Serum glycated albumin, but not glycated hemoglobin, is low in relation to glycemia in men with hypertriglyceridemia

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ABSTRACT

Aims/Introduction: Serum glycated albumin (GA) and glycated hemoglobin (HbA$_{1c}$) are influenced by plasma glucose levels, and are used for monitoring chronic glycemic control in diabetic patients. Both glycated proteins are known to be influenced by various factors other than plasma glucose levels. In the present study, we examined the effects of hypertriglyceridemia on them.

Materials and Methods: The present study comprised 273 non-diabetic men. They were grouped into men with normotriglyceridemia (serum triglyceride [TG] <150 mg/dL) and those with hypertriglyceridemia (serum TG ≥150 mg/dL).

Results: Body mass index (BMI) and high sensitivity C-reactive protein (hs-CRP) were significantly higher in the 160 men with hypertriglyceridemia than the 113 men with normotriglyceridemia. In men with hypertriglyceridemia, as compared with those with normotriglyceridemia, fasting plasma glucose, 2-h plasma glucose after 75 g oral glucose tolerance test, and HbA$_{1c}$ were significantly higher. By contrast, serum GA was significantly lower in men with hypertriglyceridemia. BMI-adjusted serum GA was also significantly lower in these men. In a multivariate analysis, serum TG was an inverse explanatory variable for serum GA.

Conclusions: Serum GA is low in relation to plasma glucose levels in men with hypertriglyceridemia. This might be caused by increased albumin metabolism associated with hypertriglyceridemic state. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00049.x, 2010)

KEY WORDS: Glycated albumin, Glycated hemoglobin, Triglyceride

INTRODUCTION

Glycation of proteins is increased in diabetic patients compared with non-diabetic subjects. Some glycated proteins have been shown to play a role in the development and progression of chronic diabetic complications[1]. Among various glycated proteins, glycated hemoglobin (HbA$_{1c}$) is widely used as a clinical parameter of chronic glycemic control[2,3]. From the results of the Diabetes Control and Complications Trial (DCTT), it is that HbA$_{1c}$ be maintained at <7.0% in order to prevent the development and progression of diabetic complications[4]. As the average lifespan of erythrocytes is approximately 120 days, the HbA$_{1c}$ level reflects the glycemic control state over the past 1–2 months. HbA$_{1c}$ values are affected not only by plasma glucose (PG) levels, but also by the shortened lifespan of erythrocytes (e.g., hemolytic anemia, renal anemia and hepatic cirrhosis) and variant hemoglobin. Thus, under these conditions, HbA$_{1c}$ gives erroneous values and is unsuitable as a glycemic control marker[5,6].

Serum glycated albumin (GA) has recently become used as another glycemic control marker. As the half-life of serum albumin is shorter than that of erythrocytes (17 days), GA reflects shorter-term glycemic control (about 2 weeks) as compared with HbA$_{1c}$. Thus, serum GA has been positioned as a more useful indicator than HbA$_{1c}$ for assessing shorter-term changes in glycemic control[7]. HbA$_{1c}$ is inadequate for the evaluation of glycemic control states in patients who receive hemodialysis for chronic renal insufficiency and pregnant women, because its levels are affected by anemia. In contrast, serum GA is not affected by hemoglobin metabolism[8] and thus it has been shown to be useful as a glycemic control marker in these conditions[9–11]. However, serum GA does not accurately reflect glycemic control in disorders influencing serum albumin metabolism (e.g., nephrotic syndrome, hepatic cirrhosis and thyroid dysfunction)[12–14].

Serum GA has been shown to set low in relation to PG levels in obese subjects[14–16]. We previously reported a significant inverse correlation between body mass index (BMI) and serum GA in non-diabetic subjects, independent of PG levels[17]. High sensitivity C-reactive protein (hs-CRP), which was elevated in obese subjects, also showed an inverse correlation with serum GA levels. It shows that chronic microinflammation leads to

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increased albumin catabolism[18] and thereby set serum GA lower in relation to PG levels[17]. Furthermore, we have shown that in smoking subjects and hyperuricemic subjects, both of whom showed elevated hs-CRP, serum GA was low relative to PG levels[19,20]. Thus, we speculated that the same mechanism might be involved in lower serum GA levels relative to PG levels in obese subjects, smoking subjects and hyperuricemic subjects.

