

# Associations Between Thyroid Hormones and Glycated Albumin in Euthyroid and Subclinical Hypothyroid Individuals: Results of an Observational Study

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**Purpose:** Although overt thyroid dysfunction has been found to influence the level of glycated albumin (GA), the associations between thyroid hormones and GA in individuals with euthyroidism and subclinical hypothyroidism (SHypo) are still unknown. The present study aimed to investigate whether thyroid hormones were related to GA in euthyroid and SHypo individuals.

**Methods:** We recruited 685 euthyroid and 103 SHypo subjects with normal weight from communities in Shanghai. Electrochemiluminescence immunoassay was used to detect the serum levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone. GA was detected by the enzymatic method. Glycated hemoglobin (HbA<sub>1c</sub>) was detected by high-performance liquid chromatography.

**Results:** Among the 788 subjects (age range 31–81 years old), 307 were men and 481 were women. In the Spearman correlation analysis and multiple stepwise regression analysis, FT3 was negatively correlated with both GA and GA/HbA<sub>1c</sub> in euthyroid subjects (all  $P < 0.05$ ). The values of GA and GA/HbA<sub>1c</sub> were reduced by approximately 0.30 and 0.05, respectively, for each 0.50 pmol/L increment in FT3. In SHypo subjects, FT4 was negatively associated with both GA and GA/HbA<sub>1c</sub> (all  $P < 0.05$ ). The values of GA and GA/HbA<sub>1c</sub> were reduced by approximately 0.23 and 0.03, respectively, for each 1.00 pmol/L increment in FT4.

**Conclusion:** In euthyroid and SHypo subjects, more attention should be paid to the potential effects of individual differences in thyroid hormones on GA.

**Keywords:** glycated albumin, glycated hemoglobin, free triiodothyronine, free thyroxine

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## Introduction

Diabetes and thyroid diseases are closely related.<sup>1</sup> The prevalence of thyroid dysfunction in diabetic patients is about 13–37%.<sup>2–4</sup> Approximately one-third of patients with type 1 diabetes may develop thyroid dysfunction.<sup>5</sup> On the other hand, thyroid dysfunction not only increases the risk of diabetes,<sup>6,7</sup> but also affects the glycemic control of diabetic patients.<sup>1</sup>

Glycated albumin (GA) is a common indicator used for glucose monitoring and therapeutic evaluation. As an important complementary indicator of HbA<sub>1c</sub>, GA is characterized by higher sensitivity to short-term glucose fluctuation and as being free of disturbance from hemoglobin (Hb). GA is generated from

a nonenzymatic glycation reaction between glucose and albumin (ALB). Factors that influence the turnover rate of ALB, such as thyroid dysfunction, may also influence the level of GA.<sup>8</sup> Koga et al found that the level of GA was significantly higher in nondiabetic subjects with hypothyroidism than in euthyroid controls, while the level of GA was significantly lower in individuals with hyperthyroidism.<sup>9</sup> Kim et al reported that thyroid hormone replacement decreased the level of GA.<sup>10</sup> Recently, Miyamoto et al found that, compared to nondiabetic euthyroid controls, the GA to HbA<sub>1c</sub> ratio (GA/HbA<sub>1c</sub>) was significantly higher in individuals with hypothyroidism and was significantly lower in individuals with hyperthyroidism.<sup>11</sup>

Although the manifestation of subclinical hypothyroidism (SHypo) is often silent and obscure, SHypo is related to an increased risk of fracture, cardiovascular disease and all-cause mortality.<sup>12,13</sup> The prevalence of SHypo is much higher than that of overt hypo- or hyperthyroidism.<sup>14</sup> However, the relationships of thyroid hormones with GA and GA/HbA<sub>1c</sub> in euthyroid and SHypo individuals have not been reported previously. Since obesity is also an influencing factor of GA and thyroid hormones,<sup>15–17</sup> the present study aimed to investigate the relationships of thyroid hormones with GA, HbA<sub>1c</sub> and GA/HbA<sub>1c</sub> in normal-weight euthyroid and SHypo subjects.

## Methods

### Study Design and Participant Enrollment

Subjects were recruited from communities in Shanghai from October 2015 to July 2016. The details of participant recruitment and data collection were described in our previous study.<sup>18</sup> All participants completed questionnaires, physical examinations and laboratory tests. The inclusion criteria included voluntary participation and normal weight. The exclusion criteria included free triiodothyronine (FT3) or free thyroxine (FT4) out of the reference range; thyroid stimulating hormone (TSH) below the lower limit of the reference range or >10 mIU/L; thyroid hormone supplement or anti-thyroid therapy; a history of diabetes or cardiovascular disease; moderate to severe anemia; hypoalbuminemia; severe kidney or liver dysfunction; malignancy; acute infection; and use of lipid-lowering drugs, hypotensive drugs, glucocorticoids, sex hormones, amiodarone or lithium. All participants written informed consent. The study was approved by the Ethics Committee of the Shanghai Jiao Tong University

Affiliated Sixth People's Hospital and was conducted in accordance with the Declaration of Helsinki.

