ORIGINAL ARTICLE

Glycated albumin to glycated hemoglobin ratio reflects postprandial glucose excursion and relates to beta cell function in both type 1 and type 2 diabetes

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Abstract The glycated albumin (GA) to HbA1c ratio (GA/HbA1c ratio) has been proposed as a marker of postprandial glucose excursion. The aim of this study was to explore the correlation between the GA/HbA1c ratio and beta cell function. Three hundred sixteen subjects with type 2 diabetes who had been admitted to our hospital were examined. Blood samples were obtained after fasting and 2 h after breakfast. Beta cell function was assessed by the serum C-peptide immunoreactivity (CPR) to plasma glucose ratio. Similarly, the correlation between the GA/HbA1c ratio and beta cell function was also estimated in 61 subjects with type 1 diabetes. As a result, the GA/HbA1c ratio was significantly correlated with the postprandial plasma glucose ($r = 0.274$, $p < 0.001$) and postprandial increment of plasma glucose ($r = 0.269$, $p < 0.001$), but not fasting plasma glucose level ($r = 0.081$, $p = 0.15$). Among HbA1c, GA and GA/HbA1c ratio, the GA/HbA1c ratio showed the highest correlation with beta cell function in subjects with type 2 diabetes ($r = -0.455$, $p < 0.001$). A robust association between beta cell function and the GA/HbA1c ratio was shown by multiple regression analysis adjusting for confounders. Similar correlations were also observed in subjects with type 1 diabetes. In conclusion, we confirmed a negative association between beta cell function and the GA/HbA1c ratio, a marker of postprandial glucose excursion, in this study using a relatively large sample size. These results indicate that beta cell dysfunction is associated with larger glucose excursions in subjects with both type 1 and type 2 diabetes.

Keywords Glycated albumin · Glycated hemoglobin · Type 2 diabetes · Beta cell function · C-peptide

Abbreviations
GA	Glycated albumin
CPR	C-peptide immunoreactivity
JDS	Japan Diabetes Society
GAD	Glutamate decarboxylase
IA-2	Insulinoma-associated antigen-2
IAA	Insulin autoantibody
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
SPIDDM	Slowly progressive type 1 diabetes

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Introduction

Type 2 diabetes is characterized by beta cell dysfunction and insulin resistance, resulting in chronic hyperglycemia [1]. Chronic hyperglycemia leads to development of diabetic microvascular complications such as retinopathy, nephropathy and neuropathy. In addition, subjects with type 2 diabetes are at risk of development of cardiovascular disease.

Glycated hemoglobin (HbA1c) reflects the mean blood glucose level over 1–2 months and is widely used as a marker of glycemic control [2]. A higher HbA1c has been shown to be associated with diabetic microvascular

complications and cardiovascular disease, and lowering the HbA1c level by intensive treatment has been shown to reduce these complications in subjects with both type 1 and type 2 diabetes [3, 4]. However, recent studies aiming at further reduction of HbA1c failed to show any benefit on overall mortality [5–7], raising the possibility that HbA1c may not be the only marker of glycemic control.

Glucose variability, especially postprandial glucose excursion, has also been shown to correlate with oxidative stress [8], atherosclerosis [9] and cardiovascular death [10–12]. In type 1 diabetes, loss of beta cell function has been reported to correlate with greater blood glucose variability [13–15]. In contrast, although recent studies have led to the emergence of the concept that beta cell dysfunction is a central pathophysiological feature of type 2 diabetes [1, 16], the impact of beta cell dysfunction on blood glucose variability in type 2 diabetes remains to be established.

Glycated albumin (GA) is another glycemic index that reflects the mean blood glucose level over a shorter period than does HbA1c [17]. Recently, glycated albumin (GA) or the GA/HbA1c ratio has been proposed as a marker of postprandial glucose excursion [18, 19]. Since postprandial hyperglycemia has been shown to correlate with cardiovascular death [10–12], it is important to explore the factors affecting postprandial glucose excursions. Although a recent study showed a correlation between beta cell function and GA/HbA1c in subjects with type 2 diabetes [20], no report has confirmed this result using a larger sample size. Therefore, in this study, using our cohort with a large sample size and detailed measurements of beta cell function, we investigated the correlation between the GA/HbA1c ratio and beta cell function in subjects with type 1 and type 2 diabetes.

