Increased glycated albumin levels in patients with acromegaly related to glucose fluctuation caused by growth hormone excess but not albumin metabolism

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Abstract. Acromegaly is often complicated by impaired glucose tolerance. The accuracy of glycated hemoglobin (HbA_{1c}) and glycated albumin (GA) levels in representing glycemic profiles in patients with endocrine disorders, such as acromegaly, is unclear. This retrospective study reviewed data from patients whose GA levels had been recorded. 14 patients with acromegaly without diabetes mellitus (DM) (the acromegaly group), 15 patients with severe adult GH deficiency without DM (the growth hormone deficiency (GHD) group), and 55 nondiabetic patients (the control group) were included in this study. GA levels were significantly increased in the acromegaly group compared with the control and GHD groups, but no significant differences were observed between the control and GHD groups. The three groups were matched using propensity score matching (13 patients with acromegaly, 13 with GHD, and 13 control patients). Nonetheless, the results after matching were the same as those before matching. GA levels in the acromegaly group were significantly associated with plasma glucose (PG) levels at 0, 30, and 120 min after a 75-g oral glucose tolerance test (OGTT). Further, GH levels at 120 min after a 75-g OGTT in the acromegaly group were significantly correlated with GA levels and the difference in PG levels at baseline and 30 min. Our findings suggest that increases in PG levels attributable to excess GH after glucose loading are related to increases in GA levels in patients with acromegaly without DM. Hence, both HbA_{1c} and GA should be checked to accurately assess impaired glucose tolerance in patients with acromegaly.

Key words: Acromegaly, Growth hormone deficiency, Glycated albumin, Growth hormone, 75-g oral glucose tolerance test

LOWERING glycated hemoglobin (HbA_{1c}) levels has long been the primary focus of diabetic therapy. However, many studies have reported that the role of postprandial hyperglycemia and glucose variability, which promotes hypoglycemia, may contribute to the risk of cardiovascular disease [1, 2]. Although HbA_{1c} is a measure of the mean blood glucose level over the preceding 1–2 months [3], it does not reflect unexpectedly high or low blood glucose levels. In contrast, glycated albumin (GA) levels are expected to reflect mean blood glucose levels over the preceding few weeks [4]. Moreover, given that the glycation rate of albumin is faster than that of hemoglobin [5], serum GA levels may also be easily influenced by blood glucose fluctuations. GA can also be more useful than HbA_{1c} for estimating glycemic control among hemodialysis patients and pregnant patients,

given that HbA_{1c} levels can easily decrease due to erythropoietin injection or anemia [6, 7]. However, since some hormones affect albumin metabolism and the half-life of erythrocytes, markers of glycemic control, such as GA and HbA_{1c} levels, may be impacted such that accurate evaluation of glycemic control is difficult [8, 9].

Acromegaly is a chronic disease caused by the excessive production of GH by pituitary adenomas. It is associated with high mortality and comorbidities, such as diabetes mellitus (DM), hypertension, and heart failure [10]. In contrast, adult GH deficiency (AGHD) is most commonly caused by a pituitary tumor or hypothalamus disease [11]. The clinical features of AGHD include increased visceral fat content, reduced bone mineral density, nonalcoholic fatty liver disease, and depression. Additionally, patients with AGHD often have insulin resistance [12]. High GA levels in patients with acromegaly have been reported as related to plasma glucose (PG) levels [13], but no studies have investigated the relationship between AGHD and GA levels.

In this study, we compared GA and HbA_{1c} levels in patients with acromegaly and patients with severe AGHD without DM with those in nondiabetic control

Submitted Jul. 16, 2021; Accepted Sep. 4, 2021 as EJ21-0439

Released online in J-STAGE as advance publication Sep. 28, 2021

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subjects. Thus, we revealed the association between GA levels and PG levels in 75-g oral glucose tolerance test (OGTT) of patients with acromegaly. Lastly, we determined the correlations between GA level and the difference in PG levels at 30 min and at baseline (Δ PG) and between GA level and GH level after 75-g OGTT.