### Anthropometric and Biochemical Assessments

Height, body weight and blood pressure were measured according to standard methods described in our previous study.<sup>18</sup> Body mass index (BMI) = body weight (kg)/height<sup>2</sup> (m<sup>2</sup>).

All subjects underwent a 75-g oral glucose tolerance test in the morning after an overnight fast of 10 hrs. Fasting plasma glucose (FPG), 2 hr plasma glucose (2hPG), fasting insulin (FINS), triglyceride (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), serum creatinine and C-reactive protein (CRP) were detected according to methods described previously.<sup>18</sup> Insulin resistance was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula: HOMA-IR = FINS (mU/L) × FPG (mmol/L)/22.5.<sup>19</sup>

Electrochemiluminescence immunoassay was used to measure FT3, FT4 and TSH on a Cobas e601 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The intra-assay coefficients for FT3, FT4 and TSH were <7.0%, <5.0% and <3.0%, respectively. The inter-assay coefficients for FT3, FT4 and TSH were <8.0%, <7.0% and <8.0%, respectively. The thyroid stimulating hormone index (TSHI) = lnTSH (mIU/L) + 0.1345 × FT4 (pmol/L).<sup>20</sup> The thyrotroph thyroxine resistance index (TT4RI) = FT4 (pmol/L) × TSH (mIU/L).<sup>21</sup> Serum levels of ALB were detected by the bromocresol green method (Kehua Bio-Engineering Co., Ltd., Shanghai, China). The enzymatic method (Lucica GA-L; Asahi Kasei Pharma Corporation, Tokyo, Japan) was used to detect GA on a 7600 analyzer (Hitachi, Tokyo, Japan). The intra- and inter-assay coefficients of GA were <3.30% and <4.73%, respectively. Hb was measured by sodium dodecyl sulfate colorimetry. High-performance liquid chromatography was used to detect HbA<sub>1c</sub> on a Variant II HbA<sub>1c</sub> analyzer (Bio-Rad Inc., Hercules, CA, USA). The intra- and inter-assay coefficients of HbA<sub>1c</sub> were <2.58% and <3.39%, respectively.

### Definitions

According to the 1998 criteria of the World Health Organization,<sup>22</sup> normal weight was defined as 18.50 kg/m<sup>2</sup> ≤ BMI < 25.00 kg/m<sup>2</sup>. In this study, euthyroid was defined as

FT3, FT4 and TSH levels within the reference range. The reference ranges of FT3, FT4 and TSH were 3.10–6.80 pmol/L, 12.00–22.00 pmol/L and 0.27–4.20 mIU/L, respectively. SHypo was defined as  $0.42 \text{ mIU/L} < \text{TSH} \leq 10.00 \text{ mIU/L}$  with FT3 and FT4 levels within the reference range.<sup>23</sup>

## Statistical Analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the distribution of all continuous variables. Normally distributed variables were expressed as the mean  $\pm$  standard deviation. Variables with a skewed distribution were expressed as the median (interquartile range). For normally distributed variables, independent sample *T*-test was used for comparisons between two groups. For skewed variables, Mann–Whitney *U*-test and Kruskal–Wallis *H*-test were used for comparisons between two groups and trend analyses, respectively. For categorical variables, the chi-square test was used for comparisons among groups. The correlations between variables were assessed by Spearman correlation analysis. To explore the independent influencing factors of GA and GA/HbA<sub>1c</sub>, multiple stepwise regression analysis was applied. SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) statistical software was used for all data analyses. A two-tailed *P* value  $< 0.05$  was considered statistically significant.

## Results

### The Clinical Characteristics of Subjects

The clinical characteristics of the subjects are listed in Table 1. A total of 788 participants (307 men and 481 women) were included in the final database. The average age was  $59 \pm 7$  years (range from 31 to 81 years). The medians (interquartile range) of BMI, GA, HbA<sub>1c</sub> and GA/HbA<sub>1c</sub> were 22.41 (20.83–23.56) kg/m<sup>2</sup>, 13.65 (12.97–14.52) %, 5.70 (5.40–5.90) % and 2.43 (2.27–2.60), respectively.

