Effects of alogliptin on the ratio of glycated albumin to HbA1c in patients with type 2 diabetes mellitus

Norio Masumoto¹ · Hiroaki Otsuki¹ · Seigo Iwakawa² · Shinya Inada³ · Kayoko Goya⁴ · Hiroyuki Sho⁵ · Satoko Suzuki⁵ · Shogo Kurebayashi⁴ · Kunihiro Hashimoto⁵ · Masafumi Koga⁶

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Abstract The ratio of glycated albumin (GA) to HbA1c (the GA/HbA1c ratio) has been used as a glycemic control indicator that reflects postprandial plasma glucose levels or glycemic variability. In this study, we investigated the effects of alogliptin, a DPP-4 inhibitor, on the GA/HbA1c ratio in patients with type 2 diabetes mellitus. Thirty-eight patients with type 2 diabetes mellitus whose glycemic control was stable were enrolled, and alogliptin (12.5 or 25 mg/day) was then administered to them for 24 weeks. HbA1c and GA levels both significantly decreased after 24 weeks ($P < 0.0001$), whereas the GA/HbA1c ratio did not ($P = 0.129$). No correlation was observed between the change in the GA/HbA1c ratio (the Δ GA/HbA1c ratio) and HbA1c or GA level before the administration of alogliptin; however, a negative correlation was found between the Δ GA/HbA1c ratio and the GA/HbA1c ratio before the administration of alogliptin ($R = -0.322$, $P = 0.049$). Although the GA/HbA1c ratio in the low-value group (<2.80) was not significantly affected by the administration

of alogliptin, that in the high-value group (≥ 2.80) significantly decreased ($P = 0.008$). The administration of alogliptin significantly decreased the GA/HbA1c ratio in the high-value group after 24 weeks. Alogliptin may be more useful for patients with high postprandial plasma glucose levels than in those with low postprandial plasma glucose levels.

Keywords Glycated albumin · HbA1c · Alogliptin · DPP-4 inhibitor · Glycemic variability

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors decrease the inactivation of incretins by inhibiting DPP-4, thereby increasing plasma incretin levels. Therefore, DPP-4 inhibitors enhance the glucose-dependent stimulation of insulin secretion along with the suppression of glucagon secretion, resulting in improved glycemic control in diabetic patients [1]. DPP-4 inhibitors rarely cause hypoglycemia in monotherapy [2] and may effectively reduce postprandial plasma glucose (PPPG) levels [3, 4]. The findings of the DECODE study [5] and Funagata study [6] suggest that diabetes mellitus increases the risk of cardiovascular disease due to the hyperglycemic state after glucose loading. Furthermore, the STOP-NIDDM trial and the MeRIA study, in which acarbose, an α -glucosidase inhibitor, was administered to patients with impaired glucose tolerance or diabetes mellitus, reported significant reductions in the occurrence of cardiovascular events in patients treated with acarbose [7–9]. Glinide suppresses increases in intima-media thickness (IMT) in the carotid artery by correcting postprandial hyperglycemia in its early stages [10]. Furthermore, several studies have indicated that DPP-4

✉ Norio Masumoto
masumoto246@gaia.eonet.ne.jp

¹ Department of Pharmacy, Kawanishi City Hospital, 5-21-1, Higashiuneno, Kawanishi, Hyogo 666-0195, Japan

² Department of Pharmaceutics, Kobe Pharmaceutical University, Kobe, Japan

³ Department of Internal Medicine, Kawanishi City Hospital, Kawanishi, Hyogo, Japan

⁴ Department of Internal Medicine, Nishinomiya Municipal Hospital, Nishinomiya, Hyogo, Japan

⁵ Department of Internal Medicine, NTT West Osaka Hospital, Osaka, Japan

⁶ Department of Internal Medicine, Hakuhokai Central Hospital, Amagasaki, Hyogo, Japan

inhibitors effectively attenuate the progression of carotid IMT in patients with type 2 diabetes mellitus [11, 12].