Materials and Methods

Study design and patients

This retrospective study reviewed hospital electronic medical records to collect data of patients whose GA levels had been recorded. Data were obtained from 14 patients with untreated acromegaly without DM (the acromegaly group) and 15 patients with severe AGHD without DM (the growth hormone deficiency (GHD) group) diagnosed at the Department of Endocrinology, Diabetes and Metabolism at Kitasato University Hospital between April 2006 and March 2021 (Table 1). The acromegaly group included 10 patients with normal fasting glucose and 4 patients with impaired fasting glucose, whereas the GHD group included 15 patients with normal fasting glucose. Acromegaly and severe AGHD were diagnosed according to the guidelines of the Endocrine Society [14, 15]. The guidelines for the diagnosis of AGHD in Japan also include the GH-releasing peptide-2 test as a stimulation test [16]. All patients with severe AGHD were administered replacement therapy with hydrocortisone or levothyroxine if they had adrenal insufficiency or thyroid dysfunction, respectively. The control data were obtained from 55 nondiabetic patients who visited our hospital between April 2019 and March 2021. The control subjects included 32 healthy people, 5

people with hypertension, 11 with dyslipidemia, 1 with simple obesity, and 1 with diabetes insipidus. The control group included 46 patients with normal fasting glucose and 9 patients with impaired fasting glucose. We diagnosed diabetes according to the guideline published by the Japan Diabetes Society [17]. Control patients included in this study were determined to have normal endocrine function and normal glucose tolerance by conducting certain tolerance tests, although they were suspected to have endocrine disorders, such as hypopituitarism, adrenal insufficiency, Cushing disease, and primary aldosteronism. Moreover, some control patients visited our hospital because they were suspected of having dyslipidemia or impaired glucose tolerance by the general doctors. However, they were determined to be healthy on the basis of their laboratory data results that were deemed as normal after our assessment. We checked their HbA_{1c}, GA levels, and fasting glucose levels on the day of their first visit to our department. The exclusion criteria were anemia, liver dysfunction, renal impairment, pregnancy, and thyroid disease, all of which might influence albumin and glucose metabolism. Subjects who were receiving any drug known to influence glucose metabolism were also excluded. The study was approved by the Ethics Committee of Kitasato University hospital (approval number: B21-049), and it was conducted according to the Helsinki Declaration and the ethical guidelines for medical and health research involving human subjects from the Ministry of Health, Labour and Welfare.

Laboratory tests

All patients with acromegaly underwent the 75-g

Table 1 Clinical characteristics of the study participants before propensity score matching

	Control <i>n</i> = 55	GHD <i>n</i> = 15	Acromegaly <i>n</i> = 14	Overall <i>p</i> -value
Male (%)	29 (52.7)	6 (40)	3 (21.4)	ns
Age (years)	53.4 ± 19.1	55.5 ± 16.5	58.9 ± 13.3	ns
Height (cm)	162.4 ± 8.7	160.2 ± 9.3	157.1 ± 7.8	ns
Body Weight (kg)	63.7 ± 24.5	60.1 ± 12.7	62.1 ± 11.9	ns
BMI (kg/m ²)	23.9 ± 7.67	23.6 ± 3.1	25.1 ± 4.3	ns
Serum GH (μg/dL)	n.d	0.16 ± 0.24	5.82 ± 4.36*	<.0001
Serum IGF-1 (ng/dL)	n.d	62 ± 31	398 ± 176*	<.0001
Serum albumin (g/dL)	4.19 ± 0.62	4.16 ± 0.24	3.80 ± 0.48	ns
Hemoglobin (g/dL)	13.4 ± 2.03	13.3 ± 0.91	12.4 ± 1.36	ns
Fasting glucose (mg/dL)	98.7 ± 12.5	94.9 ± 6.7	103.8 ± 15.3	ns

* *p* < 0.0001 vs. GHD

Data are presented as means ± standard deviations.

Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; n.d., no data; ns, not significant.