Subjects were further divided into a euthyroid group (685 out of 788) and a SHypo group (103 out of 788). FT4, 2hPG and Hb in SHypo subjects were significantly lower than those in euthyroid subjects, while the percentage of women and the levels of FT3/FT4, TSH, TSHI and TT4RI were significantly higher in SHypo subjects than in euthyroid subjects (all  $P < 0.05$ ). There were no significant differences between the two groups in terms of age, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), FT3, FPG, GA,

HbA<sub>1c</sub>, GA/HbA<sub>1c</sub>, HOMA-IR, TC, TG, HDL-c, LDL-c, CRP and ALB (all  $P > 0.05$ ).

### Covariance Analysis on the Difference of GA Between Euthyroid and SHypo Subjects

Covariance analysis was further used to evaluate the difference of GA between euthyroid and SHypo subjects (Figure 1). There was no difference in GA between euthyroid and SHypo subjects without adjustment ( $P = 0.311$ ). After adjusting for gender and HbA<sub>1c</sub>, there was still no difference in GA between euthyroid and SHypo subjects ( $P = 0.960$ ).

### Correlations of Thyroid Hormones with GA, HbA<sub>1c</sub> and GA/HbA<sub>1c</sub>

Spearman correlation analysis was used to explore the correlations of thyroid hormones with GA, HbA<sub>1c</sub> and GA/HbA<sub>1c</sub> (Table 2). In euthyroid subjects, GA and GA/HbA<sub>1c</sub> were negatively correlated with FT3 and FT3/FT4 (all  $P < 0.05$ ), but were not correlated with FT4, TSH, TSHI or TT4RI (all  $P > 0.05$ ). HbA<sub>1c</sub> was not correlated with FT3, FT4, FT3/FT4, TSH, TSHI or TT4RI (all  $P > 0.05$ ). ALB and Hb were both positively correlated with FT3 and FT4, while ALB was also positively correlated with TSH, TSHI and TT4RI, Hb was also positively correlated with FT3/FT4 (all  $P < 0.05$ ).

In SHypo subjects, GA was negatively correlated with FT4 and TSHI (all  $P < 0.05$ ), but was not correlated with FT3, FT3/FT4, TSH or TT4RI (all  $P > 0.05$ ). Hb was positively correlated with FT3, FT4, TSHI and TT4RI (all  $P < 0.05$ ), but was not correlated with FT3/FT4 or TSH (all  $P > 0.05$ ). HbA<sub>1c</sub>, GA/HbA<sub>1c</sub> and ALB were not correlated with FT3, FT4, FT3/FT4, TSH, TSHI or TT4RI (all  $P > 0.05$ ).

As shown in Figure 2, according to 0.50 pmol/L increments in FT3, euthyroid subjects were divided into 6 subgroups: 3.10–4.00 pmol/L ( $N = 16$ ), 4.01–4.50 pmol/L ( $N = 125$ ), 4.51–5.00 pmol/L ( $N = 242$ ), 5.01–5.50 pmol/L ( $N = 226$ ), 5.51–6.00 pmol/L ( $N = 67$ ) and 6.01–6.80 pmol/L ( $N = 9$ ). Both GA and GA/HbA<sub>1c</sub> showed significant decreasing trends with increasing FT3 (all  $P$  for trend  $< 0.05$ ).

According to 1.00 pmol/L increments in FT4, SHypo subjects were also divided into 6 subgroups: 12.00–13.50 pmol/L ( $N = 15$ ), 13.51–14.50 pmol/L ( $N = 15$ ), 14.51–15.50 pmol/L ( $N = 22$ ), 15.51–16.50 pmol/L ( $N = 18$ ), 16.51–17.50 pmol/L ( $N = 16$ ) and 17.51–22.00 pmol/L ( $N = 17$ ). GA showed a significant decreasing trend with

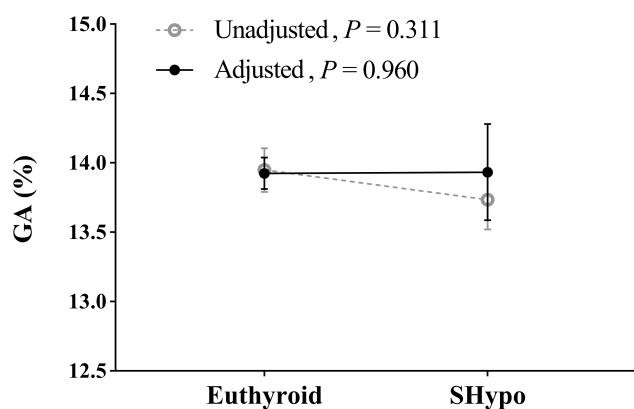
**Table 1** Clinical Characteristics of Subjects

