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The Ratio of Glycated Albumin to HbA1c is Correlated with Diabetes Duration According to Decreases in Insulin Secretion in Patients with Autoimmune Type 1 Diabetes and Type 2 Diabetes

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Abstract

Glycated albumin (GA) is a marker of glycemic control that reflects postprandial plasma glucose levels and glycemic excursions better than HbA1c. However, no reports have examined correlations between diabetes duration and the ratio of glycated albumin to HbA1c (GA/HbA1c ratio) in patients with autoimmune type 1 diabetes (T1AD) or type 2 diabetes (T2D). We conducted a cross-sectional study involving 219 patients with T1AD and 141 patients with T2D. We evaluated correlations between diabetes duration, the GA/HbA1c ratio and fasting serum C-peptide immunoreactivity (CPR), index of insulin secretion capacity. The GA/HbA1c ratio was significantly correlated with diabetes duration in both T1AD and T2D patients (T1AD; R=0.139, p<0.001, T2D; R=0.340, p<0.001). Fasting serum CPR was inversely correlated with diabetes duration (T1AD: R=-0.280, p<0.001; T2D: R=-0.349, p<0.001) as well as the GA/HbA1c ratio (T1AD: R=-0.240, p<0.001; T2D: R=-0.378, p<0.001) in both T1AD and T2D patients. We firstly reported that the GA/HbA1c ratio was positively correlated with diabetes duration in both T1AD and T2D patients. Insulin secretion capacity might influence this relationship.

Abbreviations: T1AD: Autoimmune Type 1 Diabetes; T2D: Type 2 Diabetes; BMI: Body Mass Index; GA: Glycated Albumin; GA/HbA1c ratio: Ratio of GA to Hba1c; CPR: C-Peptide Immunoreactivity

Introduction

Insulin secretion in pancreatic β cells progressively decreases with longer disease duration in both autoimmune type 1 diabetes (T1AD) and type 2 diabetes (T2D) [1,2] Cardiovascular disease and microvascular complications also increase with longer diabetes duration [3] and decrease quality of life. An association between glycemic excursions with the onset and progression of cardiovascular disease and microvascular complications has recently been reported [4-6]. Therefore, treatment to prevent glycemic excursions with drugs that improve postprandial plasma glucose levels is now considered important. HbA1c is currently used as the main determinant of glycemic control in diabetes treatment [7]. However, HbA1c primarily reflects mean blood glucose levels over time and does not reflect glycemic excursions. On the other hand, glycated albumin (GA), another glycemic control indicator, correlates with maximum blood glucose levels in both T1AD and T2D and reflects glycemic excursions as well as mean blood glucose [8,9]. Recent interest has focused on the usefulness of the GA/HbA1c ratio (corrected for HbA1c) in diabetes treatment as a marker to reflect glycemic excursions [8,10-12].

We previously reported that decreased endogenous insulin secretion in pancreatic β cells is associated with an increase in the GA/HbA1c ratio [13,14]. Considering that both T1AD and T2D is associated with a progressive decrease in endogenous insulin secretion, an increase in the GA/HbA1c ratio would be expected among patients with a longer duration of diabetes. Although the time until insulin dependence in T1AD patients is shorter than in T2D patients, endogenous insulin secretion would also be expected to influence the

relationship between the GA/HbA1c ratio and diabetes duration in T1AD patients. However, a correlation between the GA/HbA1c ratio and diabetes duration has not previously been reported in not only T2D patients but also T1AD patients.

In this study, we investigated whether there is a correlation between the GA/HbA1c ratio and diabetes duration in T1AD and T2D patients. We also examined whether endogenous insulin secretion influenced this relationship.

