**Glycated Albumin is a Better Indicator for Glucose Excursion than Glycated Hemoglobin in Type 1 and Type 2 Diabetes**

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**Abstract.** To determine the impact of blood glucose profile, involving fluctuation and excursion of blood glucose levels, on glycated proteins, we evaluated the association among the daily profile of blood glucose, and glycated albumin (GA) and HbA1c levels in patients with type 1 diabetes (n = 93) and type 2 diabetes (n = 75). GA levels were strongly correlated with HbA1c levels in type 1 (r = 0.85, P<0.0001) and type 2 diabetes (r = 0.61, P<0.0001), respectively. HbA1c levels were similar between patients with type 1 and type 2 diabetes, while GA levels were significantly higher in type 1 diabetes. Thus the ratio of GA levels to HbA1c levels was significantly higher in type 1 diabetes than that in type 2 diabetes (3.32 ± 0.36 vs. 2.89 ± 0.44, P<0.001). The degrees of GA levels and HbA1c levels correlated with maximum and mean blood glucose levels in patients with type 1 and type 2 diabetes. Stepwise multivariate analysis revealed that GA levels independently correlated with maximum blood glucose levels in type 1 diabetes (F = 43.34, P<0.001) and type 2 diabetes (F = 41.57, P<0.001). HbA1c levels also independently correlated with maximum blood glucose levels in type 1 diabetes (F = 34.78, P<0.001), as well as being correlated with mean blood glucose levels in type 2 diabetes (F = 11.28, P<0.001). In summary, GA could be a better marker for glycemic control than glycated hemoglobin in diabetic patients, especially for evaluating glycemic excursion, which is considered to be a major cause of diabetic angiopathy.

**Key words:** Glycated albumin, HbA1c, Glycemic excursion

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**THE** predominant component of glycated hemoglobin, HbA1c, is most widely used to evaluate the long-term glycemic control and the risk for the development of complications in patients with type 1 [1] and type 2 diabetes [2, 3]. Circulating glucose combines with hemoglobin via a slow irreversible non-enzymatic reaction, the rate of which is determined by serum glucose concentrations [4, 5]. However, glycated hemoglobin is known to be affected by various conditions, especially by the modification of erythrocyte survival and glycation. For example, lower HbA1c levels are observed in subjects with shortened erythrocyte survival or decreased mean erythrocyte age. Hyperglycemia is also known to reduce the survival of erythrocytes and to underestimate HbA1c levels in diabetic patients under poor glycemic control [6, 7].

The Diabetes Control and Complications Trial demonstrated that intensive insulin treatment markedly reduces the risk of retinopathy compared with conventional insulin treatment in type 1 diabetic patients, even with identical levels of HbA1c [8]. The authors suggested that intensive treatment with multiple insulin injections could decrease glucose fluctuation and excursion, and that such an effect on glucose profile might decrease the incidence of diabetic microangiopathy. We also reported that postprandial glucose level is a better predictor of diabetic retinopathy than HbA1c in type 2 diabetes [9]. In addition, increased glycemic fluctuation and/or postprandial glucose ex-
cursion has been shown to increase the risk for diabetic macro-angiopathy [10, 11]. Therefore a good indicator for glucose fluctuation and excursion is necessary to predict the development of diabetic complications.

Among various glycated proteins, serum glycated albumin (GA) has been reported to be a useful and rapid indicator of glycemic control for diabetic patients, since the turnover of serum albumin is much shorter (half-life of 17 days) than that of HbA1c [12, 13, 14]. Circulating albumin is strongly glycated at four sites of lysine residues, and the glycation reaction occurs ten times more rapidly than the glycation of hemoglobin [15, 16]. It is, therefore, possible that glycemic fluctuation and excursion could influence glycation reaction in albumin strongly compared with hemoglobin.

In this study, we evaluated the effect of the daily profile of blood glucose levels on GA and HbA1c levels in patients with type 1 and type 2 diabetes, because the glycemic fluctuation and excursion in type 1 diabetes could be larger than that of type 2 diabetes.

Patients and Methods

Study subjects

Ninety-three patients with type 1 diabetes (28 males and 65 females, age 26.7 ± 7.4 years with a duration of diabetes of 15.6 ± 6.7 years) and 75 patients with type 2 diabetes (54 males and 21 females, age 60.5 ± 10.6 years with a duration of diabetes of 13.0 ± 7.9 years) were enrolled in this study (Table 1). These patients were not suffering from advanced micro- or macro-diabetic angiopathy. All patients with type 1 diabetes were being treated with insulin injections at least 4 or 5 times daily. On the other hand, among the type 2 diabetic patients, 38 and 37 patients were treated with oral anti-diabetic agents and insulin, respectively. In these patients, treatment for diabetes went unchanged for at least three months prior to enrolling in this study. After a full explanation of this study, written informed consent was obtained from each subject. Furthermore, the study was approved by the Ethical Committee for Human Studies at Osaka University Graduate School of Medicine.

