Body Mass Index Negatively Influences Glycated Albumin, but not Glycated Hemoglobin, in Diabetic Patients

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Abstract. Measurement of serum glycated albumin (GA) is accepted as an alternative method to evaluate chronic glycemic control in diabetic patients in whom measurement of HbA1c is inadequate for some reason. Although GA levels are known to be influenced by serum albumin turnover besides glycemia, little is known about the physiological and pathological conditions affecting GA levels. This study was aimed to prove the effects of body mass index (BMI) on GA measurement in diabetic patients. We studied 209 patients with type 2 diabetes mellitus whose HbA1c levels had been stable for at least the past three months. In the study patients HbA1c and GA levels were found to be correlated to one another. Fasting plasma glucose (FPG) was significantly correlated with HbA1c and GA. BMI showed a significant negative correlation with GA levels, whereas there was no correlation of BMI with HbA1c levels. Multivariate regression analyses revealed that only FPG was positively correlated with HbA1c, while FPG was positively and BMI was negatively correlated with GA. Only BMI was negatively correlated with the ratio of GA to HbA1c. These results clearly demonstrate that GA levels are negatively influenced by BMI in diabetic patients.

Key words: Glycated albumin, HbA1c, Body mass index

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serum GA levels in diabetic patients.

In this investigation, we elucidated for the first time that body mass index (BMI) negatively influences GA levels but not HbA$_{1c}$ levels in adult diabetic patients.

### Subjects and Methods

**Patients studied**

A total of 426 Japanese patients (248 males and 178 females) with diabetes mellitus (20 patients with type 1 diabetes mellitus and 406 patients with type 2 diabetes mellitus) as defined by American Diabetes Association criteria [15] were studied. The study patients were randomly selected from patients visiting the Kinki Central Hospital during the period from August 2004 to January 2005. Their GA and HbA$_{1c}$ levels were measured. Among them, we excluded patients with malignant diseases, chronic liver diseases, thyroid disorders or hematological diseases, and those with systemic corticosteroid use. We also excluded patients having renal diseases except for diabetic nephropathy with microalbuminuria. Microalbuminuria was defined on the basis of the determination of urinary albumin excretion from at least two subsequent specimens of randomly collected urine samples as 30–299 µg per mg creatinine [16].

In order to minimize the effects of diabetic treatments on time-dependent variations of HbA$_{1c}$ and GA levels, we selected patients whose HbA$_{1c}$ levels had been stable for at least the past three months: The variations of HbA$_{1c}$ in the past three monthly-determinations were less than 0.5%. There were 209 patients (124 males and 85 females; 7 with type 1 diabetes mellitus and 202 with type 2 diabetes mellitus) who satisfied the above admission criteria. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. The institutional review board approved this study, and all the patients gave their informed consent.

**Laboratory methods**

Blood samples were obtained after overnight fasting. Plasma glucose levels were determined by standard laboratory assays. HbA$_{1c}$ was measured by HPLC [17] with use of ADAMS-A$_{1c}$ HA-8160 (Arkray Inc., Kyoto, Japan). Interassay coefficient variations were 0.85% and 0.67%, respectively, as determined by representative blood samples (5.3% and 10.4% of HbA$_{1c}$). GA was determined by enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [18, 19], with the use of Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan). Interassay coefficient variations were 1.38% and 1.32%, respectively, as determined in representative serum samples (13.3% and 34.9% of GA).

**Analytical methods**

Data represent means ± SD. To analyze the effects of confounding variables on HbA$_{1c}$, GA and ratio of GA to HbA$_{1c}$, univariate regression analysis as well as stepwise multivariate regression analysis was performed with StatView computer program (Abacus Concepts, Berkeley, CA, USA). In the stepwise multivariate regression analyses, the F-value for the inclusion of the variables was set at 4.0. In these regression analyses, the explanatory variables were age, sex (setting of female at 0 and of male at 1), BMI and FPG. P<0.05 was considered to be statistically significant.

