The Glycated Albumin (GA) to HbA1c Ratio Reflects Shorter-Term Glycemic Control than GA: Analysis of Patients with Fulminant Type 1 Diabetes

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Background: Glycated albumin (GA) reflects shorter-term glycemic control than HbA1c. We have reported that HbA1c is paradoxically increased in diabetic patients whose glycemic control deteriorated before ameliorating. In this study, we analyzed paradoxical increases of glycemic control indicators after treatment in patients with fulminant type 1 diabetes (FT1D). We also investigated whether the GA/HbA1c ratio may reflect shorter-term glycemic control than GA. **Methods:** Five FT1D patients whose post-treatment HbA1c and GA levels were measured were enrolled. We also used a formula to estimate HbA1c and GA from the fictitious models of changes in plasma glucose in FT1D patients. In this model, the periods during which HbA1c, GA, and the GA/HbA1c ratio were higher than at the first visit were compared. In addition, the half-

life for the GA/HbA1c ratio was calculated in accordance with the half-lives for HbA1c and GA (36 and 14 days, respectively). **Results:** In all FT1D patients, HbA1c levels 2–4 weeks after treatment were increased, with three patients (60%) experiencing an increase of GA levels. In contrast, an increase of the GA/HbA1c ratio was observed in only one patient. In all of the different models of changes in plasma glucose in FT1D patients, the length of time during which the values were higher than at the first visit was in the order of HbA1c > GA > GA/HbA1c ratio. The half-life for the GA/HbA1c ratio was 9 days, shorter than GA. **Conclusions:** These findings suggest that the GA/HbA1c ratio reflects shorter-term glycemic control than GA. *J. Clin. Lab. Anal.* 31:e22023, 2017. © 2016 Wiley Periodicals, Inc.

Key words: GA/HbA1c ratio; glycated albumin; half-life; HbA1c; paradoxical increase

INTRODUCTION

HbA1c, a long-term indicator of glycemic control, reflects glycemic control in a 1- or 2-month period. Glycated albumin (GA) is an intermediate-term indicator of glycemic control that reflects it in a 2- to 4-week period (1, 2). For this reason, GA measurement is useful in patients with unstable glycemic control or at the initiation of diabetes treatment (3). Recently, we have reported a phenomenon in which the intensification of treatment (e.g., the initiation, addition, or change of diabetes treatment) in patients whose glycemic control status has deteriorated rapidly results in an increase in the HbA1c level but a decrease in

the GA level despite an improvement in glycemic control shortly after the intensification of treatment (4). As the HbA1c levels in these patients subsequently dropped following the GA levels, the elevation of the HbA1c level was judged to be a paradoxical response (4).

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Fulminant type 1 diabetes (FT1D) is a new subtype of type 1 diabetes that was reported by Imagawa et al. in 2000. The condition of FT1D is diabetes that results from very rapid and almost complete pancreatic beta-cell destruction (5, 6). While plasma glucose levels rise significantly at the time of the onset of FT1D, HbA1c levels show a disproportionately normal or mild elevation. Because FT1D presents with diabetic ketoacidosis and a remarkably high level of plasma glucose at the first visit, effort is needed to improve plasma glucose immediately with insulin therapy. This may suggest that HbA1c and other indicators of glycemic control rise paradoxically because plasma glucose in FT1D patients ameliorates relatively quickly after a rapid elevation of plasma glucose levels.

In this study, the occurrence or absence of a paradoxical increase among HbA1c, GA, and the GA/HbA1c ratio was analyzed in the FT1D patients whose HbA1c and GA levels before and after treatment were observed. We also investigated whether the GA/HbA1c ratio reflects shorter-term glycemic control than GA.

MATERIALS AND METHODS

Five FT1D patients whose HbA1c and GA levels before and after treatment were observed (two men and three women; age: 55 ± 22 years; BMI 21.5 ± 2.7 kg/m²) were enrolled (Table 1). None of these patients had a kidney disease, chronic liver disease, or thyroid disease that could have an influence on their HbA1c and GA levels. Three of the five patients were reported (7–9), whereas the remaining two (patients No. 4 and No. 5) were not reported. After the onset of FT1D, each of these patients was hospitalized and underwent intensive insulin therapy. After their systemic condition stabilized, they underwent continuous outpatient treatment with insulin. This study was approved by the Ethics Committee at

Kawanishi City Hospital, and the study complied with the ethical guidelines of the Helsinki Declaration as revised in 2000.