Hypertriglyceridemia is also known to be a condition associated with elevated hs-CRP[21]. Therefore, we hypothesized that serum GA is low in relation to PG levels in hypertriglyceridemic subjects and analyzed their serum GA levels, in comparison with HbA_{1c}.

MATERIALS AND METHODS

Subjects
The present study comprised 273 non-diabetic men recruited from subjects undergoing routine medical examinations at Kinki Central Hospital, Hyogo, Japan, between July and August 2008. Subjects with diabetes were excluded, because measurement of glycated protein is greatly affected in them. A 75-g oral glucose tolerance test (OGTT) was carried out in all subjects, and glucose tolerance status was evaluated according to American Diabetes Association criteria[22]. Subjects being treated with medications for dyslipidemia were excluded. Mean age was 48.4 ± 6.4 years, and mean body mass index (BMI) was 24.5 ± 2.9 kg/m^2. Subjects with serum triglyceride (TG) <150 mg/dL were defined as those with normotriglyceridemia, and ≥150 mg/dL as those with hypertriglyceridemia. The institutional committee approved the protocol of this study and all participants gave their written informed consent.

Laboratory Methods
Height, bodyweight and waist circumstance were measured on the same day at the health examination. Blood pressure was measured with an automatic sphyngmanometer in the sitting position after 5 min of rest. Fasting blood was collected from subjects between 9.00 and 11.00 h, and was centrifuged immediately for measurements. Plasma glucose, serum uric acid, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and serum TG were determined by means of standard laboratory assays. HbA_{1c} was measured with ADAMS-A_{1c} HA-8160 (Arkray, Kyoto, Japan), by high performance liquid chromatography[16,23]. Inter-assay coefficient variations were 0.85 and 0.67%, respectively, as determined in representative blood samples (5.3 and 10.4% HbA_{1c}). Serum GA was determined by Hitachi 7600 autoanalyzer (Hitachi Instruments Service, Tokyo, Japan), by the enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan)[16,24]. Inter-assay coefficient variations were 1.38 and 1.32%, respectively, as determined in representative serum samples (13.3 and 34.9% GA). We previously reported that BMI negatively regulates serum GA levels[16,17]. Therefore, we calculated the BMI-adjusted serum GA levels using the data from non-diabetic

subjects[17]. High sensitivity-CRP was determined by means of latex-enhanced immunonephelometrics on a BNII Analyzer (Dade Behring, Marburg, Germany), as described previously[25].

Statistical Analysis
All data are shown as means ± SD. To correct for skewed distributions, plasma hs-CRP concentrations were logarithmically transformed. For statistical analyses, unpaired Student's t-test was used to compare the two groups. To analyze the effects of explanatory variables on HbA_{1c}, GA or hs-CRP, univariate regression analysis as well as stepwise multivariate regression analysis was carried out using STATVIEW software (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA, USA). In the stepwise multiple regression analysis, the F-value for the inclusion of the variables was set at 4.0. A P-value of <0.05 was considered to be statistically significant.

RESULTS
HbA_{1c}, but not serum GA, showed a significant positive association with fasting plasma glucose (FPG) and OGTT 2 h-PG. HbA_{1c} also showed a significant positive association with body-weight, BMI, waist circumference, hs-CRP and serum TG, whereas serum GA showed a significant inverse association with these variables. In addition, HbA_{1c} was inversely but serum GA was positively associated with HDL cholesterol (Table 1).

