

# Glycated Albumin, Rather than HbA1c, Reflects Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

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## Abstract

**Background:** It has recently been shown that glycated albumin (GA) has some different aspects from HbA1c as an indicator of chronic glycemic control, besides it reflects shorter periods of glycemia. In this study, we investigated whether both indices of chronic glycemia are differently influenced by diabetic duration and diabetic vascular complications.

**Methods:** The present study included 63 patients with type 2 diabetes mellitus (40 men, 23 women) in whom HbA1c and GA were simultaneously measured every other month during a year. Annual mean levels of HbA1c, GA, and the GA/HbA1c ratio were determined, and the associations of these values with diabetes duration, diabetic retinopathy, and diabetic nephropathy were analyzed.

**Results:** Annual mean levels of the GA/HbA1c ratio were significantly correlated with diabetes duration, whereas those of HbA1c and GA were not associated with it. Annual mean levels of GA and the GA/HbA1c ratio were significantly higher in the patients with diabetic retinopathy than in those without it, whereas those of HbA1c were not different between both groups. Annual mean levels of HbA1c, GA and the GA/HbA1c ratio were not different between the patients with diabetic nephropathy and those without it. By multivariate regression analysis, GA as well as diabetic duration were explanatory variables for diabetic retinopathy.

**Conclusion:** These results indicate that GA, rather than HbA1c, reflects diabetic retinopathy in patients with type 2 diabetes mellitus.

**Keywords:** Type 2 diabetes mellitus; HbA1c; Glycated albumin; Diabetic retinopathy

**Abbreviations:** GA: Glycated Albumin; DCCT: Diabetes Control and Complications Trial; UKPDS: U.K. Prospective Diabetes Study; ACR: Urinary Albumin Creatinine Ratio; ARIC: Atherosclerosis Risk in Communities

## Introduction

Glycation is accelerating on various proteins in patients with diabetes mellitus, and some of the glycated proteins are indicated to be involved in the development and progression of chronic diabetic complications [1]. Of these glycated proteins, HbA1c is clinically used as a gold standard indicator of chronic glycemic control in diabetic patients [2,3]. Clinical studies such as Diabetes Control and Complications Trial (DCCT) study [4], the U.K. Prospective Diabetes Study (UKPDS) [5] and Kumamoto study [6] demonstrated that setting HbA1c at lower levels by strict glycemic control resulted in lowering risks of the development and progression of some diabetic complications.

Glycated albumin (GA) has been recently used as another clinical indicator of glycemic control [7]. Since the half-life of serum albumin is around 2 weeks, shorter than that of erythrocytes, GA reflects shorter terms of glycemic control than HbA1c [8]. Reflecting such characteristics, it has been recently shown that changes in GA can predict change in HbA1c after diabetes treatment [9,10]. In addition, there have been accumulating evidences that HbA1c mainly reflects mean plasma glucose levels while GA also reflects plasma glucose excursions and/or postprandial glucose levels better than HbA1c [11-

16]. Furthermore, we have shown that GA reflects endogenous insulin secretion more sensitively than HbA1c [17]. Thus, it has become evident that GA has some different aspects from HbA1c as an indicator of chronic glycemic control, besides it reflects shorter periods of glycemia.

We hypothesized that HbA1c and GA differently predict some clinical characteristics of diabetes mellitus such as diabetic vascular complications and diabetes duration. Based on this hypothesis, the present study was aimed to investigate the relation of both indices with diabetic retinopathy, diabetic nephropathy, and diabetes duration in Japanese patients with type 2 diabetes mellitus.

## Methods

### Patients

This study consisted of 63 patients with type 2 diabetes mellitus (40

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men and 23 women) visiting Nissay Hospital. The study patients were randomly selected from patients with diabetes duration of more than 5 years, in whom HbA1c and GA were simultaneously measured every other month between November, 2010 and October, 2011. Patients with liver disease (chronic hepatitis and liver cirrhosis), anemia, or thyroid disease were excluded in this study. Patients who had serum creatinine  $\geq 110 \mu\text{mol/L}$  were also excluded. Among the study patients, 2 patients were treated with diet therapy alone, 39 patients with oral hypoglycemic agent(s), 1 patient with glucagon-like peptide-1 (GLP-1) receptor agonist and 21 patients with insulin.

