ORIGINAL

The glycated albumin to HbA1c ratio is elevated in patients with fulminant type 1 diabetes mellitus with onset during pregnancy

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Abstract : Fulminant type 1 diabetes mellitus (FT1DM) develops as a result of very rapid and almost complete destruction of pancreatic β cell. The most common form of type 1 diabetes mellitus with onset during pregnancy has been shown to be FT1DM at least in Japan. We previously reported that the ratio of glycated albumin (GA) to HbA1c (GA/HbA1c ratio) is elevated in FT1DM patients at the diagnosis. In the present study, we investigated whether the GA/HbA1c ratio is also elevated in FT1DM with onset during pregnancy (P-FT1DM). The study subjects consisted of 7 patients with P-FT1DM. Ten patients with untreated type 2 diabetes mellitus (T2DM) discovered during pregnancy (P-T2DM) and 9 non-pregnant women with untreated T2DM (NP-T2DM) were used as controls. All study patients satisfied HbA1c < 8.7%, the diagnostic criteria for FT1DM. The GA/HbA1c ratio in the P-FT1DM patients at the diagnosis was significantly higher than that in the P-T2DM patients and the NP-T2DM patients. The GA/HbA1c ratio was ≥ 3.0 in all P-FT1DM patients, whereas it was < 3.0 in 8 of 10 P-T2DM patients and all NP-T2DM patients. The GA/HbA1c ratio was also elevated in P-FT1DM patients at the diagnosis compared with T2DM with or without pregnancy. J. Med. Invest. 60 : 41-45, February, 2013

Keywords **:** *glycated albumin, HbA1c, fulminant type I diabetes mellitus, pregnancy*

INTRODUCTION

Fulminant type 1 diabetes mellitus (FT1DM) is a new subtype of type 1 diabetes mellitus (T1DM) reported by Imagawa *et al.* in 2000 (1). FT1DM is characterized by a very rapid onset and develops due to nearly complete destruction of pancreatic β cells (1, 2). FT1DM accounts for about 20% of T1 DM in Japanese patients (2). Moreover, in a nationwide survey in Japan, the most common form of T1DM with onset during pregnancy has been shown to be FT1DM (3). FT1DM that develops during

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pregnancy affects not only the mother, but also the fetus, and is associated with a high rate of stillbirths (4). Therefore, FT1DM developing during pregnancy should be diagnosed and be treated immediately.

In diabetic patients, glycation of various proteins is known to be increased, and some of these glycated proteins are thought to be involved in the onset and progression of chronic diabetic complications (5). Of these proteins, HbA1c is widely used clinically as a marker of glycemic control (6). As the half-life of serum albumin is shorter than that of erythrocytes, glycated albumin (GA) is used as a marker of plasma glucose levels over a shorter period (about 2 weeks) (7-9). Thus, GA reflects shorter term control of plasma glucose than HbA1c.

We previously reported that HbA1c is only mildly elevated in FT1DM patients because of the abrupt rise in plasma glucose, whereas GA is clearly elevated (10). Therefore, the ratio of GA to HbA1c (GA/HbA1c ratio) is elevated in FT1DM patients at the diagnosis, being ≥3.2 in most FT1DM patients [using the HbA1c-Japan Diabetes Society (JDS) value ; ≥3.0 using the HbA1c-National Glycohemoglobin Standardization Program (NGSP) value]. However, in most patients with type 2 diabetes mellitus (T2DM), the GA/HbA1c ratio is <3.2 (using the HbA1c-JDS value ; <3.0 using the HbA1c-NGSP value) (10).

From mid through late pregnancy, HbA1c levels are increased (11, 12), whereas GA levels are not changed (13, 14). This has been shown to be due to iron deficiency (13, 14), which occurs in most women in late pregnancy. Because HbA1c, but not GA, is increased under the influence of iron deficient conditions (15, 16), the GA/HbA1c ratio is decreased from mid through late pregnancy (13, 14).

In this study, we investigated whether the GA/HbA1c ratio is also elevated in FT1DM patients with onset during pregnancy compared with T2DM patients under these situations.