There were 113 men with normotriglyceridemia and 160 with hypertriglyceridemia. Age did not significantly differ between both groups, but BMI and waist circumference were significantly higher in men with hypertriglyceridemia (BMI 25.6 ± 2.9 vs

Table 1 | Univariate regression analyses on HbA_{1c} and serum glycated albumin in 273 non-diabetic men

	HbA_{1c}		GA	
	R	P	R	P
Bodyweight	0.287	<0.0001	−0.241	<0.0001
BMI	0.308	<0.0001	−0.288	<0.0001
Waist circumstance	0.295	<0.0001	−0.284	<0.0001
hs-CRP (log transformed)	0.178	0.0033	−0.226	0.0002
Systolic blood pressure	0.148	0.0146	−0.039	0.5184
Diastolic blood pressure	0.189	0.0017	0.021	0.7336
Serum TG	0.125	0.0392	−0.271	<0.0001
LDL cholesterol	0.180	0.0028	−0.118	0.0523
HDL cholesterol	−0.153	0.0115	0.205	0.0007
FPG	0.480	<0.0001	0.117	0.0531
OGTT 2-h PG	0.476	<0.0001	0.090	0.1361
HbA_{1c}	–	–	0.248	<0.0001
Serum GA	0.248	<0.0001	–	–
BMI-adjusted serum GA	0.356	<0.0001	–	–

BMI, body mass index; FPG, fasting plasma glucose; GA, glycated albumin; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PG, plasma glucose; TG, triglyceride.
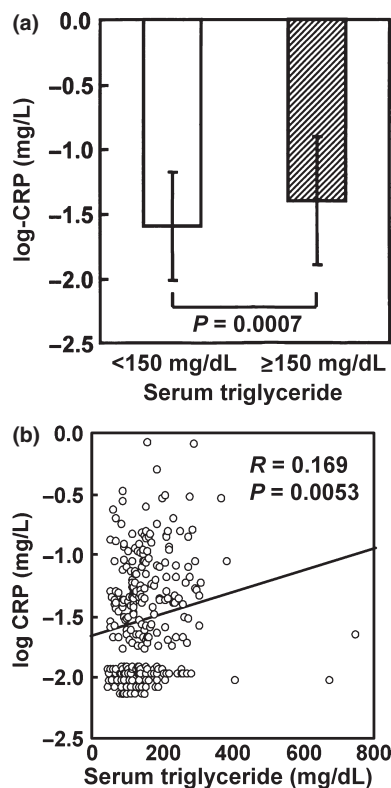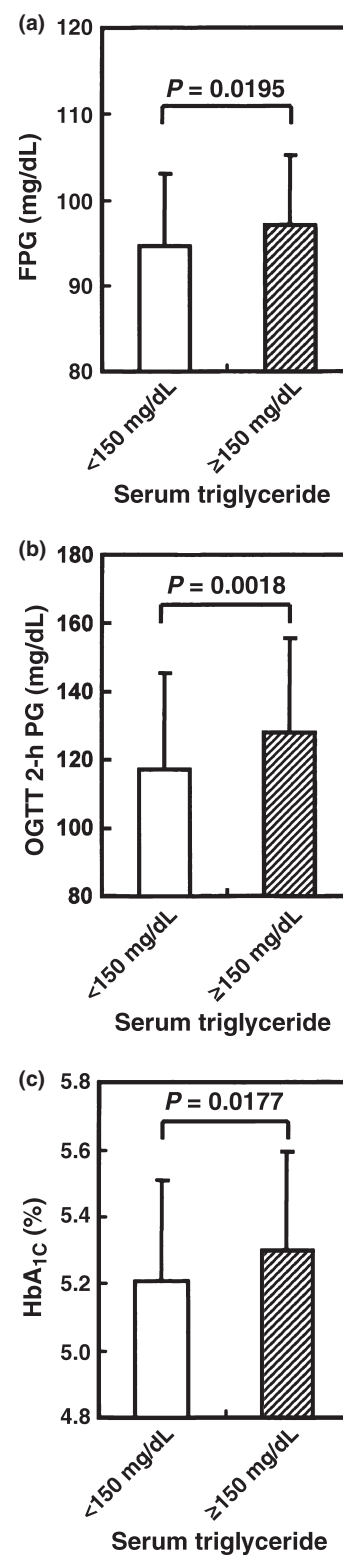
Figure 1 | (a) High sensitivity C-reactive protein levels in 113 men with normotriglyceridemia (serum triglyceride <150 mg/dL; open column) and 160 men with hypertriglyceridemia (serum triglyceride ≥150 mg/dL; closed column) and (b) their correlation with serum triglyceride.

