

Sitagliptin Significantly Decreases the Ratio of Glycated Albumin to HbA1c in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Since glycated albumin (GA) is a glycemic control marker which reflects more postprandial plasma glucose (PPPG) and/or glycemic excursions than HbA1c, the GA/HbA1c ratio is a useful indicator for PPPG and/or glycemic excursions. In this study, we investigated the clinical significance of the GA/HbA1c ratio by administration of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, in patients with type 2 diabetes mellitus.

Methods: Sitagliptin (50 mg/day) was administered for 24 weeks to 69 patients with type 2 diabetes mellitus with stable glycemic control.

Results: With sitagliptin administration, both HbA1c and GA significantly decreased from baseline to the periods of week 4 and week 24. The GA/HbA1c ratio also significantly decreased (baseline 2.72 ± 0.42 vs. 24 weeks 2.60 ± 0.38 , $P < 0.0001$). The change in the GA/HbA1c ratio with the sitagliptin administration for 24 weeks was inversely correlated with baseline GA ($R = -0.425$, $P < 0.001$) and baseline GA/HbA1c ratio ($R = -0.354$, $P = 0.003$), but not with baseline HbA1c ($R = -0.222$, $P = 0.066$). By tertile analysis based on the baseline GA/HbA1c ratio, the GA/HbA1c ratios were significantly associated with GA ($P < 0.0001$), but not fasting plasma glucose (FPG) and HbA1c. Furthermore, changes in GA ($P = 0.010$), but not FPG and HbA1c, were significantly correlated with the baseline GA/HbA1c ratio.

Conclusions: Sitagliptin significantly decreased the GA/HbA1c ratio and this effect was more pronounced in patients with the higher baseline GA/HbA1c ratio. Our findings suggest that the effect of sitagliptin on the GA/HbA1c ratio might reflect improvement of PPPG levels and/or glycemic excursion.

Keywords: Glycated albumin; HbA1c; Sitagliptin; DPP-4 inhibitor; Type 2 diabetes mellitus

Abbreviations: BMI: Body Mass Index; CGM: Continuous Glucose Monitoring; DPP-4: Dipeptidyl Peptidase-4; FPG: Fasting Plasma Glucose; GA: Glycated Albumin; HOMA- β : Homeostasis Model Assessment for β -cell Function; HOMA-R: Homeostasis Model Assessment of Insulin Resistance; PPPG: Postprandial Plasma Glucose

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors decrease degradation of incretins by inhibiting DPP-4, thus increasing plasma incretin levels. This enhances glucose-dependent stimulation of insulin secretion and glucagon-lowering effects, resulting in improved glycemic control [1]. Incretins stimulate glucose-dependent insulin secretion, and because these actions occur during hyperglycemia, but not during fasting or hypoglycemia, they improve postprandial plasma glucose (PPPG) and glycemic excursions [2,3]. These effects have recently been confirmed by assessment using continuous glucose monitoring (CGM) [4].

Many epidemiologic studies to date have shown that hyperglycemia after a glucose load is a risk factor for cardiovascular disease. The DECODE study [5] and Funagata study [6] have shown that plasma glucose levels after a glucose tolerance test (GTT) are a stronger risk factor than fasting plasma glucose (FPG) levels for cardiovascular events. In addition, in the STOP NIDDM trial, in which the α -glucosidase inhibitor acarbose was administered to patients with impaired glucose tolerance (IGT) or diabetes mellitus, a significant reduction in the risk

of cardiovascular events in the drug treatment group was reported [7,8]. Recently, DPP-4 inhibitors, known to improve PPPG, have been reported to reduce cardiovascular events similarly to α -glucosidase inhibitors [9].