HbA1c reflects the mean plasma glucose level of the previous 1–2 months, and abnormal HbA1c levels have been reported in patients with diseases that show a shortened red blood cell turnover or patients with variant hemoglobin [13–16]. Glycated albumin (GA) reflects the short-term (approximately one- to two-week) control of fasting plasma glucose levels [17–19] as well as PPPG [20–24]. Therefore, the GA/HbA1c ratio has been used as a glycemic control indicator that reflects PPPG levels or glycemic variability [25]. A positive correlation has been observed between glycemic variability indices measured by continuous glucose monitoring (CGM) and the GA/HbA1c ratio [26]. We previously reported that the GA/HbA1c ratio was significantly decreased by the administration of metformin or sitagliptin, a DPP-4 inhibitor [27, 28]. In this study, we retrospectively investigated the effects of alogliptin on the GA/HbA1c ratio in patients with type 2 diabetes mellitus.

Methods

Patients and study design

Thirty-eight outpatients with type 2 diabetes mellitus were enrolled [21 males and 17 females; mean age 69.4 ± 10.2 years; mean body mass index (BMI) 24.4 ± 4.9 kg/m²] (Table 1) in this study. Nine patients received alogliptin for the first time as an oral hypoglycemic drug, while 29 patients received it in addition to

other oral hypoglycemic drugs. HbA1c and GA levels were measured at the initiation of the administration of alogliptin and after 24 weeks. Patients were divided into two groups based on the mean value of the GA/HbA1c ratio in this study (2.80 ± 0.30) before the administration of alogliptin: a high-value group (≥ 2.80) and low-value group (< 2.80). Among the other concomitant diabetes drugs, sulfonylureas were being taken by 7 patients, biguanide by 9 patients, thiazolidine by 1 patient, and α -glucosidase inhibitors by 7 patients in the low-value group. On the other hand, sulfonylureas were being taken by 14 patients, biguanide by 6 patients, thiazolidine and insulin by 1 patient each, α -glucosidase inhibitors by 7 patients, and glinide by 2 patients in the high-value group. Alogliptin was administered at 12.5 or 25 mg/day for 24 weeks, and the addition of or changes to other diabetes drugs was not allowed during the study period. Patients who showed more than a 0.5% change in HbA1c levels 4 weeks before the administration of alogliptin were excluded from this study. Furthermore, patients with liver cirrhosis, renal disease (eGFR < 30 mL/min/1.73 m² and/or overt proteinuria), or anemia were excluded, as were those administered glucocorticoids that affected the glycemic control indicators. When DPP-4 inhibitors such as alogliptin were used concomitantly with sulfonylureas for type 2 diabetes patients, we followed the recommendation of the Japan Diabetes Society, which indicated that the maximum sulfonylurea dose should be reduced [29]. The present study was approved by the ethics committees at Kawanishi City Hospital, Nishinomiya Municipal Hospital, and NTT West Osaka Hospital. The aim of the study was explained to all patients, and informed consent was obtained from them.

Table 1 Characteristics of the patients included in the study

Variable	Total	Low GA/HbA1c ratio group	High GA/HbA1c ratio group	<i>P</i>
<i>n</i>	38	19	19	
Male (%)	21 (55.3)	12 (63.2)	9 (47.4)	0.341
Age (years)	69.4 ± 10.2	64.9 ± 10.7	72.9 ± 8.5	0.031
Diabetes duration (years)	11.6 ± 6.1	9.9 ± 5.6	13.2 ± 6.2	0.103
BMI (kg/m ²)	24.4 ± 4.9	26.2 ± 5.9	22.4 ± 2.5	0.016
HbA1c (%)	8.1 ± 1.0	8.0 ± 1.0	8.2 ± 1.0	0.477
GA (%)	22.7 ± 3.7	20.5 ± 3.2	24.8 ± 3.0	< 0.001
GA/HbA1c ratio	2.80 ± 0.30	2.57 ± 0.21	3.02 ± 0.19	< 0.0001
(range)	2.14–3.46	2.14–2.79	2.80–3.46	
New dosage/additional dosage	9/29	7/12	2/17	0.056
Baseline treatment (SU/BG/TZD/ α -GI/GN/Ins)	21/15/2/14/2/1	7/9/1/7/0/0	14/6/1/7/2/1	0.022*
Dosage (12.5/25 mg)	29/9	13/6	16/3	0.252

SU sulfonylurea, BG biguanide, TZD thiazolidinedione, α -GI α -glucosidase inhibitor, GN glinide, Ins insulin

* The number of patients administered SU were compared between the high GA/HbA1c ratio group and the low GA/HbA1c ratio group

Measurements

HbA1c was measured using HPLC and indicated based on the scale of the National Glycohemoglobin Standardization Program (NGSP). GA was measured by an enzymatic method (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [30].

