

Glycated Albumin and Glycated Hemoglobin Are Influenced Differently by Endogenous Insulin Secretion in Patients With Type 2 Diabetes

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OBJECTIVE — Glycated albumin (GA) relative to A1C is a useful marker of short-term glycemic control. We investigated whether endogenous insulin secretion in type 2 diabetes has different effects on GA and A1C levels.

RESEARCH DESIGN AND METHODS — A1C, GA, and GA-to-A1C ratio were compared in 202 type 2 diabetic patients by type of treatment. Effect of β -cell function determined by homeostasis model assessment (HOMA-% β) on GA-to-A1C ratio was examined. In addition, GA-to-A1C ratio was compared between type 2 diabetic patients and 16 patients with type 1 diabetes.

RESULTS — In type 2 diabetic patients, GA-to-A1C ratio was significantly higher in those treated with insulin than in those treated with diet or oral hypoglycemic agents. HOMA-% β showed a significant inverse correlation with GA-to-A1C ratio. This ratio was higher in type 1 diabetic patients than in type 2 diabetic patients.

CONCLUSIONS — In diabetic patients with decreased insulin secretion, serum GA levels are higher relative to A1C.

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A1C is used clinically as a parameter of glycemic control state over the previous 1–2 months (1). Measurement of A1C may be affected by conditions that shorten the life span of erythrocytes and variant hemoglobin, causing erroneous values for glycemic control (2). As other markers of glycemic control, serum glycated albumin (GA) and serum fructosamine are useful to reflect shorter-term glycemic control (~2 weeks) (3). However, these glycated proteins do not accurately reflect glycemic control in disorders of albumin metabolism.

Recently, GA-to-A1C ratio has been reported to be significantly higher in patients with type 1 diabetes than in those with type 2 diabetes, indicating that se-

rum GA is a more sensitive marker than A1C for glucose excursions (4). The underlying mechanism may involve marked fluctuation in plasma glucose levels associated with decreased insulin secretion in type 1 diabetic patients (4). The present study investigated whether endogenous insulin secretion has different effects on GA and A1C levels.

RESEARCH DESIGN AND METHODS

This study enrolled 202 outpatients with type 2 diabetes (119 male subjects and 83 female subjects) as diagnosed based on American Diabetes Association criteria (5). Exclusion criteria were variation >0.5% in A1C values during the previous 3 months, chronic liver disease, renal disease, thyroid disorder, ane-

mia, and corticosteroid treatment. The mean age was 64.2 ± 10.7 years, BMI was 24.2 ± 3.7 kg/m², and duration of diabetes was 13.1 ± 9.7 years. Treatment involved diet alone in 41 patients, oral hypoglycemic agents (OHAs) in 112 patients, and insulin in 49 patients. Fasting C-peptide and fasting plasma glucose were measured, and β -cell function was quantified using homeostasis model assessment (HOMA-% β) (6). In addition, GA-to-A1C ratio was compared between the 202 type 2 diabetic patients and 16 type 1 diabetic patients (8 male subjects and 8 female subjects, aged 60.6 ± 14.0 years, BMI 22.7 ± 2.8 kg/m², and all receiving insulin therapy).

Serum fasting C-peptide was determined by chemiluminescent enzyme-immunoassay (Fujirebio, Tokyo, Japan). A1C was measured with an ADAMS-A_{1C} HA-8160 automatic A1C analyzer (Arkray, Kyoto, Japan) based on high-performance liquid chromatography. Serum GA was determined by a Hitachi 7600 autoanalyzer (Hitachi Instruments Service, Tokyo, Japan) based on an enzymatic method using an albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan).

RESULTS — We compared A1C, GA, and GA-to-A1C ratio in 202 type 2 diabetic patients with type of treatment. Both A1C and GA were significantly higher in 49 patients treated with insulin and in 112 patients treated with OHAs than in 41 patients treated with diet alone (data not shown). By contrast, GA-to-A1C ratio did not differ between patients treated with OHAs (2.86 ± 0.34) and those treated with diet alone (2.79 ± 0.28), and it was significantly higher in patients treated with insulin (3.00 ± 0.37) than in those treated with OHAs ($P < 0.05$) and those treated with diet alone ($P < 0.01$). In multivariate analysis performed with sex, age, BMI, and insulin therapy as explanatory variables for GA-to-A1C ratio in type 2 diabetic patients, BMI, age, and insulin treatment were identified as inde-

