

## Research Article

# Glycated Albumin Levels in Patients with Type 2 Diabetes Increase Relative to HbA<sub>1c</sub> with Time

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We recently reported that glycated albumin (GA) is increased in subjects with longer duration of diabetes and with decreased insulin secretory function. Based on this, we investigated whether GA increases with time relative to glycated hemoglobin (HbA<sub>1c</sub>) and the association between GA and beta-cell function. We analyzed 340 type 2 diabetes patients whose serum GA and HbA<sub>1c</sub> levels had been repeatedly measured over 4 years. We assessed the pattern of changes with time in glycemic indices (GA, HbA<sub>1c</sub>, and GA/HbA<sub>1c</sub> ratio) and their relationship with beta-cell function. In all patients, glycemic indices decreased and maintained low levels around 15 and 27 months. However, from 39 months to 51 months, GA significantly increased but HbA<sub>1c</sub> tended to increase without statistical significance. We defined  $\Delta\text{GA}/\text{HbA}_{1c}$  as the difference between the nadir point (at 15 to 27 months) and the end point (at 39 to 51 months) and found that  $\Delta\text{GA}/\text{HbA}_{1c}$  was positively correlated with diabetes duration and negatively related to beta-cell function. In multivariable linear regression analyses,  $\Delta\text{GA}/\text{HbA}_{1c}$  was independently associated with diabetes duration. In conclusion, this study demonstrated that serum GA levels increase relative to HbA<sub>1c</sub> levels with time.

## 1. Introduction

Glucose monitoring is essential for the appropriate care and treatment of patients with diabetes in order to avoid diabetic complications and hypoglycemia. An accurate measure of glucose level allows physicians and patients to make optimal decisions about food, physical activity, and medications [1]. Of the glycemic indices, the American Diabetes Association recommends glycated hemoglobin (HbA<sub>1c</sub>) testing in all diabetic patients as an initial assessment and then as a part of continuing care [2]. This recommendation is derived from clinical data that shows that HbA<sub>1c</sub> reflects average glycemic status over 2-3 months and predicts diabetic complications [3, 4]. Although HbA<sub>1c</sub> provides useful information, it might be inadequate in clinical situations such as anemia, renal insufficiency, and gestational diabetes. Glycated albumin

(GA) has been gaining popularity as an indicator in several physiologic and pathologic conditions [5] because it provides more information than the gold standard HbA<sub>1c</sub>. In line with this trend, we have demonstrated the clinical relevance of GA in type 2 diabetes mellitus (T2D) with insulin secretory dysfunction rather than insulin resistance [6], fluctuating or poorly controlled glycemic excursions [7], and progressing atherosclerosis [8].

In the natural course of T2D, however, beta-cell function decreases as duration of diabetes increases [9]. Moreover, glycemic excursions worsen due to decreased beta-cell function [10]. In a recent cross-sectional study, we reported that the levels of GA/HbA<sub>1c</sub> were significantly elevated in subjects with long diabetic duration, largely attributed to the inverse relationships between GA and pancreatic beta-cell secretory indices [11], and suggested that clinicians should be careful

in interpreting GA as only an indicator of glycemic control in T2D cases of longer duration. However, no longitudinal studies investigating the change in GA and HbA<sub>1c</sub> over time in patients with T2D have been published.

In this longitudinal observational study, we investigated the changing pattern of glycemic indices such as GA, HbA<sub>1c</sub>, and GA/HbA<sub>1c</sub> over 4 years in order to determine whether GA increases more with time relative to HbA<sub>1c</sub> in subjects with T2D. We also investigated which clinical and biochemical parameters are associated with changes in the GA/HbA<sub>1c</sub> ratio.

## 2. Research Design and Methods

**2.1. Subjects and Data Collection.** In this longitudinal observational study, we recruited patients with T2D who had enrolled in previous studies [6, 7] between May 2009 and June 2011 and who were followed up in June 2014. Using electronic medical records, we reviewed and rechecked demographic and clinical data for age, gender, metabolic parameters, and duration of diabetes. The diabetic duration was defined from the date the patients were first diagnosed with diabetes by blood tests or by patient recall from interviews.

To investigate the changes in glycemic indices with time, we tried to include patients whose duration of diabetes was less than 5 years. Patients were included if they were (1) aged  $\geq 20$  years, (2) had repeated laboratory data for both HbA<sub>1c</sub> and GA up to the final follow-up point, and (3) had undergone a baseline standardized liquid meal test (Ensure, Meiji Dairies Corporation, Tokyo, Japan; 500 kcal, 17.5 g fat (31.5%), 68.5 g carbohydrate (54.5%), and 17.5 g protein (14.0%)) after an overnight fast. Patients were excluded if they had any medical conditions that could alter HbA<sub>1c</sub> or GA levels such as liver cirrhosis or chronic kidney diseases (estimated glomerular filtration rate (GFR) by chronic kidney disease epidemiology collaboration formula  $< 60 \text{ mL/min/1.73 m}^2$ ), pregnancy, or hematologic disorders or if they were being treated with steroids.