Statistical analysis

The results obtained are shown as the mean $\pm$ standard deviation. The paired Student's *t* test, unpaired Student's *t* test, or chi-squared test was used to compare the two groups. A univariate regression analysis was performed to analyze the relationship between two parameters. To analyze the effects of various parameters on the Δ GA/HbA1c ratio, a stepwise multivariate regression analysis was performed. The *F* value for the inclusion of the variables was set at 4.0 in the stepwise multiple regression analysis. These analyses were performed with the StatView computer program (version 5.0 for Windows, Abacus Concepts, Berkeley, CA, USA). Values of *P* < 0.05 were considered significant.

Results

HbA1c levels decreased significantly from 8.1 ± 1.0 to $6.9 \pm 0.7\%$ 24 weeks after the administration of alogliptin (*P* < 0.0001) (Table 2). GA levels also significantly decreased from 22.7 ± 3.7 to $19.1 \pm 2.8\%$ 24 weeks after the administration of alogliptin (*P* < 0.0001). The GA/HbA1c ratio changed from 2.80 ± 0.30 to 2.75 ± 0.30 after 24 weeks (*P* = 0.129). A significant negative correlation was observed between HbA1c or GA level before the administration of alogliptin and the change in HbA1c level

Fig. 1a–c Relationships of HbA1c, GA, and the GA/HbA1c ratio before the administration of alogliptin to Δ HbA1c upon the administration of alogliptin for 24 weeks. The correlations of HbA1c (a), GA (b), and the GA/HbA1c ratio (c) before the administration of alogliptin with the change in HbA1c (Δ HbA1c) upon the administration of alogliptin for 24 weeks are shown

(Δ HbA1c) (HbA1c; *R* = −0.806, *P* < 0.0001, GA; *R* = −0.713, *P* < 0.0001), whereas no significant correlation was found between the GA/HbA1c ratio before the administration of alogliptin and Δ HbA1c (*R* = −0.172, *P* = 0.302) (Fig. 1). On the other hand, no significant association was observed between HbA1c or GA level before the administration of alogliptin and change in the GA/HbA1c ratio (Δ GA/HbA1c ratio) (HbA1c; *R* = 0.040, *P* = 0.801, GA; *R* = −0.230, *P* = 0.164) (Fig. 2a, b). A significant negative correlation was noted between the GA/HbA1c ratio before the administration of alogliptin and the Δ GA/HbA1c ratio (*R* = −0.322, *P* = 0.049) (Fig. 2c). We performed stepwise multivariate regression analysis with Δ GA/HbA1c ratio as an objective variable and with age, sex, BMI, diabetes duration, and baseline GA/HbA1c ratio as explanatory variables. Age, sex, BMI, and diabetes duration were not significant explanatory variables for Δ GA/HbA1c ratio; only baseline GA/HbA1c ratio was a significant explanatory variable [standard regression

Table 2 Effects of the administration of alogliptin on HbA1c, GA, and the GA/HbA1c ratio

	0 week	24 weeks	P*	Δ (24 week – 0 week)
HbA1c (%)	8.1 ± 1.0	6.9 ± 0.7	<0.0001	-1.2 ± 1.1
GA (%)	22.7 ± 3.7	19.1 ± 2.8	<0.0001	-3.6 ± 3.7
GA/HbA1c ratio	2.80 ± 0.30	2.75 ± 0.30	0.129	-0.05 ± 0.19
GA/HbA1c ratio in low-value group	2.57 ± 0.21	2.60 ± 0.26	0.426	0.03 ± 0.17
GA/HbA1c ratio in high-value group	3.02 ± 0.19	2.90 ± 0.27	0.008	-0.13 ± 0.19

*: 24 weeks vs. 0 week, #: *P* = 0.010; low-value group vs. high-value group.