Parameters	Total	Euthyroid	SHypo
N (women)	788 (481)	685 (401)	103 (80)**
Age (years)	59 (55–64)	59 (55–64)	59 (55–64)
BMI (kg/m <sup>2</sup> )	22.41 (20.83–23.56)	22.38 (20.83–23.55)	22.57 (21.15–23.77)
SBP (mmHg)	126 (115–138)	127 (115–138)	126 (116–139)
DBP (mmHg)	76 (70–83)	77 (70–83)	75 (68–82)
FT3 (pmol/L)	4.92 ± 0.49	4.93 ± 0.49	4.90 ± 0.50
FT4 (pmol/L)	16.48 ± 1.76	16.61 ± 1.70	15.64 ± 1.90**
FT3/FT4	0.299 (0.274–0.326)	0.297 (0.273–0.324)	0.316 (0.280–0.346)**
TSH (mIU/L)	2.33 (1.63–3.31)	2.16 (1.54–2.87)	5.18 (4.52–6.42)**
TSHI	3.07 ± 0.54	2.96 ± 0.47	3.81 ± 0.31**
TT4RI	38.89 (27.18–53.54)	36.15 (25.61–47.41)	84.58 (70.85–100.59)**
FPG (mmol/L)	5.63 (5.30–6.01)	5.63 (5.31–6.03)	5.61 (5.25–5.94)
2hPG (mmol/L)	6.96 (5.69–8.21)	7.02 (5.75–8.30)	6.58 (5.36–7.81)*
GA (%)	13.65 (12.97–14.52)	13.65 (12.97–14.55)	13.67 (13.09–14.28)
HbA <sub>1c</sub> (%)	5.70 (5.40–5.90)	5.70 (5.40–5.90)	5.60 (5.40–5.90)
GA/HbA <sub>1c</sub>	2.43 (2.27–2.60)	2.43 (2.26–2.61)	2.44 (2.27–2.56)
HOMA-IR	1.92 (1.39–2.66)	1.92 (1.37–2.66)	1.98 (1.50–2.89)
TC (mmol/L)	5.45 ± 0.97	5.43 ± 0.96	5.55 ± 1.03
TG (mmol/L)	1.26 (0.92–1.86)	1.25 (0.91–1.85)	1.38 (0.97–2.00)
HDL-c (mmol/L)	1.44 (1.21–1.69)	1.45 (1.21–1.70)	1.42 (1.22–1.69)
LDL-c (mmol/L)	3.29 ± 0.83	3.28 ± 0.82	3.33 ± 0.85
CRP (mg/L)	0.74 (0.35–1.40)	0.72 (0.35–1.41)	0.83 (0.40–1.39)
ALB (g/L)	49 (48–51)	49 (48–51)	50 (48–51)
Hb (g/L)	142 (135–153)	143 (135–153)	138 (131–146)**

**Notes:** Data were mean ± standard deviation or medians (interquartile range). \* $P < 0.05$  and \*\* $P < 0.01$  compared with euthyroid. Euthyroid was defined as normal FT3, FT4 and TSH. SHypo was defined as  $4.20 \text{ mIU/L} < \text{TSH} \leq 10.00 \text{ mIU/L}$  with normal FT3 and FT4.

**Abbreviations:** 2hPG, 2 hr plasma glucose; ALB, albumin; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GA, glycated albumin; Hb, hemoglobin; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SHypo, subclinical hypothyroidism; TC, total cholesterol; TG, triglyceride; TSH, thyroid stimulating hormone; TSHI, thyroid stimulating hormone index; TT4RI, thyrotroph thyroxine resistance index.

increasing FT4 levels ( $P$  for trend  $< 0.05$ ). However, the decreasing trend of GA/HbA<sub>1c</sub> with increasing FT4 was marginally significant ( $P$  for trend = 0.05).



**Figure 1** Covariance analysis on the difference of GA between euthyroid and SHypo subjects. The lines and bars indicate to the means and 95% confidence intervals. Gender and HbA<sub>1c</sub> were adjusted. Euthyroid was defined as normal FT3, FT4 and TSH levels. SHypo was defined as  $4.20 \text{ mIU/L} < \text{TSH} \leq 10.00 \text{ mIU/L}$  with normal FT3 and FT4 levels.

