Clinical Biochemistry 47 (2014) 279–282

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Serum albumin-adjusted glycated albumin is an adequate indicator of glycemic control in patients with Cushing's syndrome

Tetsuhiro Kitamura [a], Michio Otsuki [a], Daisuke Tamada [a], Yukiko Tabuchi [a], Kosuke Mukai [a], Shinya Morita [b], Soji Kasayama [b], Yukihiro Bando [c], Iichiro Shimomura [a], Masafumi Koga [d,*]

[a] Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Japan
[b] Department of Medicine, Nissay Hospital, Japan
[c] Department of Internal Medicine, Fukui-ken Saiseikai Hospital, Japan
[d] Department of Internal Medicine, Kawanishi City Hospital, 5-21-1 Higashi-Uneno, Kawanishi, Hyogo 666-0195, Japan

ARTICLE INFO

Article history:
Received 30 April 2014
Received in revised form 3 September 2014
Accepted 4 September 2014
Available online 16 September 2014

Keywords:
Cushing's syndrome
Glucocorticoid
Glycated albumin
HbA1c
Albumin

ABSTRACT

Objectives: We recently reported that glycated albumin (GA) in patients with Cushing's syndrome is low. In the present study, we examined whether serum albumin (SA)-adjusted GA (SAaGA) is an adequate indicator of glycemic control in patients with Cushing's syndrome.

Design and methods: We studied 26 patients with Cushing's syndrome (13 patients without diabetes and 13 patients with diabetes). Twenty six non-diabetic subjects and 26 patients with type 2 diabetes mellitus matched for age, sex and BMI were used as the controls. SAaGA was calculated using the regression formula between SA and GA in non-diabetic patients with Cushing's syndrome and non-diabetic subjects.

Results: SA showed a significant correlation with GA in non-diabetic patients with Cushing's syndrome and non-diabetic subjects. GA, but not SAaGA, in non-diabetic patients with Cushing's syndrome was significantly lower than that in the non-diabetic controls. Furthermore, the GA/HbA1c ratio, but not the SAaGA/HbA1c ratio, in diabetic patients with Cushing's syndrome was significantly lower than that in the diabetic controls. The measured GA in the patients with Cushing's syndrome was significantly lower than the estimated GA, but there was no difference between SAaGA and the estimated GA.

Conclusions: The present findings suggest that SAaGA is an adequate indicator of the glycemic control in patients with Cushing's syndrome.

Introduction

It is known that nonenzymatic glycation of various proteins increases in diabetic patients compared with non-diabetic subjects, and it has been suggested that these glycated proteins contribute to the onset and progression of diabetic complications [1]. Among these glycated proteins, HbA1c is frequently used as an indicator of glycemic control in clinical practice [2,3]. Since the lifespan of erythrocytes is about 120 days, HbA1c reflects glycemic control during the previous 1 to 2 months. However, it is known that HbA1c level is influenced by variant hemoglobin and the diseases that shorten the lifespan of erythrocytes such as hemolytic anemia and renal anemia. Thus HbA1c does not accurately reflect the state of glycemic control in such cases [4,5].

In addition to HbA1c, glycated albumin (GA) is used as an indicator of glycemic control [6]. Since the half-life of albumin is shorter than that of erythrocytes, GA reflects the intermediate-term (about two weeks) of glycemic control. It is known that GA is not affected by disorders of hemoglobin metabolism [6]. However, GA shows a low value in nephrotic syndrome [7] and hyperthyroidism [8] in which the half-life of albumin is shortened, and a high value in liver cirrhosis [9] and hypothyroidism [8] in which the half-life of albumin is prolonged. While glucocorticoid is known to enhance the catabolism of albumin [10,11], we reported that GA shows a low value in patients with Cushing's syndrome [12].