The protocol of this study was approved by the Institutional Review Board at Severance Hospital (IRB numbers 4-2009-0656, 4-2012-0398, and 4-2014-0507). Written informed consent for this study was not required by the Institutional Review Board because researchers only accessed the database for analysis purposes, and personal information was not used.

**2.2. Laboratory Measurements.** The baseline glycemic indices (GA, HbA<sub>1c</sub>, and GA/HbA<sub>1c</sub>) were defined as the values measured at enrollment. Subsequently, serum GA and HbA<sub>1c</sub> were measured every 3 or 6 months. The end point glycemic indices of each subject were measured between 39 and 51 months. For glucose and C-peptide analyses, blood samples were collected at 0 and 90 min (basal and stimulated values) as part of the standardized liquid meal test. Pancreatic beta-cell functions in the context of ambient insulin secretory function were assessed using the following indices: (1) PCGR (stimulated C-peptide level/stimulated glucose level  $\times$

100), (2) C-peptide increment ( $\Delta\text{C-peptide} = \text{stimulated C-peptide} - \text{basal C-peptide}$ ), and (3) C-peptide-genic index [ $\text{CGI} = (\text{stimulated C-peptide} - \text{basal C-peptide})/(\text{stimulated glucose} - \text{basal glucose})$ ]. Measurement techniques included the hexokinase method for glucose and high-performance liquid chromatography using Variant II Turbo (Bio-Rad Laboratories, Hercules, CA) for HbA<sub>1c</sub>. Serum GA was analyzed by an enzymatic method using an albumin-specific proteinase, ketoamine oxidase, an albumin assay reagent (LUCICA GA-L; Asahi Kasei Pharma Co., Tokyo, Japan), and a Hitachi 7699 P module autoanalyzer (Hitachi Instruments Service, Tokyo, Japan). GA values were calculated from the ratio of GA to total serum albumin and expressed as a percentage. Serum C-peptide levels were measured in duplicate using an immunoradiometric assay method (Beckman Coulter, Fullerton, CA).

**2.3. Statistical Analysis.** All continuous variables were presented as mean  $\pm$  standard deviation (SD) or median (quartiles) or as mean  $\pm$  standard error (SE) for variables on the graphs. Categorical variables were described as *N* (%). Differences were analyzed using Student's *t*-test for the continuous variables and the chi-square test for categorical variables.

Repeated measured analysis of variance (ANOVA) with Bonferroni correction and paired *t*-test were used to determine the significance of differences in glycemic indices according to duration of diabetes. We compared GA, HbA<sub>1c</sub>, and GA/HbA<sub>1c</sub> levels at baseline and 3, 15, 27, and 39 to 51 months after enrollment in all patients who had glycemic values available at that time point. Because all glycemic indices reached their lowest level between 15 and 27 months (arbitrarily defined nadir point), we defined  $\Delta\text{GA}/\text{HbA}_{1c}$  as the difference in GA/HbA<sub>1c</sub> between the end point (39 to 51 months) and nadir point (15 to 27 months). One-way ANOVA with Tukey correction was used to compare the differences of duration of diabetes and PCGR according to the tertiles of  $\Delta\text{GA}/\text{HbA}_{1c}$  ratio. Multivariable linear regression analysis was performed to determine the independent relationship of the studied variables including duration of diabetes associated with  $\Delta\text{GA}/\text{HbA}_{1c}$  increase. Statistical analyses were performed using PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

## 3. Results

**3.1. Study Population Characteristics.** A total of 340 subjects (71% men, mean age  $61.3 \pm 11.6$  years) were enrolled in this study. The patient characteristics of the cohort are shown in Table 1. The mean body mass index (BMI) was  $25.4 \pm 3.6 \text{ kg/m}^2$  and the prevalence of hypertension was 57% ( $n = 195$ ). Median duration of diabetes and levels of mean HbA<sub>1c</sub> were 1 (range: 0–5.0) year and  $7.0\% \pm 0.9\%$ , respectively. We also measured baseline insulin secretory beta-cell function indices such as PCGR ( $3.24 \pm 2.1$ ),  $\Delta\text{C-peptide}$  level ( $4.13 \pm 2.6$ ), and CGI ( $0.08 \pm 0.4$ ). All glycemic indices, GA ( $19.3 \pm 6.6$  versus  $16.5 \pm 4.9$ ), HbA<sub>1c</sub> ( $7.7 \pm 1.6$  versus  $7.0 \pm 1.2$ ), and GA/HbA<sub>1c</sub> ( $2.47 \pm 0.5$  versus  $2.33 \pm 0.4$ ), were decreased at

TABLE 1: Baseline characteristics of the study population.