OGTT, and blood samples for measuring PG and GH levels were collected before and 30, 60, and 120 min after glucose intake. GA and HbA_{1c} levels were measured in patients with acromegaly or severe AGHD before GH levels were normalized by specific treatments such as resection of a GH-producing adenoma or GH replacement therapy. PG level was measured using the glucose oxidase method (Glucose analyzer GA 08, A&T Corporation, Kanagawa, Japan; percentage coefficient of variation [%CV] of intra-assay variability <0.8%). GA level was measured by enzymatic synthesis using the automated system LucicaTM glycated albumin-L assay kit (Asahi Kasei Pharma, Tokyo, Japan; %CV of intra-assay variability <0.51). HbA_{1c} levels were expressed as National Glycohemoglobin Standardization Program (NGSP) values and measured by high-performance liquid chromatography using an automated HLC-728G8 system (Tosoh Corp., Tokyo, Japan; %CV of intra-assay variability <0.3%). The reference ranges of HbA_{1c} and GA are 4.6%–6.2% and 11.0%–16.0%, respectively. Serum GH level was measured by electrochemiluminescence immunoassay using Cobas 8000 analyzer series module e801 (Roche Diagnostics, Mannheim, Germany; %CV of intra-assay variability <15%).

Statistical analysis

We used GraphPad Prism 9.1.0 software (GraphPad Software Inc., San Diego, CA, USA) for statistical analysis. Data are presented as mean $\pm$ standard deviation, unless otherwise indicated. Univariate tests for differences in values among the three groups were performed using one-way analysis of variance. *Post hoc* comparison

was performed using Tukey's honestly significant difference test. Moreover, the three groups were matched for age, sex, body mass index, albumin, and hemoglobin using propensity score matching with JMP 16 software (SAS Institute, Cary, NC, USA). The correlations between GA level and PG level and between GA level and GH level were determined using linear regression analysis. Statistical significance was set at less than 5%.

Results

The demographic characteristics of each group before propensity score matching is shown in Table 1. There were no significant differences in the male/female ratio, age, height, body weight, body mass index, fasting glucose, serum albumin level, and hemoglobin level between the groups. Serum GH and insulin-like growth factor 1 (IGF-1) levels were higher in the acromegaly group (5.82 ± 4.36 μ g/dL and 398 ± 176 ng/dL) than in the GHD group (0.16 ± 0.24 μ g/dL and 62 ± 31 ng/dL).

GA level was significantly higher in the acromegaly group than in the control and GHD groups (control group *versus* acromegaly group, $p < 0.0004$; GHD group *versus* acromegaly group, $p = 0.0057$), and there were no significant differences in GA levels between the control group and the GHD group (control group *versus* GHD group, $p = 0.9987$) (Fig. 1A). Further, there were no significant differences in HbA_{1c} levels between the three groups (control group *versus* GHD group, $p = 0.8458$; control group *versus* acromegaly group, $p = 0.5811$; GHD group *versus* acromegaly group, $p = 0.9273$) (Fig. 1B). Furthermore, GA/HbA_{1c} was comparable to GA level and was significantly higher in the acromegaly group,

Fig. 1 Comparison of glycated albumin (GA) levels, glycated hemoglobin (HbA_{1c}) levels, and the GA/HbA_{1c} ratio among the groups before propensity score matching. (A) GA levels, (B) HbA_{1c} levels, and (C) GA/HbA_{1c} in the control group, growth hormone deficiency (GHD) group, and acromegaly group. Data are presented as mean $\pm$ standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

with no significant differences between the control group and the GHD group (control group *versus* acromegaly group, $p < 0.0046$; GHD group *versus* acromegaly group, $p = 0.0125$; control group *versus* GHD group, $p = 0.9253$) (Fig. 1C).

Next, we analyzed the patient characteristic data after propensity score matching. The demographic characteristics of each group after propensity score matching are shown in Table 2 and Table 3. The GA level and GA/HbA_{1c} were significantly higher in the acromegaly group than in the control groups after the matching (control group *versus* acromegaly group; GA $p = 0.0429$; HbA_{1c} $p = 0.7727$; GA/HbA_{1c} $p = 0.0319$) (Fig. 2A–2C). Furthermore, there was no significant difference between the GHD group and control group after the matching (control group *versus* GHD group; GA $p = 0.6716$; HbA_{1c} $p = 0.6337$; GA/HbA_{1c} $p = 0.04592$) (Fig. 2D–

2F).