### Results

The clinical characteristics of 209 study patients are shown in Table 1. Their age averaged 64.0 ± 10.9 years and BMI 24.1 ± 3.7 kg/m$^2$. Known duration for diabetes mellitus was 12.9 ± 9.6 years. Twenty-eight patients were treated with diet therapy alone, 120 with

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>209</th>
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<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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<tr>
<td>Known diabetes duration (years)</td>
<td>12.9 ± 9.6 (0–50)</td>
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<tr>
<td>Diabetes treatment at study</td>
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<tr>
<td>diet</td>
<td>28</td>
<td></td>
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<tr>
<td>oral hypoglycemic agents (OHA)</td>
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<td></td>
</tr>
<tr>
<td>insulin</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>OHA + insulin</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>7.8 ± 2.0 (4.2–18.6)</td>
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<tr>
<td>HbA$_{1c}$ (%)</td>
<td>7.1 ± 0.9 (4.7–10.7)</td>
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<tr>
<td>GA (%)</td>
<td>20.6 ± 3.6 (12.4–33.3)</td>
<td></td>
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<tr>
<td>Ratio of GA to HbA$_{1c}$</td>
<td>2.88 ± 0.36 (2.07–4.04)</td>
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</table>

Data are means ± SD (ranges) or number.

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KOGA et al.
oral hypoglycemic agents (OHA), 40 with insulin and 21 with OHA plus insulin. Averaged fasting plasma glucose (FPG) was 7.8 ± 2.0 mmol/l. HbA$_{1c}$ and GA levels were 7.1 ± 0.9% and 20.6 ± 3.6%, respectively.

As shown in Fig. 1A, there was a positive correlation between FPG and HbA$_{1c}$ levels ($R = 0.485$, $P<0.0001$). There was also a positive correlation between FPG and GA levels ($R = 0.406$, $P<0.0001$) (Fig. 1B). GA was strongly correlated with HbA$_{1c}$ in the study patients ($R = 0.690$, $P<0.0001$) (Fig. 2).

Surprisingly, we found a significant negative correlation of BMI with GA levels ($R = 0.252$, $P<0.001$) (Fig. 3A). A significant negative correlation of BMI with ratio of GA to HbA$_{1c}$ was also observed ($R = 0.354$, $P<0.0001$) (Fig. 3B). Stepwise multivariate regression analyses revealed that, among confounding variables, only FPG was positively correlated with HbA$_{1c}$ while BMI was negatively correlated with GA (Table 2). Only BMI was negatively correlated with ratio of HbA$_{1c}$ to GA, by stepwise multivariate regression analysis (Table 2).

**Discussion**

In this study, we aimed to clarify the effects of confounding variables on measurement of HbA$_{1c}$ and GA levels in 209 diabetic patients. In order to avoid disparate results of HbA$_{1c}$ and GA levels related to recent fluctuation of plasma glucose levels, we selected patients whose glycemic control had been stable for at least the past three months. In our study patients there

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![Fig. 1](image1.png) Correlation of FPG with HbA$_{1c}$ levels (A) and GA levels (B) in 209 diabetic patients.

![Fig. 2](image2.png) Correlation of HbA$_{1c}$ levels with GA levels in 209 diabetic patients.

![Fig. 3](image3.png) Correlation of BMI with HbA$_{1c}$ levels (A), GA levels (B) and ratio of GA to HbA$_{1c}$ levels (C) in 209 diabetic patients.
was a strong positive correlation between HbA\textsubscript{1c} and GA, indicating that the study populations were relatively uniform in terms of their ability to glycate hemoglobin and albumin. Although FPG was positively correlated with both glycated proteins, the correlation of FPG with GA was found to be slightly weaker than that with HbA\textsubscript{1c}. It lead us to speculate that variable(s) other than plasma glucose levels are also involved in the GA measurement. Among the other confounding variables of age, sex and BMI, only BMI was found to be negatively correlated with GA. The negative correlation was independent of the other variables by stepwise multivariate regression analysis. On the other hand, BMI was never correlated with HbA\textsubscript{1c}.

