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Glycated albumin is set lower in relation to plasma glucose levels in patients with Cushing's syndrome

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ABSTRACT

Background: Glycated albumin (GA) is an indicator of glycemic control, which has some specific characters in comparison with HbA1c. Since glucocorticoids (GC) promote protein catabolism including serum albumin, GC excess state would influence GA levels. We therefore investigated GA levels in patients with Cushing's syndrome.
Methods: We studied 16 patients with Cushing's syndrome (8 patients had diabetes mellitus and the remaining 8 patients were non-diabetic). Thirty-two patients with type 2 diabetes mellitus and 32 non-diabetic subjects matched for age, sex and BMI were used as controls.
Results: In the patients with Cushing's syndrome, GA was significantly correlated with HbA1c, but the regression line shifted downwards as compared with the controls. The GA/HbA1c ratio in the patients with Cushing's syndrome was also significantly lower than the controls. HbA1c in the non-diabetic patients with Cushing's syndrome was not different from the non-diabetic controls, whereas GA was significantly lower. In 7 patients with Cushing's syndrome who performed self-monitoring of blood glucose, the measured HbA1c was matched with HbA1c estimated from mean blood glucose, whereas the measured GA was significantly lower than the estimated GA.
Conclusions: We clarified that GA is set lower in relation to plasma glucose levels in patients with Cushing's syndrome.

1. Introduction

Nonenzymatic glycation of proteins is known to increase in diabetic patients when 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 often used as a clinical indicator of long-term glycemic control [2,3]. Because erythrocytes have an average lifespan of 120 days, HbA1c reflects the glycemic control during the previous 1 to 2 months. However, HbA1c measurement is influenced by hemoglobinopathies and the diseases that shorten the erythrocyte lifespan, such as hemolytic anemia and renal anemia, and thus HbA1c does not accurately reflect the state of glycemic control in such cases [4,5].

In addition to HbA1c, glycated albumin (GA) has also been used as an indicator of glycemic control [6]. Because the half-life of serum albumin is much shorter than that of erythrocytes, GA reflects glycemic control over the previous 2 weeks. GA measurement is not affected by disorders of hemoglobin metabolism [6], but it gives a low value in nephrotic syndrome [7] and hyperthyroidism [8], in both of which the half-life of serum albumin are reduced, and a high value in liver cirrhosis [9] and hypothyroidism [8], in both of which that of albumin are prolonged.

Glucose intolerance occurs in patients with Cushing's syndrome and diabetes mellitus is present in 20 to 50% of these patients [10]. In addition to hypertension, diabetes mellitus is another important risk factor for cardiovascular diseases in Cushing's syndrome [11,12]. For this reason, the careful evaluation and treatment of glucose intolerance and diabetes mellitus associated with Cushing's syndrome are recommended.

Since glucocorticoids (GC) are known to promote protein catabolism including serum albumin [13,14], there is a possibility that GC excess state would influence GA levels. However, it is unknown whether GA levels are influenced besides plasma glucose levels in patients with Cushing's syndrome. This study was aimed to prove this issue.

2. Patients and methods

2.1. Patients

We enrolled 16 patients with Cushing's syndrome [4 males and 12 females; Cushing's disease in 5 patients, cortisol-producing adrenal

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adenoma in 9 patients and ACTH-independent macronodular adrenal hyperplasia (AIMAH) in 2 patients]. The mean age of these patients was 49.9 ± 10.2 y and mean body mass index (BMI) was 24.9 ± 5.2 kg/m^2. Half of these patients were diagnosed to have diabetes mellitus (Table 1). Serum cortisol levels in these subjects were high at 22.9 ± 8.0 μg/dl. Thirty-two patients with type 2 diabetes mellitus and 32 non-diabetic subjects matched for age, sex and BMI were used as controls. All of these patients were diagnosed based on American Diabetes Association criteria [15]. Plasma glucose, HbA1c and GA were measured in the morning with the fasting state.

2.2. Laboratory methods

Blood glucose was measured in 7 patients with Cushing's syndrome (3 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 HbA1c was calculated from MBG using the formula developed by Rohlfing et al. [16] (estimated HbA1c = MBG × 1.11/35.6 + 2.17), and the estimated GA was calculated using the GA/HbA1c ratio in Type 2 diabetes mellitus reported by Ogawa et al. [17] (estimated GA = 2.7 × estimated HbA1c).

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 using a Hitachi 7600 analyzer (Hitachi Instruments Service Co., Tokyo, Japan) by the enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [19,20]. The normal reference values 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 RIA.

2.3. Statistical analyses

All data are shown as means ± SD. For statistical analyses, paired or unpaired Student's *t* test was used to compare 2 groups, as appropriate. To analyze the effects of explanatory variables on GA, univariate regression analysis was performed with the StatView computer program (Ver 5.0 for Windows; Abacus Concepts, Berkeley, CA). A $P < 0.05$ were considered to be statistically significant.