For the purpose of estimating the length of the period during which HbA1c, GA, and the GA/HbA1c ratio in FT1D patients were higher than they had been at the first visit, we used a formula that we had created for estimating the changes in HbA1c and GA levels from the previous plasma glucose levels (10). Some fictitious models of changes in plasma glucose in FT1D patients were created, and the changes in HbA1c, GA, and the GA/HbA1c ratio accompanying the changes in plasma glucose levels were calculated. Based on the results of the calculations, a comparison was performed in terms of the length of the period during which the different values were higher than they had been at the first visit.

In accordance with our previous report (10), the calculation of the HbA1c and GA levels involved the use of formulas 1 and 2, respectively.

Calculated HbA1c =

$$\sum_{n=1}^{140} (\text{Estimated HbA1c}_t / 2^{t/36}) / \sum_{n=1}^{140} 1/2^{t/36} \quad (1)$$

Calculated GA =

$$\sum_{n=1}^{140} (\text{Estimated GA}_t / 2^{t/14}) / \sum_{n=1}^{140} 1/2^{t/14} \quad (2)$$

For t , continuous plasma glucose levels from the time of the first visit to 140 days before the first visit were used. The pre-onset mean plasma glucose (MPG) level and the MPG level in a post-treatment stable condition were set as 105 and 150 mg/dl, respectively. Estimated HbA1c (eHbA1c_t) and estimated GA (eGA_t) levels for t days were calculated with the use of formulas 3 (11) and 4 (12) based on the MPG level determined t days before.

TABLE 1. Clinical Characteristics in Study Patients with Fulminant Type 1 Diabetes

Patient No.	Age (years)	Sex	BMI (kg/m ²)	At first visit			
				PG (mg/dl)	HbA1c (%)	GA (%)	GA/HbA1c ratio
1	43	Male	21.7	567	6.0	21.5	3.61
2	30	Female	20.8	1,191	6.2	23.0	3.73
3	70	Female	24.2	453	6.7	22.4	3.36
4	75	Male	23.5	1,037	7.5	31.1	4.15
5	72	Female	17.4	853	6.2	22.7	3.66
Mean ± SD	55 ± 22		21.5 ± 2.7	820 ± 310	6.5 ± 0.6	24.1 ± 3.9	3.70 ± 0.29

PG, plasma glucose.

$$eHbA1ct = MPGr \times 1.11/35.6 + 2.17 \quad (3)$$

$$eGA_t = eHbA1ct \times 2.7 \quad (4)$$

We reported the half-lives for HbA1c and GA to be 36 and 14 days, respectively (10). Based on this result, we sought the half-life for the GA/HbA1c ratio using the following method. Pretreatment HbA1c and GA levels were assumed to be 10% and 27%, respectively. When plasma glucose has been normalized, HbA1c and GA were assumed to be 5.4% and 15%, respectively. Assuming that plasma glucose has been normalized very quickly with intensive insulin therapy, HbA1c, and GA for t days later can be found using the following formulas.

$$\log(HbA1ct - 5.4) = -[\log(10 - 5.4) - \log(10 - 5.4)/2] / 36 \times t + \log(10 - 5.4) \quad (5)$$

$$\log(GA_t - 15) = -[\log(27 - 15) - \log(27 - 15)/2] / 14 \times t + \log(27 - 15) \quad (6)$$

The GA/HbA1c ratio at t days later was calculated by HbA1c and GA sought by formulas 5 and 6, and the half-life for the GA/HbA1c ratio was sought from changes in the GA/HbA1c ratio.

Plasma glucose was determined using the glucose oxidase method. HbA1c, expressed as the National Glycohemoglobin Standardization Program value (13), was measured by high-performance liquid chromatography. GA was determined by enzymatic methods using albumin-specific protease, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) (14).

RESULTS

In the FT1D patients before treatment, HbA1c was $6.5 \pm 0.6\%$; GA was $24.1 \pm 3.9\%$; and the GA/HbA1c ratio was 3.70 ± 0.29 (Table 1). HbA1c rose in all patients 2–4 weeks after the initiation of insulin treatment (Fig. 1A). GA was decreased in two of the five patients after the initiation of treatment and rose in the remaining three patients (Fig. 1B). The GA/HbA1c ratio rose in only one of the five patients (patient No. 5) (Fig. 1C).

Fictitious models of changes in plasma glucose in different FT1D patients, as shown in Table 2, were created (Model No. 1–4). We then used estimation formulas (formulas 1 and 2) for HbA1c and GA calculated from previous plasma glucose levels to analyze the changes in HbA1c, GA, and the GA/HbA1c ratio

Fig. 1. Changes in post-treatment HbA1c, GA, and the GA/HbA1c ratio levels in patients with fulminant type 1 diabetes (FT1D). The figure shows changes in HbA1c (A), GA (B), and the GA/HbA1c ratio (C) from before treatment to after treatment in five FT1D patients: ○; case 1, △; case 2, ▲; case 3, ●; case 4, ■; case 5.