To determine if GA levels are reflective of PG levels after 75-g OGTT, the correlation between GA and PG levels in the acromegaly group after 75-g OGTT was evaluated. Pearson's univariate correlation analysis revealed that, in the acromegaly group, GA levels were significantly associated with PG levels at 0 min ($y = 4.050x + 37.55$, $r^2 = 0.4272$, $p = 0.0112$), 30 min ($y = 8.067x + 35.91$, $r^2 = 0.3502$, $p = 0.0258$), and 120 min ($y = 10.77x - 9.427$, $r^2 = 0.2958$, $p = 0.0444$) after 75-g OGTT (Fig. 3A–3C). However, GA levels did not correlate with PG levels at 60 min after 75-g OGTT in the acromegaly group ($r^2 = 0.1874$, $p = 0.1220$) (data not shown). We also examined the correlation between HbA_{1c} and PG levels after 75-g OGTT. HbA_{1c} levels were significantly associated with PG levels at 30 min ($y = 53.80x - 143.5$, $r^2 = 0.3682$, $p = 0.0214$) and not

Table 2 Clinical characteristics of the control group and acromegaly group after propensity score matching

	Control $n = 13$	Acromegaly $n = 13$	Overall p -value
Male (%)	1 (7.7)	3 (23.0)	ns
Age (years)	55.0 ± 22.3	57.9 ± 13.2	ns
Height (cm)	158.8 ± 9.00	158.0 ± 7.23	ns
Body Weight (kg)	56.7 ± 16.2	62.6 ± 12.2	ns
BMI (kg/m ²)	22.3 ± 5.46	25.1 ± 4.44	ns
HbA _{1c} (%)	5.66 ± 0.46	5.73 ± 0.35	ns
Serum albumin (g/dL)	4.08 ± 0.54	3.97 ± 0.48	ns
Hemoglobin (g/dL)	12.6 ± 1.55	12.2 ± 1.16	ns
Fasting glucose (mg/dL)	93.3 ± 8.70	95.0 ± 5.44	ns

Data are presented as means $\pm$ standard deviations.

Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; n.d., no data; ns, not significant.

Table 3 Clinical characteristics of the control group and GHD group after propensity score matching

	Control $n = 13$	GHD $n = 13$	Overall p -value
Male (%)	6 (46.1)	5 (34.1)	ns
Age (years)	60.4 ± 22.2	56.1 ± 17.5	ns
Height (cm)	159.8 ± 11.2	159.8 ± 9.99	ns
Body Weight (kg)	56.8 ± 13.1	61.3 ± 13.7	ns
BMI (kg/m ²)	22.1 ± 4.39	23.8 ± 3.27	ns
Serum albumin (g/dL)	4.02 ± 0.54	4.10 ± 0.20	ns
Hemoglobin (g/dL)	13.3 ± 1.75	13.2 ± 0.84	ns
Fasting glucose (mg/dL)	99.3 ± 11.6	94.0 ± 5.20	ns

Data are presented as means $\pm$ standard deviations.

Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; n.d., no data; ns, not significant.

correlated with PG levels at any other time (data not shown).

To determine if GA levels are reflective of GH levels after 75-g OGTT, the correlation between GA and GH levels after 75-g OGTT was evaluated in the acromegaly group. Pearson's univariate correlation analysis revealed that, in the acromegaly group, GA levels were significantly correlated with GH levels at 120 min ($y = 0.8474x - 7.595$, $r^2 = 0.3359$, $p = 0.0298$) after 75-g OGTT

(Fig. 4A), but no such correlation was observed at 0 min ($r^2 = 0.1560$, $p = 0.1662$), 30 min ($r^2 = 0.01124$, $p = 0.7182$), or 60 min ($r^2 = 0.2032$, $p = 0.1057$) after 75-g OGTT (data not shown). Furthermore, we estimated the correlation between GH levels and Δ PG. GH levels at 120 min after 75-g OGTT correlated significantly with Δ PG ($y = 0.1090x - 0.8014$, $r^2 = 0.4868$, $p = 0.0055$) (Fig. 4B). However, there was no correlation between Δ PG and GH levels at 0 min ($r^2 = 0.1895$, $p = 0.1198$),