PATIENTS AND METHODS

Patients

This study included 7 patients with FT1DM with onset during pregnancy (P-FT1DM), all cases by JDS's Comittee on Research of T1DM or reported cases, in whom HbA1c and GA were simultaneously measured at initial evaluation (Table 1). As controls, we included 10 patients with untreated T2DM discovered during pregnancy (P-T2DM) and 9 non-pregnant women with untreated T2DM (NP-T2DM) evaluated at Kinki Central Hospital, in whom HbA1c and GA were simultaneously measured before treatment. T2DM was diagnosed based on JDS criteria (17). In pregnancy, oral glucose tolerance test (OGTT) was performed for diagnosis of diabetes mellitus. All study patients satisfied HbA1c <8.3% (using the JDS value ; <8.7% using NGSP value), one of the diagnostic criteria for FT1DM (18). Patients with liver, renal or thyroid disease and those taking glucocorticoid therapy were excluded. For the P-T2DM patients, patients with gestational diabetes mellitus (19) were excluded. The institutional review board approved this

Table 1 Clinical characteristics of study patients in this study

	Fulminant type 1 diabetes with onset in pregnancy (P-FT1DM)	Type 2 diabetes with onset in pregnancy (P-T2DM)	Type 2 diabetes in non-pregnant women (NP-T2DM)
Total number	7	10	9
Age (years)	29.6± 3.0	35.2± 5.0$^{\#}$	49.4± 18.1$^{\#}$
Body mass index (kg/m^2)	19.3± 1.8	27.7± 6.4$^{\#\#}$	23.6± 4.4$^{\#}$
Duration of pregnancy (weeks)	20.3± 12.6 (5-36)	18.0± 8.8 (6-36)	-
Disease duration (days)	2.6± 2.9	-	-
Plasma glucose (mg/dl)	764± 213* (505-983)	135± 62**,$^{\#\#\#}$ (81-227)	135± 24** (113-181)
HbA1c (%)	6.0± 0.4 (5.6-6.5)	6.5± 0.7 (5.5-7.9)	7.2± 0.7$^{\#\#}$ (6.4-8.3)
GA (%)	20.5± 1.9 (17.1-22.9)	17.5± 3.4 (13.2-23.1)	19.1± 1.7 (17.6-23.0)

$^{\#}$: $p< 0.05$, $^{\#\#}$: $p< 0.01$, $^{\#\#\#}$: $p< 0.001$ vs. P-FT1DM, * : randomly measured plasma glucose,
** : fasting plasma glucose, parentheses denote range

study, and all T2DM patients as control group provided written informed consent.

Laboratory analysis

HbA1c was measured by high performance liquid chromatography. The value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%), as measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) (17). Serum GA was determined by an enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) (20).

Statistical analysis

All data are presented as means ± SD. For statistical analyses, the Mann-Whitney *U* test was used to compare two groups. Simple regression analyses were employed in order to assess the association between continuous variables. A p value of < 0.05 was considered to be statistically significant.

RESULTS

The P-FT1DM patients were significantly younger than the P-T2DM patients and the NP-T2DM patients (Table 1). Body mass index (BMI) in the P-FT1DM patients was significantly lower than that in the P-T2DM patients and the NP-T2DM patients. Randomly measured plasma glucose levels in the P-FT1DM patients were markedly higher than that in the P-T2DM patients and in the NP-T2DM patients. HbA1c levels in the P-FT1DM patients and that in the P-T2DM patients did not significantly differ. It was significantly lower in the P-FT1DM patients than in the NP-T2DM patients. On the other hand, GA did not significantly differ among the 3 groups (Table 1).

In each group, HbA1c was significantly correlated with GA, but the regression line for HbA1c and GA in the P-FT1DM patients showed an upward shift in comparison with that in the P-T2DM patients and that in the NP-T2DM patients (Fig. 1). The GA/HbA1c ratio in the P-FT1DM patients was significantly higher compared with the P-T2DM patients and the NP-T2DM patients (P-FT1DM : 3.4 ± 0.2 vs. P-T2DM : 2.7 ± 0.4 ; $p < 0.01$, vs. NP-T2DM : 2.7 ± 0.2 ; $p < 0.01$) (Fig. 2). The GA/HbA1c ratio was ≥ 3.0 in all P-FT1DM patients, whereas that was < 3.0 in 8 of 10 P-T2DM patients and in all NP-T2DM patients.