(Fig. 2). We calculated the length of the period during which these values would be higher than at the first visit. In some models, HbA1c levels remained high for a long period, and sometimes during the course, they did not fall below the value at the time of the first visit (Table 2, Model No. 2). In each of the models, the length of the period with the high GA/HbA1c ratio (5–11 days) was shorter than the length of the period with high GA (11–26 days) or HbA1c (37–∞ days).

Figure 3A shows changes in the HbA1c and GA levels after plasma glucose was quickly normalized with the use of intensive insulin therapy and formulas 5 and 6 described in the Methods section, on the assumption that pretreatment HbA1c and GA levels were 10% and 27%, respectively. Figure 3B shows changes in the GA/HbA1c ratio calculated by changes in HbA1c and GA. The GA/HbA1c ratio dropped temporarily and then increased. The GA/HbA1c ratio at the first visit was 2.7 and hit the bottom, at 2.2, 5 weeks after the initiation of treatment. The mean of the value recorded at the first visit and the bottom value is 2.45. The period with the GA/HbA1c ratio at 2.45 may be the half-life for the GA/HbA1c ratio. As shown in Figure 3B, the half-life for the GA/HbA1c ratio was 9 days, which was shorter than the half-life for GA (14 days).

DISCUSSION

We analyzed changes in the indicators of glycemic control after treatment in the five FT1D patients. In all the patients, HbA1c rose 2–4 weeks after the initiation of treatment, whereas GA rose in nearly half of the patients. On the other hand, the GA/HbA1c ratio rose in only one of the five patients.

TABLE 2. Conditions of a Model of Changes in Plasma Glucose in Fulminant Type 1 Diabetes (FT1D) (Rate of Plasma Glucose Elevation, Plasma Glucose at the First Visit and Rate of Plasma Glucose Decrease); HbA1c, GA, and the GA/HbA1c Ratio at the First Visit; and Estimated Length of Period with Higher Values than Those Determined at the First Visit

Model No.		1	2	3	4
Increasing rate of PG	(mg/dl/day)	120	150	190	600
PG at first visit	(mg/dl/day)	1,100	800	1,100	2,000
Decreasing rate of PG	(mg/dl/day)	180	180	180	180
Data at first visit	HbA1c (%)	8.3	6.7	7.4	8.0
	GA (%)	31.6	22.3	26.6	30.4
	GA/HbA1c ratio	3.8	3.4	3.6	3.8
Period demonstrating higher value than that at first visit (days)	HbA1c	37	∞	76	85
	GA	11	15	16	26
	GA/HbA1c ratio	5	6	7	11

We created different models of changes in plasma glucose in FT1D patients (Model No. 1–4). The pre-onset mean plasma glucose level and the post-treatment mean plasma glucose level in a stable condition were set as 105 and 150 mg/dl, respectively. For the rate of the plasma glucose increase, the plasma glucose at the first visit and the rate of the plasma glucose decrease; we used the numerical values shown at the top. Using the formulas described in the procedure section, we sought the estimated HbA1c, GA, and the GA/HbA1c ratio at the first visit (middle) and the estimated values for the period with higher glycemic control indicators than at the first visit (bottom). PG, plasma glucose.

Fig. 2. Changes in estimated HbA1c, GA, and the GA/HbA1c ratio from a fictitious model of change in plasma glucose (Model No. 1) in patients with fulminant 1 diabetes (FT1D). Using the formula described in an already-reported study (10), we sought changes in HbA1c (B: solid line) and GA (B: dotted line) for Model No. 1 (pre-onset mean plasma glucose: 105 mg/dl, rate of pretreatment plasma glucose increase: 120 mg/dl/day, plasma glucose at the first visit: 1,100 mg/dl, rate of post-treatment plasma glucose decrease: 180 mg/dl/day, post-treatment mean plasma glucose in a stable condition: 150 mg/dl) where changes in plasma glucose in FT1D patients (A: solid line) are as shown in Table 2. Based on the HbA1c and GA obtained therefrom, we calculated the GA/HbA1c ratio (A: dotted line). An estimated period with higher HbA1c, GA, and GA/HbA1c ratios than at the first visit is also shown.

