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Thyroid-Stimulating Hormone Levels Are Positively Associated with Insulin Resistance

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: It has been reported that overt and mild thyroid dysfunctions are associated with insulin resistance (IR). We performed this retrospective study to evaluate the relationships between thyroid-stimulating hormone (TSH) levels within the reference range and IR.

Material/Methods: A total of 447 outpatients were enrolled in this study: 298 with type 2 diabetes mellitus and 149 nondiabetic individuals. Based on a cutoff HbA1c value of 7%, diabetic patients were additionally divided into 2 groups: a high-HbA1c group (n=240) and a low-HbA1c group (n=58). The relationships of TSH levels and HOMA-IR were computed using linear regression models.

Results: TSH levels were positively and linearly associated with HOMA-IR in both the nondiabetic and diabetic groups (r=0.210, p=0.011 and r=0.451, p<0.001), as well as in the high- and low-HbA1c groups (r=0.507, p<0.001 and r=0.259, p=0.048). A better correlation between TSH levels and HOMA-IR was found in the diabetic group and in the high-HbA1c group when compared with the nondiabetic group and the low-HbA1c group, respectively. Linear regression analysis showed that TSH levels were independently associated with HOMA-IR (p=0.034, =0.049 and <0.001 in nondiabetic, low-, and high-HbA1c groups, respectively).

Conclusions: Our data suggest that TSH is independently associated with insulin resistance.

MeSH Keywords: Diabetes Mellitus, Type 2 • Insulin Resistance • Thyrotropin

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Background

Patients with overt hyperthyroidism and overt hypothyroidism are more likely to develop insulin resistance [1]. Mild thyroid dysfunctions involving subclinical hyperthyroidism and subclinical hypothyroidism are also associated with insulin resistance [2,3]. These might indicate that abnormal thyroid hormones and thyroid-stimulating hormone (TSH) levels affect the development of insulin resistance. A study by Lambadiari et al. showed a positive association between thyroid hormone levels and insulin resistance in type 2 diabetes mellitus (DM) patients [4]. Moreover, higher TSH levels tended to be associated with higher homeostasis model of assessment for insulin resistance index (HOMA-IR) values in women with polycystic ovary syndrome [5]. There are no published reports investigating the relations between TSH and insulin resistance in non-DM and type 2 DM patients. The aim of our study was to evaluate the associations between TSH levels within the reference range and insulin resistance among euthyroid type 2 DM patients and non-DM individuals.

Material and Methods

We included 298 outpatients diagnosed with type 2 DM patients in Huai'an Xuyi Hospital in this observational study from January 2015 to December 2015. All patients had known diabetes duration of 4–10 years. Exclusion criteria were: (1) overt and subclinical thyroid dysfunction, including overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism, and subclinical hypothyroidism; (2) diabetic acute complications; (3) thyroid tumor or thyroid operations; (4) requirement of exogenous insulin; (5) treatment of synthetic thyroid hormones, antithyroid drugs, or any other medicines which could possibly influence thyroid functions; (6) concomitant severe diseases, such as heart failure, serious infection, and malignant tumor; (7) age <30 or >80 years. We included 149 age- and sex-matched non-DM individuals as a control group. This study was approved by the Ethics Committee of Huai'an Xuyi Hospital. All patients signed the informed consent.

Clinical data included age, sex, weight, height, concomitance hypertension, coronary heart disease (CHD) and stroke, smoking status, and drugs. Hypertension was defined as a systolic BP ≥140 mmHg, a diastolic BP ≥90 mmHg, a history of hypertension, or current use of antihypertensive medicines. CHD was defined as: symptoms such as angina, myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery. Current smokers were defined as any who had smoked at least 1 cigarette per day for at least 1 year or who had stopped less than 6 months before recruitment.

All laboratory examinations were performed on the day of the second visit. Blood samples were collected at 6 AM for the measurement of thyroid function, HbA1c, fasting blood glucose, fasting insulin, and serum lipids, including total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c). TSH, and fasting insulin were measured using an immunoradiometric assay (Tosho Corp, Tokyo, Japan). The reference ranges were: TSH, 0.4–4.0 mIU/L and insulin, 17.8–173.0 pmol/L. HbA1c was measured using high-performance liquid chromatography instruments (HLC-723; Tokyo, Japan) with a reference range of 4.5–6.3%. Fasting blood glucose was measured by the colorimetry method using an autoanalyzer (Hitachi 911; Mito, Japan, normal range, 3.6–6.2 mmol/L). HOMA-IR was used to estimate insulin resistance, calculated by the equation: (fasting blood glucose×fasting serum insulin)/22.5 [6]. Serum lipid levels were measured by an autoanalyzer (Hitachi 911; Mito, Japan). TC and TG levels were measured using an enzymatic method, and LDL-c was measured using the turbidimetry method. The reference ranges were: TC, 2.9–6.0 mmol/L; TG, 0.2–1.7 mmol/L; and LDL-c, 1.3–3.6 mmol/L.