Fig. 2a–c Relationships of HbA1c, GA, and the GA/HbA1c ratio before the administration of alogliptin to the Δ GA/HbA1c ratio upon the administration of alogliptin for 24 weeks. The correlations of HbA1c (**a**), GA (**b**), and the GA/HbA1c ratio (**c**) before the administration of alogliptin with the change in the GA/HbA1c ratio (Δ GA/HbA1c ratio) upon the administration of alogliptin for 24 weeks are shown

coefficient (β) = -0.322 , exclusion F value (F) = 4.16 , $P = 0.009$].

We then investigated the effects of alogliptin on HbA1c and GA after dividing patients into two groups based on the GA/HbA1c ratio before the administration of alogliptin: a high-value group (GA/HbA1c ratio ≥ 2.80) and a low-value group (GA/HbA1c ratio < 2.80) (Table 1). Patients were significantly older in the high-value group than in the low-value group, and BMI was significantly lower in the high-value group than in the low-value group. No significant differences were observed in sex, the duration of diabetes, or HbA1c level before the administration of alogliptin between the two groups. Sulfonylureas were administered to more than half of the patients (55%), and the number of patients who were administered sulfonylureas was larger in the high GA/HbA1c ratio group than in the low GA/HbA1c ratio group ($P = 0.022$). The GA/HbA1c ratio in the low-value group did not change significantly between 0 weeks (2.57 ± 0.21) and 24 weeks after the administration of alogliptin (2.60 ± 0.26) ($P = 0.426$), whereas that in the high-value group significantly decreased from 3.02 ± 0.19 at 0 weeks to 2.90 ± 0.27 at 24 weeks after the administration of alogliptin ($P = 0.008$) (Table 2). The Δ GA/HbA1c ratio in the low-value group between 0 and 24 weeks was 0.03 ± 0.17 , while that in the high-value group was significantly lower (-0.13 ± 0.19) ($P = 0.010$). We compared the Δ GA/HbA1c ratio after categorizing patients based on different criteria: alogliptin dosages of 12.5 and 25 mg, alogliptin for the first time or in addition to other treatments, obese (BMI ≥ 25 kg/m²) and not obese (BMI < 25 kg/m²), and elderly (≥ 70 years) and not elderly (< 70 years). For each comparison, the Δ GA/HbA1c ratios of the groups were not significantly different (data not shown).

Discussion

In the present study, we investigated the effects of the administration of alogliptin on the GA/HbA1c ratio in patients with type 2 diabetes mellitus. The GA/HbA1c ratio in the high-value group was significantly decreased by the administration of alogliptin. These results suggest that improvements in PPPG upon the administration of alogliptin appear to be more prominent in patients with high PPPG levels.

HbA1c mainly reflects the mean plasma glucose level, while GA reflects glycemic variability as well as the mean plasma glucose level [20–24]. Therefore, the GA/HbA1c ratio is regarded as a glycemic control indicator that reflects glycemic variability [25].

We have already reported that the GA/HbA1c ratio is decreased by administering metformin or sitagliptin to patients with type 2 diabetes mellitus [27, 28]; however, few studies have examined the effects of the administration of alogliptin on the GA/HbA1c ratio. Therefore, in the present study, we investigated the effects of the administration of alogliptin on the GA/HbA1c ratio. A significant correlation was not observed between the Δ GA/HbA1c ratio and the HbA1c or GA level before the administration of alogliptin, whereas a significant negative correlation was found between the GA/HbA1c ratio before the administration of alogliptin and the Δ GA/HbA1c ratio, similar to what was seen with sitagliptin administration (Fig. 2). Mori et al. previously reported a negative correlation between MAGE (mean amplitude of glycemic excursions) before the administration of sitagliptin and change in MAGE level [31]. These findings suggest that alogliptin has a profound effect on improvements in glycemic variability in patients who show high glycemic variability. The GA/HbA1c ratio, which reflects glycemic variability, was significantly decreased in the high-value group.