## Independent Influencing Factors of GA and GA/HbA<sub>1c</sub>

Multiple stepwise regression analysis was used to investigate the independent influencing factors of GA and GA/HbA<sub>1c</sub> (Table 3). The initial independent variables included gender, age, BMI, FT3, FT4, TSH, HbA<sub>1c</sub> (only for GA), SBP, DBP, TG, HDL-c, LDL-c, CRP, ALB and Hb.

In euthyroid subjects, FT3 was independently and negatively correlated with both GA and GA/HbA<sub>1c</sub> (standardized  $\beta = -0.14$  for GA, standardized  $\beta = -0.19$  for GA/HbA<sub>1c</sub>, all  $P < 0.01$ ). Moreover, HbA<sub>1c</sub>, BMI, TG and gender were independent influencing factors of GA (all  $P < 0.01$ ). The independent influencing factors of GA/HbA<sub>1c</sub> also included BMI, TG, gender, ALB and Hb (all  $P < 0.05$ ). Men had significantly higher GA and GA/HbA<sub>1c</sub> than women (all  $P < 0.01$ ).

In SHypo subjects, FT4 was independently and negatively correlated with both GA and GA/HbA<sub>1c</sub> (standardized  $\beta = -0.39$  for GA, standardized  $\beta = -0.22$  for GA/HbA<sub>1c</sub>, all

**Table 2** Spearman Correlation Analysis for GA, HbA<sub>1c</sub> and GA/HbA<sub>1c</sub>

Parameters	FT3		FT4		FT3/FT4		TSH		TSHI		TT4RI	
	r	P	r	P	r	P	r	P	r	P	r	P
Euthyroid												
GA	-0.15	<0.01	-0.03	0.49	-0.10	0.01	0.05	0.17	0.03	0.50	0.04	0.26
ALB	0.17	<0.01	0.14	<0.01	0.02	0.63	0.09	0.02	0.16	<0.01	0.13	<0.01
HbA <sub>1c</sub>	0.07	0.09	0.01	0.72	0.04	0.31	-0.03	0.49	-0.02	0.58	-0.02	0.59
Hb	0.40	<0.01	0.19	<0.01	0.15	<0.01	-0.04	0.26	0.07	0.09	0.01	0.78
GA/HbA <sub>1c</sub>	-0.21	<0.01	-0.06	0.13	-0.12	<0.01	0.07	0.07	0.03	0.48	0.05	0.20
SHypo												
GA	-0.18	0.08	-0.33	<0.01	0.17	0.10	0.05	0.62	-0.25	0.01	-0.14	0.17
ALB	-0.02	0.81	0.02	0.83	-0.02	0.84	0.10	0.30	0.12	0.25	0.13	0.18
HbA <sub>1c</sub>	-0.13	0.20	-0.10	0.33	0.03	0.74	-0.01	0.90	-0.06	0.54	-0.06	0.55
Hb	0.38	<0.01	0.27	<0.01	0.04	0.68	0.12	0.25	0.31	<0.01	0.25	0.01
GA/HbA <sub>1c</sub>	-0.05	0.65	-0.17	0.09	0.09	0.36	-0.00	0.97	-0.19	0.06	-0.11	0.28

**Notes:** Euthyroid was defined as normal FT3, FT4 and TSH. SHypo was defined as 4.20 mIU/L < TSH ≤ 10.00 mIU/L with normal FT3 and FT4.

**Abbreviations:** ALB, albumin; FT3, free triiodothyronine; FT4, free thyroxine; GA, glycated albumin; Hb, hemoglobin; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; TSH, thyroid stimulating hormone; TSHI, thyroid stimulating hormone index; TT4RI, thyrotroph thyroxine resistance index.

$P < 0.05$ ). Moreover, BMI was an independent influencing factor of GA ( $P < 0.01$ ), while ALB was an independent influencing factor of GA/HbA<sub>1c</sub> ( $P = 0.04$ ).

We further evaluated the extent of the influence of thyroid hormones on GA and GA/HbA<sub>1c</sub> values. In euthyroid subjects, the values (95% CI) of GA and GA/HbA<sub>1c</sub> were reduced by 0.30 (0.17, 0.42) and 0.05 (0.03, 0.07), respectively, for each 0.50 pmol/L increment in FT3. In SHypo subjects, the values (95% CI) of GA and GA/HbA<sub>1c</sub> were reduced by 0.23 (0.13, 0.33) and 0.03 (0.00, 0.05) for each 1.00 pmol/L increment in FT4 (Figure 3).