Methods

Subjects

In our retrospective study, we included 316 patients with type 2 diabetes who had been admitted to our hospital between 2000 and 2007 [207 men and 109 women, age 64 ± 13 years (mean $\pm$ SD), duration of diabetes 12 ± 10 years, BMI 24.6 ± 4.1 kg/m^2; Table 1]. Before admission, 156 subjects (49%) were treated with sulfonylureas, 8 (3%) with glinides, 36 (11%) with biguanides, 38 (12%) with thiazolidinedione, 88 (28%) with α-glucosidase inhibitors and 49 (16%) with insulin. Ninety-six subjects (30%) were receiving no medication. Most patients had been admitted to the hospital because of poor glycemic control, and received basal-bolus insulin therapy using regular and NPH insulin during admission. We excluded subjects in whom GA was not available. We also excluded subjects with renal failure

defined as serum creatinine level ≥ 2 mg/dl [corresponding to glomerular filtration rate (GFR) $\leq \sim 30$ ml/min/1.73 m^2] and subjects with liver cirrhosis. Beta cell function may be transiently impaired by marked hyperglycemia, so-called glucose toxicity. It has been reported that the beta cell response to glucose is blunted above a plasma glucose level of 180 mg/dl [21]. Therefore, subjects with fasting plasma glucose (FPG) levels ≥ 200 mg/dl on the day of CPR measurement ($\sim 15\%$ of our whole cohort) were also excluded. In addition, we also examined 61 subjects with type 1 diabetes who had been admitted to our hospital between 2000 and 2009 (22 men and 39 women, age 51 ± 18 years, duration of diabetes 11 ± 9 years, BMI 22.1 ± 4.1 kg/m^2; Table 1). The diagnosis of type 1 and type 2 diabetes was made according to the diagnostic criteria of the Japan Diabetes Society (JDS) [22]. Especially type 1 diabetes was diagnosed with the presence of clinical manifestations such as polyuria, polydipsia, weight loss and ketosis if (1) the patient was positive for at least one of the islet-related autoantibodies [glutamate decarboxylase (GAD) antibody, islet cell antibody, insulinoma-associated antigen-2 (IA-2) antibody and/or insulin autoantibody (IAA)] and/or (2) the patient was in an insulin-dependent state and required insulin therapy within 6 months of the onset of diabetes. Other types of diabetes such as diabetes related to pancreatic disease, mitochondrial diabetes, maturity-onset diabetes of the young (MODY) and drug-induced diabetes were carefully excluded from the diagnosis of type 1 or type 2 diabetes. This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the ethics review committee of Keio University School of Medicine, Tokyo, Japan.

Measurements

All measurements were conducted during admission and assayed by the Department of Laboratory Medicine, Keio University School of Medicine. Plasma glucose and serum CPR levels were measured after overnight fasting and 2 h after breakfast during admission, usually within a few days after admission under basal-bolus insulin therapy. All patients received the ideal dietary caloric intake calculated from their ideal body weight [i.e. height (m)^2 × 22 × 25 kcal/kg] when blood samples were obtained. Plasma glucose was measured by glucose oxidase method, and CPR was measured by enzyme immunoassay (ST AIA-PACK C-Peptide, TOSOH, Tokyo, Japan). CV of the within-run and between-day precision of CPR was 2.39 and 2.97%, respectively. ΔPG was calculated as: postprandial plasma glucose (PPG, mg/dl) — fasting plasma glucose (FPG, mg/dl). Fasting and postprandial CPR indices were calculated as previously reported [23, 24], i.e., fasting or postprandial serum CPR (ng/ml)/fasting or postprandial

Table 1 Characteristics of subjects

	Type 2 diabetes ($n = 316$)	Type 1 diabetes ($n = 61$)	p value
Sex (male/female)	207/109	22/39	<0.001
Age (years)	64 ± 13	51 ± 18	<0.001
Duration of diabetes (years)	12 ± 10	11 ± 9	0.35
BMI	24.6 ± 4.1	22.1 ± 4.1	<0.001
HbA1c (%)	9.8 ± 1.8	9.7 ± 2.2	0.23
GA (%)	28.0 ± 7.6	31.4 ± 8.5	0.001
GA/HbA1c	2.97 ± 0.56	3.42 ± 0.59	<0.001
FPG (mg/dl)	144 ± 29	170 ± 59	0.001
FCPR (ng/ml)	1.70 ± 0.99	0.51 ± 0.64	<0.001
FCPRI	1.19 ± 0.68	0.38 ± 0.60	<0.001
PPG (mg/dl)	238 ± 66	260 ± 97	0.04
PCPR (ng/ml)	4.37 ± 2.48	1.24 ± 1.81	<0.001
PCPRI	1.95 ± 1.22	0.59 ± 1.14	<0.001
UCPR (μg/day)	62.5 ± 47.4	23.7 ± 47.8	<0.001