23.7 ± 2.6 kg/m^2, $P < 0.0001$; waist circumference 89.0 ± 7.8 *vs* 84.0 ± 7.7 cm, $P < 0.0001$). In men with hypertriglyceridemia, hs-CRP was significantly higher than in those with normotriglyceridemia ($-0.4 ± 0.5$ *vs* $-1.6 ± 0.4$ log-mg/L, $P = 0.0007$). There was a significant positive correlation between serum TG and hs-CRP ($R = 0.169$, $P = 0.0053$; Figure 1).

In men with hypertriglyceridemia, as compared with men with normotriglyceridemia, FPG (97 ± 8 *vs* 95 ± 8 mg/dL, $P = 0.0195$), OGTT 2-h PG (128 ± 28 *vs* 117 ± 29 mg/dL, $P = 0.0018$) and HbA$_{1c}$ (5.3 ± 0.3 *vs* 5.2 ± 0.3%, $P = 0.0177$) were significantly higher (Figure 2). In contrast, serum GA was significantly lower in men with hypertriglyceridemia (13.7 ± 0.9 *vs* 14.3 ± 1.2%, $P < 0.0001$; Figure 3a). BMI-adjusted serum GA was also significantly lower in men with hypertriglyceridemia, as compared with men with normotriglyceridemia (14.3 ± 1.1 *vs* 14.7 ± 1.1%, $P = 0.0045$; Figure 3b). In men with normotriglyceridemia, HbA$_{1c}$ ($R = 0.405$, $P < 0.0001$) and serum GA ($R = 0.207$, $P = 0.0277$) showed a significant positive association with FPG, whereas in men with hypertriglyceridemia, HbA$_{1c}$ ($R = 0.512$, $P < 0.0001$), but not serum GA ($R = 0.128$, $P = 0.1059$), showed significant positive association with FPG.

Stepwise multivariate regression analyses were carried out with HbA$_{1c}$ and serum GA as objective variables. The results

Figure 2 | (a) Fasting plasma glucose (FPG), (b) oral glucose tolerance test (OGTT) 2-h plasma glucose (PG) and (c) glycated hemoglobin (HbA$_{1c}$) levels in 113 men with normotriglyceridemia (serum triglyceride <150 mg/dL; open column) and 160 men with hypertriglyceridemia (serum triglyceride ≥150 mg/dL; closed column).
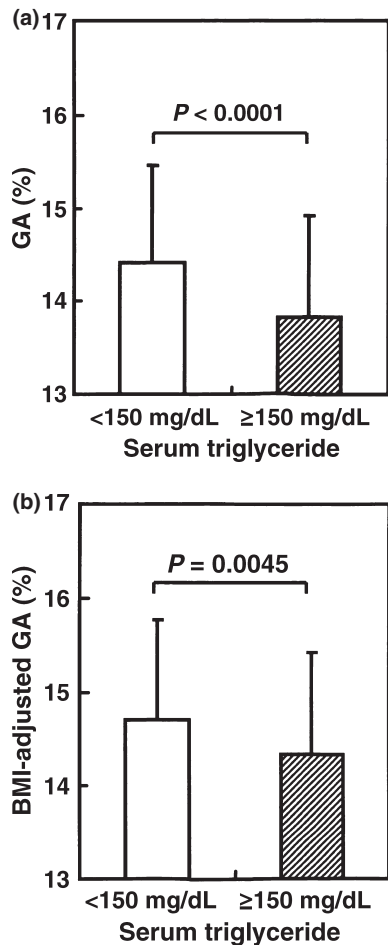
Figure 3 | (a) Serum glucose albumin (GA) and (b) body mass index (BMI)-adjusted serum GA levels in 113 men with normotriglyceridemia (serum triglyceride <150 mg/dL; open column) and 160 men with hypertriglyceridemia (serum triglyceride ≥150 mg/dL; closed column).

Table 2 | Stepwise multivariate regression analyses on glycated hemoglobin levels in 273 non-diabetic men

	β	F	P
Serum GA	0.274	29.8	<0.0001
OGTT 2-h PG	0.272	26.7	<0.0001
FPG	0.268	25.9	<0.0001
BMI	0.228	19.0	<0.0001
LDL cholesterol	0.136	8.2	0.0096

An objective variable is glycated hemoglobin (HbA_{1c}) and explanatory variables are age (years), body mass index (BMI; kg/m^2), serum glucose albumin (GA; %), fasting plasma glucose (FPG; mg/dL), oral glucose tolerance test (OGTT) 2-h plasma glucose (PG; mg/dL), serum triglyceride (TG; mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and serum uric acid (mg/dL). $R^2 = 0.421$, $F = 38.8$ and $P < 0.0001$.