Measurement of HbA\textsubscript{1c} is known as a valuable tool for monitoring chronic glycaemia over the preceding 2–3 months and has become a mainstay of clinical testing for evaluation of glycemic control in diabetic patients [20]. By contrast, measurement of GA has yet to be adopted in wide spread clinical use. Serum GA levels reflect shorter-term glycemic control than HbA\textsubscript{1c} and are not affected by erythrocyte turnover [4]. Additionally, it has been shown that GA is a more sensitive index than HbA\textsubscript{1c} [21] and probably responds more quickly than HbA\textsubscript{1c} to changes in glycaemia because of a shorter half-life and a greater tendency of serum albumin to become glycated [6, 22, 23]. Thus, GA measurement provides additional information to HbA\textsubscript{1c} measurement, and has some advantages to monitor glycemic control more accurately especially in diabetic patients with abnormalities of erythrocyte turnover.

GA measurement is also influenced by the half-life of serum albumin [13]. Increased turnover of serum albumin results in lower GA levels in relation to glycaemia and conversely serum GA levels may be higher in conditions of decreased albumin turnover [14]. Therefore, serum GA levels should be interpreted cautiously in cases with disorders showing abnormal albumin turnover, such as nephrotic syndrome, hypothyroidism, hyperthyroidism and liver cirrhosis [14]. Our results clearly demonstrated that BMI is a factor negatively influencing serum GA levels independent of plasma glucose levels in diabetic patients but it never affects HbA\textsubscript{1c} levels. Thus the influence of BMI on glycated protein levels was not uniform. This is supported by evidence that BMI also independently showed a negative correlation with the ratio of GA to HbA\textsubscript{1c}.

At present, the reasons for the negative influence of BMI on GA but not HbA\textsubscript{1c} are unknown. A possible explanation is that turnover of serum albumin may be increased in obese subjects, which sets serum GA at lower levels relative to plasma glucose concentrations. Chronic low-grade systemic inflammation is involved in obesity [24]. Inflammation is known to decrease the rate of albumin synthesis and to increase its catabolic rate [25]. Thus, chronic inflammatory process may provide a mechanism for increased turnover of serum albumin in obese subjects. Another possibility is the effect of obesity on serum albumin levels. It is known that the serum albumin level influences its own catabolism in such a way that lower serum concentrations of albumin are catabolized substantially more slowly [26]. We found that serum albumin levels showed a weak but significant negative correlation with serum GA levels (R = −0.158, P = 0.024), which seems consistent with previous observations [13]. However, we failed to find a significant correlation between serum albumin level and BMI in our study patients (R = 0.046, P = 0.500). Thus, it is unlikely that increased serum albumin levels per se contribute to increased turnover of serum albumin in obese diabetic patients.

After submission of our manuscript, it has been reported that serum GA levels are low in obese, non-diabetic children compared with non-obese, non-diabetic children [27]. Thus, the negative influences of obesity on serum GA levels are observed in both adult diabetic patients and non-diabetic children.

In conclusion, we demonstrated for the first time that BMI is negatively correlated with GA but not with HbA\textsubscript{1c} in adult patients with diabetes mellitus. This observation provides important information for clinical care of diabetic patients. For the interpretation of serum GA levels of the diabetic patients, their BMI should be considered.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial regression coefficient</th>
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<tbody>
<tr>
<td>HbA\textsubscript{1c}</td>
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<tr>
<td>FPG (mmol/l)</td>
<td>0.485</td>
<td>41.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>GA</td>
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<tr>
<td>FPG (mmol/l)</td>
<td>0.417</td>
<td>30.0</td>
<td>&lt;0.0001</td>
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<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>−0.237</td>
<td>9.75</td>
<td>&lt;0.01</td>
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<tr>
<td>Ratio of GA to HbA\textsubscript{1c}</td>
<td>−0.285</td>
<td>12.0</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
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Confounding variables are age (years), sex (female, 0; male, 1), BMI (kg/m\textsuperscript{2}) and fasting plasma glucose (FPG) (mmol/l).
Acknowledgements

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References