GA glycoalbumin, *FPG* fasting plasma glucose, *FCPR* fasting C-peptide immunoreactivity, *FCPRI* FCPR index, *PPG* postprandial plasma glucose, *PCPR* postprandial CPR, *PCPRI* PCPR index, *UCPR* urinary CPR

plasma glucose (mg/dl) × 100, respectively. Homeostasis model assessment (HOMA2) was also calculated from fasting plasma glucose and CPR values (HOMA2 calculator, http://www.dtu.ox.ac.uk/homacalculator/index.php). In addition, 24 h urinary CPR was also measured within a few days after admission. HbA1c and GA were measured at the time of admission. HbA1c was measured by HPLC and expressed as international standard value, i.e., HbA1c (JDS) + 0.4%, as defined by JDS [22]. GA was measured by enzymatic method. The coefficients of variance (CV) of within-run and between-day precision were 0.4–1.0% and 0.5–0.9% for HbA1c, and 0.9–1.2% and 0.6–0.7% for GA, respectively.

Statistical analysis

Descriptive statistics were calculated for the baseline characteristics. Homogeneity of distributions between the two groups was examined with Mann-Whitney's U test or Fisher's exact test. The association between two variables was estimated with Pearson's correlation coefficient. The difference in two slopes of the CPR index against GA/HbA1c between the type 1 and type 2 diabetes groups was examined with an ANOVA model that contained an interaction term between the CPR index and diabetes type. Multiple regression analysis adjusting for confounders was performed to evaluate the robustness of results. These analyses were performed with the Statistical Package for the Social Sciences (version 17.0; SPSS, Chicago, IL). All

data were expressed as mean ± SD, and values of $p < 0.05$ were considered statistically significant.

Results

Correlation between plasma glucose levels and GA/HbA1c ratio

Correlations among HbA1c, GA, GA/HbA1c and other glycemic indices are shown in Figs. 1 and 2. There were significant positive correlations between GA and HbA1c ($r = 0.684$, $p < 0.001$, Fig. 1a) and GA/HbA1c ($r = 0.716$, $p < 0.001$, Fig. 1c), but not HbA1c and GA/HbA1c ($r = 0.001$, $p = 0.98$, Fig. 1b). GA/HbA1c was significantly positively correlated with postprandial glucose level ($r = 0.274$, $p < 0.001$, Fig. 2h) and ΔPG ($r = 0.269$, $p < 0.001$, Fig. 2i), but not FPG ($r = 0.081$, $p = 0.15$, Fig. 2g). GA also showed stronger correlations with PPG ($r = 0.318$, $p < 0.001$, Fig. 2e) and ΔPG ($r = 0.284$, $p < 0.001$, Fig. 2f) than with FPG ($r = 0.151$, $p = 0.007$, Fig. 2d), while HbA1c showed comparable correlations with PPG ($r = 0.170$, $p = 0.002$, Fig. 2b), ΔPG ($r = 0.119$, $p = 0.04$, Fig. 2c) and FPG ($r = 0.146$, $p = 0.009$, Fig. 2a).