Table 3 | Stepwise multivariate regression analyses on serum glycated albumin levels in 273 non-diabetic men

	β	F	P
HbA_{1c}	0.307	28.7	<0.0001
BMI	−0.268	19.9	<0.0001
Age	0.182	11.4	0.0020
Serum uric acid	−0.126	5.0	0.0225
Serum TG	−0.131	5.0	0.0243
HDL cholesterol	0.116	4.3	0.0826

An objective variable is serum glycated albumin and explanatory variables are age (years), body mass index (BMI; kg/m^2), glycated hemoglobin (HbA_{1c}; %), fasting plasma glucose (FPG; mg/dL), oral glucose tolerance test (OGTT) 2-h plasma glucose (PG; mg/dL), serum triglyceride (TG; mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and serum uric acid (mg/dL). $R^2 = 0.300$, $F = 19.0$ and $P < 0.0001$.

showed that serum GA and HbA_{1c} were significant positive explanatory variables for each other. Fasting plasma glucose, OGTT 2h-PG, BMI and LDL cholesterol were significant positive variables for HbA_{1c} (Table 2), whereas serum TG, in addition to BMI and serum uric acid, was a significant negative explanatory variable for serum GA (Table 3).

DISCUSSION
Hypertriglyceridemia, in addition to diabetes, hypertension and hyperuricemia, is more prevalent in obese subjects[26], and it has been proposed to be an element of metabolic syndrome[27]. In the present study, BMI and waist circumference were higher in men with hypertriglyceridemia than in those with normotriglyceridemia. This suggests that visceral fat accumulation was accelerated in men with hypertriglyceridemia. Thus, in these subjects, impaired glucose tolerance would be expected to be more prevalent. In the present study targeted non-diabetic men, FPG, 2-h PG and HbA_{1c}, were higher in men with hypertriglyceridemia

than those with normotriglyceridemia. In contrast to these results, serum GA was significantly lower in men with hypertriglyceridemia, suggesting that some factor(s) independent of PG levels affect serum GA in men with hypertriglyceridemia. As serum GA is shown to be inversely correlated with BMI[15–17], we also determined BMI-adjusted values. The results showed that BMI-adjusted serum GA remained significantly lower in men with hypertriglyceridemia than in men with normotriglyceridemia. Multivariate analysis showed serum TG to be an independent negative factor for serum GA. The discrepant results between HbA_{1c} and GA in men with hypertriglyceridemia raise a question as to which is a suitable glycemic index in these subjects. To reveal this, a continuous glucose monitoring system[28] could clearly show the role of triglyceridemia on HbA_{1c} and GA levels.

Hypertriglyceridemia is considered a risk factor for arteriosclerosis[29,30], and patients with hypertriglyceridemia have been

shown to have elevated hs-CRP levels[21]. The present study also showed that hs-CRP was higher in men with hypertriglyceridemia, compared with those with normotriglyceridemia, and serum TG was a significant positive explanatory variable for hs-CRP. Furthermore, there has been a shown significant inverse association of hs-CRP with serum GA, but not with HbA_{1c}[17,18]. The present findings suggest that low serum GA levels are related to chronic inflammation associated with conditions showing hypertriglyceridemia.

In conclusion, the present study showed that serum TG levels influenced serum GA, but not HbA_{1c}, independent of PG levels in non-diabetic men. The present study was carried out in non-diabetic men, and thus the results cannot be simply extrapolated in diabetic patients. However, if similar results are also observed in diabetic patients, caution is necessary for evaluating serum GA levels in diabetic patients with hypertriglyceridemia. Furthermore, most patients with type 2 diabetes are overweight or obese and have metabolic syndrome traits including hypertriglyceridemia, and thus serum GA levels might be set lower in relation to glycemia in these patients.

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