Evaluation of glycated proteins and daily glucose profile

HbA1c levels were determined using high performance liquid chromatography, and glycated serum albumin levels were measured using the enzymatic glycated albumin assay kit (Lucica GA-L, Asahi Kasei Pharma, Tokyo, Japan) [17]. The daily profile of glucose levels was determined by self-monitored blood glucose testing before and 2-hours after each meal and at bedtime on the day before blood sampling for glycated proteins, from which data the mean blood glucose levels and the mean amplitude of glucose excursion (MAGE) were calculated [18].

Statistical analysis

Data were presented as means ± SD. Data between the groups of type 1 and type 2 diabetes were compared by the Mann-Whitney U-test. Stepwise multivariate regression analyses were performed to evaluate the relationship among glycated proteins and various parameters of the diurnal glucose profile. For the stepwise multivariate regression analyses, the F value for the inclusion and exclusion of variables was set at 4.0. The analysis was performed with StatView computer program (Abacus Concepts, Berkeley, CA).

Results

Age and body mass index (BMI) in type 1 diabetic patients were significantly lower than those in type 2
diabetic patients, and the duration of diabetes in type 1 diabetic patients was significantly longer than that in type 2 diabetic patients (Table 1). Fasting, mean and maximum blood glucose levels, and MAGE determined from the daily blood glucose profile were similar between type 1 and type 2 diabetes. However, the difference between maximum and minimum blood glucose levels ($\Delta BG$), representing glycemic fluctuation, was significantly higher in type 1 diabetes than that in type 2 diabetes.

HbA1c levels were similar between type 1 and type 2 diabetes, while GA levels were significantly higher in type 1 diabetes than that in type 2 diabetes. GA levels were strongly correlated with HbA1c levels in type 1 ($r = 0.85$, $P<0.0001$) and type 2 diabetic patients ($r = 0.61$, $P<0.0001$), respectively (Fig. 1). The ratio of GA levels to HbA1c levels in type 1 diabetes was significantly higher than that of type 2 diabetes ($P<0.001$).

A previous report demonstrated that BMI correlated negatively with GA [19], but we could not find any correlation between BMI and GA or HbA1c in type 1 (GA, $r = -0.152$; HbA1c, $r = -0.043$) and type 2 diabetes (GA, $r = -0.178$; HbA1c, $r = 0.206$). On the other hand, the ratio of GA levels to HbA1c levels correlated negatively with BMI in type 2 diabetic patients ($r = -0.466$, $P<0.001$), but not in type 1 diabetic ones ($r = -0.231$, $P = 0.07$).

In patients with type 1 diabetes, GA and HbA1c levels correlated with fasting, mean and maximum glucose, MAGE and $\Delta BG$ levels (Table 2). On the other hand, in type 2 diabetes, GA levels correlated with fasting, mean and maximum glucose, and $\Delta BG$ levels, and HbA1c levels correlated with mean and maximum glucose, and $\Delta BG$ levels. Stepwise multivariate analysis revealed that GA levels independently correlated with maximum blood glucose levels in type 1 and type 2 diabetes (Table 2). HbA1c levels also independently correlated with maximum blood glucose levels in type 1 diabetes, while HbA1c levels correlated with mean blood glucose levels in type 2 diabetes. Since $\Delta BG$ were highly correlated with maximum glucose levels, $\Delta BG$ was excluded from stepwise multivariate analysis.

### Table 2. Association between glycated proteins and parameters of daily glucose profile in patients with type 1 and type 2 diabetes

| Factors | Parameters | Type 1 diabetes | | | Type 2 diabetes | | |
|---------|------------|----------------|---|---|----------------|---|
|         |            | Univariate     | Multivariate | | Univariate     | Multivariate | |
|         |            | R   P           | F   P       | | R   P           | F   P       | |
| GA      | FBG        | 0.321 0.002 | 1.31 NE | | 0.446 <0.001 | 3.37 NE | |
|         | MBG        | 0.535 <0.001 | 0.70 NE | | 0.601 <0.001 | 0.15 NE | |
|         | MAXBG      | 0.568 <0.001 | 43.34 <0.001 | | 0.605 <0.001 | 41.57 <0.001 | |
|         | MAGE       | 0.328 0.001 | 0.02 NE | | 0.219 0.060 | 0.153 NE | |
|         | $\Delta BG$ | 0.376 <0.001 | | | 0.452 <0.001 | |
| HbA1c   | FBG        | 0.352 <0.001 | 2.96 NE | | 0.107 NS | |
|         | MBG        | 0.511 <0.001 | 1.24 NE | | 0.366 0.001 | 11.28 <0.001 | |
|         | MAXBG      | 0.526 <0.001 | 34.87 <0.001 | | 0.359 0.001 | 0.43 NE | |
|         | MAGE       | 0.346 <0.001 | 0.21 NE | | 0.172 NS | |
|         | $\Delta BG$ | 0.271 0.020 | | | 0.382 0.003 | |