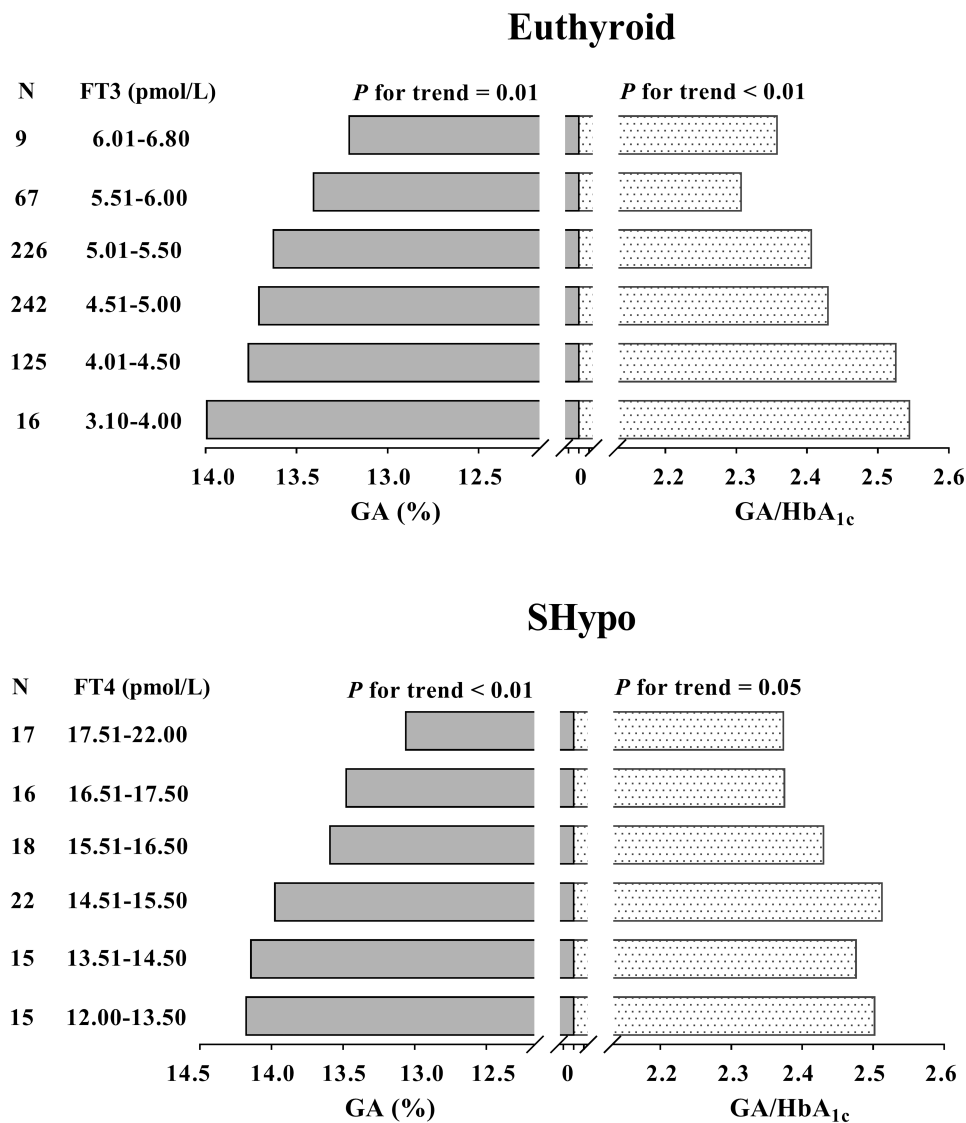
## Discussion

The present study found that FT3 was independently and negatively related to GA and GA/HbA<sub>1c</sub> in euthyroid subjects, while FT4 was independently and negatively related to GA and GA/HbA<sub>1c</sub> in SHypo subjects. The results suggested that in euthyroid and SHypo subjects, more attention should be paid to the potential effects of individual differences in thyroid hormones on GA.

Glycation is the nonenzymatic reaction between glucose and the amino acid residues of proteins. Chronic hyperglycemia increases the concentration of glycated proteins which includes HbA<sub>1c</sub> and GA.<sup>24</sup> Compared to HbA<sub>1c</sub>, GA is more sensitive to short-term glucose fluctuation and is not influenced by the erythrocyte lifespan or iron deficiency.<sup>25</sup> Considering the importance of GA in clinical application, elucidating the influencing factors of GA is essential for glucose monitoring. Our previous study found that obesity

was an influencing factor of GA.<sup>16</sup> Since obesity is a factor that influences both GA and thyroid hormones,<sup>15,17</sup> overweight and obese subjects were excluded from this study. Moreover, factors that influence the turnover rate of ALB may also influence the level of GA.