Cushing's syndrome is a clinical state caused by hypercortisolemia. Autonomic and inappropriate cortisol secretion is mostly caused by ACTH producing pituitary adenoma and cortisol producing adrenal adenoma [13]. In these patients, hypercortisolemia caused not only pathognostic features but also metabolic abnormalities. Glucose intolerance occurs in patients with Cushing's syndrome and diabetes mellitus is present in 20 to 50% of these patients [14]. In addition to hypertension, diabetes mellitus is another important risk factor for cardiovascular diseases in Cushing's syndrome [15,16]. The careful evaluation and treatment of glucose intolerance and diabetes mellitus associated with Cushing's syndrome is recommended.

It is known that serum albumin (SA) shows a low value in patients with Cushing's syndrome [17]. We therefore hypothesized that, if SA decreases because of enhanced catabolism of albumin in patients with Cushing's syndrome, SA-adjusted GA (SAaGA) may reflect the glycemic

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

http://dx.doi.org/10.1016/j.clinbiochem.2014.09.007
0009-9120/

control state in patients with Cushing's syndrome. The aim of this study is to verify this hypothesis.

Materials and methods

Patients

We retrospectively enrolled 26 patients with Cushing's syndrome [6 males and 20 females; Cushing's disease in 10 patients, cortisol-producing adrenal adenoma in 14 patients and ACTH-independent macronodular adrenal hyperplasia (AIMAH) in 2 patients] (Table 1). The mean age of these patients was 50.5 ± 12.8 years and mean body mass index (BMI) was 26.0 ± 5.6 kg/m^2. Thirteen patients were diagnosed to have diabetes mellitus. Serum cortisol levels in these subjects were high at 23.8 ± 9.9 μg/dL. Twenty six non-diabetic subjects and 26 patients with type 2 diabetes mellitus matched for age, sex and BMI were used as the controls. Plasma glucose, HbA1c, GA, SA and serum cortisol were measured in the morning with the fasting state. This study was approved by the ethics committees at each participating hospital.

Laboratory methods

Plasma glucose levels were determined by glucose oxidase methods for fasting plasma glucose. HbA1c was measured by high performance liquid chromatography (HPLC). HbA1c values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values in accordance with the official equation [18]. GA was determined by a 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) [19]. The normal reference ranges of HbA1c were between 4.6% and 6.2% (27.5 mmol/mol and 43.8 mmol/mol), while those of GA were between 11.7% and 16.0%. Serum cortisol was measured by solid-phase radioimmunoassay.

Blood glucose was measured in 6 patients with Cushing's syndrome (2 with diabetes mellitus and 4 without it) 7 times a day (before and after each meal and before bed) using self-monitoring of blood glucose (SMBG), and mean blood glucose (MBG) was calculated from these blood glucose values.

The estimated Hb1Ac was calculated from MBG using the formula developed by Rohlfing et al. as described previously (Formula 1) [12,20]. The estimated GA was calculated from the estimated HbA1c using the data of the GA/HbA1c ratio in patients with type 2 diabetes mellitus reported by Hirata et al. [12,21] (Formula 2). SAaGA was calculated using the formula (Formula 3) based on the regression line [GA (%) = 1.77 × SA (g/dL) + 6.26] between GA and SA in the non-diabetic patients with Cushing's syndrome and the non-diabetic subjects (Fig. 1) and the mean GA levels (14.0%) in the non-diabetic subjects.

$$\text{Estimated HbA1c}\ (\%) = \text{MBG}\ (\text{mg/dL}) \times 1.11/35.6 + 2.17 \quad \text{(Formula 1)}$$

Table 1
Clinical characteristics of study patients.

