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Effects of growth hormone excess on glycated albumin concentrations: Analysis in acromegalic patients

Daisuke Tamada [a], Michio Otsuki [a], Tetsuhiro Kitamura [a], Satoru Oshino [b], Youichi Saitoh [b], Iichiro Shimomura [a], Masafumi Koga [c,*]

[a] Departments of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[b] Departments of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan
[c] Department of Internal Medicine, Kawanishi City Hospital, Hyogo, Japan

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ABSTRACT

Background: Glycated albumin (GA) does not reflect glycemic control in patients with disorders of albumin metabolism. In the present study, we examined GA concentrations in acromegalic patients with growth hormone (GH) excess.
Methods: We studied the hormonal status of 29 acromegalic patients (10 patients had diabetes mellitus and the remaining 19 patients were non-diabetic), 20 patients with type 2 diabetes mellitus and 38 non-diabetic subjects matched for age, sex and body mass index.
Results: Serum GA concentrations, but not those of fasting plasma glucose, 2-h post-load plasma glucose and HbA1c, were significantly higher in non-diabetic acromegalic patients compared with non-diabetic control subjects. Serum GA concentrations, but not those of fasting plasma glucose and HbA1c, were significantly higher in diabetic acromegalic patients compared with patients with type 2 diabetes mellitus.
Conclusions: This is the first report describing higher GA concentrations in acromegalic patients relative to plasma glucose concentrations. Special care should be taken when evaluating glycemic control using GA because acromegaly is frequently complicated with diabetes mellitus.

1. Introduction

It is known that nonenzymatic glycation of protein increases in diabetic patients compared with non-diabetic subjects, and it is suggested that certain types of these glycated proteins may contribute to the onset and progression of diabetic complications [1]. Among these glycated proteins, HbA1c and glycated albumin (GA) are used as clinical indicators of glycemic control [2,3]. However, in diseases affecting the life span of erythrocytes and albumin metabolism, HbA1c and GA are not suitable markers since they do not accurately reflect the state of glycemic control [4,5]. Since some hormones affect erythrocyte life span and albumin metabolism, they may also affect the markers of glycemic control. For example, testosterone indirectly reduces HbA1c by stimulating erythropoiesis [6], similar to the effects of thyroid hormone and glucocorticoid on GA [7,8].

Acromegaly is caused by hypersecretion of growth hormone (GH) from pituitary adenoma. In acromegalic patients, the prevalence of diabetes mellitus ranges from 19% to 56% [9], and these complications are associated with the prognosis of acromegalic patients [10]. Therefore, glucose intolerance should be managed appropriately in these patients. GH is a strong anabolic hormone, which is essential for maintenance of muscle mass not only in childhood but also in adulthood [11]. Therefore, GH regulates the metabolism of various proteins, including albumin, a major serum protein. Accordingly, GH excess may affect GA concentrations.

2. Patients and methods

2.1. Study patients

The study subjects were 29 patients with active acromegaly diagnosed at Osaka University Hospital between April 2010 and March 2013 (Table 1). The diagnosis of acromegaly was based on the following criteria: (1) clinical features (acral enlargement, acromegalic features and macroglossia); (2) lack of suppression of serum GH concentrations below 1 μg/l after 75 g oral glucose tolerance test (OGTT), with serum insulin-like growth factor-I (IGF-I) concentrations above the upper limit of the normal range; and (3) identification of a pituitary mass on magnetic resonance imaging. Among the study subjects, we excluded patients with chronic liver diseases, chronic renal disease including overt proteinuria, anemia, thyroid dysfunction or adrenal dysfunction, which are known to influence the measurements of HbA1c and/or GA. Thus, data were collected from 20 patients with type 2 diabetes mellitus

* Corresponding author. Tel.: +81 72 794 2321; fax: +81 72 794 6321.
E-mail address: m-koga@kawanishi-city-hospital.com (M. Koga).

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Table 1
Clinical characteristics of subjects of the 4 study groups.