Thyroid dysfunction was reported to affect the metabolic rate of ALB.<sup>8</sup> Previous studies have found that overt thyroid dysfunction significantly affected the level of GA. Moriyama et al reported a case of type 2 diabetes patient who had inhibited thyroid function due to overeating seaweed. The level of GA increased markedly with increasing TSH, while HbA<sub>1c</sub> and FPG remained within the normal range. After the patient stopped eating seaweed, the level of GA declined together with that of TSH. However, HbA<sub>1c</sub> remained within the normal range despite the changes in TSH and GA levels.<sup>26</sup> Koga et al recruited 23 untreated nondiabetic patients with hypo- or hyperthyroidism and 25 subjects with euthyroid as a control. They found that GA in individuals with hypothyroidism was significantly higher than that in controls, and GA in individuals with hyperthyroidism was significantly lower than that in controls. There were no differences in HbA<sub>1c</sub> among the three groups. Furthermore, GA was positively related to TSH but negatively related to FT3 and FT4.<sup>9</sup> In 45 nondiabetic hypothyroidism patients and 180 euthyroid subjects, Kim et al found that hypothyroidism patients had significantly higher HbA<sub>1c</sub> than controls. HbA<sub>1c</sub> and GA were also measured in 30 nondiabetic hypothyroidism patients before and after thyroid hormone replacement. Both GA and HbA<sub>1c</sub> decreased significantly



**Figure 2** GA and GA/HbA<sub>1c</sub> levels with increasing thyroid hormones. Euthyroid was defined as normal FT3, FT4 and TSH levels. SHypo was defined as 4.20 mIU/L < TSH ≤ 10.00 mIU/L with normal FT3 and FT4 levels.

after thyroid hormone replacement.<sup>10</sup> In a recent study, Miyamoto et al recruited 92 nondiabetic hypo- or hyperthyroidism patients and 80 euthyroid controls. They found that, compared with euthyroid controls, hypothyroidism patients had significantly higher GA/HbA<sub>1c</sub>, while hyperthyroidism patients had significantly lower GA/HbA<sub>1c</sub>.<sup>11</sup>

In the basal and unstimulated condition, the thyroid gland produces relatively low level of thyroid hormones, a majority of which is prohormone FT4.<sup>27</sup> The bioactive form FT3 exerts genomic effects by directly binding to the nuclear receptor. In the human body, up to 85% of circulating FT3 is produced by the extrathyroidal pathways including type 2 iodothyronine deiodinase (DIO2) and DIO1.<sup>28</sup> Because of the expression of different types of

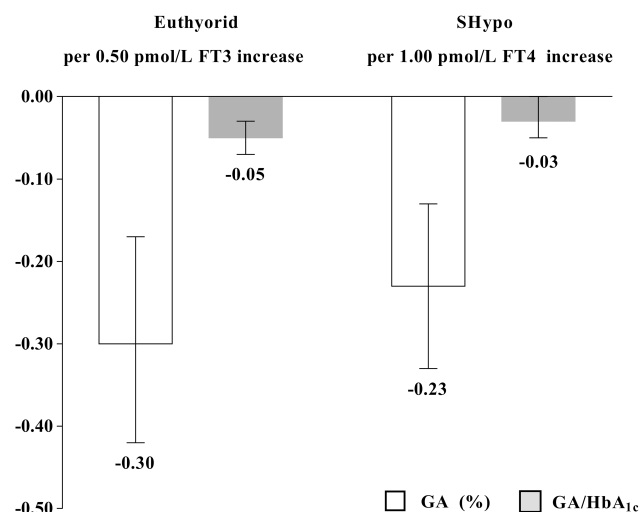
transporters, FT4 is easier to get through the blood-brain barrier than FT3.<sup>29</sup> Previous study has indicated that the hypothalamus-pituitary-thyroid axis is controlled by the DIO2-mediated conversion from FT4 to FT3 in hypothalamus.<sup>30</sup> The regulation of DIO2 is conserved and steady, and transducing minor change of the circulating FT4 levels. The interplay between TSH and FT4 forms the so called “set point”. Thus, in euthyroidism, the change of TSH and FT4 is subtle and tightly controlled. In this case, FT3 may contribute to the DIO-mediated adaptive response. In our study, we also found that, in euthyroid subjects, GA and GA/HbA<sub>1c</sub> were all significantly and negatively correlated with FT3 and FT3/FT4, but not correlated with FT4 or TSH.

