Association of glycated albumin with the presence of carotid plaque in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: Postprandial hyperglycemia is a potent risk factor for cardiovascular disease. Serum glycated albumin (GA) has been reported to reflect postprandial blood glucose fluctuations. In the present study, we assessed the possible correlation of GA with the presence of carotid plaque to evaluate the potential clinical usefulness of GA for predicting atherosclerotic cardiovascular complications in patients with type 2 diabetes.

Materials and Methods: Patients with type 2 diabetes ($n = 236$) admitted to Nippon Medical School Hospital (Tokyo, Japan) for glycemic control (aged 19–86 years, 81 females and 155 males) were examined. Clinical measurements were taken on admission. The presence of carotid plaque was assessed by ultrasonography.

Results: In patients with carotid plaque ($n = 154$), GA ($P = 0.023$) was higher than those without carotid plaque ($n = 82$). In contrast, neither fasting plasma glucose ($P = 0.48$) nor glycated hemoglobin ($P = 0.41$) was significantly different between the groups. The results of logistic regression analysis showed that GA (age- and sex-adjusted odds ratio [95% confidence interval], 1.05 [1.01–1.09]; $P = 0.017$) and glycated hemoglobin (1.17 [1.01–1.37]; $P = 0.036$) were significantly associated with the presence of carotid plaque.

Conclusions: The positive correlation of serum GA with the presence of carotid plaque in type 2 diabetes suggests that GA will serve as a useful clinical marker for predicting diabetic cardiovascular complications. (J Diabetes Invest, doi: 10.1111/jdi.12085, 2013)

KEY WORDS: Carotid plaque, Glycated albumin, Type 2 diabetes mellitus

INTRODUCTION

Glycated hemoglobin (HbA_{1c}) is regarded as a gold standard for monitoring glycemic control. Most expert committees now recommend the use of HbA_{1c} in the diagnosis of diabetes[1]. Although the overall usefulness of HbA_{1c} is well accepted, epidemiological data suggest that HbA_{1c} is not always versatile for predicting all types of diabetic complication; namely, whereas HbA_{1c} is a good predictor of microvascular complications, it appears to be less so for macrovascular outcomes[2]. One interpretation is that the fluctuation of blood glucose contributes more to macrovascular diabetic complications than time-averaged blood glucose concentration represented by HbA_{1c}[2]. Postprandial acute glucose fluctuations are postulated to contribute to the pathogenesis of atherosclerotic cardiovascular complications through the induction of oxidative stress and consequent endothelial dysfunction[3–5].

Whereas glycation of hemoglobin in erythrocytes (i.e., HbA_{1c}) might not reflect blood glucose fluctuations, several reports have shown that glycation of serum albumin reflects the glycemic excursions[6,7]. The glycation of serum proteins has been long assessed by the measurement of fructosamine; however, the reduction reaction-based colorimetric assay is influenced by protein concentration and other coexisting substances in serum[8]. For assessing serum protein glycation more accurately, glycated albumin (GA) assay has been developed. GA was originally analyzed by high-performance liquid chromatography (HPLC), but it can currently be determined with automated clinical analyzers by a rapid and specific enzymatic method[9]. The measurement of GA is now available for monitoring glycemic control in patients with diabetes under public health insurance coverage in Japan. GA can be a potential index for predicting cardiovascular events, as it reflects blood glucose fluctuations better than HbA_{1c}[6,7]. Postprandial hyperglycemia is epidemiologically a more potent risk factor for diabetic cardiovascular complications than fasting plasma glucose (FPG)[10,11].

In the present study, we assessed the association of GA with the presence of carotid plaque, a surrogate marker for atherosclerotic disease, to evaluate the potential usefulness of the measurement of GA for predicting cardiovascular complications in type 2 diabetes.