All patients had a complete physical and laboratory examination during the study. Diabetic retinopathy was diagnosed by ophthalmologists on fundus examination and photography. There were 32 patients without diabetic retinopathy, 21 patients with non-proliferative diabetic retinopathy and 10 patients with proliferative diabetic retinopathy. Diabetic nephropathy was defined as the following way: normoalbuminuria (no diabetic nephropathy) [urinary albumin creatinine ratio (ACR) of  $<30 \text{ mg/g creatinine}$ ], 36 patients; microalbuminuria (ACR of  $<300 \text{ mg/g creatinine}$ ), 17 patients; macroalbuminuria (ACR of  $\geq 300 \text{ mg/g creatinine}$ ) but not elevated serum creatinine ( $<110 \mu\text{mol/L}$ ), 10 patients. Normoalbuminuria, microalbuminuria and macroalbuminuria were defined on the basis of the determination of ACR from at least two subsequent specimens of randomly collected urine samples.

Annual mean levels of HbA1c, GA and the GA/HbA1c ratio were determined. Associations of these values with diabetes duration, diabetic retinopathy and diabetic nephropathy were analyzed. The institutional committee approved the protocol of this study, and all participants gave their informed consent.

### Measurements

HbA1c was measured with HLC-723G8 (Tosoh Co., Tokyo, Japan), by high performance liquid chromatography (HPLC) [18]. HbA1c values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values in accordance with the official equation [19]. Serum GA was determined by Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan), by enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [20].

### Statistical analysis

All data are shown as means  $\pm$  SD. For statistical analyses, unpaired Student's t test was used to compare two groups. To analyze the associations of HbA1c, GA and the GA/HbA1c ratio with diabetes duration, univariate regression analysis was performed with StatView computer program (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA). In the stepwise multivariate regression analyses, the F-value for the inclusion of the variables was set at 4.0. Since diabetes duration was not normally distributed, the logarithmically transformed value was entered into these analyses. P value of  $<0.05$  was considered to be statistically significant.

### Results

Mean age of the study patients was  $64.9 \pm 11.8$  years (range, 29-86 years) and mean diabetes duration was  $14.3 \pm 8.1$  years (range, 5-34 years). Whereas annual mean levels of HbA1c and GA were not associated with diabetes duration (HbA1c;  $R=0.036$ ,  $P=0.782$ , GA;  $R=0.224$ ,  $P=0.077$ ), those of the GA/HbA1c ratio ( $R=0.329$ ,  $P=0.009$ ) were significantly correlated with diabetes duration (Figure 1).

In the patients with diabetic nephropathy, there were more men than women (81.5% vs. 50.0%;  $P=0.010$ ) and diabetes duration was longer but not significantly ( $16.6 \pm 9.4$  years vs.  $12.5 \pm 6.6$  years;  $P=0.051$ ), compared with the patients without diabetic nephropathy (Table 1). Annual mean levels of HbA1c ( $7.1 \pm 1.0\%$  vs.  $7.1 \pm 1.0\%$ ;  $P=0.851$ ), GA ( $21.6 \pm 4.3\%$  vs.  $20.7 \pm 4.3\%$ ;  $P=0.409$ ), the GA/HbA1c ratio ( $3.0 \pm 0.4$  vs.  $2.9 \pm 0.3$ ;  $P=0.173$ ) were not different between the patients with diabetic nephropathy and those without it.

In the patients with diabetic retinopathy, diabetes duration was significantly longer ( $17.5 \pm 8.4$  years vs.  $11.1 \pm 6.5$  years;  $P=0.001$ ) and more were treated with insulin (48.4% vs. 18.8%;  $P=0.013$ ), compared with the patients without diabetic retinopathy. Annual mean levels of GA ( $22.6 \pm 4.6\%$  vs.  $19.7 \pm 3.6\%$ ;  $P=0.008$ ) and the GA/HbA1c ratio ( $3.1 \pm 0.4$  vs.  $2.8 \pm 0.3$ ;  $P=0.003$ ) were significantly higher in the patients with diabetic retinopathy than in those without it, whereas annual mean levels of HbA1c were not different between both groups ( $7.3 \pm 1.0\%$  vs.  $7.0 \pm 0.9\%$ ;  $P=0.219$ ).