Negative correlation between beta cell function and GA/HbA1c ratio

Next we assessed the correlation between beta cell function and GA/HbA1c (Fig. 3). There were significant negative correlations between indices of beta cell function and GA/HbA1c. Both fasting and postprandial CPR indices were more strongly correlated with GA ($r = -0.365$, $p < 0.001$ and $r = -0.421$, $p < 0.001$, Fig. 3b, e) than with HbA1c ($r = -0.109$, $p = 0.05$ and $r = -0.134$, $p = 0.02$, Fig. 3a, d), and most strongly correlated with GA/HbA1c ($r = -0.410$, $p < 0.001$ and $r = -0.455$, $p < 0.001$, Fig. 3c, f). There was also a modest but significant negative correlation between urinary CPR and GA ($r = -0.127$, $p = 0.03$) and GA/HbA1c ($r = -0.228$, $p < 0.001$), but not HbA1c ($r = 0.057$, $p = 0.31$). Significant negative correlations between GA/HbA1c and the postprandial CPR index were consistently observed irrespective of the treatment before admission ($r = -0.378$, $p < 0.001$; $r = -0.579$, $p < 0.001$; $r = -0.428$, $p = 0.002$ for diet only, oral hypoglycemic agents and insulin treatment, respectively). The correlation between GA/HbA1c and postprandial CPR index remained significant after adjustment for sex, age, duration of diabetes, family history of diabetes, BMI, FPG, PPG, creatinine and medication for diabetes (sulfonylureas, biguanides, thiazolidinediones, glinides, α-glucosidase inhibitors and insulin) ($\beta = -0.351$,
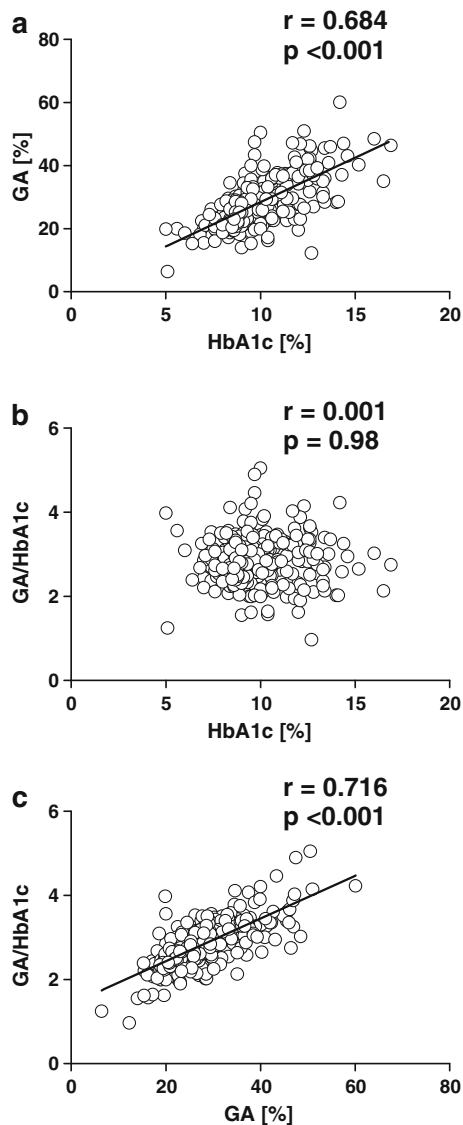
Fig. 1 Correlations among HbA1c, GA and GA/HbA1c ratio. There were significant positive correlations between GA and HbA1c (**a**), and GA and GA/HbA1c ratio (**c**), but no correlation between HbA1c and GA/HbA1c ratio (**b**)

$p < 0.001$, Table 2). In this analysis, BMI, age and PPG were also significantly associated with GA/HbA1c (Table 2).

Beta cell function (HOMA-β%) was also assessed by HOMA2. HOMA-β% was strongly correlated with fasting and postprandial CPR indices ($r = 0.858$, $p < 0.001$ and $r = 0.639$, $p < 0.001$, respectively). The correlation between HOMA-β% and GA/HbA1c was the strongest ($r = -0.379$, $p < 0.001$) compared to those between HOMA-β% and GA ($r = -0.316$, $p < 0.001$) and HbA1c ($r = -0.155$, $p = 0.006$). Insulin resistance (HOMA-IR) was modestly correlated with GA/HbA1c ($r = -0.316$, $p < 0.001$) and GA ($r = -0.251$, $p < 0.001$), but not with HbA1c ($r = -0.034$, $p = 0.55$).

Comparable relationship between beta cell function and GA/HbA1c ratio in type 1 diabetes

Finally we examined whether the relationship between beta cell function and GA/HbA1c in subjects with type 2 diabetes is comparable to that in subjects with type 1 diabetes. The characteristics of subjects with type 1 diabetes in comparison with subjects with type 2 diabetes are shown in Table 1. Mean HbA1c was comparable, but GA was higher in subjects with type 1 diabetes than in those with type 2 diabetes, resulting in a higher GA/HbA1c ratio in subjects with type 1 diabetes than in those with type 2 diabetes (3.42 ± 0.59 vs. 2.97 ± 0.56, $p < 0.001$). There were significant negative correlations between beta cell function and HbA1c, GA and GA/HbA1c, with the strongest association between GA/HbA1c and beta cell function in subjects with type 1 diabetes, which was consistent with the findings in those with type 2 diabetes (Fig. 4). Moreover, the relationships between beta cell function and GA/HbA1c were comparable between subjects with type 1 and type 2 diabetes (Fig. 4c, f). It is of note that higher CPR levels were mainly seen in the subjects classified as having slowly progressive type 1 diabetes (SPIDDM). Comparable slopes of the CPR index against GA/HbA1c between subjects with type 1 and type 2 diabetes were confirmed ($p = 0.88$ and $p = 0.90$; for interaction between fasting or postprandial CPR index and diabetes type, respectively).