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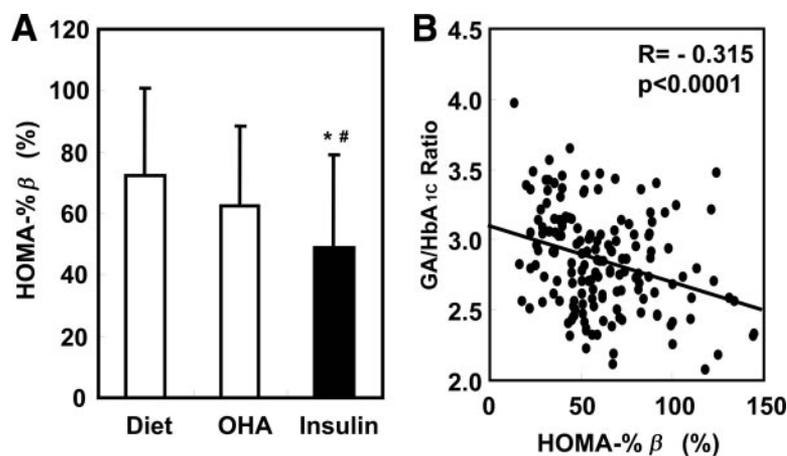


Figure 1—HOMA-% β by treatment type in patients with type 2 diabetes (A) and its correlation between this score and GA-to-A1C ratio (B). The HOMA-% β was calculated from fasting plasma glucose and serum fasting C-peptide concentrations using the correct HOMA evaluation and a computer program (7). Treatment involved diet alone in 41 patients, OHA in 112 patients, and insulin in 49 patients. * $P < 0.001$ vs. diet, # $P < 0.001$ vs. OHA.

pendent explanatory variables (data not shown). GA-to-A1C ratio was significantly higher in 16 type 1 diabetic patients (3.15 ± 0.26) than in 202 type 2 diabetic patients (2.87 ± 0.36) ($P < 0.001$) but showed no significant difference compared with 49 type 2 diabetic patients treated with insulin. By power analyses, each number of patients was found statistically adequate to make the conclusions when the analytical power was set at 80%.

HOMA-% β was significantly lower in type 2 diabetic patients treated with insulin than in those treated with diet alone and those treated with OHAs (Fig. 1A). A significant inverse correlation was observed between GA-to-A1C ratio and HOMA-% β (Fig. 1B). Stepwise multivariate analysis including HOMA-% β , sex, age, and BMI to identify explanatory variables for GA-to-A1C ratio showed that BMI ($\beta = -0.203$, $F = 9.6$, $P = 0.015$), age ($\beta = 0.215$, $F = 8.2$, $P = 0.006$), and HOMA-% β ($\beta = -0.237$, $F = 6.4$, $P = 0.020$) were found to be independent explanatory variables.

CONCLUSIONS— Our findings suggest that decreased endogenous insulin secretion is involved in elevated GA-to-A1C ratios. Yoshiuchi et al. (4) reported that in type 1 diabetic patients, glucose excursions or maximum glucose levels based on diurnal plasma glucose variations influence GA-to-A1C ratios. In addition, GA-to-A1C ratio in 158 subjects with normal glucose tolerance was 2.73 ± 0.22 in our previous study (7), significantly lower than that in 202 type 2

diabetic patients in the present study. Together with these findings, it is suggested that decreased insulin secretion may increase the GA-to-A1C ratio by causing marked glucose excursions.

The reasons why serum GA reflects postprandial hyperglycemia better than A1C are unknown. The shortened life span of erythrocytes in patients with diabetes and poor glucose control (8), lagging GLUT1-mediated glucose uptake by erythrocytes resulting in a relatively lower degree of rise in A1C (9), different glycation rates between albumin and hemoglobin (10), and the direct effect of insulin and OHAs on serum albumin metabolism (11) may be involved.

In the present study, BMI was an independent negative risk for GA-to-A1C ratio, as we previously reported (7,12), and was significantly lower in type 2 diabetic patients treated with insulin and type 1 diabetic patients than in type 2 diabetic patients treated with OHA or diet alone. Thus, elevated GA-to-A1C ratio in type 2 diabetic patients treated with insulin and type 1 diabetic patients may be caused by a lower BMI. However, adjustment of GA-to-A1C ratio by BMI gave the same conclusions (data not shown).

In the Diabetes Control and Complications Trial (DCCT), type 1 diabetic patients treated with intensive insulin therapy had a markedly reduced prevalence of diabetic retinopathy and macrovascular complications compared with those who had the same A1C levels treated with conventional insulin therapy (13). The reason proposed was that intensive insulin therapy decreased glycemic

excursions thus emphasizing the need to reduce glucose fluctuations. If serum GA levels had been measured in that study, the relationship between serum GA levels and the diabetes complications in intensive versus conventional insulin therapy would have been an interesting observation.

Postprandial hyperglycemia reportedly increases the prevalence of cardiovascular diseases (14). If serum GA is higher relative to A1C in the state of postprandial hyperglycemia, serum GA may offer a better surrogate marker of cardiovascular risk. Along this line, it has recently been reported that serum GA was significantly elevated in patients with coronary artery stenosis (15).

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