Variables	All (N = 340)
<b>Demographics</b>	
Age (years)	61.3 ± 11.6
Male, N (%)	204 (71)
BMI (kg/m <sup>2</sup> )	25.4 ± 3.6
Waist circumference (cm)	88.1 ± 9.0
Hypertension, N (%)	195 (57)
Duration of diabetes (years)	1.0 (0–5.0)
<b>Biochemistry profiles</b>	
Creatinine (mg/dL)	0.93 ± 0.2
Estimated GFR (mL/min/1.73 m <sup>2</sup> )	81.5 ± 17.7
Albumin (g/dL)	4.6 ± 0.4
Total cholesterol (mg/dL)	177.2 ± 48.5
Triglyceride (mg/dL)	152.5 ± 110.7
HDL-cholesterol (mg/dL)	47.7 ± 14.3
LDL-cholesterol (mg/dL)	99.7 ± 38.7
<b>Beta-cell function indices at baseline</b>	
Basal glucose (mg/dL)	138.0 ± 50.9
Stimulated glucose (mg/dL)	231.8 ± 87.3
Basal C-peptide (ng/mL)	2.35 ± 1.2
Stimulated C-peptide (ng/mL)	6.50 ± 3.3
ΔC-peptide (ng/ml)	4.13 ± 2.6
PCGR	3.24 ± 2.1
CGI	0.08 ± 0.4
<b>Glycemic indices</b>	
GA at baseline (%)	19.3 ± 6.6
HbA <sub>1c</sub> at baseline (%)	7.7 ± 1.6
HbA <sub>1c</sub> at baseline (mmol/mol)	60.8 ± 16.9
GA/HbA <sub>1c</sub> ratio at baseline	2.47 ± 0.5
GA at end point (%)	16.5 ± 4.9
HbA <sub>1c</sub> at end point (%)	7.0 ± 1.2
HbA <sub>1c</sub> at end point (mmol/mol)	53.2 ± 13.1
GA/HbA <sub>1c</sub> ratio at end point	2.33 ± 0.4
Mean GA (%)	16.5 ± 4.0
Mean HbA <sub>1c</sub> (%)	7.0 ± 0.9
<b>Medications at baseline</b>	
Insulin, N (%)	63 (19)
Metformin, N (%)	221 (65)
DPP-IV inhibitor, N (%)	59 (17)
Thiazolidinediones, N (%)	40 (12)
Sulfonylurea, N (%)	88 (26)
<b>Medications at 27 months</b>	
Insulin, N (%)	52 (15)
Metformin, N (%)	254 (75)
DPP-IV inhibitor, N (%)	98 (29)
Thiazolidinediones, N (%)	65 (19)
Sulfonylurea, N (%)	99 (29)

Continuous variables were described as mean ± SD or median (quartiles), N (%) for categorical variables.

BMI, body mass index; GFR, glomerular filtration rate; GA, glycated albumin; CGI, C-peptide-genic index; PCGR, postprandial C-peptide to glucose ratio.

final follow-up compared to those at baseline. At the time of enrollment, the patients were being treated with metformin (221 patients; 65% of the study population), sulfonylurea (88; 26%), DPP-IV inhibitors (59; 17%), or insulin (63; 19%).

TABLE 2: Univariate linear regression analysis to determine the variables associated with ΔGA/HbA<sub>1c</sub>.

Variables	STD β	p
Age (year)	0.063	0.246
BMI (kg/m <sup>2</sup> )	-0.063	0.251
Waist circumference (cm)	0.004	0.940
Estimated GFR (mL/min/1.73 m <sup>2</sup> )	-0.032	0.552
Albumin (g/dL)	0.008	0.886
Total cholesterol (mg/dL)	-0.029	0.599
Triglyceride (mg/dL)	-0.080	0.141
HDL-cholesterol (mg/dL)	0.023	0.674
LDL-cholesterol (mg/dL)	-0.007	0.903
GA at baseline (%)	<b>0.166</b>	<b>0.002</b>
HbA <sub>1c</sub> at baseline (%)	0.017	0.753
Mean GA (%)	<b>0.345</b>	<b>&lt;0.001</b>
Mean HbA <sub>1c</sub> (%)	<b>0.128</b>	<b>0.018</b>
Duration of diabetes (year)	<b>0.187</b>	<b>0.001</b>
ΔC-peptide (ng/mL)	<b>-0.139</b>	<b>0.011</b>
PCGR	<b>-0.145</b>	<b>0.007</b>
CGI	-0.059	0.284

BMI, body mass index; GFR, glomerular filtration rate; GA, glycated albumin; PCGR, postprandial C-peptide to glucose ratio; CGI, C-peptide-genic index. Values with statistical significance are printed in bold.