MATERIALS AND METHODS

Participants

Patients with type 2 diabetes who were admitted to Nippon Medical School Hospital (Tokyo, Japan) for glycemic control during 2005–2012 were enrolled in the present study ($n = 236$, aged 19–86 years, 81 females and 155 males). Exclusion criteria included diabetic nephropathy stage 3 or higher (urinary albumin exertion ≥300 mg/g·Cr [spot], or ≥300 mg/day; Joint Committee of the Japan Diabetes Society and the Japanese Society of Nephrology[12]), uncontrolled endocrine disease, steroid treatment, ketoacidosis, estimated primary hyperlipidemia, malignant disease, anemia (hemoglobin <10.0 g/dL) and other systemic disorders. The present study was approved by the Institutional Review Board, and all participants were enrolled after giving informed consent.

Clinical Measurements

All participants underwent a physical examination including height, bodyweight and blood pressure on the first morning of admission. Blood sample was taken after an overnight fast. FPG, HbA_{1c} and serum GA were measured by the glucose oxidase method (ADAMS Glucose GA-1170; Arkray, Kyoto, Japan), HPLC (ADAMS A1c HA-8160; Arkray) and an enzymatic method using albumin-specific proteinase and ketoamine oxidase (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan), respectively. HbA_{1c} level was expressed as the percentage value of the National Glycohemoglobin Standardization Program according to the guideline of the Japan Diabetes Society[13,14]. GA was expressed as a percentage of total serum albumin. Serum total cholesterol, high-density lipoprotein (HDL)-cholesterol and triacylglycerol were measured enzymatically (Sekisui Medical, Tokyo, Japan). Low-density lipoprotein cholesterol concentration was calculated by the Friedewald formula[15]. Smoking habit (current, past or never) and type 2 diabetes duration were assessed by interview.

Carotid Ultrasonography

Carotid artery status was examined with high-resolution B-mode ultrasound systems (SDU-2000; Shimadzu, Kyoto, Japan; iU22 and EnVisor; Philips Healthcare, Andover, MA, USA; LOGIQ 7; GE Healthcare, Little Chalfont, England, UK) equipped with linear transducers with a frequency of 3–12 MHz as previously described[16]. Carotid plaque was defined as a focal intima-media thickening ≥1.0 mm with marked protrusion into the lumen.

Statistical Analysis

Continuous variables are expressed as means ± standard deviation or median (interquartile range) for variables with normal or skewed distribution, respectively. Differences in clinical data between participants with and without carotid plaque were assessed by Student's t-test, Mann–Whitney U-test or χ^2-test as appropriate. Correlations between GA and other continuous variables were examined by Pearson's correlation analysis. A logistic regression model was applied to determine the odds ratio for the presence of carotid plaque. A P-value of <0.05 was considered as significant. All analyses were carried out with JMP software (version 9.0; SAS Institute, Cary, NC, USA).

RESULTS

Of 236 participants enrolled in the present study, 154 (65%) had carotid plaque. The clinical characteristics for each group are shown in Table 1. In the participants with carotid plaque, age was higher and the duration of type 2 diabetes was longer than in those without carotid plaque. Body mass index (BMI) was lower in the participants with carotid plaque compared with those without. In glycemic control indices, GA and GA-to-HbA_{1c} ratio (GA/HbA_{1c}) were higher in the participants with carotid plaque than in those without, whereas neither FPG nor HbA_{1c} was significantly different between the two groups. With regard to diabetic complications, the participants with carotid plaque had a higher incidence of retinopathy or abnormal Achilles tendon reflex than those without. Regarding prehospital medication, a higher population of the participants with carotid plaque had been treated with an antihypertensive agent or antiplatelet agent than those without.

Table 2 shows Pearson's correlation coefficients between GA and other continuous variables. GA was positively correlated with FPG, HbA_{1c} and HDL-cholesterol, whereas inversely with systolic blood pressure, diastolic blood pressure and BMI.

Table 3 shows the results of logistic regression analysis for the presence of carotid plaque. Age, duration of type 2 diabetes, GA and GA/HbA_{1c} were positively associated with the presence of carotid plaque in unadjusted univariate analysis, whereas BMI was inversely associated with that. After the analysis was adjusted for age and sex, GA and HbA_{1c} were significant predictors of the carotid plaque presence. In contrast, no significant association was found between GA/HbA_{1c} and the presence of carotid plaque after the adjustment. To address the discrepancies between these glycemic control indices (GA, HbA_{1c} and GA/HbA_{1c}) and the carotid plaque presence with or without the adjustment, we analyzed the correlations between these glycemic control indices and age. Whereas no correlation was found between GA and age (Figure 1a), HbA1c was inversely correlated with age (Figure 1b). As a consequence, GA/HbA1c was positively correlated with age (Figure 1c).

