

Glycosylated albumin and glycosylated hemoglobin are differently influenced by endogenous insulin secretion in patients with type 2 diabetes mellitus

Running title: Endogenous insulin secretion and glycosylated proteins

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Objective: Glycated albumin (GA) relative to glycosylated hemoglobin (HbA_{1C}) is a useful marker of short-term glycemic control. We investigated whether endogenous insulin secretion in type 2 diabetes mellitus (T2DM) has different effects on GA and HbA_{1C} levels.

Research Design and Methods: HbA_{1C}, GA and GA/HbA_{1C} ratio were compared in 202 T2DM patients by type of treatment. Effect of beta-cell function determined by homeostasis model assessment (HOMA-%β) on GA/HbA_{1C} ratio was examined. In addition, GA/HbA_{1C} ratio was compared between T2DM patients and 16 patients with type 1 diabetes mellitus (T1DM).

Results: In T2DM patients, GA/HbA_{1C} 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/HbA_{1C} ratio. This ratio was higher in T1DM patients than in T2DM patients.

Conclusions: In diabetic patients with decreased insulin secretion, serum GA levels are higher relative to HbA_{1C}.

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

Recently, GA/HbA_{1C} ratio has been reported to be significantly higher in patients with type 1 diabetes mellitus (T1DM) than in those with type 2 diabetes mellitus (T2DM), indicating that serum GA is a more sensitive marker than HbA_{1C} for glucose excursions (4). The underlying mechanism may involve marked fluctuation in plasma glucose levels associated with decreased insulin secretion in T1DM patients (4). The present study investigated whether endogenous insulin secretion has different effects on GA and HbA_{1C} levels.

RESEARCH DESIGN AND METHODS

This study enrolled 202 outpatients with T2DM (119 men and 83 women), as diagnosed based on the American Diabetes Association (ADA) criteria (5). Exclusion criteria were: variation >0.5% in HbA_{1C} values during the previous 3 months; chronic liver disease; renal disease; thyroid disorder; anemia; and corticosteroid treatment. Age was 64.2±10.7 years, body mass index (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 beta-cell function was quantified using homeostasis model assessment (HOMA-%β) (6). In addition, GA/HbA_{1C} ratio was compared between the 202 T2DM patients and 16 T1DM patients (8 men and 8 women; age: 60.6±14.0 years; BMI: 22.7±2.8 kg/m²; all receiving insulin therapy).

Serum fasting C-peptide was determined by chemiluminescent enzyme-immunoassay (CLEIA) (Fujirebio Inc., Tokyo, Japan). HbA_{1C} was measured with an ADAMS-A_{1C} HA-8160 automatic HbA_{1C} analyzer (Arkray Inc., Kyoto, Japan) based on high-performance liquid chromatography. Serum GA was determined by a Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., 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 Co., Tokyo, Japan).

RESULTS

We compared HbA_{1C}, GA and GA/HbA_{1C} ratio in 202 T2DM patients by type of treatment. Both HbA_{1C} and GA were significantly higher in 49 patients treated with insulin and in 112 patients with OHA than in 41 patients with diet alone (data not shown). By contrast, GA/HbA_{1C} ratio did not differ between patients treated with OHA (2.86±0.34) and those with diet alone (2.79±0.28), and was significantly higher in patients treated with insulin (3.00±0.37) than in those with OHA (p<0.05) and those with diet alone (p<0.01). In multivariate analysis performed with sex, age, BMI, and insulin therapy as explanatory

variables for GA/HbA_{1C} ratio in T2DM patients, BMI, age, and insulin treatment were identified as independent explanatory variables (data not shown). GA/HbA_{1C} ratio was significantly higher in 16 T1DM patients (3.15±0.26) than in 202 T2DM patients (2.87±0.36) ($p<0.001$), but showed no significant difference compared to 49 T2DM 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 T2DM patients treated with insulin than in those treated with diet alone and those treated with OHA (Fig. 1A). A significant inverse correlation was observed between GA/HbA_{1C} ratio and HOMA-%β (Fig. 1B). Stepwise multivariate analysis including HOMA-%β, sex, age and BMI to identify explanatory variables for GA/HbA_{1C} 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/HbA_{1C} ratios. Yoshiuchi *et al.* (4) reported that in T1DM patients, glucose excursions or maximum glucose levels, based on diurnal plasma glucose variations, influence GA/HbA_{1C} ratios. In addition, we previously showed that GA/HbA_{1C} ratio 2.73±0.22 in 158 subjects with normal glucose tolerance (NGT) (7), which was significantly lower than that in 202 T2DM patients in the present study. Together with these findings, it is suggested that decreased insulin secretion may increase the GA/HbA_{1C} ratio by causing marked glucose excursions.

The reasons why serum GA reflects postprandial hyperglycemia better than HbA_{1C} are unknown. The shortened lifespan of erythrocytes in patients with diabetes and poor glucose control (8), lagging GLUT1-mediated glucose uptake by erythrocyte resulting in a relatively lower degree of rise in HbA_{1C} (9), different glycation rates between albumin and hemoglobin (10), and a 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/HbA_{1C} ratio, as we previously reported (7,12), and was significantly lower in T2DM patients treated with insulin and T1DM patients than in T2DM patients treated with OHA or with diet alone. Thus, elevated GA/HbA_{1C} ratio in T2DM patients treated with insulin and T1DM patients may be caused by a lower BMI. However, adjustment of GA/HbA_{1C} ratio by BMI gave the same conclusions (data not shown).

In the Diabetes Control and Complications Trial, T1DM patients treated with intensive insulin therapy had a markedly reduced prevalence of diabetic retinopathy and macrovascular complications, compared to those who had the same HbA_{1C} levels treated with conventional insulin therapy (13). The reason proposed was because 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 diabetic complications in intensive vs. 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 HbA_{1C} in the state of postprandial hyperglycemia, serum GA may offer a better surrogate marker of cardiovascular risk. Along this line, it has been recently reported that serum GA was significantly elevated in patients with coronary artery stenosis (15).

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FIGURE LEGENDS

Figure 1: HOMA-%β by treatment type in patients with T2DM (A) and its correlation between this score and GA/HbA_{1C} 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, oral hypoglycemic agent (OHA) in 112 patients, and insulin in 49 patients. *p<0.001 vs. diet, #p<0.001 vs. OHA.

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Figure 1.