**3.2. Glycated Albumin and GA/HbA<sub>1c</sub> Ratio Levels Increased Relative to HbA<sub>1c</sub> Levels over Time.** In all patients, both levels of GA (16.1% ± 4.0%) and GA/HbA<sub>1c</sub> ratio (2.30 ± 0.4) improved and reached the nadir points on glucose control at 15 months (Figure 1). From 15 months to 39 months, the nadir glycemic indices were stably maintained. From 39 months to 51 months, GA significantly increased (16.1% ± 4.8% to 17.5% ± 4.9%, *p* = 0.028), but HbA<sub>1c</sub> tended to increase without statistical significance (6.9% ± 1.0% to 7.1% ± 1.2%, *p* = 0.389). The levels of GA at 27 and 39 months (*p* = 0.029 and 0.028, resp.) as well as GA/HbA<sub>1c</sub> ratio at 15 and 27 months (*p* = 0.038, *p* = 0.039) were significantly lower than at 51 months (Figures 1(a) and 1(b)). However, statistical differences in HbA<sub>1c</sub> between each time point (3, 15, 27, and 39 months) and the last time point (51 months) were not significant except for baseline (Figure 1(c)). In sum, GA levels and the GA/HbA<sub>1c</sub> ratio, but not HbA<sub>1c</sub> levels, were significantly increased at the final follow-up compared with those at the nadir time point (Figure 1(d)).

**3.3. Associations between ΔGA/HbA<sub>1c</sub> and Clinical and Biochemical Parameters.** Since the GA/HbA<sub>1c</sub> ratio significantly increased from the nadir point to the final follow-up point, which was designated as ΔGA/HbA<sub>1c</sub> (Figure 1(e)), we tried to determine the clinical and biochemical parameters that are associated with ΔGA/HbA<sub>1c</sub> (Table 2). In the univariate linear regression analysis, duration of diabetes (standardized β coefficient (STD β) = 0.187, *p* = 0.001), mean GA (STD β = 0.345, *p* < 0.001), and mean HbA<sub>1c</sub> (STD β = 0.128, *p* = 0.018) were positively associated with ΔGA/HbA<sub>1c</sub>. On the other hand, beta-cell function indices were negatively related to ΔGA/HbA<sub>1c</sub>. In particular, PCGR (STD β = -0.145,

