Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

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

Effects of thyroid hormone on serum glycated albumin levels: Study on non-diabetic subjects

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ARTICLE INFO

Article history:
Received 11 December 2008
Received in revised form
27 January 2009
Accepted 28 January 2009
Published on line 24 February 2009

Keywords:
Glycated albumin
Glycated hemoglobin (HbA_{1C})
Thyroid hormone
Hypothyroidism
Thyrotoxicosis

ABSTRACT

Glycated albumin (GA) is used alongside glycated hemoglobin (HbA_{1C}) as an indicator of glycemic control. Although serum GA levels are affected mainly by plasma glucose, they are also influenced by serum albumin metabolism. Thyroid hormone is known to promote albumin catabolism, and it is thus thought to affect serum GA levels. In the present study, the effects of thyroid hormone on serum GA measurements were investigated in patients with thyroid dysfunction. Six patients with untreated hypothyroidism and 17 patients with untreated thyrotoxicosis were investigated. Patients who had anemia or diabetes were excluded. A total of 25 non-diabetic, euthyroid individuals were enrolled as controls. HbA_{1C}, serum GA, thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), and free thyroxine (T_4) levels were measured in all these subjects, and their relationships were examined. Although no intergroup differences were observed for HbA_{1C}, serum GA was significantly higher among patients with hypothyroidism than controls, and significantly lower among patients with thyrotoxicosis. Serum GA had a significant positive correlation with serum TSH and significant inverse correlations with free T_3 and free T_4.

Thyroid hormone levels are inversely associated with serum GA levels. Cautions are necessary when evaluating serum GA levels in patients with thyroid dysfunction.

1. Introduction

Glycation of various proteins is known to increase in diabetic patients compared to non-diabetic individuals, and is thought to be involved in the onset and progression of some chronic diabetic complications [1]. Among the glycated proteins, glycated hemoglobin (HbA_{1C}) is commonly used clinically as an indicator of glycemic control [2,3]. Based on the results of the Diabetes Control and Complications Trial (DCCT), an HbA_{1C} level of <7% has been recommended for preventing the onset and progression of chronic diabetic complications [4]. Because the lifespan of erythrocytes is approximately 120 days, HbA_{1C} is thought to reflect blood glucose levels for the past 1–2 months. However, HbA_{1C} measurement is known to be affected by diseases in which the lifespan of erythrocytes is shortened, such as hemolytic anemia and renal anemia, as well as hemoglobin variants, and may thus not be an accurate indicator of glycemic control [5,6].

Serum glycated albumin (GA) is a measure of the proportion of serum albumin that has been glycated, and it has been used as an indicator of glycemic control alongside HbA_{1C} [7]. Serum albumin has a shorter half-life than erythrocytes, and thus is thought to reflect shorter term blood glucose levels (approximately 2 weeks) compared with HbA_{1C}. Therefore, serum GA is more useful than HbA_{1C} in patients whose glycemic control change rapidly [8]. Although, serum GA is

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0168-8227/$ – see front matter
doi:10.1016/j.diabres.2009.01.013

known to decrease in patients with nephrotic syndrome, which shortens the half-life of serum albumin, and to increase in patients with liver cirrhosis, which prolongs the half-life of serum albumin [9], serum GA measurement is not affected by abnormal hemoglobin metabolism [7]. Recently, HbA_{1C} has been reported to be inadequate for the evaluation of glycemic control states in patients who receive hemodialysis for chronic renal insufficiency and cases with pregnancy, because its levels are affected by anemia. Instead, utility of serum GA as a glycemic control marker is also reported in these conditions [10–12].

Thyroid hormone is known to promote albumin metabolism [13] and therefore is presumed to affect serum GA levels. Recently a case with hypothyroidism who appeared to have a high serum GA has been reported [14]. However, serum GA measurements in patients with thyroid dysfunction have not yet been systematically analyzed. In the present study, we aimed to investigate the effects of thyroid hormone on serum GA levels in patients with thyroid dysfunction.