DISCUSSION

HbA_{1c} and GA basically provide similar clinical information on recent glycemic control. However, owing to the shorter half-life of serum albumin than erythrocyte hemoglobin, GA reflects shorter-term blood glucose concentration (over 2–3 weeks) compared with HbA_{1c}, which reflects that over 2–3 months[17].

Table 1 | Clinical characteristics of the participants

Variable	All participants	Carotid plaque		P-value*
	(n = 236)	+ (n = 154)	− (n = 82)	
Age (years)	56 ± 13	60 ± 11	50 ± 14	<0.0001
Sex (female/male)	81/155	52/102	29/53	0.81
Duration of type 2 diabetes (years)	5 [0–11]	6 [1–15]	3 [0–10]	0.0069
Systolic blood pressure (mmHg)	127 ± 15	128 ± 15	125 ± 15	0.073
Diastolic blood pressure (mmHg)	75 ± 11	75 ± 10	74 ± 11	0.58
BMI (kg/m^2)	25.4 ± 4.9	24.8 ± 4.5	26.4 ± 5.6	0.014
Smoking habit, current or past (n [%])	148 [63]	102 [66]	46 [56]	0.13
Fasting plasma glucose (mmol/L)	9.79 ± 2.99	9.89 ± 3.04	9.60 ± 2.89	0.48
HbA$_{1c}$ (%)	10.3 ± 2.1	10.4 ± 2.1	10.1 ± 1.9	0.41
GA (%)	28.5 ± 8.4	29.4 ± 8.9	26.8 ± 7.0	0.023
GA/HbA$_{1c}$	2.74 ± 0.45	2.80 ± 0.45	2.63 ± 0.43	0.0037
Total cholesterol (mmol/L)	5.31 ± 1.06	5.28 ± 1.06	5.37 ± 1.07	0.55
HDL-cholesterol (mmol/L)	1.27 ± 0.35	1.26 ± 0.32	1.27 ± 0.41	0.89
LDL-cholesterol (mmol/L)†	3.26 ± 0.89	3.26 ± 0.89	3.25 ± 0.88	0.93
Non HDL-cholesterol (mmol/L)	4.05 ± 1.05	4.02 ± 1.04	4.10 ± 1.08	0.58
Triacylglycerols (mmol/L)	1.72 ± 0.94	1.68 ± 0.88	1.81 ± 1.05	0.31
Retinopathy (n [%])	49 [21]	41 [27]	8 [10]	0.0014
Albuminuria, >30 mg/mg·Cr (n [%])	36 [15]	26 [17]	10 [12]	0.33
Abnormal Achilles tendon reflex (n [%])	98 [42]	75 [49]	23 [28]	0.0019
Prehospital medication				
Insulin (n [%])	29 [12]	23 [15]	6 [7]	0.078
Oral hypoglycemic agent (n [%])	120 [51]	81 [53]	39 [48]	0.46
Statin (n [%])	47 [20]	36 [23]	11 [13]	0.061
Antihypertensive agent (n [%])	75 [32]	57 [37]	18 [22]	0.016
Antiplatelet agent (n [%])	26 [11]	23 [15]	3 [4]	0.0043

Continuous variables are expressed as means ± SD or median [interquartile range]. *For differences between the subjects with (+) and without (−) carotid plaque. †As low-density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula, three participants (one in + and two in –) with hypertriacylglycerolemia (≥4.5 mmol/L) were excluded from the statistical analysis of LDL-cholesterol. BMI, body mass index; GA, glycated albumin; GA/HbA$_{1c}$, glycated albumin-to-glycated hemoglobin ratio; HbA$_{1c}$, glycated hemoglobin; HDL, high-density lipoprotein.