Pearson’s univariate correlation coefficients and stepwise multivariate regression analysis were performed. $P<0.05$, NS, not significant; NE, not entered
Discussion

In the present study, GA levels were strongly correlated with HbA1c levels in type 1 and type 2 diabetes, and these glycated proteins were well correlated with mean blood glucose levels determined from a 7-point blood glucose measurement per day. Thus GA levels, as well as glycated hemoglobin levels, are a useful marker of glycemic control as previously reported [14]. Since GA in patients with type 2 diabetes showed a better correlation with various parameters of glycemic profiles than HbA1c, GA could be a more accurate marker for evaluating glycemic control than HbA1c in these patients. In addition, an independent determinant of GA was maximum glucose levels in type 2 diabetes, thus GA might predominantly reflect glucose excursion. On the other hand, in type 1 diabetes, both GA and HbA1c were similarly correlated with various parameters of glycemic profiles, and were independently correlated with maximum glucose levels. However, the coefficient and F-value of correlation of GA with maximum glucose levels were higher than those of HbA1c in type 1 diabetes. Therefore, GA is a better marker for evaluating glucose excursion than HbA1c in type 1 diabetes, as well as type 2 diabetes.

An independent determinant of HbA1c was maximum glucose in type 1 diabetes, and mean blood glucose in type 2 diabetes. This finding implied that the impact of glycemic excursion on HbA1c was stronger in type 1 diabetes than that in type 2 diabetes. Monnier et al. demonstrated in type 2 diabetic patients that the contribution of postprandial glucose excursion to glycated hemoglobin gradually decreased in contrast to increase in HbA1c levels [20]. In the present study, however, the average HbA1c levels were identical between type 1 and type 2 diabetic patients. We, therefore, speculated that increased glycemic fluctuation in type 1 diabetic patients may increase the contribution of postprandial glucose excursion to HbA1c levels.

Interestingly, the ratio of GA levels to HbA1c levels was significantly higher in type 1 diabetic patients than in type 2 diabetic patients. A previous report demonstrated that a higher ratio of GA levels to HbA1c levels was observed in patients with poor glycemic control than good glycemic control, and that acute glycemic control decreased this ratio [14]. In the present study, mean blood glucose levels and glycated hemoglobin levels were similar between type 1 and type 2 diabetic patients and treatment for diabetes remained unchanged for at least three months prior to enrolling in this study. Thus acute change and degree of glycemic control is unlikely to affect the ratio of GA levels to HbA1c levels in this study. Moreover, Koga et al. recently reported that BMI negatively influenced glycated albumin levels and the ratio of GA levels to HbA1c levels in diabetic patients [19]. In the present study, we failed to find a correlation between BMI and GA levels in patients with type 1 and type 2 diabetes, and BMI negatively correlated with the ratio of GA levels to HbA1c levels only in type 2 diabetic patients. Thus, in patients with type 2 diabetes, higher BMI might partially contribute to lower ratio of GA levels to HbA1c levels.

Since ΔBG and MAGE were the predominant determinants for the ratio of GA levels to HbA1c levels among the various parameters of daily glucose profiles (F = 25.4 and F = 4.8, respectively), large glucose fluctuation in type 1 diabetes could enhance the glycation and oxidation reaction of albumin, which are known to be major reactions to produce GA, and increase the ratio of GA levels to HbA1c levels. In addition, hyperglycemia is known to reduce the survival of hemoglobin [6, 7], thus a higher glucose fluctuation in type 1 diabetics may decrease HbA1c and increase the ratio of GA levels to HbA1c levels.

In conclusion, GA could be a better marker for glycemic control than glycated hemoglobin, especially for evaluating glycemic excursion in type 1 and type 2 diabetes. Postprandial glucose excursion is known to be a risk factor for diabetic micro- and macro-angiopathy in diabetic patients. Further studies are required to determine the usefulness of GA as an indicator of diabetic complications.

Acknowledgements

We wish to thank Dr. Takuji Kouzuma (Asahi Kasei Pharma) for technical assistance and critical discussion. We also thank Ms. Chikayo Yokogawa for excellent secretarial work.
References