3. Results

Fasting plasma glucose, HbA1c and GA in patients with Cushing's syndrome did not differ from the controls, but the GA/HbA1c ratio was significantly lower ($P < 0.001$) (Table 1). GA was correlated significantly with HbA1c in the patients with Cushing's syndrome and controls, but the regression line in the patients with Cushing's syndrome shifted downwards as compared with controls (Fig. 1). In the diabetic patients with Cushing's syndrome, HbA1c and GA did not differ from the patients with type 2 diabetes mellitus without Cushing's syndrome [HbA1c: 8.2 ± 1.6% (65.6 ± 17.1 mmol/mol) vs. 7.6 ±1.0% (59.6 ± 11.2 mmol/mol), P = 0.229; GA: 18.5 ± 4.2% vs. 19.4 ±3.0%, P = 0.502], whereas the GA/HbA1c ratio was significantly lower (2.27 ± 0.33 vs. 2.56 ± 0.33, P = 0.031) (Fig. 2). When the non-diabetic patients with Cushing's syndrome were compared with the non-diabetic controls, HbA1c did not differ significantly [5.6 ± 0.4% (37.3 ± 4.0 mmol/mol) vs. 5.5 ± 0.4% (36.2 ± 3.7 mmol/mol), P = 0.543], whereas GA and the GA/HbA1c ratio were significantly lower in the patients with Cushing's syndrome (GA: 12.5 ± 2.0% vs. 14.1 ± 1.2%, P = 0.004, GA/HbA1c ratio: 2.24 ± 0.31 vs. 2.59 ± 0.23, P = 0.007) (Fig. 3).

MBG was calculated from SMBG measurements in seven blood samples on a day from 7 patients with Cushing's syndrome (3 with diabetes mellitus and 4 without it). The measured HbA1c in the patients with Cushing's syndrome was matched for HbA1c estimated from MBG [6.3 ± 1.2% (45.3 ± 12.6 mmol/mol) vs. 6.2 ± 1.3% (44.1 ± 14.3 mmol/mol), P = 0.597], whereas the measured GA levels was significantly lower than the estimated GA (14.0 ± 4.1% vs. 16.7 ± 5.3%, P = 0.016) (Fig. 4).

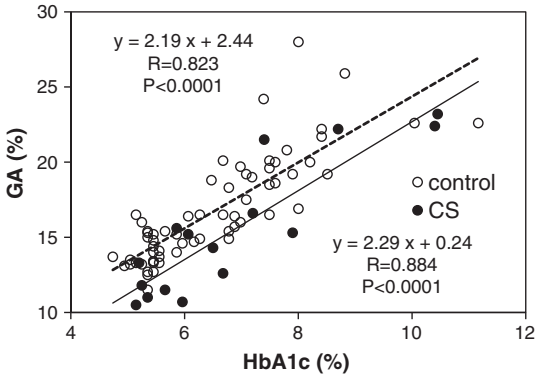

Fig. 1. Correlation between HbA1c and GA in the patients with Cushing's syndrome. Correlations between HbA1c and GA were observed in the patients with Cushing's syndrome (CS) (closed symbols) and the controls with or without type 2 diabetes mellitus (open symbols).

Table 1
Clinical characteristics of study patients.

	Cushing's syndrome	Control	P value
n	16	64	–
Male (%)	4 (23.5)	16 (23.5)	–
Diabetes mellitus (%)	8 (50.0)	32 (50.0)	–
Age (y)	49.9 ± 10.2	50.6 ± 5.5	NS
BMI (kg/m^2)	24.9 ± 5.2	24.6 ± 3.5	NS
Serum cortisol (μg/dl)	22.9 ± 8.0	–	–
Fasting plasma glucose (mg/dl)	105 ± 41	118 ± 33	NS
HbA1c (%)	6.9 ± 1.7	6.5 ± 1.3	NS
HbA1c (mmol/mol)	51.4 ± 18.9	47.9 ± 14.4	NS
GA (%)	16.5 ± 4.5	16.8 ± 3.5	NS
GA/HbA1c ratio	2.25 ± 0.31	2.58 ± 0.28	<0.001

NS: not significant.

4. Discussion

We demonstrated in this study that GA in the patients with Cushing's syndrome is low relative to the estimated levels from MBG. To our knowledge, this is the first report that GA levels are influenced in patients with Cushing's syndrome. When the non-diabetic patients with Cushing's syndrome were compared with the non-diabetic controls, HbA1c was not different, but GA was significantly lower. Furthermore, the measured HbA1c in the patients with Cushing's syndrome was matched for HbA1c estimated from MBG, but the measured GA levels were significantly lower than the estimated GA. This result shows that whereas HbA1c can be used as an indicator of glycemic control in patients with Cushing's syndrome, GA gives an apparently low value in relation to plasma glucose levels, and is therefore unsuitable for use as a glycemic control indicator. This phenomenon may be caused by the increased catabolism in serum albumin in Cushing's syndrome [13,14].

We previously reported that thyroid hormones (free T3 and free T4) showed a significantly negative correlation with GA in non-diabetic patients with abnormal thyroid function [8]. Here, we investigated the correlation between GA or the GA/HbA1c ratio and urinary cortisol, which reflects cortisol secretion levels, in Cushing's syndrome, but found no correlation among them (data not shown). This may be because of the small number of patients in this study. Further investigation in a larger sample size is needed.