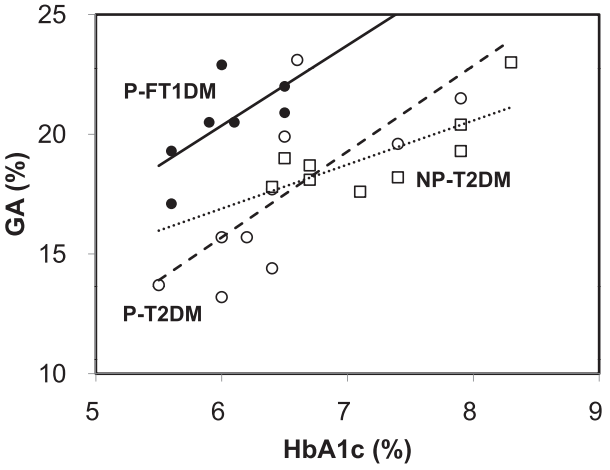

Figure 1 Correlation between HbA1c and GA in each group.
Relationship between HbA1c and GA in the patients with fulminant type 1 diabetes mellitus with onset during pregnancy (P-FT1DM) (closed circles), the patients with type 2 diabetes mellitus with onset during pregnancy (P-T2DM) (open circles), and the patients with type 2 diabetes mellitus in non-pregnant women (NP-T2DM) (open squares). Regression line is shown for each group.

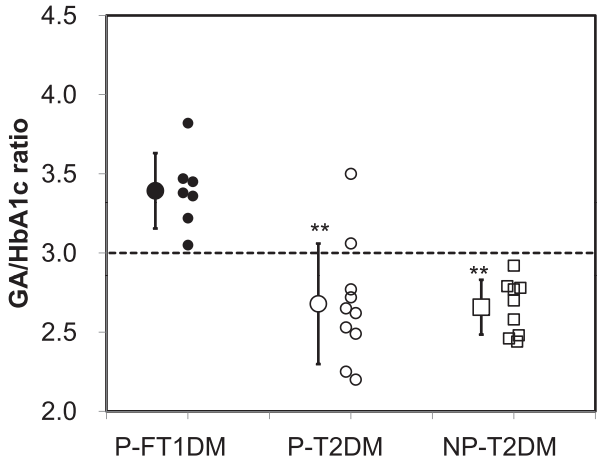

Figure 2 The GA/HbA1c ratio in each group.
The GA/HbA1c ratio in the patients with fulminant type 1 diabetes mellitus with onset during pregnancy (P-FT1DM) (closed circles), the patients with type 2 diabetes mellitus with onset during pregnancy (P-T2DM) (open circles), and the patients with type 2 diabetes mellitus in non-pregnant women (NP-T2DM) (open squares). Mean ± SD values and individual values of the GA/HbA1c ratio in each group are shown. Dotted line indicates the GA/HbA1c ratio of 3.0.

DISCUSSION

In T2DM patients, the GA/HbA1c ratio is reported to be about 3.0, with a range of 2.0 to 4.0 (9, 21). In diabetic patients with poor glycemic control,

when plasma glucose rapidly improves, the GA/HbA1c ratio is decreased because the degree of decrease in GA is larger than that in HbA1c (8, 9). Conversely, when glycemic control rapidly worsens, the degree of increase in GA is also expected to be larger compared with HbA1c. In this study, based on a higher GA/HbA1c ratio in the FT1DM patients with onset during pregnancy, a high GA/HbA1c ratio at the time of acute plasma glucose elevation could be confirmed.

FT1DM with onset during pregnancy must be diagnosed and be treated immediately. In most patients with FT1DM, its diagnosis is relatively easy due to the presence of marked hyperglycemia and ketoacidosis in addition to hyperglycemic symptoms. However, only mildly elevated plasma glucose has been reported at the time of onset in some patients with FT1DM (22). Based on the findings in this study, if HbA1c is $< 8.9\%$ and the GA/HbA1c ratio is ≥ 3.0 in diabetic patients with onset during pregnancy, FT1DM is strongly suspected.

Because HbA1c is increased under the influence of iron deficiency, which occurs in most women in late pregnancy, the GA/HbA1c ratio is decreased from mid through late pregnancy (13, 14). Although the GA/HbA1c ratio (3.4 ± 0.2) in the P-FT1DM patients was slightly lower than that (3.7 ± 0.5) in the FT1DM patients without pregnancy described previously (10), there was no significant difference between both groups. Thus, the influence of iron deficiency in pregnancy on the GA/HbA1c ratio is negligible compared with the influence of FT1DM.

BMI in the P-FT1DM patients was significantly lower than that in the P-T2DM patients and the NP-T2DM patients. We reported that BMI negatively influences GA, but not HbA1c, in non-diabetic subjects and diabetic patients (21, 23). The differences of BMI might influence the GA/HbA1c ratio in each group. However, similar results were obtained when the GA/HbA1c ratio was adjusted by BMI (data not shown).

Because P-FT1DM is a relatively rare condition, the number of P-FT1DM patients was small in this study. In the future, the GA/HbA1c ratio in P-FT1 DM patients should be examined using a large number of patients.

CONFLICT OF INTEREST

The authors declared no conflict of interest relevant to this manuscript

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