Stepwise multivariate regression analyses were performed with diabetic nephropathy and diabetic retinopathy as objective variable and with age (years), sex (setting of female at 0 and of male at 1), diabetes duration (years), HbA1c (%) and GA (%) as explanatory variables. The results showed that GA, in addition to diabetes duration, was a significant positive explanatory variable for diabetic retinopathy,

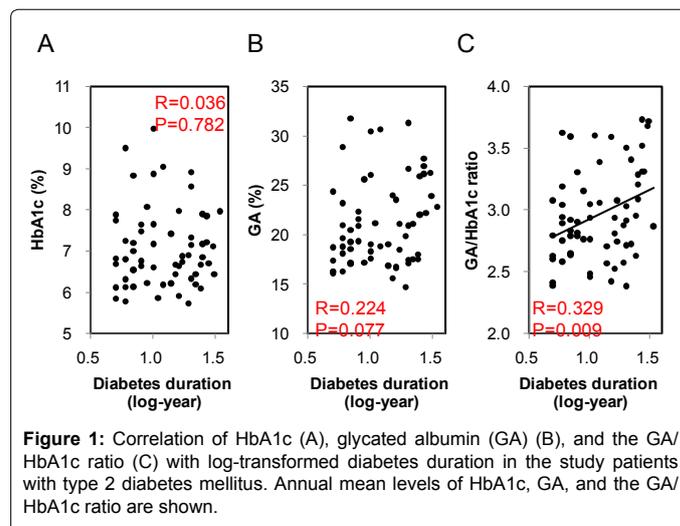


Figure 1: Correlation of HbA1c (A), glycated albumin (GA) (B), and the GA/HbA1c ratio (C) with log-transformed diabetes duration in the study patients with type 2 diabetes mellitus. Annual mean levels of HbA1c, GA, and the GA/HbA1c ratio are shown.

	Diabetic nephropathy			Diabetic retinopathy		
	absent	present	P	absent	present	P
n	36	27	-	32	31	-
Male (%)	50.0	81.5	0.010	59.4	67.7	0.490
Age (years)	62.8 $\pm$ 12.0	67.7 $\pm$ 11.2	0.103	64.0 $\pm$ 10.8	65.8 $\pm$ 12.9	0.541
Diabetes duration (years)	12.5 $\pm$ 6.6	16.6 $\pm$ 9.4	0.051	11.1 $\pm$ 6.5	17.5 $\pm$ 8.4	0.001
Insulin therapy (%)	30.6	37.0	0.589	18.8	48.4	0.013
HbA1c (%)	7.1 $\pm$ 1.0	7.1 $\pm$ 1.0	0.851	7.0 $\pm$ 0.9	7.3 $\pm$ 1.0	0.219
GA (%)	20.7 $\pm$ 4.3	21.6 $\pm$ 4.3	0.409	19.7 $\pm$ 3.6	22.6 $\pm$ 4.6	0.008
GA/HbA1c ratio	2.9 $\pm$ 0.3	3.0 $\pm$ 0.4	0.173	2.8 $\pm$ 0.3	3.1 $\pm$ 0.4	0.003

Values are mean  $\pm$  SD or percent

Table 1: Clinical and biochemical characteristics of the patients with or without diabetic nephropathy and those with or without diabetic retinopathy.

A. Diabetic nephropathy			
Variables	$\beta$	F	P
Sex (female, 0; male, 1)	0.351	8.73	0.004
Diabetes duration (years)	0.246	4.29	0.246

Explanatory variables are age (years), sex (female, 0; male, 1), log-transformed diabetes duration (years), HbA1c (%) and GA (%).  $R^2 = 0.406$ ,  $F = 5.90$  and  $P < 0.005$

B. Diabetic retinopathy			
Variables	$\beta$	F	P
Diabetes duration (years)	0.350	9.07	0.002
GA (%)	0.255	4.82	0.016

Explanatory variables are age (years), sex (female, 0; male, 1), log-transformed diabetes duration (years), HbA1c (%) and GA (%).  $R^2 = 0.478$ ,  $F = 8.87$  and  $P < 0.001$

**Table 2:** Stepwise multivariate regression analyses on diabetic nephropathy (A) and diabetic retinopathy (B) in 63 patients with type 2 diabetes mellitus.

while sex was a significant positive explanatory variable for diabetic nephropathy (Table 2).

## Discussion

As serum GA reflects shorter terms of glycemic control than HbA1c, GA changes more rapidly than HbA1c as glycemic control changes [8-10]. The GA/HbA1c ratio also decreases as glycemic control improves [21] and increases as glycemic control worsens [22]. In the present study, to avoid the influences of interval changes of glycemic control, we determined annual mean levels of HbA1c, GA and the GA/HbA1c ratio in 63 patients with type 2 diabetes mellitus.

The results showed that annual mean levels of the GA/HbA1c ratio had significant association with diabetes duration but those of HbA1c and GA did not. Insulin secretory function is estimated to be decreased to about 50% of healthy subjects at diagnosis of type 2 diabetes mellitus, and it gradually declines during the course of diabetes duration [23]. When the insulin secretory function is more depressed, the continued improved glycemic control is difficult to be obtained by treatment with oral hypoglycemic agents alone, and insulin treatment is often needed.