Materials and Methods

Study patients, Study design and Setting

We conducted a cross-sectional study of 219 patients with T1AD and 141 patients with T2D in Saitama Social Insurance Hospital and Kinki Central Hospital, respectively. The T1D patients were positive for anti-glutamic acid decarboxylase antibodies and/or anti-islet antigen 2 antibodies. We only included participants with stable glycemic control, defined as HbA1c level changes within 0.5%, with no change of medication, and stable body weight, defined as body weight change within 1 kg, during the previous 3 months. We excluded participants

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complicated with chronic liver disease; renal disease (including ≥ stage 3 diabetic nephropathy); thyroid disorder; anemia; malignant tumor; and corticosteroid treatment because these disorders (conditions) may lead to abnormal HbA1c and/or GA levels [10]. This study was approved by the Ethics Committee of Saitama Social Insurance Hospital and Kinki Central Hospital, and written informed consent was obtained from all patients.

Measurements

Clinical characteristics such as gender, age, height, and diabetes duration were obtained from medical records. Body weight was measured at outpatient visits, and body mass index (BMI) was calculated. Blood tests were performed during outpatient visits to measure serum GA, HbA1c, and serum C-peptide immunoreactivity (CPR) levels after overnight fasting at registration. 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. Serum GA levels were determined by enzymatic methods using albumin-specific protease, ketoamine oxidase, and albumin assay reagents (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) [16]. Fasting serum CPR levels were determined using a chemiluminescent enzyme immunoassay (Fujirebio, Inc., Tokyo, Japan) as described previously [13].

Statistical analysis

Data are presented as mean ± SD for continuous variables or numbers and percentages for categorical variables. We used the Mann Whitney's U test for continuous variables and the chi-square test for categorical variables to compare patient characteristics between the T1AD and T2D groups. We analyzed correlations of diabetes duration, GA/HbA1c ratio, and fasting serum CPR using the Pearson correlation coefficient. A p value of <0.05 was considered statistically significant. All analyses were performed using Stata SE 11 data analysis and statistical software (StataCorp LP, College Station, TX, USA).

Results

Clinical characteristics of participants

Clinical characteristics of participants are shown in Table 1. Compared with the T2D group, the T1AD group had significantly more females, was significantly younger, and had a significantly lower BMI. However, diabetes duration did not differ significantly between the groups.

In terms of glycemic control markers, HbA1c did not differ significantly between the groups (T1AD: 7.5 ± 1.0%, T2D: 7.6 ± 0.9%, p=0.415), but GA was significantly higher in the T1AD patients than the T2D patients (T1AD: 23.3 ± 4.5%, T2D: 20.7 ± 3.4%, p<0.001). As a result, the GA/HbA1c ratio was also significantly higher in the T1AD patients than the T2D patients (T1AD: 3.08 ± 0.34, T2D: 2.72 ± 0.35, p<0.001). In addition, the fasting serum CPR, measured as an index of endogenous insulin secretion, was significantly lower in the T1AD patients (T1AD: 0.16 ± 0.33 ng/mL, T2D: 2.29 ± 1.02 ng/mL, p<0.001).

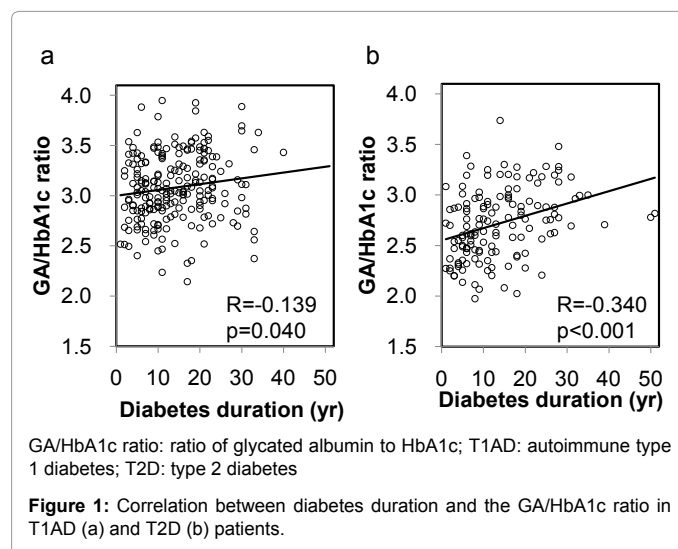### Correlation among diabetes duration, GA/HbA1c ratio, and serum CPR

The GA/HbA1c ratio was significantly positively correlated with diabetes duration in both T1AD and T2D patients (T1AD: R=0.139, p=0.040, T2D: R=0.340, p<0.001). In addition, for both groups combined (T1AD and T2D), the GA/HbA1c ratio was significantly positively correlated with diabetes duration (R=0.209, p<0.001).