	Control		Acromegaly	
	Without DM	With DM	Without DM	With DM
n	38	20	19	10
Male (%)	19 (50.0)	10 (50.0)	9 (47.4)	5 (50.0)
Age (years)	49.4 ± 5.9	57.8 ± 6.8	49.4 ± 10.8	58.1 ± 10.0
Body mass index (kg/m^2)	23.2 ± 3.0	24.2 ± 2.8	23.0 ± 2.7	24.1 ± 2.7
Serum GH (μg/l)	n.d.	n.d.	8.9 (3.9–13.8)	11.7 (5.3–19.8)
Serum IGF-1 (μg/l)	n.d.	n.d.	695 (487–1140)	913 (564–1220)
Serum albumin (g/l)	42.0 ± 6.0	43.0 ± 4.0	39.0 ± 3.0	39.0 ± 3.0$^{\#\#}$
Hemoglobin (g/l)	137 ± 16	140 ± 13	133 ± 11	132 ± 12
Serum creatinine (μmol/l)	65.4 ± 10.6	67.2 ± 16.8	49.5 ± 11.5**	49.5 ± 15.9$^{\#}$
Serum uric acid (μmol/l)	339 ± 95	321 ± 77	286 ± 54*	256 ± 48$^{\#}$
Serum albumin/ creatinine ratio	0.97 ± 0.24	1.01 ± 0.25	1.24 ± 0.29**	1.29 ± 0.44$^{\#}$

Data are mean ± SD, or median (interquartile range).
The two groups were compared using the unpaired *t*-test.
$^{*}P < 0.05$, $^{**}P < 0.001$ vs. non-diabetic control subjects, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. diabetic control subjects.
DM, diabetes mellitus; n.d., not done.

and 38 control non-diabetic subjects matched for age, gender and body mass index (BMI). Diabetes mellitus was diagnosed based on the diagnostic criteria of the American Diabetes Association [12]. The study was performed was approved by the Ethics Committee of Osaka University School of Medicine (approval number: 13080) and conducted according to the Helsinki Declaration

2.2. Laboratory tests

Blood samples were taken in the early morning after overnight fast. The 75-g OGTT was performed in all acromegalic patients and control subjects, and plasma glucose concentrations were measured before and 2 h after the glucose tolerance test.

HbA1c was measured by high-performance liquid chromatography (HPLC) with an HLC-723G8 (Tosoh Co.). The HbA1c values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values using the official equation [13]. GA was measured by the enzymatic method with a Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co.) using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co.) [14]. The standard range was 4.6–6.2% for HbA1c and 11.7–16.0% for GA. Serum GH was measured using a chemiluminescent enzyme immunoassay kit (Beckman Coulter Inc.), and IGF-1 was determined by immunoradiometric assay (Daiichi Radioisotope Laboratories) [15].

2.3. Statistical analysis

Data were expressed as mean ± SD for parameters with normal distribution and as medians and interquartile range for those with skewed distribution (GH and IGF-1). The unpaired *t*-test and the χ^2 test were used for intergroup comparisons, and Pearson's correlation coefficient was used for testing the correlation between fasting plasma glucose and HbA1c and GA. The concentration of statistical significance was established as less than 5%. Statistical analysis was performed using JMP 9.0.2 (SAS Institute Inc.).

3. Results

The acromegalic patients consisted of 14 males (48.3%) and 15 females, aged 52.4 ± 11.3 years with BMI of 23.4 ± 2.7 kg/m^2. Ten of these patients (34.5%) were diagnosed with diabetes mellitus while the remaining 19 patients were non-diabetic (Table 1). Serum GH and serum IGF-1 were high at 10.4 μg/l (4.6–14.1) and 834 μg/l (535–1155), respectively.