As an exploratory analysis, multiple regression analysis for GA/HbA1c in the subjects with type 1 diabetes was performed. The model included sex, age, duration of diabetes, BMI, FPG, PPG, creatinine and postprandial CPR index as independent variables. The analysis revealed that the postprandial CPR index ($r = -0.396$, $p < 0.001$) as well as BMI ($r = -0.225$, $p < 0.001$), age ($r = 0.213$, $p < 0.001$), PPG ($r = 0.127$, $p = 0.01$) and duration of diabetes ($r = -0.114$, $p = 0.02$) was independently correlated with GA/HbA1c.

Discussion

Here, we report that (1) the GA/HbA1c ratio was significantly positively correlated with postprandial glucose excursion but not FPG, (2) there was a significant negative correlation between GA/HbA1c ratio and beta cell function in subjects with type 2 diabetes, and (3) the relationship between the GA/HbA1c ratio in subjects with type 2 diabetes was comparable to that in subjects with type 1 diabetes.

GA and the GA/HbA1c ratio have been reported to be markers of postprandial glucose excursion [18, 19]. We confirmed those previous findings in our study population with a larger sample size. On the other hand, HbA1c has been reported to have a stronger association with the
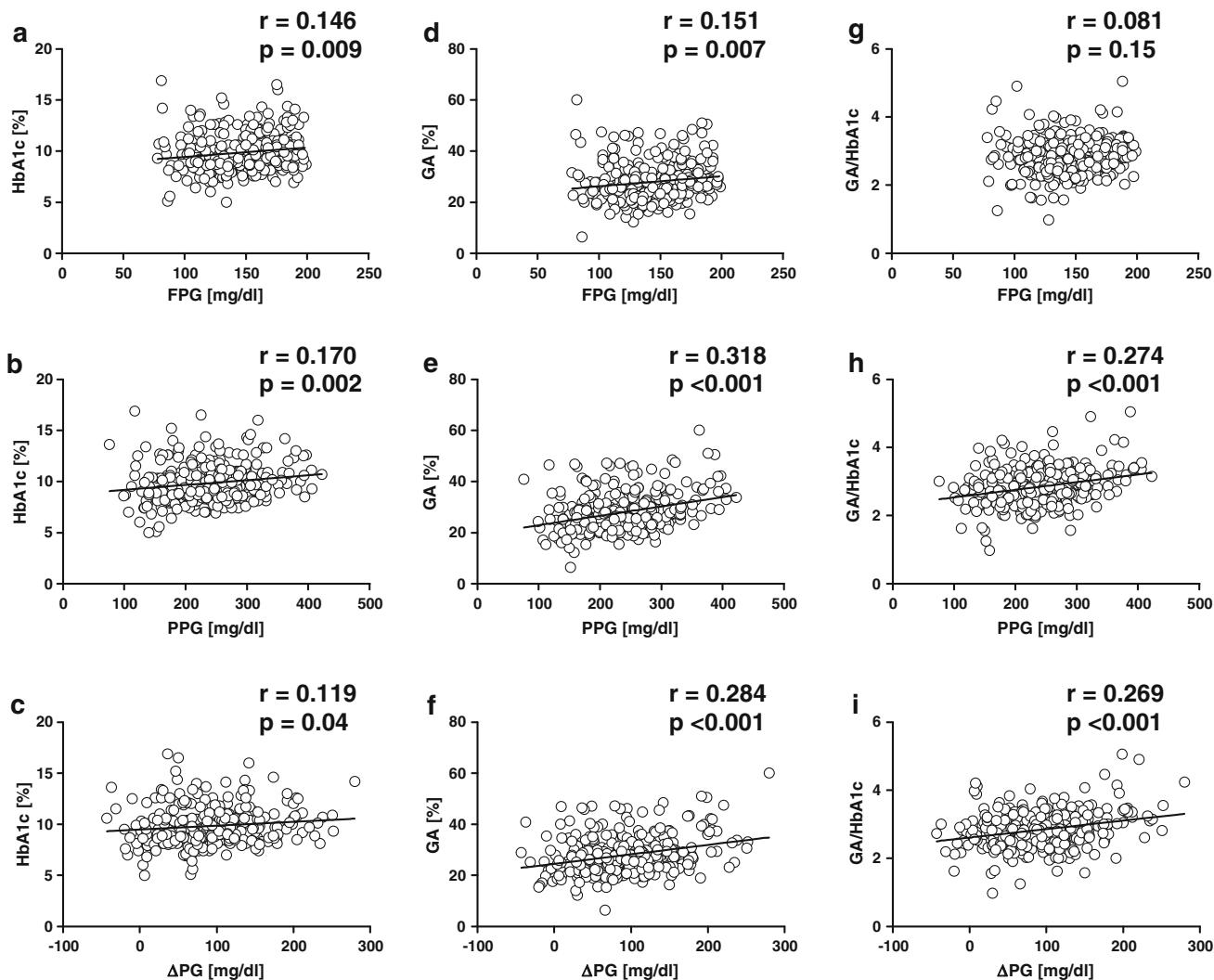
Fig. 2 Correlations among HbA1c, GA, GA/HbA1c ratio and other glycemic indices. There was a significant positive correlation between either postprandial plasma glucose (PPG) (h) or ΔPG (i.e., PPG–FPG) (i) and GA/HbA1c ratio, but no correlation between FPG and GA/HbA1c ratio (g)