GA should therefore be a more suitable index of glycemic control than HbA$_{1c}$ in cases where rapid changes might occur in blood glucose concentration; for example, when starting or changing diabetes treatments[6,9,18]. GA is also proposed as a useful measure of glycemic control in populations for whom HbA$_{1c}$ might not reflect glycemic status accurately; that is, anemics, those with hemoglobinopathies or neonates[19]. More intriguingly, GA has been reported to reflect blood glucose fluctuations[7,20]. A recent report clearly showed that GA, but not HbA$_{1c}$, was positively associated with glycemic excursions, which were assessed with 48-h continuous glucose monitoring[20].

Because GA has been reported to reflect blood glucose fluctuations and individuals with greater postprandial glycemic excursions are more likely to develop cardiovascular disease[10,11], GA might serve as a useful marker for predicting diabetic cardiovascular complications. A recent study actually reported that GA, but not HbA$_{1c}$, was associated with the increasing degree of coronary stenosis in type 2 diabetes[21]. The higher GA level in subjects with carotid plaque among the present participants (Table 1) also supports the clinical

usefulness of GA for evaluating the risk of cardiovascular complications.

The positive correlations of GA with other glycemic indices (FPG and HbA$_{1c}$) suggest that GA increases with the deterioration of overall glycemic control (Table 2). Furthermore, GA was associated with the presence of carotid plaque, and the association remained significant after the logistic regression model was adjusted for age and sex (Table 3). As a recent meta-analysis of prospective cohorts[22] and an additional relevant report[23] showed, there is no doubt that higher HbA$_{1c}$ level is associated with the risk of cardiovascular events in the general population without diabetes. However, in subjects with type 2 diabetes, epidemiological evidence indicates a weaker association of HbA$_{1c}$ with macrovascular outcomes than that with microvascular complications[24]. Ishizaka *et al.*[25] actually demonstrated that HbA$_{1c}$ level was strongly associated with the presence of carotid plaque in normal subjects (normal FPG and normal glucose tolerance); however, the association was not observed in subjects with diabetes or prediabetes. Similar to that report, no significant difference was found in HbA$_{1c}$ between the subjects with

Table 2 | Pearson's correlation coefficients between glycated albumin and other continuous variables

Variable	r	P-value
Age	0.0077	0.91
Duration of type 2 diabetes	−0.041	0.53
Systolic blood pressure	−0.19	0.0028
Diastolic blood pressure	−0.13	0.046
BMI	−0.39	<0.0001
Fasting plasma glucose	0.71	<0.0001
HbA$_{1c}$	0.83	<0.0001
Total cholesterol	0.11	0.10
HDL-cholesterol	0.15	0.022
LDL-cholesterol*	0.083	0.20
Non HDL-cholesterol	0.056	0.39
Triacylglycerols	−0.044	0.50

*Three participants were excluded from the statistical analysis of low-density lipoprotein (LDL)-cholesterol (see the footnote to Table 1). BMI, body mass index; HbA$_{1c}$, glycated hemoglobin; HDL, high-density lipoprotein.

and without carotid plaque in the present study (Table 1). As patients with poor glycemic control were enrolled in the present study, their higher HbA$_{1c}$ levels within a narrow range might be one reason for the lack of association. However, age- and sex-adjusted logistic regression analysis showed the association between HbA$_{1c}$ and carotid plaque prevalence (Table 3).

Even though we excluded patients with anemia (hemoglobin <10.0 g/dL) and renal failure (stage 3 or higher), HbA$_{1c}$ showed a significant inverse correlation with age in the present participants (Figure 1b). Several reports suggested that HbA$_{1c}$

can be affected by age[26,27] and ethnic group[28,29]. Recently, Khoo et al.[30] reported a discrepancy between the oral glucose tolerance test (OGTT) and HbA$_{1c}$ to diagnose diabetes in elderly populations. They suggested a higher false negative rate when diagnosing diabetes by HbA$_{1c}$ alone as compared with by OGTT. These results suggest that HbA$_{1c}$ alone is not enough to evaluate glycemic control, especially in elderly patients with type 2 diabetes. Conversely, as GA was not affected by age (Figure 1a), the measurement of GA might have clinical value for evaluating glycemic control more accurately, and for predicting atherosclerotic cardiovascular outcomes, especially in patients with type 2 diabetes.