Fig. 2 Comparison of glycated albumin (GA) levels, glycated hemoglobin (HbA_{1c}) levels, and the GA/HbA_{1c} ratio among the groups after propensity score matching. (A) GA levels, (B) HbA_{1c} levels, and (C) GA/HbA_{1c} in the control group and acromegaly group. (D) GA levels, (E) HbA_{1c} levels, and (F) GA/HbA_{1c} in the control group and growth hormone deficiency (GHD) group. Data are presented as mean $\pm$ standard deviation. * $p < 0.05$.

Fig. 3 Correlation between glycated albumin (GA) levels and plasma glucose (PG) levels after oral glucose loading. Plots showing the correlation between GA levels and PG levels before (A) and at 30 min (B) and 120 min (C) after 75-g OGTT. A linear regression model was used for the analysis.

Fig. 4 Correlation between glycated albumin (GA) and GH levels after oral glucose loading, between baseline plasma glucose (Δ PG) and GH, and between GA and HOMA- β . Plots showing the correlation of serum GH levels at 120 min after 75-g OGTT with glycated albumin (GA) levels (A) and Δ PG (B). (C) Plot showing the correlation of GA levels and HOMA- β . Δ PG was calculated as follows: PG level at 30 min – PG level at baseline. A linear regression model was used for the analysis.

30 min ($r^2 = 0.01822$, $p = 0.6454$), or 60 min ($r^2 = 0.2691$, $p = 0.0574$) after 75-g OGTT. Although we examined the correlation between HbA_{1c} and GH levels after 75-g OGTT, HbA_{1c} levels were not significantly associated with GH levels at any time.

We examined whether there was any correlation between GA levels or HbA_{1c} and HOMA-R or HOMA- β . HOMA- β was significantly associated with GA levels ($y = -8.647x + 202.4$, $r^2 = 0.5890$, $p = 0.0014$) (Fig. 4C). HOMA-R was not associated with GA and HbA_{1c}, and HOMA- β was not correlated with HbA_{1c}.

Discussion

The results of this study confirm those of a previous study that reported higher GA levels in patients with acromegaly than in patients without acromegaly [13]. Moreover, our study revealed that GA/HbA_{1c} is higher in nondiabetic patients with acromegaly than in nondiabetic control patients and patients with AGHD. We also found that there were no significant differences in GA level, HbA_{1c} level, and GA/HbA_{1c} between nondiabetic patients with severe AGHD and nondiabetic control patients. It also showed that in nondiabetic patients with acromegaly, PG levels and GH levels after 75-g OGTT correlate with GA levels.

This study included only nondiabetic patients. Diabetic patients are often prescribed oral antidiabetic agents that may influence glucose markers, and GA level correlates with fluctuations in glucose level. Reports have shown that glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter 2 inhibitors are more effective at alleviating glucose fluctuations than sulfonylureas and basal insulin [18–20]. If the patients evaluated in this study had been prescribed an antidiabetic agent, we would have needed to exclude the effect of the antidia-

betic agent on GA levels. We reckoned that the physiological effects of GH on blood glucose levels are greater in nondiabetic patients than in diabetic patients, and it is easier to understand the relationship between GH and glucose metabolism because patients with DM have higher plasma glucagon and cortisol levels than patients with normal glucose tolerance [21, 22]. We can exclude the unexpected effects of counterregulatory hormones if only nondiabetic patients are included in this study.

There are many benefits of GA level in terms of glucose control monitoring. GA level is not influenced by abnormal hemoglobin and is useful for the estimation of postprandial glucose level and glucose excursions [23, 24]. GA/HbA_{1c}, which also serves as a clinical index for predicting blood glucose variability [25], increases when β -cell function is reduced, whereas glycemic variability is correlated with β -cell dysfunction [26]. We found that GA levels and GA/HbA_{1c}, which is known to represent glucose variability, are higher in the acromegaly group than in the other two groups. However, in our study, GA/HbA_{1c} was not found to correlate with PG level after 75-g OGTT.