HbA1c, which is currently widely used as a glycemic control marker, mainly reflects mean plasma glucose levels. By contrast, glycated albumin (GA), another glycemic control marker, reflects mean plasma glucose as well as PPPG [10-14]. In type 1 diabetes mellitus as compared to type 2 diabetes mellitus, and among patients with type 2 diabetes mellitus, in those on insulin therapy compared to those not on insulin therapy, GA is higher than HbA1c in relation to glycemia because of larger glycemic excursions [12,13]. Recently, GA has been shown to be a more significant explanatory variable than other markers

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like HbA1c and 1,5-AG for glucose excursions as assessed by CGM [14]. Therefore, because GA is higher than HbA1c in patients with marked postprandial hyperglycemia, the GA/HbA1c ratio is also higher; when postprandial hyperglycemia is improved by drugs that improve PPPG, the GA/HbA1c ratio might decrease.

Thus, the GA/HbA1c ratio is a useful indicator for PPPG and/or glycemic excursions. In this study, we investigated the clinical significance of the GA/HbA1c ratio and the related factors involved in the change of this ratio by administration of sitagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes mellitus.

Methods

Patients

For this 24 week, multi-center, prospective, open-label study, we recruited 88 Japanese outpatients with type 2 diabetes mellitus between January, 2011 and December, 2012. These patients met the following inclusion criteria: more than 20 years old, no anemia, no corticosteroid administration, no macro-albuminuria, serum creatinine concentrations <2.0 mg/dl, serum transaminases concentrations less than twice the upper limit of control ranges, and no viral hepatitis. Patients with more than a 1.0% change in HbA1c in the 2-month period preceding the sitagliptin administration were excluded. This study was approved by the ethics committees at each participating medical institution. The aim of the study was explained to all patients and informed consent was obtained from them. This study is registered with the University Hospital Medical Information Network (UMIN) clinical trial registry, number 000006004.

Study protocol

The recruited patients received 50 mg/day of sitagliptin for 24 weeks and during the study period no additions or changes in other diabetes drugs were permitted. Before and after treatment for 4, 8, 12 and 24 weeks, the patients were scheduled to undergo a physical examination,

laboratory analyses, and assessment of medication compliance. Blood tests were performed during outpatient visits to measure FPG, HbA1c, GA, and insulin levels after overnight fasting. These clinical data of the 69 patients who completed the 24-week follow-up were analyzed in this study. The baseline clinical characteristics of the 69 patients are shown in Table 1. The treatment of diabetes consisted of diet therapy alone for 16 patients and one or a combination of oral hypoglycemic agents for 53 patients (sulfonylureas for 34, thiazolidinediones for 12, biguanides for 32, glinides for 1, α -glucosidase inhibitors for 10).

Measurements

Plasma glucose was determined by glucose oxidase methods. HbA1c, expressed as National Glycohemoglobin Standardization Program (NGSP) values [15], was measured by high performance liquid chromatography. GA was determined by the enzymatic method using albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [16]. Serum insulin concentrations were determined by enzyme immunoassay using guinea pig antihuman insulin antibody. Pancreatic β cell function and insulin sensitivity were assessed by the homeostasis model assessment (HOMA) of pancreatic β -cell function (HOMA- β), and insulin resistance was assessed by the HOMA of insulin resistance (HOMA-R) [17].

Statistical analyses

Continuous variables are shown as means \pm SD when distribution was normal and as medians with interquartile range when distribution was skewed (HOMA-R and HOMA- β). Effects of treatment were analyzed by means of paired Student's t-test for normally distributed variables. Analysis of variance was used for normally distributed variables among tertiles for the GA/HbA1c ratio, and the Bonferroni method was used to estimate the level of significance of differences between means. The Kruskal-Wallis test was used to compare patient characteristics among tertiles for skewed distributed variables