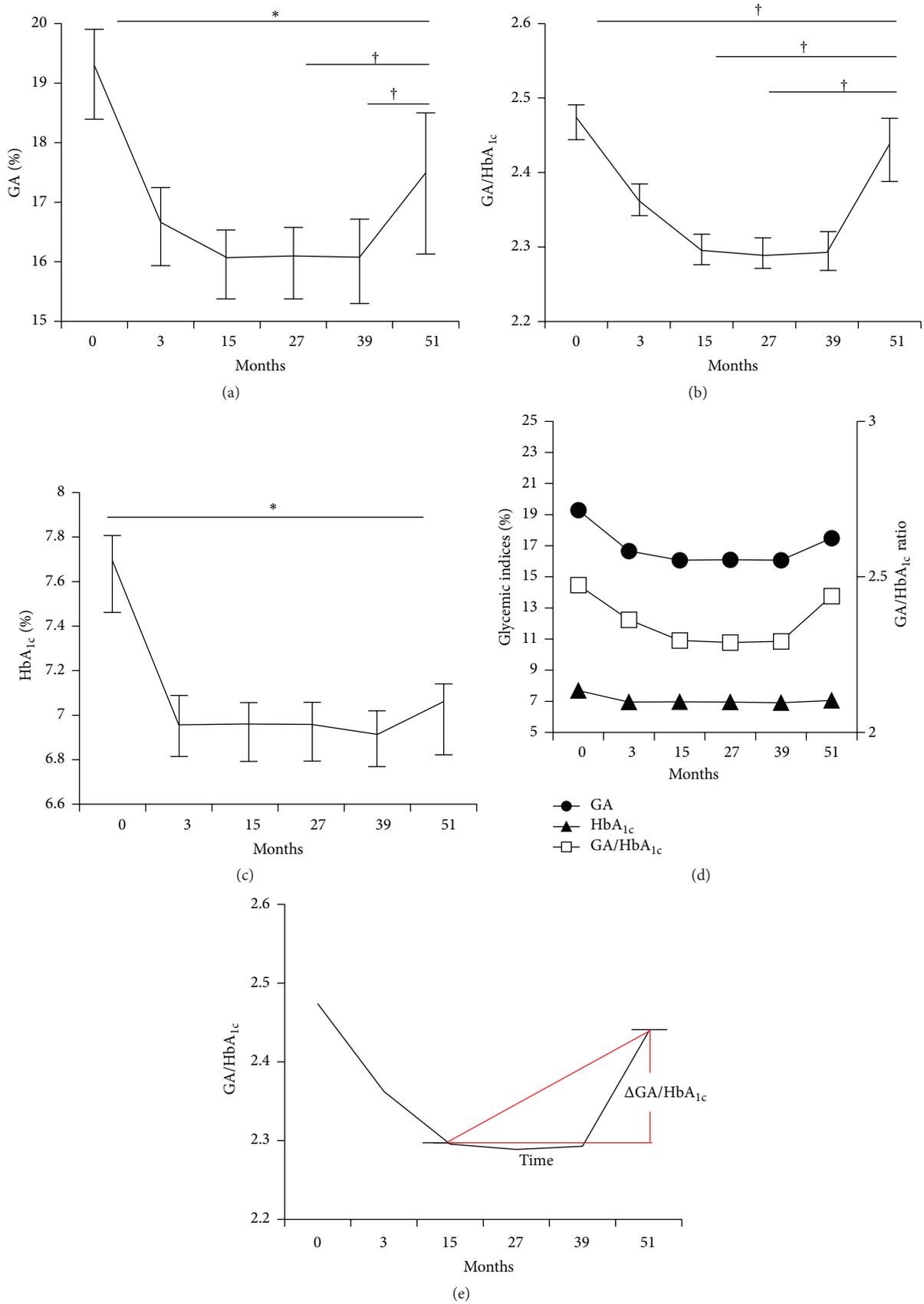


FIGURE 1: Changing patterns of glycemic indices over 4 years. (a) GA, (b) GA/HbA<sub>1c</sub> ratio, (c) HbA<sub>1c</sub>, (d) changing patterns of glycemic indices, (e)  $\Delta$ GA/HbA<sub>1c</sub>, calculated by end point GA/HbA<sub>1c</sub> - nadir point GA/HbA<sub>1c</sub>. Data are presented as mean with SE. \* $p < 0.001$ ,  $\dagger p < 0.05$  for the comparison with 51 months.