preprandial glucose level than with the postprandial glucose level in subjects with both type 1 and type 2 diabetes in the A1C-Derived Average Glucose (ADAG) study [25]. We also found that HbA1c showed comparable associations with FPG and postprandial glucose levels in our population, which was different from GA and the GA/HbA1c ratio. Thus, based on our results, we can safely conclude that the GA/HbA1c ratio reflects postprandial glucose excursion and is a potential marker of postprandial glucose excursion. The mean HbA1c of the subjects in our study (9.8 ± 1.8%) was much higher than that in previous studies (7–8%) [18, 19]. It has also been reported that the relative contribution of postprandial glucose excursion versus fasting glucose decreases with higher HbA1c [26]. Nonetheless, we showed a significant positive association between postprandial glucose and GA/HbA1c, indicating that the GA/HbA1c ratio reflects postprandial glucose

excursion even if the overall glycemic control is poor. On the contrary, since the contribution of postprandial glucose excursion to overall hyperglycemia increases in cases with lower HbA1c (≤ ∼7%), the GA/HbA1c ratio may be affected in such cases.

The mechanism by which the GA/HbA1c ratio reflects glucose excursion remains unknown. Albumin has been reported to be more susceptible to glycation than hemoglobin [27]. A shortened life span of erythrocytes in subjects with diabetes and poor glycemic control has also been reported [28]. Other conditions that affect the turnover of erythrocytes or albumin, such as anemia, proteinuria and liver cirrhosis, could also affect the GA/HbA1c ratio. However, patients with renal failure or liver cirrhosis were excluded from this study.

Our study showed that GA itself also reflects glucose excursion. However, the GA level reflects not only glucose

Fig. 3 Correlations of HbA1c (**a**), GA (**b**) and GA/HbA1c ratio (**c**) with fasting CPR index in subjects with type 2 diabetes. The GA/HbA1c ratio showed the strongest correlation with fasting CPR index compared to HbA1c and GA in subjects with type 2 diabetes. Similar results were observed for postprandial CPR index (**d**–**f**)
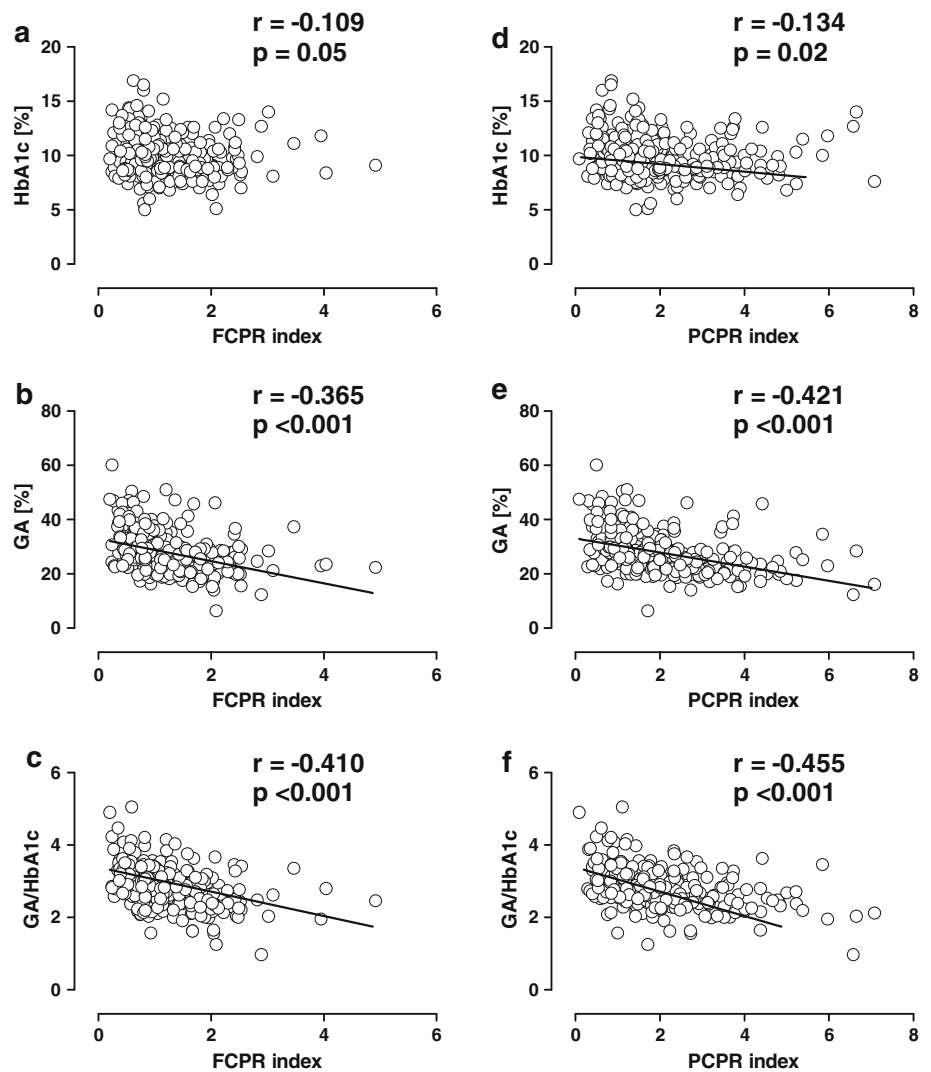
Table 2 Multiple regression analysis for GA/HbA1c ratio