	Control	Cushing's syndrome	P value
n	52	26	–
Male (%)	19 (36.5)	6 (23.1)	0.230
Diabetes mellitus (%)	26 (50.0)	13 (50.0)	1.0
Age (years)	51.6 ± 6.4	50.5 ± 12.8	0.650
Body mass index (kg/m^2)	25.1 ± 4.1	26.0 ± 5.6	0.446
Fasting plasma glucose (mg/dL)	117 ± 31	107 ± 37	0.184
HbA1c (%)	6.6 ± 1.3	6.8 ± 1.6	0.586
GA (%)	16.8 ± 3.7	15.2 ± 4.0	0.092
Serum albumin (g/dL)	4.3 ± 0.4	3.8 ± 0.5	<0.0001

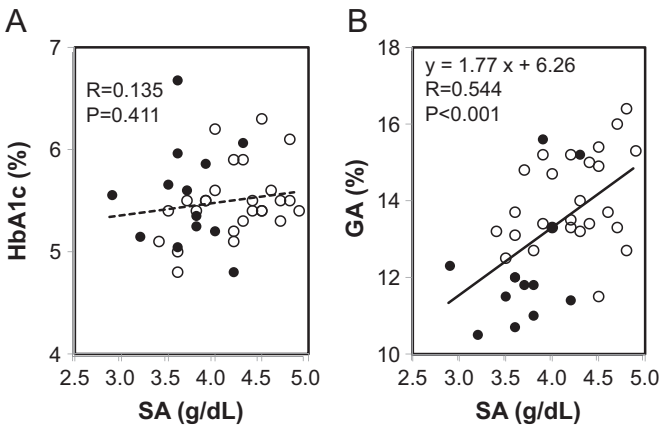

Fig. 1. Correlation between serum albumin (SA) and the indicators of glycemic control (HbA1c and GA) in the non-diabetic patients with Cushing's syndrome (CS) and the non-diabetic subjects. Correlations between SA and HbA1c (A), and correlations between SA and GA (B) in 13 non-diabetic subjects with CS (closed symbols) and 26 non-diabetic subjects (open symbols) are shown.

$$\text{Estimated GA}(\%) = 2.7 \times \text{Estimated HbA1c}(\%) \quad \text{(Formula 2)}$$

$$\text{SAaGA}(\%) = \text{GA}(\%) \times 14.1/[1.77 \times \text{SA}(\text{g/dL}) + 6.26] \quad \text{(Formula 3)}$$

Statistical analysis

All data are shown as mean ± SD. For statistical analyses, unpaired Student's *t* test paired Student's *t* test or chi-square test were used to compare two groups, as appropriate. To analyze the effects of explanatory variables on HbA1c, GA, or SAaGA, univariate regression analysis was performed with the StatView computer program (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA). A P value of <0.05 was considered to be statistically significant.

Results

SA in the patients with Cushing's syndrome was significantly lower than that in the control (3.8 ± 0.5 g/dL vs. 4.3 ± 0.4 g/dL, $P < 0.0001$) (Table 1). It was less than 4.0 g/dL in 18 (69.2%) of 26 patients with Cushing's syndrome, which was a significantly higher proportion than 14 (25.0%) of 56 controls ($P < 0.001$). SA less than 3.5 g/dL was only one (1.8%) in 56 controls, whereas such values were observed in 6 (25.0%) of 26 patients with Cushing's syndrome ($P < 0.0001$).

Next, the correlation between SA and the indicators of glycemic control (HbA1c and GA) was examined in 13 non-diabetic patients with Cushing's syndrome and 26 non-diabetic subjects without Cushing's syndrome (Fig. 1). SA did not show a significant correlation with HbA1c ($R = 0.135$, $P = 0.411$), but a significant positive correlation with GA ($R = 0.544$, $P < 0.001$). Therefore, SAaGA was calculated using the formula shown in the Methods section based on the regression formula between SA and GA.

HbA1c in the non-diabetic patients with Cushing's syndrome showed no significant difference from that in the non-diabetic subjects (5.6 ± 0.6% vs. 5.5 ± 0.4%, $P = 0.628$); however, GA was significantly lower (12.2 ± 1.6% vs. 14.0 ± 1.2%, $P < 0.0001$) (Table 2A). On the other hand, SAaGA showed no significant difference between both groups (13.4 ± 1.5% vs. 14.0 ± 1.2%, $P = 0.182$).

Whereas HbA1c and GA in the diabetic patients with Cushing's syndrome were not significantly different from that in the type 2 diabetic patients, the GA/HbA1c ratio was significantly lower than that in the