As GA reflects blood glucose fluctuations better than HbA$_{1c}$[6,7], GA/HbA$_{1c}$ might reflect the postprandial glycemic response and could be useful for predicting diabetic complications[31]. Most recently, possible clinical use of both GA and GA/HbA$_{1c}$ for predicting the presence of carotid atherosclerosis[32] and the progression of intima-media thickness[33] were also reported in outpatients with type 2 diabetes. However, in the present study, the association between GA/HbA$_{1c}$ and the presence of carotid atherosclerosis was not significant after the adjustment for age and sex. Similarly, no significant correlation was found between GA/HbA$_{1c}$ and intima-media thickness after the adjustment (data not shown). One of the possible reasons for the differences from the previous reports[32,33] is the age distribution. Relative to the participants in those reports (aged 40–70 years and 53–68 years in the reports of Moon et al.[32] and Song et al.[33], respectively), the present participants had a wider age distribution (19–86 years). As HbA$_{1c}$ was inversely correlated with age (Figure 1b), GA/HbA$_{1c}$ (the index defined by reciprocal

Table 3 | Odds ratios of variables for the presence of plaque

Variable	Unadjusted		Age- and sex-adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per 1 year)	1.07 (1.04–1.09)	<0.0001		
Sex (male)*	1.07 (0.61–1.88)	0.81		
Duration of type 2 diabetes (per 1 year)	1.05 (1.01–1.09)	0.0050	1.01 (0.98–1.05)	0.51
BMI (per 1 kg/m^2)	0.93 (0.88–0.99)	0.015	0.98 (0.92–1.04)	0.49
Smoking habit (current or past)†	1.54 (0.89–2.66)	0.13	1.80 (0.97–3.37)	0.062
Fasting plasma glucose (per 1 mmol/L)	1.03 (0.94–1.13)	0.48	1.06 (0.96–1.17)	0.24
HbA$_{1c}$ (per 1%)	1.06 (0.93–1.21)	0.41	1.17 (1.01–1.37)	0.036
GA (per 1%)	1.04 (1.01–1.08)	0.020	1.05 (1.01–1.09)	0.017
GA/HbA$_{1c}$ (per 1)	2.57 (1.36–5.05)	0.0032	1.74 (0.87–3.60)	0.12
Total cholesterol (per 1 mmol/L)	0.93 (0.72–1.19)	0.55	1.00 (0.76–1.32)	0.98
HDL-cholesterol (per 1 mmol/L)	0.95 (0.45–2.05)	0.89	0.42 (0.17–1.01)	0.052
Non HDL-cholesterol (per 1 mmol/L)	0.93 (0.72–1.20)	0.58	1.09 (0.82–1.44)	0.56
LDL-cholesterol (per 1 mmol/L)‡	1.01 (0.75–1.38)	0.93	1.08 (0.78–1.52)	0.63
Triacylglycerols (per 1 mmol/L)	0.87 (0.65–1.15)	0.31	1.15 (0.85–1.59)	0.37

