Effects of Thyroid Hormone on A1C and Glycated Albumin Levels in Nondiabetic Subjects With Overt Hypothyroidism

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OBJECTIVE — We aimed to determine the effects of thyroid hormone on A1C and glycated albumin (GA) in nondiabetic patients with overt hypothyroidism.

RESEARCH DESIGN AND METHODS — A1C levels were measured in 45 nondiabetic patients with overt hypothyroidism and 180 euthyroid control subjects. A1C, GA, fasting blood glucose (FBG), 1,5-anhydroglucitol, and erythrocyte indexes were determined in 30 nondiabetic patients with overt hypothyroidism before and after thyroid hormone replacement.

RESULTS — A1C levels were higher in patients with hypothyroidism compared with control subjects. A1C levels were decreased by thyroid hormone replacement. Thyroid hormone replacement increased serum erythropoietin, reticulocyte count, and mean corpuscular hemoglobin (MCH). The change in A1C level was significantly correlated with the change in reticulocyte count or MCH. Thyroid hormone replacement decreased serum levels of albumin and GA. However, FBG and 1,5-anhydroglucitol levels were not altered.

CONCLUSIONS — Levels of A1C and GA are spuriously high in nondiabetic patients with overt hypothyroidism.

A1C is widely used for assessment of glycemic control, and the American Diabetes Association (ADA) recently recommended its use for diagnosing diabetes and pre-diabetes (1). Serum glycated albumin (GA) has been introduced as a marker of short-term glycemia (2). However, A1C or GA is subject to certain limitations. Conditions that affect erythrocyte turnover or survival lead to falsely high or low A1C levels (3–6). GA levels might be influenced by serum albumin metabolism (2).

Thyroid hormone stimulates erythrocyte production, and hypothyroidism often results in hypoproliferative erythropoiesis (7–8). In addition, thyroid hormone promotes albumin metabolism, and albumin degradation is reduced in hypothyroidism (9). We therefore hypothesized that A1C or GA levels do not accurately reflect glycemia in hypothyroidism. Thus, we aimed to determine the effects of thyroid hormone on A1C and GA levels in nondiabetic patients with overt hypothyroidism.

RESEARCH DESIGN AND METHODS — First, we performed a cross-sectional study (study 1) in 45 nondiabetic patients with thyroid cancer who underwent thyroid hormone withdrawal (THW) during radioiodine treatment. Pa-

RESULTS — In study 1, TSH levels were significantly higher in patients with overt hypothyroidism compared with the control subjects. A1C levels were higher...
Table 1—Laboratory characteristics of 30 non-diabetic patients with overt hypothyroidism before and after thyroid hormone replacement in study 2

|                     | Before thyroid hormone replacement | After thyroid hormone replacement | P     |
|---------------------|-----------------------------------|----------------------------------|-------|
| Age (years)         | 47.3 ± 12.3                       | —                                |       |
| Sex (male/female)   | 7/23                              | —                                |       |
| A1C (%)             | 5.57 ± 0.26                       | 5.37 ± 0.32                      | <0.001|
| GA (%)              | 13.18 ± 1.35                      | 12.52 ± 1.16                     | 0.027 |
| GA-to-A1C ratio     | 2.38 ± 0.29                       | 2.35 ± 0.28                      | 0.987 |
| Glucose (mmol/l)    | 4.95 ± 0.41                       | 5.24 ± 0.92                      | 0.174 |
| 1.5-AG (μg/ml)      | 20.03 ± 6.92                      | 21.42 ± 7.45                     | 0.086 |
| Hb (g/dl)           | 14.05 ± 1.35                      | 13.64 ± 1.23                     | 0.004 |
| MCV (fl)            | 88.29 ± 4.73                      | 90.78 ± 4.75                     | <0.001|
| MCH (pg)            | 29.48 ± 2.04                      | 30.25 ± 1.95                     | <0.001|
| Reticulocyte (%)    | 0.64 ± 0.18                       | 1.09 ± 0.34                      | <0.001|
| Ferritin (ng/ml)    | 74.34 ± 64.30                     | 76.31 ± 57.58                    | 0.689 |
| EPO (mIU/ml)        | 12.93 ± 4.97                      | 16.41 ± 6.44                     | 0.022 |
| Albumin (g/l)       | 43.5 ± 1.7                        | 42.6 ± 1.6                       | 0.009 |
| Total cholesterol (mmol/l) | 6.21 ± 1.23          | 4.37 ± 0.75                      | <0.001|
| Triglyceride (mmol/l) | 1.57 ± 1.01                   | 1.62 ± 1.15                      | 0.802 |