It was reported that HbA1c in some patients paradoxically rose after diabetes treatment was initiated, added, or changed in the patients whose glycemic control quickly deteriorated (4). However, most of the FT1D patients showed a paradoxical increase of HbA1c because the deterioration and subsequent amelioration of the glycemic control status occurred very quickly. It is considered that a paradoxical increase of

Fig. 3. Calculation of half-life for the GA/HbA1c ratio. Assuming that pretreatment HbA1c and GA levels were 10% and 27%, respectively, and that plasma glucose was normalized very quickly after day 0 with intensive insulin therapy, and based on the half-lives for HbA1c and GA (36 and 14 days), we used the method described in the procedure section to trace changes in HbA1c and GA and created a decrease curve for each (A). The GA/HbA1c ratio was calculated from changes in GA and HbA1c, and the changes are shown in B. Because the pretreatment GA/HbA1c ratio was 2.7 and hit the bottom at 2.2, we defined the half-life, namely the period during which the GA/HbA1c ratio remains at 2.45, as 9 days.

GA generally does not occur because GA reflects shorter-term glycemic control than HbA1c. However, we firstly reported that a paradoxical increase of GA may have occurred in the FT1D patients in which a rapid increase of plasma glucose is followed by an amelioration of glycemic control in this study. No elevation of the GA/HbA1c ratio was observed in most of the patients, but one patient (patient No. 5) showed a paradoxical increase. This may be because patient No. 5 underwent the measurement of the GA/HbA1c ratio shortly after treatment (after 4 days). The above

findings suggested that the GA/HbA1c ratio reflects shorter-term glycemic control than GA or HbA1c.

We reported a formula for estimating HbA1c and GA from the previous plasma glucose levels (10). The original method involved a formula using MPG for a 1-week period. However, plasma glucose fluctuates very quickly in FT1D patients, which makes it impossible to use a formula for estimating MPG for a 1-week period. For this reason, we employed a formula for estimating HbA1c and GA in FT1D patients by using the plasma glucose MPG level for a 1-day period. Using the formula can estimate HbA1c, GA, and the GA/HbA1c ratio for consecutive days with the use of fictitious changes in plasma glucose levels. Accordingly, using the estimation formula can estimate the paradoxical increase of the indicators of glycemic control in FT1D patients. Several models of changes in plasma glucose in FT1D patients were used to determine the length of the period with a paradoxical increase, which was in the order of $\text{HbA1c} > \text{GA} > \text{GA/HbA1c}$ ratio in each of the models. The length of the period may reflect the half-life for the corresponding indicators.

We reported the half-lives for HbA1c and GA to be 36 and 14 days, respectively (10). Based on the data, the half-life of the GA/HbA1c ratio was 9 days, shorter than that of HbA1c or GA. When glycemic control deteriorates or ameliorates, the GA/HbA1c ratio reflects fluctuations of glycemic control (3). In other words, when glycemic control deteriorates, the GA/HbA1c ratio rises because the extent of the elevation of GA, which reflects shorter-term glycemic control, is larger than that of HbA1c. When glycemic control ameliorates, the GA/HbA1c ratio drops because the extent of the decrease of GA is larger than that of HbA1c. The GA/HbA1c ratio may be useful in judging whether glycemic control has deteriorated or ameliorated in patients whose glycemic control is unstable and undergoes repeated deterioration and amelioration, because the GA/HbA1c ratio reflects shorter-term glycemic control than GA.

With respect to a mechanism whereby the GA/HbA1c ratio reflects shorter-term glycemic control than GA, in the cases in which both GA and HbA1c have risen by a paradoxical increase after the deteriorated glycemic control has ameliorated, the increase of GA is higher than HbA1c after the deterioration, while the subsequent increase of GA becomes smaller than that of HbA1c. This is accompanied by a decrease in the GA/HbA1c ratio. In other words, the GA/HbA1c ratio already shifts from an increase to a decrease while the paradoxical phenomenon of GA continues. As a consequence, the GA/HbA1c ratio may reflect a shorter-term glycemic control than GA does.

This study has some limitations. First, it had relatively few patients. The findings from the study need to be verified with a large number of FT1D patients. Second, the measurement of HbA1c and GA varied among the patients due to the retrospective nature of the study. The measurement was performed shortly after treatment in patient No. 5, which made it possible to observe a paradoxical increase of the GA/HbA1c ratio. None of the other patients underwent measurement within 1 week after treatment. In the future, the measurement of HbA1c and GA will need to be performed frequently during a short post-treatment period so that we can confirm that a paradoxical increase of the GA/HbA1c ratio actually does occur.

In conclusion, the present studies suggested that the GA/HbA1c ratio reflects shorter-term glycemic control than GA. The GA/HbA1c ratio is firstly reported to be a short-term indicator of glycemic control. However, the measurement of plasma glucose is more practical and the HbA1c and GA should not be measured in such a short-term period shown in this study.

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