very limited ( $n = 12$ ). In addition, the duration of the study may have been another limitation, because the extent of the glycemic response may not have been fully elucidated over this time frame. Furthermore, other markers, such as waist circumference as a marker of central obesity, markers for assessment of  $\beta$ -cell function in homeostatic models, and basal active GLP-1 levels, that could have contributed to the HbA1c reduction with sitagliptin were not measured in the present study. Therefore, increased numbers of subjects and more detailed clinical parameters are needed in future to avoid overestimation of the data.

In conclusion, the present 12-week retrospective study of Japanese patients with type 2 diabetes mellitus and inadequate glycemic control on diet and/or drug therapy demonstrated that once-daily sitagliptin, at a dose of 25 or 50 mg once daily,

provided significant and clinically important reductions in HbA1c. Furthermore, our analysis provides evidence that increased BMI may contribute, in part, to attenuation of the HbA1c-lowering effect of sitagliptin in Japanese patients with type 2 diabetes. Analysis of a larger population over a longer period of time is warranted to confirm these findings.

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The authors declare no conflict of interest.

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