GA is indicated to reflect plasma glucose excursions and/or postprandial glucose levels better than HbA1c [11-15]. We previously demonstrated that endogenous insulin secretion had inverse correlation with the GA/HbA1c ratio in patients with type 2 diabetes mellitus [17], suggesting that in diabetic patients with decreased insulin secretion, GA levels are set higher relative to HbA1c because of marked plasma glucose excursions. This was proved by recent observations that the GA/HbA1c ratio is positively associated with postprandial glucose levels, but not fasting plasma glucose levels [13,14]. Taken all together, it is indicated that in patients with longer diabetes duration, decreased insulin secretion results in marked plasma glucose excursions, causing higher levels of the GA/HbA1c ratio.

In DCCT study [4], UKPDS [5], and Kumamoto study [6], setting HbA1c at lower levels by strict glycemic control resulted in preventing the development and progression of diabetic nephropathy and diabetic retinopathy. In the present study, we performed cross-sectional analyses in order to compare annual mean levels of HbA1c, GA and the GA/HbA1c ratio as to the relation with diabetic nephropathy and diabetic retinopathy, in patients with type 2 diabetes mellitus who had diabetes duration of more than 5 years. Our data showed that any of annual mean levels of HbA1c, GA and the GA/HbA1c ratio were not related to diabetic nephropathy. It suggests that long-term glycemic control status after the onset of diabetes, but not recent glycemic

control status, is rather important for the development of diabetic complications. Recently, it has been shown in a cross-sectional analysis of the Atherosclerosis Risk in Communities (ARIC) Study that both HbA1c and GA were significantly associated with albuminuria and also with chronic kidney disease [24]. This study was performed on a community-based population, and 277 out of 1,600 study participants had a history of diabetes mellitus. Among them only 27.7% had chronic kidney disease and 23.0% had albuminuria. Thus, the difference in the study populations from the present study may cause the different results.

In patients with massive proteinuria, GA levels are lower in relation to glucose levels probably because of increased catabolism of serum albumin [25,26]. There were 10 patients with macro albuminuria included in the present study. Their GA levels might be set lower, which may influence the analyses of the association of GA with diabetic nephropathy. However, when we performed the analyses on the patients excluding these patients, annual mean levels of HbA1c, GA and the GA/HbA1c ratio were not different between patients with diabetic nephropathy and those without it (data not shown).

By contrast, annual mean levels of GA and the GA/HbA1c ratio were significantly higher in patients with diabetic retinopathy than in patients without diabetic retinopathy. Furthermore, stepwise multivariate regression analyses revealed that GA as well as diabetes duration were independent explanatory variables for diabetic retinopathy. It seems to be consistent with a cross-sectional analysis of the ARIC Study [24]. It has been shown that postprandial hyperglycemia is a risk of diabetic retinopathy [27,28] and GA also reflects postprandial hyperglycemia [12-15]. Taken together with these observations, patients with higher postprandial glucose levels are prone to show higher levels of GA in relation to HbA1c and to develop diabetic retinopathy. In the present study, more patients with diabetic retinopathy were given treatment with insulin than patients without diabetic retinopathy. In our previous study, in the patients with the insulin treatment lower insulin secretion was associated with marked plasma glucose excursions and also with elevated GA [17]. Thus, lower insulin secretion may be associated with the development of diabetic retinopathy, although plasma insulin levels were not determined in the present study.

Our findings surmise the association of GA and/or the GA/HbA1c ratio with diabetic complications other than diabetic retinopathy, especially influenced by postprandial hyperglycemia and/or plasma glucose excursions. Atherosclerotic vascular diseases are known to be associated with postprandial hyperglycemia [29-31]. Pu et al. [32] showed by a cross-sectional analysis of patients with type 2 diabetes mellitus that GA levels are associated with the presence and severity of coronary artery disease. According to their data,  $GA \geq 19.0\%$  was a predictor for the presence of coronary artery disease and  $GA \geq 21.0\%$  for 3-vessel disease prediction. By contrast, HbA1c levels did not differ between patients with coronary artery disease and those without it.

This study has several limitations. First, this study was a cross-sectional study. In future, therefore, prospective studies investigating the effects of serum GA levels on the development and progression of the diabetic complications are necessary. Second, this study was performed using a small number of patients in a single hospital. A multicenter, prospective clinical study with a larger number of patients is necessary to confirm our results.

From the observations that GA reflects glucose excursions more strongly than HbA1c, we speculate that GA might be a more sensitive index for some diabetic complications than HbA1c.

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