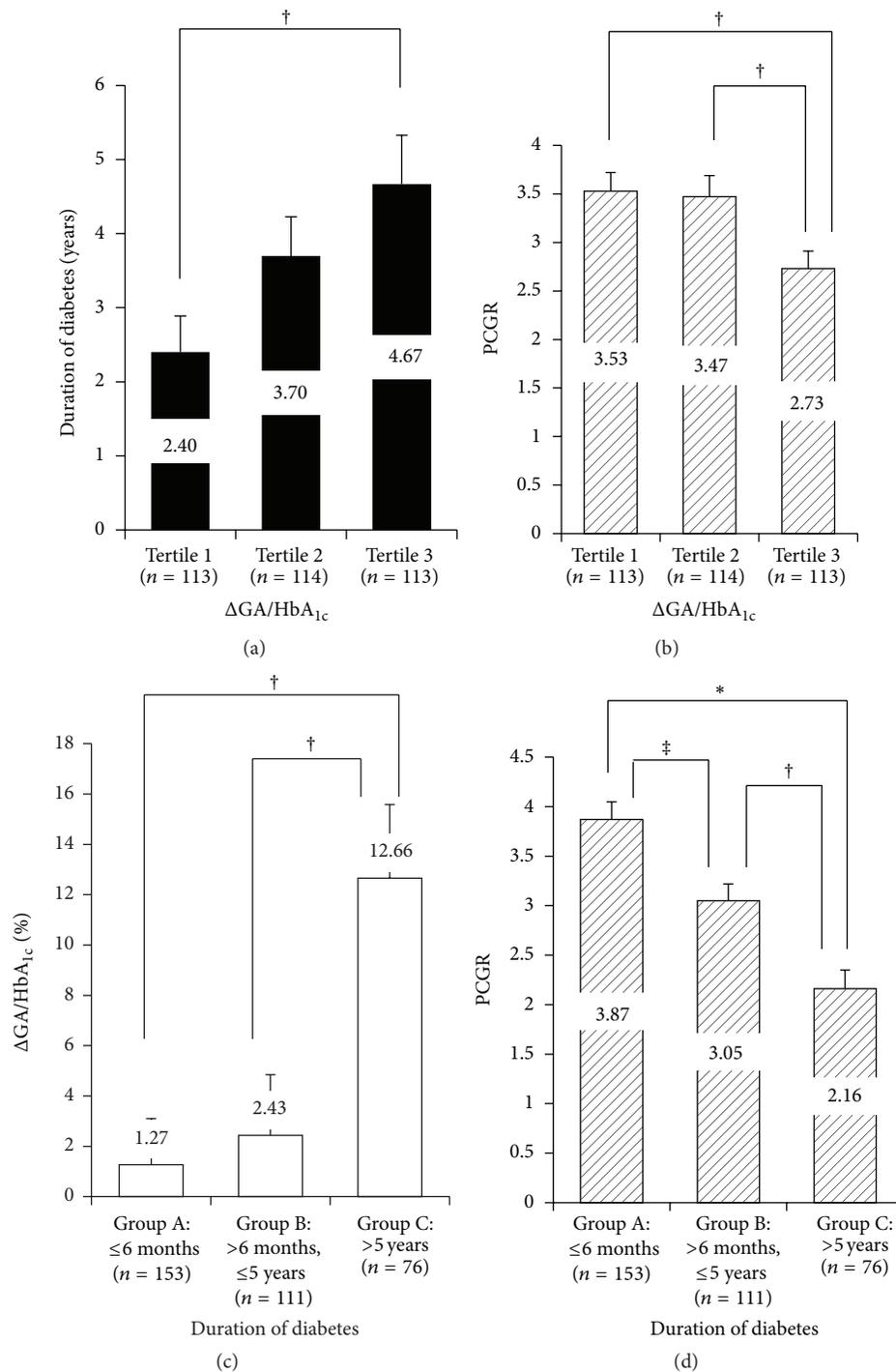


FIGURE 2: Correlations between  $\Delta\text{GA}/\text{HbA}_{1c}$  and duration of diabetes, beta-cell function. (a, b) Differences of duration of diabetes (a) and PCGR (b) in subjects according to the tertiles of  $\Delta\text{GA}/\text{HbA}_{1c}$ . (c, d) Differences of  $\Delta\text{GA}/\text{HbA}_{1c}$  (c) and PCGR (d) in subjects according to duration of diabetes. †  $p < 0.05$ , ‡  $p < 0.01$ , \*  $p < 0.001$ ;  $\Delta\text{GA}/\text{HbA}_{1c}$  (%) =  $\Delta\text{GA}/\text{HbA}_{1c}/\text{nadir point GA}/\text{HbA}_{1c} * 100$ .

$p = 0.007$ ) was more strongly associated with  $\Delta\text{GA}/\text{HbA}_{1c}$  than  $\Delta\text{C-peptide}$  (STD  $\beta = -0.139$ ,  $p = 0.011$ ).

We classified study subjects according to tertiles of  $\Delta\text{GA}/\text{HbA}_{1c}$ . Individuals in higher tertiles for  $\Delta\text{GA}/\text{HbA}_{1c}$  had longer duration of diabetes (2.4 versus 3.7 versus 4.7 years; tertile 1 versus tertile 3,  $p = 0.013$ ) and lower levels of

PCGR (3.5 versus 3.5 versus 2.7; tertile 1 versus tertile 3,  $p = 0.011$ ; tertile 2 versus tertile 3,  $p = 0.021$ ) (Figures 2(a) and 2(b)). Moreover, study subjects were categorized into three groups based on duration of diabetes (Group A:  $\leq 6$  months,  $n = 153$ ; Group B:  $>6$  months and  $\leq 5$  years,  $n = 111$ ; Group C:  $>5$  years,  $n = 76$ ) to investigate the impact of diabetes

TABLE 3: Multivariable linear regression analyses to determine the variables associated with  $\Delta\text{GA}/\text{HbA}_{1c}$ .

Models	Model 1		Model 2		Model 3		Model 4		Model 5	
Variables	Conventional confounders		Model 1 + PCGR		Model 2 + duration of diabetes		Model 3 + mean GA		Model 3 + mean $\text{HbA}_{1c}$	
	STD $\beta$	<i>p</i>	STD $\beta$	<i>p</i>	STD $\beta$	<i>p</i>	STD $\beta$	<i>p</i>	STD $\beta$	<i>p</i>
DPP-IV inhibitor use	<b>-0.111</b>	<b>0.049</b>	-0.109	0.053	-0.089	0.111	-0.084	0.133	-0.088	0.116
PCGR	—	—	<b>-0.161</b>	<b>0.009</b>	-0.111	0.080	-0.059	0.396	-0.106	0.113
Duration of diabetes	—	—	—	—	<b>0.172</b>	<b>0.005</b>	<b>0.166</b>	<b>0.007</b>	<b>0.170</b>	<b>0.007</b>

Conventional confounders: age (years), sex (0 = female, 1 = male), body mass index ( $\text{kg}/\text{m}^2$ ), waist circumference (cm), and estimated glomerular filtration rate ( $\text{mL}/\text{min}/1.73 \text{ m}^2$ ).

PCGR, postprandial C-peptide to glucose ratio; STD  $\beta$ , standardized  $\beta$  coefficient. Values with statistical significance are printed in bold.

duration on  $\Delta\text{GA}/\text{HbA}_{1c}$  ratio and PCGR. The  $\Delta\text{GA}/\text{HbA}_{1c}$  ratios (expressed as percentages) were significantly elevated in patients with diabetes of duration >5 years compared to other groups (Figure 2(c)), whereas PCGR was decreased in patients with longer duration of diabetes (Figure 2(d)).