Patients with diseases associated with irregular albumin metabolism have abnormal GA levels [9]. GH decreases proteolysis by inducing IGF-1 synthesis [27, 28]. However, in this study, no significant differences in serum albumin levels were observed between the patient groups. The GA levels in the GHD group were not significantly lower than those in the nondiabetic control patients, while the GA levels in the acromegaly group were higher than those in the two other groups. The effects of GH on protein metabolism become more pronounced during the fasting state, while they are modest in the postprandial states and include increased protein synthesis at the whole-body level [29]. High doses of GH for 7 days were reported to increase both leucine protein synthesis and leucine oxidation at the whole-body level,

demonstrating the impact of GH on protein metabolism [30]. On the other hand, 14 weeks of high-dose GH treatment had no effect on fractional muscle protein synthesis [31]. Some studies did not find any effects of prolonged GH exposure on whole-body protein turnover or albumin synthesis [32, 33]. These studies revealed that the effect of GH on albumin metabolism is unstable. It is difficult to confirm that patients with acromegaly have a disorder of albumin metabolism or GA metabolism. We thought that the increase in GA levels in patients with acromegaly was not significantly related to albumin metabolism due to GH.

Furthermore, GA levels in acromegaly are associated with PG levels after the oral glucose load. GA levels reflect daily glucose excursion [34] and medium-term variation more accurately in non-complicated diabetes [23]. Moreover, the finding that GH levels after the oral glucose load correlates with GA levels shows that GH directly affects postprandial PG and GA levels. GH is partially considered a catabolic hormone since it induces lipolysis and insulin resistance. Chronic GH treatment of differentiated 3T3-L1 cells reduces insulin-dependent 2-deoxyglucose uptake and activation of Akt [35]. Continuous infusion of 1.5 mg of GH impaired hepatic and peripheral insulin sensitivity in a normal man after 12 h [36, 37]. Furthermore, smaller GH doses can impair hepatic and peripheral insulin sensitivity after 2 h [38]. GH induces insulin resistance through increased endogenous glucose production and decreased peripheral glucose disposal in muscles [38, 39]. Interestingly, HOMA- β was significantly associated with GA levels in this study, suggesting that GA levels are also related to β cell functions. Our study results suggest that the rise in postprandial PG level through insulin resistance due to GH excess and β cell function is related to the increase in GA level but is unrelated to albumin metabolism.

Our study revealed that there were no significant differences in GA level, HbA_{1c} level, and GA/HbA_{1c} between nondiabetic patients with severe AGHD and nondiabetic control patients. Our findings are supported

by a study showing that patients with AGHD had similar fasting glucose levels to control subjects before and after a meal [40].

Because serum albumin is glycosylated more rapidly than hemoglobin, GA is a more sensitive indicator of blood glucose excursion than HbA_{1c}. Both the GA level and GA/HbA_{1c} ratio were reported as each independently correlated with the mean amplitude of glucose excursion in patients with type 1 diabetes [41]. Moreover, our previous study using continuous glucose monitoring revealed that GA/HbA_{1c} is more strongly correlated with glycemic standard deviation than single GA levels (GA: $r = 0.31$, $p = 0.0016$. GA/HbA_{1c}: $r = 0.53$, $p < 0.0001$) [25]. Thus, GA/HbA_{1c} is more sensitive to glycemic fluctuations than GA levels, and it cannot merely be explained by the susceptibility of GA and HbA_{1c} to glycemic fluctuations.

In conclusion, GA levels are significantly higher in patients with acromegaly without DM than in nondiabetic control patients and nondiabetic patients with severe AGHD. In patients with acromegaly, PG and GH levels after a glucose load correlate with the GA level. These results revealed that increased GA levels in patients with acromegaly were unrelated to albumin metabolism disorders but were related to glucose excursion due to GH excess. Moreover, we may miss impaired glucose tolerance in patients with acromegaly if we only check HbA_{1c} levels without checking GA levels. HbA_{1c} and GA levels should both be measured to detect impaired glucose tolerance in patients with acromegaly.

Acknowledgments

The authors thank Enago (www.enago.jp) for the English language review.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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