Fasting plasma glucose (5.42 ± 0.51 vs. 5.46 ± 0.49 mmol/l, $P = 0.577$) and 2-h post-load plasma glucose after OGTT (7.60 ± 1.67 vs. 7.60 ± 1.17 mmol/l, $P = 0.905$) in the non-diabetic acromegalic patients were not significantly different from those in the non-diabetic control subjects (Fig. 1A, B). HbA1c also showed no significant difference between these two groups (5.7 ± 0.4% vs. 5.5 ± 0.4%, $P = 0.150$) (Fig. 1C). On the other hand, GA in the non-diabetic acromegalic patients was significantly higher than that in the non-diabetic control subjects (16.7 ± 2.2% vs. 14.0 ± 1.1%, $P < 0.0001$) (Fig. 1D). Similar results were obtained even after adjustment of GA concentrations for age, gender, BMI and HbA1c (16.4 ± 1.7% vs. 14.2 ± 1.2%, $P < 0.0001$). HbA1c was higher than the standard value by the same proportion in 2 non-diabetic acromegalic patients (10.5%) and 4 non-diabetic control subjects (10.5%). On the other hand, GA was higher than the standard value in 12 non-diabetic acromegalic patients (63.2%) and only one non-diabetic control subject (2.6%), and the proportion of non-diabetic acromegalic patients was significantly higher compared with non-diabetic control subjects ($P < 0.0001$).

Fasting plasma glucose (7.88 ± 1.72 mmol/l) and HbA1c (7.4 ± 1.1%) in the diabetic acromegalic patients were not significantly different from those of patients with type 2 diabetes mellitus (7.94 ± 1.22 mmol/l, $P = 0.943$, 7.6 ± 1.0%, $P = 0.503$, respectively) (Fig. 2A, B). On the other hand, GA was significantly higher in the diabetic acromegalic patients (24.2 ± 4.7%) than those with type 2 diabetes mellitus (19.8 ± 3.0%, $P = 0.004$) (Fig. 2C). When GA concentrations in both groups were adjusted for age, gender, BMI and HbA1c, the mean values of the 2 groups were still statistically different (24.8 ± 2.9% vs. 19.6 ± 1.5%, $P < 0.0001$). In the diabetic acromegalic patients and the patients with type 2 diabetes mellitus, fasting plasma glucose correlated significantly with HbA1c ($y = 0.031x + 2.96$, $R = 0.856$, $P = 0.002$ vs. $y = 0.030x + 3.37$, $R = 0.645$, $P = 0.002$, respectively), and the regression formulae of the two groups were almost identical (Fig. 3A). Furthermore, GA significantly correlated with fasting plasma glucose ($y = 0.101x + 9.93$, $R = 0.655$, $P = 0.040$ vs. $y = 0.082x + 8.18$, $R = 0.615$, $P = 0.004$) (Fig. 3B) and also with HbA1c ($y = 3.64x + 2.48$, $R = 0.854$, $P = 0.002$ vs. $y = 2.41x + 1.38$, $R = 0.845$, $P < 0.0001$) (Fig. 3C) in both groups, but the regression line of the diabetic acromegalic patients was shifted upward compared with that of patients with type 2 diabetes mellitus.

Serum albumin was significantly lower in the acromegalic patients (39.0 ± 3.0 g/l) compared with the control (43.0 ± 6.0 g/l, $P = 0.006$). Furthermore, serum creatinine (49.5 ± 13.3 μmol/l) and serum uric acid (274 ± 54 μmol/l) were significantly lower in acromegalic patients than the control (66.3 ± 13.3 μmol/l, $P < 0.0001$, 333 ± 89 μmol/l, $P = 0.003$, respectively). The serum albumin/creatinine ratio was significantly higher in acromegalic patients (1.26 ± 0.34) than the control (0.99 ± 0.24, $P < 0.0001$). A comparison of the non-diabetic acromegalic patients and non-diabetic control subjects showed a significant correlation between the serum albumin/creatinine ratio and GA ($R = 0.340$, $P = 0.010$), but not between serum albumin and GA ($R = -0.078$, $P = 0.564$). Stepwise multivariate analysis showed a significant correlation between the serum albumin/creatinine ratio, but not serum albumin, and GA (data not shown).

4. Discussion

The main findings of the present study were high GA concentrations in acromegalic patients relative to plasma glucose concentrations and no significant difference in fasting plasma glucose and HbA1c between acromegalic patients and control subjects. The change in GA was observed in both acromegalic patients with and without diabetes mellitus. Patients with diseases known to be associated with abnormal albumin metabolism have abnormal GA values [5]. Patients with nephrotic