Fasting serum CPR was significantly negatively correlated with diabetes duration in both T1AD and T2D patients (T1AD: R= -0.280, p<0.001, T2D: R= -0.349, p<0.001; Figure 2). There was also a significant negative correlation between the GA/HbA1c ratio and fasting serum CPR in both groups (T1AD, R= -0.240; p<0.001, T2D, R= -0.378, p<0.001; Figure 3). Moreover, compared with results

|	T1AD patients	T2D patients	p value
Number	219	141	-
Gender (Male/Female)	85/134	91/50	<0.001
Age (years)	43.9 ± 15.4	63.7 ± 10.8	<0.001
BMI (kg/m^2)	20.1 ± 2.9	24.2 ± 3.9	<0.001
Diabetes duration (years)	14.1 ± 8.2	13.8 ± 9.7	0.718
HbA1c (%)	7.5 ± 1.0	7.6 ± 0.9	0.415
GA (%)	23.3 ± 4.5	20.7 ± 3.4	<0.001
GA/HbA1c ratio	3.08 ± 0.34	2.72 ± 0.35	<0.001
Fasting CPR (ng/mL)	0.16 ± 0.33	2.29 ± 1.02	<0.001

T1AD: Autoimmune Type 1 Diabetes; T2D: Type 2 Diabetes; BMI: Body Mass Index; GA: Glycated Albumin; GA/HbA1c ratio: Ratio of GA to Hba1c; CPR: C-Peptide Immunoreactivity

Table 1: Clinical characteristics of study patients.

GA/HbA1c ratio: ratio of glycated albumin to HbA1c; T1AD: autoimmune type 1 diabetes; T2D: type 2 diabetes

Figure 1: Correlation between diabetes duration and the GA/HbA1c ratio in T1AD (a) and T2D (b) patients.
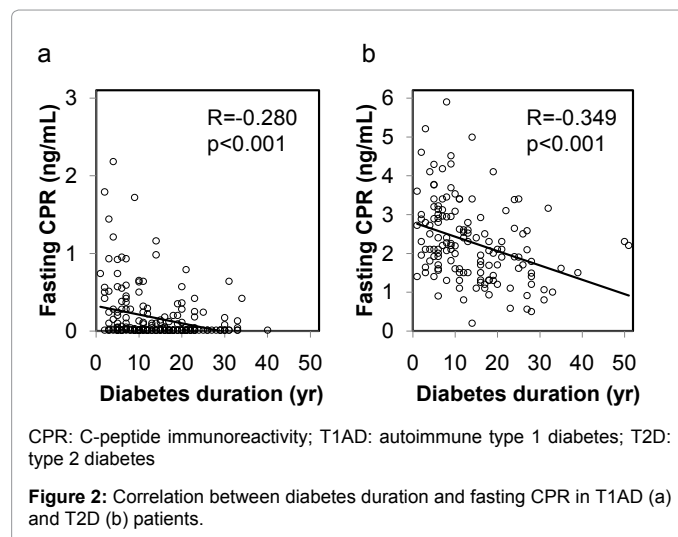
CPR: C-peptide immunoreactivity; T1AD: autoimmune type 1 diabetes; T2D: type 2 diabetes