Data are means ± SD. Hb, hemoglobin.

in patients with hypothyroidism compared with the control subjects (5.54 ± 0.43 vs. 5.34 ± 0.31%; P < 0.001). In contrast, fasting blood glucose (FBG) levels were lower in patients with hypothyroidism than in the control subjects ( supplementary Table 1 in the online appendix at http://care.diabetesjournals.org/cp/content/full/dc10-0988/DC1).

In study 2, 30 patients were consecutively enrolled. After 4 weeks of THW, serum TSH and fT4 levels were 84.5 ± 20.7 mIU/l (reference range 0.38–4.94 mIU/l) and 5.2 ± 0.1 pmol/l (reference range 9.0–24.9 pmol/l), respectively. After radioiodine treatment, patients received a standard protocol of thyroid hormone therapy. During this period, serum TSH and fT4 levels were 0.2 ± 0.5 mIU/l and 22.8 ± 5.1 pmol/l, respectively.

A1C level decreased after thyroid hormone replacement (from 5.57 ± 0.26 to 5.37 ± 0.32%; P < 0.001; Table 1). Thyroid hormone replacement increased EPO level, reticulocyte count, MCV, and MCH. Thyroid hormone replacement decreased serum albumin level and GA level. However, thyroid hormone replacement did not alter GA-to-A1C ratio, FBG, or 1.5-AG level.

The change in A1C was correlated with the change in reticulocyte count (γ = −0.381, P = 0.042) and the change in MCH (γ = −0.466, P = 0.010).

Six patients were evaluated before total thyroidectomy (euthyroidism), after THW (hypothyroidism), and after thyroid hormone replacement (euthyroidism). A1C levels tended to increase during hypothyroidism (from 5.52 ± 0.25 to 5.63 ± 0.28%; P = 0.082) and then return to baseline levels (from 5.52 ± 0.25 to 5.50 ± 0.29%; P = 0.426) (Table 1).

**CONCLUSIONS**—We found that A1C levels were significantly higher in patients with overt hypothyroidism compared with control subjects. In addition, A1C levels decreased after thyroid hormone replacement in patients with overt hypothyroidism. Serum EPO level, reticulocyte count, and MCH increased after thyroid hormone replacement, suggesting that thyroid hormone stimulates erythropoiesis. Moreover, the change in A1C level was negatively correlated with the change in reticulocyte count and MCH. These data suggest that thyroid hormone replacement is associated with a decrease in A1C level, which is influenced by increased erythropoiesis rather than by changes in glucose level.

Ten of 30 patients (33%) had an A1C ≥5.7% during overt hypothyroidism, but after thyroid hormone replacement only 4 of 30 patients (13%) had an A1C ≥5.7%. The ADA Expert Committee recently endorsed an A1C of 5.7–6.4% as indicative of pre-diabetes (1). According to these criteria, 20% of our subjects (6 of 30 patients) were misclassified as having pre-diabetes. However, use of A1C for diagnosing pre-diabetes is not universally accepted.

GA levels decrease in patients with nephrotic syndrome, which shortens the half-life of serum albumin, and increase in patients with liver cirrhosis, which prolongs the half-life of serum albumin (2). Albumin metabolism is prolonged in hypothyroidism, and thyroid hormone promotes albumin metabolism. We demonstrated that GA levels decreased, along with serum albumin levels, after thyroid hormone replacement.

Although abnormal glucose metabolism is common in thyrotoxicosis, the effect of overt hypothyroidism on glucose metabolism is still a subject of debate (10–11). In our study, GA-to-A1C ratio, FBG, and 1.5-AG level (a marker for postprandial hyperglycemia) (12) were not altered by thyroid hormone replacement.

The limitation of this study includes the fact that patient selection was narrowed by choosing iatrogenic hypothyroid patients prior to radioiodine treatment. Second, we did not measure erythrocyte life span.

In conclusion, our data suggest that non-diabetic patients with overt hypothyroidism showed spuriously high levels of A1C and GA. Therefore, the effects of thyroid hormone on A1C and GA must be considered when interpreting these parameters in patients with thyroid disorders.

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