**Table 3** Multiple Stepwise Regression Analysis Showing the Variables Independently Associated with GA and GA/HbA<sub>1c</sub>

Independent Variables	GA			GA/HbA <sub>1c</sub>		
	Standardized $\beta$	t	P	Standardized $\beta$	t	P
Euthyroid						
HbA <sub>1c</sub>	0.70	26.15	<0.01	–	–	–
BMI	–0.12	–4.45	<0.01	–0.15	–4.13	<0.01
FT3	–0.14	–4.71	<0.01	–0.19	–4.70	<0.01
TG	–0.08	–3.09	<0.01	–0.12	–3.26	<0.01
Gender <sup>a</sup>	–0.08	–2.75	<0.01	–0.19	–3.83	<0.01
ALB	–	–	–	0.08	2.17	0.03
Hb	–	–	–	–0.13	–2.44	0.02
SHypo						
FT4	–0.39	–4.42	<0.01	–0.22	–2.30	0.02
BMI	–0.26	–2.90	<0.01	–	–	–
ALB	–	–	–	0.20	2.05	0.04

**Notes:** Initial variables included gender; age; BMI; FT3; FT4; TSH; HbA<sub>1c</sub> (only for GA); SBP; DBP; TG; HDL-c; LDL-c; CRP; ALB and Hb. Euthyroid was defined as FT3, FT4 and TSH within the reference range. SHypo was defined as 4.20 mIU/L < TSH  $\leq$  10.00 mIU/L with normal FT3 and FT4.

**Abbreviations:** ALB, albumin; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FT3, free triiodothyronine; FT4, free thyroxine; GA, glycated albumin; Hb, hemoglobin; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SHypo, subclinical hypothyroidism; TG, triglyceride; TSH, thyroid stimulating hormone.



**Figure 3** The extent of the influence of thyroid hormones on the values of GA and GA/HbA<sub>1c</sub>. The columns and bars indicate to the values and 95% confidence intervals. Euthyroid was defined as normal FT3, FT4 and TSH levels. SHypo was defined as 4.20 mIU/L < TSH  $\leq$  10.00 mIU/L with normal FT3 and FT4 levels.

In SHypo subjects, the activity of DIO2 and thus the conversion rate of FT4 to FT3 are all significantly increased in almost all tissues, which coincide well with our results that FT3/FT4 was significantly higher in SHypo subjects than in euthyroid subjects. We also found that FT3/FT4 was negatively correlated with GA and GA/HbA<sub>1c</sub> in euthyroid subjects, but not in SHypo subjects, which might be resulted by the nearly full load of DIO2 in SHypo subjects. The thyroid-mediated TSH-triiodothyronine shunt may also increase in SHypo

subjects.<sup>31</sup> These mechanisms work together to maintain FT3 stability,<sup>28,32</sup> which may leave little room for additional variation of FT3. The secretion of TSH is mainly regulated by the negative feedback of FT4. In our study, we found that FT4 was decreased while TSH was increased in SHypo subjects. However, the central thyroid hormone resistance indexes, TSHI and TT4RI, were also significantly increased in SHypo subjects, suggesting that the increase of TSH was insufficient to cope with the decrease of FT4 in SHypo subjects. FT4 rather than TSH directly reflects the deficiency of thyroid hormones in peripheral tissues. This may partly explain our findings that FT4 was negatively related to GA and GA/HbA<sub>1c</sub> within the subclinical hypothyroid range, while FT3 and TSH were not.

Due to a broad role in promoting metabolism, thyroid hormones may affect the level of GA by influencing the turnover rate of ALB. Nevertheless, few studies have explored the potential mechanism of thyroid dysfunction related to GA. Parving et al found that both the anabolic and catabolic rates of ALB were decreased in individuals with hypothyroidism. Moreover, the transcapillary escape rate and the extravascular mass of ALB were increased in individuals with hypothyroidism. All the variables returned to normal after thyroid hormone replacement.<sup>8</sup> Further study is needed to clarify the potential mechanisms of thyroid hormones in relation to GA, GA/HbA<sub>1c</sub>.

To our knowledge, this is the first study to explore the relationships of thyroid hormones with GA and GA/HbA<sub>1c</sub> in euthyroid and SHypo subjects. Our study also has several limitations. Firstly, the study subjects were recruited from communities in Shanghai. Thus, to some extent, the results may be influenced by regional differences and population selection. Secondly, due to the nature of cross-sectional studies, we could not determine a causal relationship between thyroid hormones and GA and GA/HbA<sub>1c</sub>.

## Conclusions

The present study found that FT3 was inversely related to GA in euthyroid individuals, while FT4 was inversely related to GA in SHypo individuals. In euthyroid and SHypo individuals, more attention should be paid to the potential effects of individual differences in thyroid hormones on GA.

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## Disclosure

The authors report no conflicts of interest in this work.

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