A significant negative correlation of Δ HbA1c with HbA1c or GA level before the administration of alogliptin was observed. Thus, Δ HbA1c was large in patients with poor glycemic control before the administration of alogliptin. This phenomenon has been reported for most diabetes drugs [32, 33]. On the other hand, the Δ GA/HbA1c ratio did not show a significant correlation with baseline HbA1c, but it did show a significant correlation with baseline GA/HbA1c ratio (Fig. 2), which was also observed upon the administration of other DPP-4 inhibitors [28]. However, this is the first study to show a significant correlation of Δ HbA1c with baseline HbA1c but not the GA/HbA1c ratio (Fig. 1). In the present study, alogliptin improved both the mean plasma glucose level (evaluated by HbA1c) and the glycemic variability (evaluated by the GA/HbA1c ratio). In addition, these results suggest that the

improvements in mean plasma glucose level and glycemic variability caused by alogliptin may occur independently.

The GA/HbA1c ratio was significantly decreased by the administration of sitagliptin, but not by alogliptin in the present study. A suggested reason for this could be that the administration of alogliptin causes a smaller improvement in glycemic variability compared to the administration of sitagliptin, but this seems unlikely because the Δ GA/HbA1c of alogliptin was not significantly different from that of sitagliptin (-0.05 ± 0.19 vs. $-0.11 \pm 0.20\%$, $P = 0.150$). Differences between the alogliptin study (38 patients) and the sitagliptin study (69 patients) in number of patients and patient background may have contributed to the different results for the GA/HbA1c ratio seen in those two studies. Further investigation of the different behavior of the GA/HbA1c ratio seen in the two studies is necessary.

Glycemic variability is high in patients with impaired insulin secretion [26]. Furthermore, a negative correlation has been reported between insulin secretory capacity and the GA/HbA1c ratio (the GA/HbA1c ratio reflects glycemic variability) [22, 25, 26]. In the present study, patients were significantly older in the high-value group than in the low-value group, while the BMI was significantly lower in the high-value group than in the low-value group. These results are consistent with impaired insulin secretion in the elderly and in those with a low BMI. However, when the Δ GA/HbA1c ratio was compared between elderly and non-elderly patients or between those with high and low BMI following the administration of alogliptin, no significant difference was found. These results suggest that the GA/HbA1c ratio is not significantly affected by the age or BMI of the patient, in contrast to the secretion of insulin. We previously reported that the GA/HbA1c ratio was high in patients with a reduced capacity for endogenous insulin secretion [22]. The number of patients who were administered sulfonylureas was high in the high GA/HbA1c ratio group compared to the low GA/HbA1c ratio group. In the present study, diabetes duration was longer in the high-value group than in the low-value group, so the GA/HbA1c ratio in the high-value group may be increased by the decreased insulin secretion capacity.

We previously examined the effects of the dosage of alogliptin (12.5 or 25 mg) on HbA1c in type 2 diabetic patients, and found that there was no significant difference in the effects of the two dosages [34]. Therefore, a dosage of either 12.5 or 25 mg alogliptin was selected based on the judgment of the attending physician, and the dosage selected did not significantly affect the HbA1c level or the GA/HbA1c ratio in the present study.

In addition to chronic hyperglycemia, glycemic variability is considered to be an important risk factor for atherosclerosis [5, 6]. Therefore, a decrease in glycemic variability as well as a lower mean glucose level may

suppress the occurrence of cardiovascular events in diabetic patients. DPP-4 inhibitors have recently been reported to exert inhibitory effects on arteriosclerosis [11, 12]. The anti-arteriosclerotic effects of DPP-4 inhibitors may be more closely related to decreases in the GA/HbA1c ratio than decreases in the HbA1c level, because the GA/HbA1c ratio reflects glycemic variability. Future studies are needed to elucidate the contribution of the decreases in the GA/HbA1c ratio caused by DPP-4 inhibitors to the inhibition of arteriosclerotic and cardiovascular events.

There were several limitations of the present study. Since the PPPG was not measured, we were unable to investigate the relationship between the Δ GA/HbA1c ratio and the decrease in PPPG level upon the administration of alogliptin. Furthermore, we were unable to examine the effects of the administration of alogliptin on glycemic variability using CGM.

In conclusion, the administration of alogliptin significantly decreased the GA/HbA1c ratio in the high-value group after 24 weeks. Alogliptin may be more useful for patients with high PPPG levels than for patients with low PPPG levels.

Compliance with ethical standards

Conflict of interest None.

Human rights and informed consent 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. Informed consent or a substitute for it was obtained from all patients prior to their participation in this study.

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