	β	p value
PCPRI	−0.351	<0.001
BMI	−0.225	<0.001
Age	0.199	0.001
PPG	0.152	0.008

Model includes sex, age, duration of diabetes, family history of diabetes, BMI, FPG, PPG, creatinine, PCPRI and medication for diabetes (sulfonylureas, biguanides, thiazolidinediones, glinides, α-glucosidase inhibitors and insulin)

PCPRI postprandial CPR index, *PPG* postprandial plasma glucose

excursion, but also hyperglycemia per se. Indeed, GA was significantly correlated with not only postprandial glucose excursion, but also FPG and HbA1c. In contrast, GA/HbA1c was not significantly correlated with either FPG or HbA1c. These results indicate that GA/HbA1c reflects only glucose excursion independently of hyperglycemia per se. Since normally the GA/HbA1c ratio is approximately 3, we conclude that GA/HbA1c rather than GA itself is a useful marker of glucose excursion in clinical settings.

Recently, Koga et al. [20] reported a significant negative correlation between the GA/HbA1c ratio and beta cell function in subjects with type 2 diabetes. Our study confirmed their finding using a larger sample size and precise evaluation of beta cell function by fasting and postprandial CPR indices and urinary CPR measurement. Furthermore, the correlation between beta cell function and GA/HbA1c remained significant after adjustment for other confounders including age, BMI, FPG, postprandial glucose and previous medication. In this analysis, BMI, age and postprandial glucose level were also selected as independent variables. A negative correlation between BMI and GA has been reported [29, 30]. Obesity and aging may also affect the turnover of either erythrocytes or albumin, or both. The significant negative correlation between HOMA-IR and GA/HbA1c in this study may also reflect the effect of