2. Patients, materials and methods

2.1. Patients

Six patients with untreated hypothyroidism (Hashimoto's thyroiditis) and 17 patients with untreated thyrotoxicosis (Graves' disease) were studied (Table 1). Patients with anemia or diabetes mellitus were excluded in this study. As control subjects, 25 non-diabetic, euthyroid individuals who had undergone a complete medical checkup were enrolled. Patients with hypothyroidism were significantly older than controls, while those with thyrotoxicosis were significantly younger than controls. Of the 17 patients with thyrotoxicosis, 16 were women. Patients with thyrotoxicosis had a significantly lower body mass index (BMI) than controls. HbA_{1C}, serum GA, Thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), and free thyroxine (T_4) levels were measured in all subjects.

The reported investigations were performed in accordance with the principles of the Declaration of Helsinki as revised in 2000. The institutional review board approved this study, and all patients provided written informed consent.

2.2. Laboratory methods

HbA_{1C} was measured with ADAMS-A_{1C} HA-8160 (Arkray Inc., Kyoto, Japan) by HPLC [15]. Serum GA levels were measured using the Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan) by an enzymatic method using albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [16,17]. The control ranges of HbA_{1C} were between 4.3% and 5.8%, while those of GA were between 11.7% and 16.0%. Serum TSH, free T_3, and free T_4 levels were measured using the chemiluminescent immunoassay (CLIA) method. We previously reported that BMI negatively regulates serum GA levels [18]. Age and male sex are also the significant explanatory variables for serum GA levels [8,18]. Therefore, in the present study, we calculated the age-, sex-, and BMI-adjusted serum GA levels using the data from non-diabetic subjects [18] and we compared these values among three groups.

Table 1 – Background characteristics of study subjects.

	Control	Hypothyroidism	Thyrotoxicosis
n	25	6	17
Male/female	13/12	3/3	1/16
Age (years)	53.8 ± 5.9	70.7 ± 6.7**	44.9 ± 13.4*
BMI	23.4 ± 2.3	23.6 ± 5.0	20.2 ± 1.7**

Data are means ± S.D. or numbers.
* $p < 0.01$ vs. control.
** $p < 0.001$ vs. control.

2.3. Statistical analyses

All data are shown as means ± S.D. To correct for skewed distributions, serum TSH concentrations were logarithmically transformed. For statistical analyses, the unpaired Student's *t*-test was used to compare two groups, as appropriate. To analyze the effects of explanatory variables on serum GA levels, univariate regression analysis was performed using the StatView computer program (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA, USA). A p value of <0.05 was considered to be statistically significant. For simple correlation analysis, statistical analysis was performed using values of 0.01 μU/ml for TSH ≤ 0.01 μU/ml, 30 pg/ml for free $T_3 \geq 30$ pg/ml, and 6 ng/dl for free $T_4 \geq 6$ ng/dl.

3. Results

HbA_{1C} was 5.4 ± 0.6% in patients with hypothyroidism and 5.2 ± 0.3% in patients with thyrotoxicosis; these results were not significantly different compared to controls (5.1 ± 0.4%). By contrast, serum GA levels adjusted for age, sex and BMI were significantly higher in patients with hypothyroidism (16.3 ± 2.6%) and significantly lower in patients with thyrotoxicosis (11.8 ± 1.4%) compared to controls (14.1 ± 1.4%) (Fig. 1). Serum GA levels had a significant positive correlation with serum TSH levels ($R = 0.723$, $p < 0.0001$; Fig. 2) and significant inverse correlations with serum free T_3 ($R = -0.661$, $p < 0.0001$) and serum free T_4 ($R = -0.673$, $p < 0.0001$) levels (Fig. 2).

Clinical course of a patient with hypothyroidism after treatment with L-thyroxine is shown in Fig. 3. HbA_{1C} levels were not changed after the treatment, but serum GA levels which were over control ranges before the treatment were decreased to control ranges after the treatment.

4. Discussion

The present study showed that serum GA was elevated in patients with hypothyroidism and reduced in patients with thyrotoxicosis. In addition, serum GA had significant inverse correlations with serum free T_3 and free T_4, as well as a significant positive correlation with serum TSH. We observed that serum GA levels were decreased by treatment with L-T_4