	Total (n=69)	T1 (n=23)	T2 (n=23)	T3 (n=23)	p
The GA/HbA1c ratio					
Range	2.02 - 3.74	2.02 - 2.54	2.55 - 2.83	2.84 - 3.74	-
Mean	2.69 \pm 0.36	2.31 \pm 0.15	2.68 \pm 0.08	3.07 \pm 0.26	<0.0001
Male (%)	46 (66.7)	16 (69.6)	15 (62.5)	15 (62.5)	0.759
Age (years)	64.8 \pm 10.5	61.3 \pm 9.4	60.7 \pm 9.6	72.5 \pm 8.1	<0.001
Diabetes duration (years)	11.0 \pm 7.8	6.9 \pm 4.4	12.6 \pm 6.8	13.8 \pm 11.3	0.017
Body mass index (kg/m ²)	25.4 \pm 4.7	27.1 \pm 5.5	25.4 \pm 3.6	23.6 \pm 4.0	0.013
FPG (mg/dl)	146 \pm 27	141 \pm 21	145 \pm 20	151 \pm 35	0.186
HbA1c (%)	8.0 \pm 0.9	8.0 \pm 0.7	7.9 \pm 0.8	8.1 \pm 1.1	0.687
HbA1c (mmol/mol)	63.6 \pm 9.5	63.6 \pm 8.1	62.2 \pm 8.6	64.9 \pm 11.7	0.685
GA (%)	21.4 \pm 3.6	18.3 \pm 1.6	21.0 \pm 2.5	24.8 \pm 3.2	<0.0001
HOMA-R	2.4 (0.2-4.6)	3.6 (0.6-6.6)	2.4 (0.5-4.4)	1.7 (0.2-3.2)	0.010
HOMA- β (%)	34.2 (11.7-56.7)	42.3 (23.2-61.4)	31.0 (9.6-52.4)	23.8 (2.1-45.6)	0.002
Δ FPG (mg/dl)	-13 \pm 32	-13 \pm 23	-4 \pm 36	-23 \pm 34	0.318
Δ HbA1c (%)	-0.7 \pm 0.8	-0.7 \pm 0.6	-0.4 \pm 0.6	-1.1 \pm 1.1	0.383
Δ HbA1c (mmol/mol)	-7.3 \pm 9.2	-7.6 \pm 7.0	-4.4 \pm 7.1	-9.9 \pm 12.2	0.403
Δ GA (%)	-2.6 \pm 3.0	-1.9 \pm 1.4	-1.8 \pm 2.4	-4.1 \pm 4.0	0.010
Δ GA/HbA1c ratio	-0.11 \pm 0.20	-0.03 \pm 0.13	-0.09 \pm 0.17	-0.20 \pm 0.24	0.004
Δ HOMA-R	-0.1 (-1.2-1.0)	-0.3 (-1.7-1.1)	-0.1 (-1.4-1.2)	0 (-1.0-1.0)	0.744
Δ HOMA- β (%)	6.7 (-12.6-26.0)	7.1 (-8.0-22.2)	1.9(-9.2-13.0)	16.6 (-6.4-39.5)	0.067

Figures show the mean \pm SD or median (interquartile range)

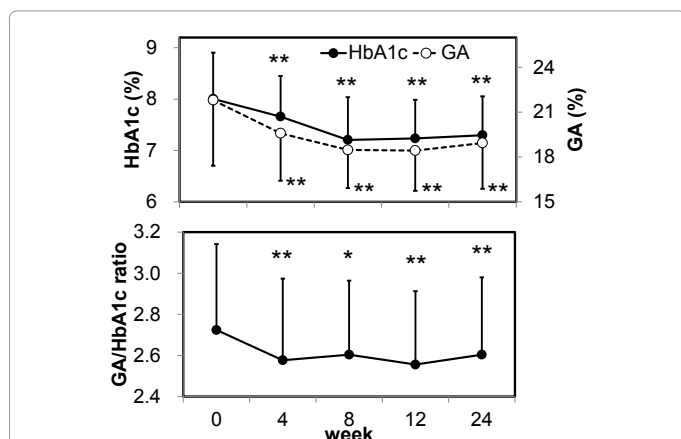
Table 1: Tertile analysis of the baseline GA/HbA1c ratios; patient characteristics and changes in laboratory values with 24 weeks of sitagliptin administration in each group

(HOMA-R and HOMA-β). The StatView computer program (Version 5.0 for Windows; Abacus Concepts, Berkeley, CA) was used for all statistical analyses. A P value of <0.05 was considered to be statistically significant.