BMI, body mass index; CI, confidence interval; GA, glycated albumin; GA/HbA$_{1c}$, glycated albumin-to-glycated hemoglobin ratio; HbA$_{1c}$, glycated hemoglobin; HDL, high-density lipoprotein; OR, odds ratio. *Female as reference. †Never as reference. ‡Three participants were excluded from the statistical analysis of low-density lipoprotein (LDL)-cholesterol (see the footnote to Table 1).
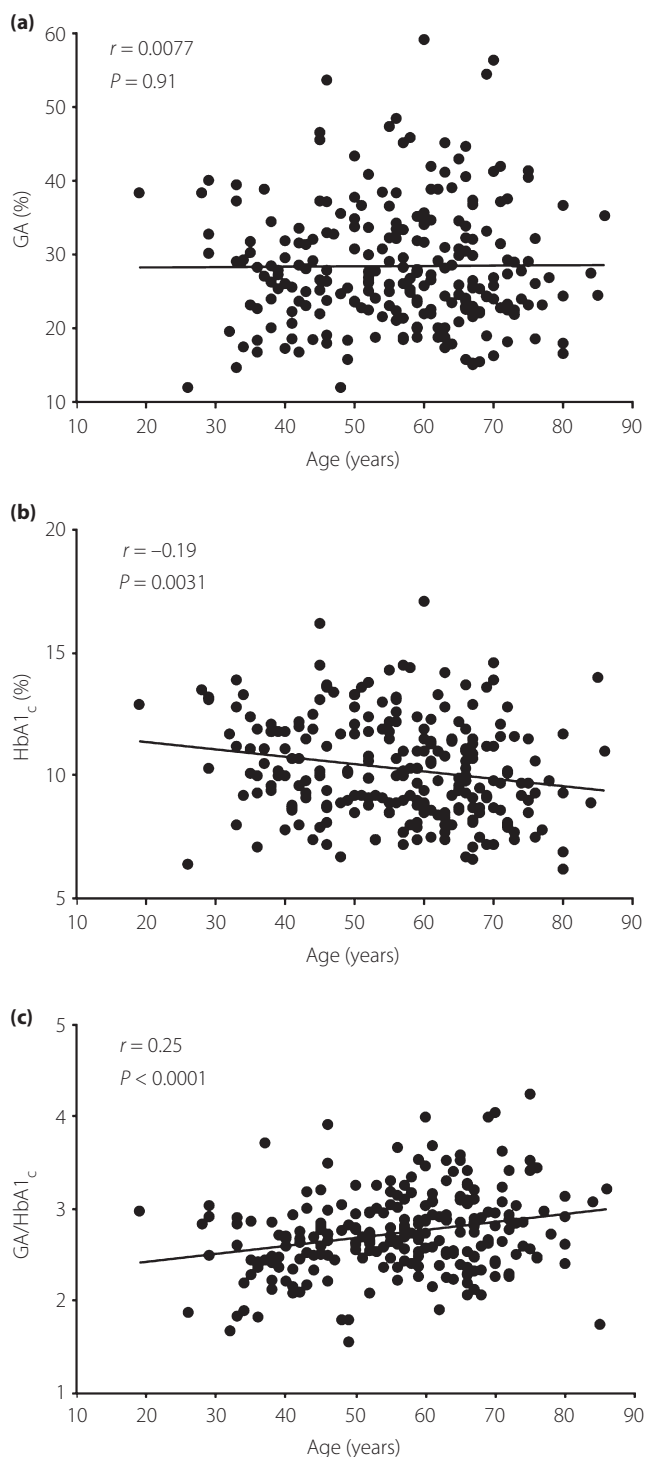
Figure 1 | Correlations of (a) glycated albumin (GA), (b) glycated hemoglobin (HbA$_{1c}$) and (c) GA-to-HbA$_{1c}$ ratio (GA/HbA$_{1c}$) with age in the participants. Pearson's correlation coefficient is shown in each panel.

value of HbA$_{1c}$) showed a positive correlation with age in the present study (Figure 1c). These results suggest that age-related differences among the glycemic control indices

should be taken into account for clinical use of GA/HbA$_{1c}$ as a surrogate marker of diabetic complications.

In the present study, BMI was inversely correlated with GA (Table 2). Although the reasons remain unknown, several reports also showed that BMI was inversely correlated with GA[34–36]. Further investigation into the causes of the relationship between GA and BMI might provide new insights into the interpretation of glycemic control indices in the research and clinical practice of diabetes and its complications.

In conclusion, the present results showed that GA and GA/HbA$_{1c}$ were higher in subjects with carotid plaque among patients with type 2 diabetes. Logistic regression analysis showed the positive association of GA and HbA$_{1c}$ with the presence of carotid plaque when the models were adjusted for age and sex. Because this was a cross-sectional study, the present data provide just a snapshot of each patient at admission; this is a limitation of the present study. As atherosclerotic lesion formation is a longitudinal event, the longstanding history of vascular conditions should be taken into account. Nevertheless, the present cross-sectional data should warrant further prospective investigation to evaluate the clinical usefulness of GA for predicting cardiovascular outcomes in patients with type 2 diabetes.

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