Figure 2: Correlation between diabetes duration and fasting CPR in T1AD (a) and T2D (b) patients.
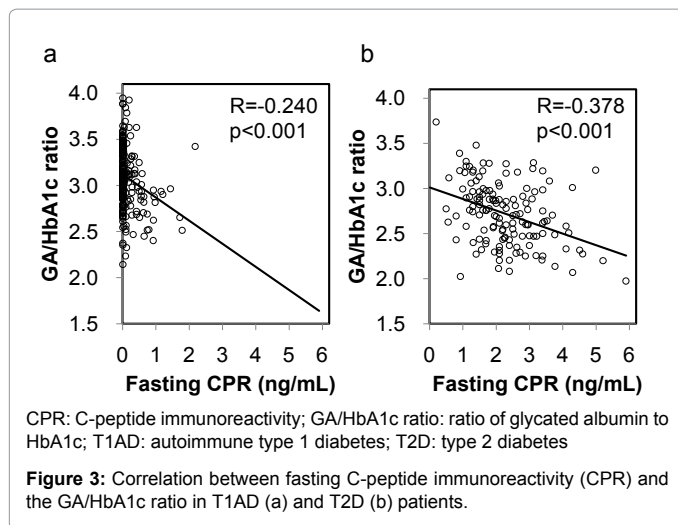
CPR: C-peptide immunoreactivity; GA/HbA1c ratio: ratio of glycated albumin to HbA1c; T1AD: autoimmune type 1 diabetes; T2D: type 2 diabetes

Figure 3: Correlation between fasting C-peptide immunoreactivity (CPR) and the GA/HbA1c ratio in T1AD (a) and T2D (b) patients.

analyzed by diabetes type, results for both groups combined showed an even stronger correlation (R= -0.529, p<0.001).

Discussion

This study was the first study to examine the correlation between the GA/HbA1c ratio and diabetes duration. We found that the GA/HbA1c ratio was significantly positively correlated with diabetes duration in both T1AD and T2D patients (Figure 1). In addition, there were significant negative correlations in both T1AD and T2D patients between fasting serum CPR and diabetes duration, and between fasting serum CPR and the GA/HbA1c ratio. These findings suggest that endogenous insulin secretion influences the relationship between the GA/HbA1c ratio and diabetes duration.

Endogenous insulin secretion is known to progressively decrease with longer disease duration in both T1AD and T2D patients [1,2]. Oxidative stress, which is related to glucose excursions, is considered to be one of the causes of the decrease in insulin secretion in pancreatic β cells in both T1AD and T2D patients [17]. Previous studies have shown a significant negative correlation between endogenous insulin secretion and the GA/HbA1c ratio (a marker for glycemic excursions) [12-14,18]. Thus, an increase in the GA/HbA1c ratio with longer diabetes duration would be expected regardless of diabetes type. However, the correlation between the GA/HbA1c ratio and diabetes duration, and the influence of endogenous insulin secretion on that relationship has not previously been investigated. Our study results are the first to support the above hypothesis.

Our study found a weaker correlation between the GA/HbA1c ratio and diabetes duration in T1AD compared with T2D patients. The reason is because in T1AD patients, as compared with T2D patients, endogenous insulin secretion decreases more rapidly, with progression to insulin dependence in a shorter time. In other words, in T1AD patients with long duration of disease, endogenous insulin secretion has already been depleted. Therefore, the GA/HbA1c ratio does not change, thus leading to a weaker correlation between the GA/HbA1c ratio and diabetes duration. In fact, in this study 116 (53.5%) of the 219 T1AD patients had complete depletion of endogenous insulin secretion (defined as fasting serum CPR ≤ 0.01 ng/mL). Diabetes duration ranged from 2 to 40 years.

A limitation of this study is that endogenous insulin secretion was assessed only using fasting serum CPR. For accurate assessment of

endogenous insulin secretion, it has recently been recommended that in addition to a fasting serum CPR, a glucagon tolerance test and a meal tolerance test also be performed, with measurement of CPR levels after loading [19]. In particular, in T1AD patients with complete depletion of endogenous insulin secretion, these tolerance tests may detect very slight differences in insulin secretion. Therefore, evaluation of insulin secretion should include these tolerance tests in future.

In conclusion, our study is the first to demonstrate a sequence of events in which insulin secretion decreases with longer diabetes duration, followed by an associated increase in the GA/HbA1c ratio, a glycemic excursions marker, in both T1AD and T2D patients. Taking into account the association between glycemic excursions and the onset and progression of diabetic complications, aggressive treatment at an early stage, in both T1AD and T2D patients, is necessary to prevent a loss of endogenous insulin secretion.

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