**3.4.  $\Delta\text{GA}/\text{HbA}_{1c}$  Was Independently Associated with Duration of Diabetes.** Multivariable linear regression models were applied to determine the clinical and laboratory variables associated with  $\Delta\text{GA}/\text{HbA}_{1c}$  (Table 3). We focused on certain parameters that can directly or indirectly reflect the insulin secretory function, such as PCGR, duration of diabetes, and medication history of DPP-IV inhibitor which can effectively reduce postprandial glucose. After adjustment for clinically important variables such as age, sex, BMI, waist circumference, and estimated GFR in model 1, history of DPP-IV inhibitor use was negatively associated with  $\Delta\text{GA}/\text{HbA}_{1c}$  (STD  $\beta = -0.111$ ,  $p = 0.049$ ). After additional inclusion of PCGR in model 2, PCGR showed significant correlation with  $\Delta\text{GA}/\text{HbA}_{1c}$  (STD  $\beta = -0.161$ ,  $p = 0.009$ ), but history of DPP-IV inhibitor use lost its significance. In model 3, duration of diabetes was further adjusted and the significant correlation of PCGR with  $\Delta\text{GA}/\text{HbA}_{1c}$  disappeared (STD  $\beta = -0.111$ ,  $p = 0.080$ ). However, duration of diabetes was still independently associated with  $\Delta\text{GA}/\text{HbA}_{1c}$  (STD  $\beta = 0.172$ ,  $p = 0.005$ ). Moreover, this association remained significant even after adjustment for glycemic status of subjects (inclusion of mean GA in model 4 and mean  $\text{HbA}_{1c}$  in model 5, resp.).

Additionally, we conducted multiple linear regression analyses to determine variables associated with PCGR at baseline (Supplementary Table 1 in Supplementary Material available online at <http://dx.doi.org/10.1155/2015/576306>). PCGR showed the strongest relationship with mean GA (STD  $\beta = -0.336$ ,  $p < 0.001$ ). It also had significant correlation with duration of diabetes (STD  $\beta = -0.133$ ,  $p = 0.010$ ) and insulin use (STD  $\beta = -0.119$ ,  $p = 0.029$ ) (model 1). To evaluate the association between PCGR and  $\Delta\text{GA}/\text{HbA}_{1c}$ , model 2 was developed, which showed a significant negative relationship (STD  $\beta = -0.107$ ,  $p = 0.032$ ).

#### 4. Discussion

Evidence has accumulated on the clinical relevance of GA as a glycemic index. However, the optimal use of GA as

a glucose monitoring tool has not been fully investigated. Based on a previous cross-sectional study that showed that GA values are significantly influenced by the duration of T2D in cases where beta-cell function gradually decreases with time, we hypothesized that the ratio of GA to  $\text{HbA}_{1c}$  might not be constant over time. In this study of more than 4 years, we assessed glycemic excursion by measuring  $\text{HbA}_{1c}$  and GA and investigated discrepancy between two glycemic indices according to multiple time points. This study has three main findings: first, we found an initial sharp decrease in these glycemic indices, followed by maintenance at a low level, and then a gradual increase. Unlike for GA, the  $\text{HbA}_{1c}$  increase was statistically insignificant. Second, the change in  $\text{GA}/\text{HbA}_{1c}$  ratios, defined as the difference between the nadir point and the end point, was independently associated with baseline duration of diabetes. Third, impaired beta-cell function accounted for the association between longer duration of diabetes and increase in GA relative to  $\text{HbA}_{1c}$ , as well as the increase in the  $\text{GA}/\text{HbA}_{1c}$  ratio.

Because  $\text{HbA}_{1c}$  is formed via a nonenzymatic glycation process of hemoglobin in erythrocytes [12], medical conditions such as pregnancy, hemolytic anemia, chronic kidney disease, or end stage renal disease with dialysis could alter  $\text{HbA}_{1c}$  levels. In those cases, GA may be a more reliable marker than  $\text{HbA}_{1c}$  [5]. In contrast to  $\text{HbA}_{1c}$  formation, which requires intracellular glucose and protein metabolism, GA is formed directly via an extracellular nonenzymatic glycation process in plasma. However, medical conditions associated with albumin metabolism such as obesity, hyperthyroidism, and nephrotic syndrome, as well as glucocorticoid treatment [5], are known to affect GA levels. To avoid complications, we did not include patients with liver cirrhosis, chronic kidney diseases, pregnancy, and hematologic disorders or those who were being treated with steroid therapy.