Fig. 4 Correlations of HbA1c
(**a**), GA (**b**) and GA/HbA1c
ratio (**c**) with fasting CPR index
in subjects with type 1 diabetes
(*white circles* and *solid line*)
overlaid on subjects with type 2
diabetes (*gray circles* and *dotted
line*). Similarly to in subjects
with type 2 diabetes, the GA/
HbA1c ratio showed the
strongest correlation with the
fasting CPR index compared to
HbA1c and GA in subjects with
type 1 diabetes. Note that the
relationships were comparable
in subjects with type 1 and type
2 diabetes. Similar results were
observed for postprandial CPR
index (**d–f**)
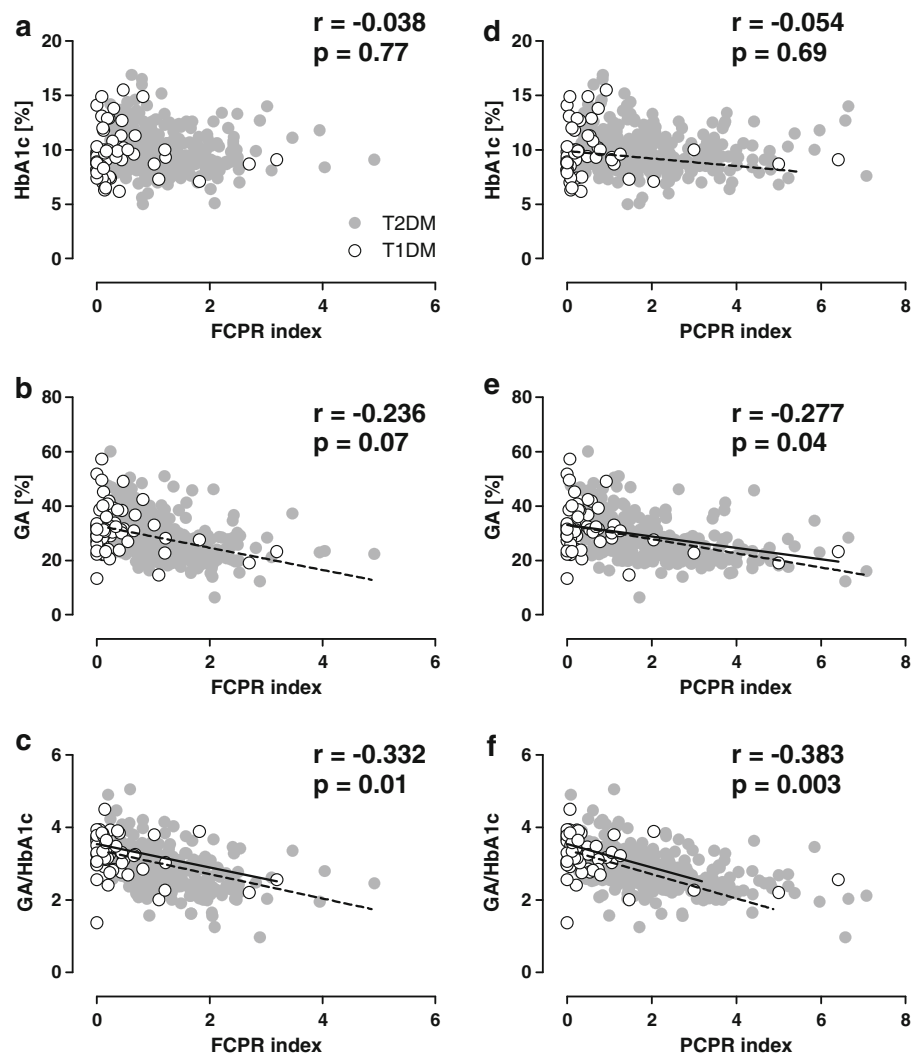
obesity on GA/HbA1c. Although medications such as
α-glucosidase inhibitors, glinides and rapid-acting insulin
analogs affect postprandial glucose excursion, those med-
ications were not selected in our analysis. It would be of
interest to examine whether medications that correct
postprandial glucose excursion decrease the GA/HbA1c
ratio.

Finally, consistent with previous studies [18, 20], our
study showed that the GA/HbA1c ratio was higher in
subjects with type 1 diabetes than in those with type 2
diabetes, suggesting greater glucose variability in subjects
with type 1 diabetes. Furthermore, a comparable relation-
ship between GA/HbA1c and beta cell function in subjects
with type 1 and type 2 diabetes was demonstrated in this
study. These findings indicate the fundamental importance
of beta cell dysfunction in postprandial glucose excursion
in both types of diabetes.

Our study limitations are as follows: (1) fasting and
postprandial blood samples were obtained during admission,

which may not fully reflect postprandial glucose excursion
in daily life. In this study, most patients were receiving
basal-bolus insulin therapy because of hyperglycemia at the
time when postprandial glucose excursion was assessed.
Since insulin therapy reduces glucose excursion as well as
FPG, we might have underestimated the correlation between
GA/HbA1c and postprandial glucose excursion. It is of note,
however, that this does not affect our qualitative conclusion.
(2) Since we did not examine hemoglobin level or thyroid
function in our study population, we cannot completely
exclude the possibility of the presence of mild iron defi-
ciency anemia or thyroid dysfunction, which have been
reported to affect GA and HbA1c in non-diabetic subjects
[31, 32]. (3) Because of the retrospective design of this
study, other confounding factors may exist. Prospective
studies will be needed to confirm our findings.

In conclusion, we report a significant negative correla-
tion between beta cell function and GA/HbA1c ratio in
subjects with both type 1 and type 2 diabetes. Postprandial

glucose excursion has been shown to associate with cardiovascular death [11]. Whether a higher GA/HbA1c level is a risk for diabetic complications in patients with diabetes is of interest. Our results indicate that preservation or recovery of beta cell function would be important to control postprandial glucose excursion, independently of HbA1c level, in patients with both type 1 and type 2 diabetes.

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