Results

With sitagliptin administration, both HbA1c and GA significantly decreased from baseline at all points from week 4 to week 24 (Figure 1). The GA/HbA1c ratio also significantly decreased from baseline at all points from week 4 to week 24 (baseline: 2.72 ± 0.42 vs. 24 weeks: 2.60 ± 0.38 , $P < 0.0001$). With sitagliptin administration for 24 weeks, HOMA-β significantly increased (baseline: $37.0 \pm 25.4\%$ vs. 24 weeks: $49.2 \pm 35.6\%$, $P < 0.0001$), but HOMA-R did not significantly change (baseline: 2.9 ± 2.0 vs. 24 weeks; 2.6 ± 1.7 , $P = 0.647$). BMI did not significantly change during treatment (baseline: 25.4 ± 4.7 vs. 24 weeks; 25.5 ± 4.5 , $P = 0.647$). The baseline GA/HbA1c ratio was significantly and inversely correlated with HOMA-β ($R = -0.422$, $P < 0.001$). In addition, the change in the GA/HbA1c ratio (Δ GA/HbA1c ratio) with sitagliptin administration was significantly and inversely correlated with baseline GA ($R = -0.425$, $P < 0.001$) and baseline GA/HbA1c ratio ($R = -0.354$, $P = 0.003$) but was not significantly correlated with baseline HbA1c ($R = -0.222$, $P = 0.066$) (Figure 2).

Sitagliptin 50 mg/day was administered for 24 weeks to 69 patients



Sitagliptin 50 mg/day was administered for 24 weeks to 69 patients with type 2 diabetes mellitus with stable glycemic control. Changes in HbA1c, GA and the GA/HbA1c ratio are shown.

*: $P < 0.001$, **: $P < 0.0001$ vs. 0 week

Figure 1: Changes in HbA1c, GA and the GA/HbA1c ratio with sitagliptin.

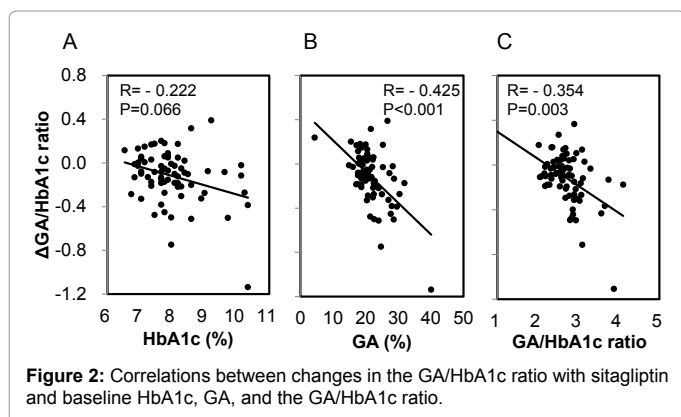


Figure 2: Correlations between changes in the GA/HbA1c ratio with sitagliptin and baseline HbA1c, GA, and the GA/HbA1c ratio.

with type 2 diabetes mellitus with stable glycemic control. Correlations between changes in the GA/HbA1c ratio (Δ GA/HbA1c ratio) and baseline HbA1c (A), GA (B) and the GA/HbA1c ratio (C) are shown.

Next, the data were examined by tertile analysis based on the baseline (before sitagliptin administration) GA/HbA1c ratio (Table 1). The higher GA/HbA1c ratios were associated with significantly higher age, diabetes duration and GA, and significantly lower baseline BMI, HOMA-R and HOMA-β. Gender was not significantly different. FPG and HbA1c were not significantly correlated. In addition, the T3 group with the higher GA/HbA1c ratios before sitagliptin administration, the degree of decrease in GA and the GA/HbA1c ratio by treatment with sitagliptin for 24 weeks was significantly greater. The baseline GA/HbA1c ratios in T1, T2 and T3 groups were 2.31 ± 0.15 , 2.68 ± 0.08 , and 3.07 ± 0.26 , respectively, and after sitagliptin for 24 weeks, the GA/HbA1c ratios in each group were 2.28 ± 0.21 ($P = 0.249$), 2.59 ± 0.15 ($P = 0.019$) and 2.88 ± 0.33 ($P < 0.0001$), respectively. The GA/HbA1c ratios in T2 and T3 groups were significantly decreased from baseline, but there were no significant changes in T1 group. Changes in GA ($P = 0.010$), but not FPG ($P = 0.318$) and HbA1c ($P = 0.383$), were significantly correlated with the baseline GA/HbA1c ratio.