With respect to the clinical relevance of the  $\text{GA}/\text{HbA}_{1c}$  ratio, it is known that the ratio is significantly correlated with insulin secretory beta-cell function but not with insulin resistance [6]. Recent study also showed that lower insulin secretory capacity predicted increased levels of  $\text{GA}/\text{HbA}_{1c}$  ratio in subjects with T2D [13]. Moreover, the  $\text{GA}/\text{HbA}_{1c}$  ratio in patients with T1D and T2D more accurately reflected glucose excursion [7, 14–16] and diabetic vasculopathy [8, 17] than  $\text{HbA}_{1c}$  alone. The  $\text{GA}/\text{HbA}_{1c}$  ratio was significantly

higher in T2D patients treated with insulin than in those treated with either diet or oral hypoglycemic agents [7, 18]. This observation might explain why history of insulin use is associated with either significant hyperglycemia or decreased beta-cell function. Our study also showed that  $\Delta\text{GA}/\text{HbA}_{1c}$  between end point and nadir point is significantly associated with decreased insulin secretory function-related clinical and laboratory variables such as baseline and mean GA, mean  $\text{HbA}_{1c}$  PCGR,  $\Delta\text{C-peptide}$ , and diabetic duration (Table 2). Of the assessed glycemic indices, baseline  $\text{HbA}_{1c}$  did not predict the changes in the  $\text{GA}/\text{HbA}_{1c}$  ratio. With respect to the effect of insulin secretory factors on GA values, a recent cross-sectional study reported that GA levels significantly increased more in patients with longer duration of T2D and impaired beta-cell function measured by  $\Delta\text{C-peptide}$  regardless of  $\text{HbA}_{1c}$  levels [11]. Consistent with this finding, our longitudinal study also showed that patients with higher levels of  $\Delta\text{GA}/\text{HbA}_{1c}$  had longer duration of diabetes and lower levels of PCGR (Figure 2). Furthermore, PCGR representing beta-cell function was associated with diabetic duration and insulin use at baseline and mean GA but not with mean  $\text{HbA}_{1c}$ . Based on these findings, we could infer that patients with T2D of longer duration and with higher  $\text{GA}/\text{HbA}_{1c}$  are more likely to have impaired beta-cell function and need insulin.

Our study had several strengths. First, this study is a longitudinal study with a long follow-up period of more than 4 years, which allowed us to investigate the changes in GA and  $\text{HbA}_{1c}$  levels over time. Second, about 80% of participants had a relatively short duration of diabetes ( $\leq 5$  years) at enrollment. Lastly, we conducted mixed meal tests to obtain basal and stimulated C-peptide levels, which were then used to calculate PCGR as a measure of beta-cell function. That allowed for standardization of the stimulation calories and glucose content. Because it can be easily calculated and is a reliable indicator of beta-cell function, the PCGR is being used more frequently to help determine the optimal antidiabetic drug treatment [19, 20]. In our study, PCGR levels were strongly associated with  $\Delta\text{C-peptide}$  ( $r = 0.808$ ,  $p < 0.001$ ) which strongly predicted beta-cell function (Supplementary Figure 1). In multivariable linear regression analyses, PCGR was also associated with  $\Delta\text{GA}/\text{HbA}_{1c}$ . However, because the duration of diabetes strongly affects  $\Delta\text{GA}/\text{HbA}_{1c}$ , after adjusting for duration of diabetes, the association between  $\Delta\text{GA}/\text{HbA}_{1c}$  and PCGR disappeared (Table 3).

This study has the following limitations. First, we did not measure beta-cell function or glucose levels during follow-up period or at the end point. Thus, we did not prove that the difference between GA and  $\text{HbA}_{1c}$  is caused by a decline in beta-cell function during the follow-up period. Second, since this is a retrospective study, the follow-up period varied among the participants. Third, because we did not assess changes in medication, we could not adjust for its effects.

## 5. Conclusions

We conclude that both impaired beta-cell function and longer duration of diabetes are associated with an increase in GA

relative to  $\text{HbA}_{1c}$  and an increase in the  $\text{GA}/\text{HbA}_{1c}$  ratio. The  $\text{GA}/\text{HbA}_{1c}$  ratio was significantly correlated with insulin secretory beta-cell function and increased as duration of diabetes increased. In this regard, clinicians should be extra careful when interpreting GA and  $\text{GA}/\text{HbA}_{1c}$  ratio values in subjects with longer duration of diabetes. Further well-designed prospective studies enrolling larger populations are warranted.

## Conflict of Interests

The authors declare that there is no competing financial interest associated with this paper.

## Authors' Contribution

Byung-Wan Lee, Yong-ho Lee, and Hye-jin Yoon carried out the concept and design of the study. Hye-jin Yoon, Yong-ho Lee, So Ra Kim, Byung-Wan Lee, and Hyun Chul Lee carried out data analysis and interpretation. Hye-jin Yoon, Yong-ho Lee, and Byung-Wan Lee were responsible for the drafting of the paper. Kwang Joon Kim, Eun Seok Kang, Bong Soo Cha, and Hyun Chul Lee were responsible for the critical revision of the paper. Hye-jin Yoon, Yong-ho Lee, and Kwang Joon Kim were responsible for the statistics. Hye-jin Yoon and Yong-ho Lee were responsible for the data collection. Hye-jin Yoon and Yong-ho Lee contributed equally to this study.

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