Discussion

In this study, we showed for the first time that sitagliptin significantly decreased the GA/HbA1c ratio as well as HbA1c and GA. This effect was more pronounced in patients with the higher baseline GA/HbA1c ratio, whereas the significant decrease in the GA/HbA1c ratio was not observed in patients with the lower baseline GA/HbA1c ratio. The effect of sitagliptin on the GA/HbA1c ratio might reflect improvement of PPPG levels and/or glycemic excursion described previously [2-4]. Our results suggest that sitagliptin might improve PPPG to a greater degree in patients with marked postprandial hyperglycemia.

The GA/HbA1c ratio decreased significantly from baseline after 4 weeks of treatment with sitagliptin, and this decrease persisted until 24 weeks of the treatment. Because GA reflects shorter-term glycemia than HbA1c, the degree of decrease in GA is greater than in HbA1c in short term after diabetes treatment. For this reason, the GA/HbA1c ratio significantly decreases in short term after starting diabetes treatment [18]. This effect can be observed for a 12-week period; thus, the decrease in the GA/HbA1c ratio up to week 12 of sitagliptin administration, at least in part, involves the fact that GA reflects short-term improvement of hyperglycemia. Because the above effect then disappears at 24 week after treatment, the decrease in the GA/HbA1c ratio after week 24 of treatment might be influenced by the fact that GA also reflects postprandial hyperglycemia and glucose excursions. Therefore, the analysis discussed below is for the 24-week results.

The baseline GA/HbA1c ratio showed a significant inverse correlation with HOMA-β, a marker for insulin secretion (Table 1). We have reported in patients with type 2 diabetes mellitus, including those treated with insulin, that the GA/HbA1c ratio and HOMA-β are significantly and inversely correlated [13]. In the present study, we also observed this phenomenon in patients with type 2 diabetes mellitus treated with oral antidiabetic agents. On tertile analysis of the GA/HbA1c ratio, in patients with the high GA/HbA1c ratio HOMA-β was significantly lower, and age and diabetes duration were significantly higher.

When insulin secretion decreases, glucose excursions increase, and as a result, the GA/HbA1c ratio increases [13,19-21]. In addition, the UKPDS study found that insulin secretion capacity in patients with type 2 diabetes mellitus decreases with longer diabetes duration [22].

This is probably why the GA/HbA1c ratio was significantly correlated with age and diabetes duration. Furthermore, tertile analysis of the GA/HbA1c ratio showed that the higher GA/HbA1c ratios were associated with significantly higher GA, lower BMI and HOMA-R, respectively, but there were no significant associations of the GA/HbA1c ratio with FPG and HbA1c. A significant inverse correlation between the GA/HbA1c ratio and BMI in patients with type 2 diabetes mellitus has already been reported [23,24]. The present results are in agreement with these reports. Since HOMA-R is higher with obesity, HOMA-R might be significantly lower in patients with the higher GA/HbA1c ratios.

The change in the GA/HbA1c ratio with the sitagliptin administration was inversely correlated with baseline GA, but not with baseline HbA1c. Thus, it is thought that changes in the GA/HbA1c ratio mainly reflect changes in GA. HbA1c mainly reflects mean plasma glucose, and GA reflects mean plasma glucose as well as PPPG and/or glucose excursions [10,12,14]. For this reason, it is assumed that the higher GA/HbA1c ratios are associated with more marked postprandial hyperglycemia and/or larger glycemic excursions. In fact, the positive correlation was observed between index of glycemic excursion and the GA/HbA1c ratio in a study using CGM [10]. The baseline GA/HbA1c ratio and the changes in the GA/HbA1c ratio with the sitagliptin administration were also significantly and inversely correlated. In other words, the higher the baseline GA/HbA1c ratio, the greater was the degree of decrease in the GA/HbA1c ratio. A similar phenomenon was observed with tertiary analysis of the GA/HbA1c ratio.

These results suggest that in patients with larger glycemic excursions, the greater the improvement in glycemic variability with the sitagliptin administration. In another recent study using CGM, the sitagliptin administration reduced mean plasma glucose and also improved glycemic excursions; the changes in these glycemic excursions were significantly and inversely correlated with baseline glycemic excursions [4]. In addition, the higher the baseline GA/HbA1c ratio, the greater the decrease in the GA/HbA1c ratio, but the degree of reduction in HbA1c and FPG was not correlated. Thus, it is thought that the effects of sitagliptin on glycemic excursions are independent of its effects on decreasing mean plasma glucose.

The mechanism involved in why the GA/HbA1c ratio decreases further in patients with the higher baseline GA/HbA1c ratios is unknown. With the sitagliptin administration, a significant increase in HOMA- β was observed, as reported previously [24,25]. However, the degree of increase in HOMA- β was not correlated with the baseline GA/HbA1c ratio. This suggests that the phenomenon of a larger decrease in the GA/HbA1c ratio in patients with the higher GA/HbA1c ratios is not due to increased stimulation of insulin secretion in these patients. In addition, with the sitagliptin administration, the insulin resistance marker HOMA-R did not significantly change, thus excluding the possibility that insulin sensitivity changed. Therefore, glucagon suppression or changes in postprandial insulin secretion capacity by sitagliptin might be involved.

Currently, assessment of glycemic control status relies mainly on measuring HbA1c. In the present study, we found that decreases in the GA/HbA1c ratio were larger in patients with the higher baseline GA/HbA1c ratio. Moreover, this decrease in the GA/HbA1c ratio was mainly due to a decrease in GA. Based on these results, because GA reflects PPPG and glycemic excursions, GA should preferably be used to assess PPPG-improving drugs and glycemic control status.

This study has several limitations. First, FPG and fasting insulin secretion were measured in this study, but PPPG and postprandial

insulin secretion were not. Therefore, the correlation between the degree of decrease in the GA/HbA1c ratio and decrease in PPPG with the sitagliptin administration could not be examined. In addition, because postprandial insulin secretion was not evaluated, the mechanism of larger decreases in the GA/HbA1c ratio in patients with the higher baseline GA/HbA1c ratios could not be elucidated. Second, the effects of sitagliptin on glucagon secretion were not assessed. Therefore, the possibility that suppressed glucagon secretion played a role in decreasing the GA/HbA1c ratio could not be evaluated. Third, the effects of sitagliptin administration on glycemic excursions could not be assessed. By evaluating the effects of sitagliptin on mean plasma glucose and glycemic excursions using CGM, their relationship to changes in the GA/HbA1c ratio could be assessed. Lastly, oral hypoglycemic agent(s) were administered in the majority of patients before and during treatment of sitagliptin. It is interesting whether the lowering effect of sitagliptin on the GA/HbA1c ratio is depending on the type of oral hypoglycemic agent(s) administered concomitantly. However, any combination of sitagliptin and oral hypoglycemic agent(s) did not significantly influence the lowering effect of sitagliptin on the GA/HbA1c ratio (data not shown).

In conclusion, treatment with sitagliptin decreased the GA/HbA1c ratio, suggesting that sitagliptin improves PPPG and/or glycemic excursion. The decrease in the GA/HbA1c ratio was more pronounced in patients with the higher baseline GA/HbA1c ratios. On the other hand, the GA/HbA1c ratio did not significantly decrease in patients with the lower baseline GA/HbA1c ratio. These findings suggest that the GA/HbA1c ratio is a useful indicator to evaluate the improvement of PPPG to a greater degree in patients with marked postprandial hyperglycemia by not only the DPP-4 inhibitor(s) other than sitagliptin but also the PPPG improving drugs other than DPP-4 inhibitor(s). This possibility should be investigated in the future.

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