Data are summarized as the mean ± standard deviation or number (percentage). Participants were classified into the DM group and non-DM group. Type 2 DM patients were furthermore categorized into the low-HbA1c group (HbA1c <7%) and the high-HbA1c group (HbA1c ≥7%). The cut-point of 7% for separating the low- and high-HbA1c groups was based on the AACE/ACE guidelines.[7] Logarithmic transformation of the data of HbA1c and TSH levels was applied to fulfill the requirement of normal distribution. Continuous variables were analyzed by the one-way ANOVA test. The data for pairs of groups were compared by LSD-t test. We used the Mann-Whitney U test after Bonferroni adjustments to estimate the differences of dichotomous data among these groups. A generalized linear model was constructed to determine the association of TSH and HOMA-IR in the non-DM group, DM group, low-HbA1c group, and high-HbA1c group. The differences in correlation coefficients were evaluated by Fisher's z-transformation. Furthermore, we used multiple regression analysis to adjust for the confounding factors. SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for our analyses. Statistical significance was considered when $p<0.05$.

Results

There were 298 type 2 DM patients (mean age 59.11±11.23 years, 172 men) and 149 control subjects (mean age 60.31±10.52 years, 84 men) eligible in this study. Clinical and laboratory characteristics are shown in Table 1. Patients in the high-HbA1c group had higher rates of hypertension and CHD when compared with those in the non-DM group (36.2% *vs.* 32.2% and 28.3% *vs.* 17.4%). The incidence of CHD was also higher in the

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Table 1. Clinical and laboratory characteristics of the subjects.

	Nondiabetic group (n=149)	High HbA1c group (n=240)	Low HbA1c group (n=58)
HbA1c, mean (SD), %	4.97±0.42	9.49±1.71*#	6.37±0.39#
Age, mean (SD), y	60.31±10.52	58.53±11.30	61.52±10.66
Male, No (%)	84 (56.4)	134 (55.8)	38 (65.5)
Hypertension, No (%)	48 (32.2)	108 (36.2)#	28 (48.3)
CHD, No (%)	26 (17.4)	68 (28.3)#	21 (36.2)#
Stroke, No (%)	8 (5.4)	17 (7.1)	4 (6.9)
TC, mean (SD), mmol/l	3.47±1.13	4.30±1.11*#	3.80±1.09
TG, mean (SD), mmol/l	1.32±0.87	1.75±0.89*#	1.46±1.21
LDL-c, mean (SD), mmol/l	2.04±0.85	2.49±0.89*#	2.23±0.82
HOMA-IR	2.56±1.14	3.05±1.23*#	2.40±1.09
TSH, mean (SD), mIU/L	1.89±0.90	1.87±0.82	1.74±0.85
BMI, mean (SD)	24.19±2.74	26.02±3.22	25.37±2.67
Current smokers, No (%)	74 (49.7)	126 (52.5)	28 (48.2)
Insulin secretagogues, No (%)	–	79 (32.9)	23 (39.7)
Metformin, No (%)	–	95 (39.6)	25 (43.1)
Aspirin, No (%)	25 (16.8)	57 (23.8)	15 (25.9)
Statin, No (%)	22 (14.8)	52 (21.7)	11 (19.0)
Antihypertensive drugs, No (%)	43 (28.9)	89 (37.1)	21 (36.2)

* Versus low-HbA1c group, # versus non-DM group, significant difference. TC – total cholesterol; TG – triglyceride; LDL-c – low-density lipoprotein cholesterol; HOMA-IR – insulin resistance index; TSH – thyroid stimulating hormone; BMI – body mass index.

low-HbA1c group than in the non-DM group (36.2% versus 17.4%). Patients in the high-HbA1c group tended to have the highest HOMA-IR values than in the other 2 groups (3.05±1.23 *vs.* 2.56±1.14 and 2.40±1.09). TC, TG, and LDL-c levels in the high-HbA1c group were also higher than in the other 2 groups. No significant differences among groups were found in the analyses of BMI, current smokers, stroke, drugs, and TSH levels.

In generalized linear analyses, HOMA-IR was positively associated with TSH levels in the non-DM group (r=0.189, p=0.021) as well as in the DM group (r=0.451, p<0.001). Among patients with diabetes, we found positive relationships between HOMA-IR and TSH levels in the high-HbA1c group (r=0.507, p<0.001) and in the low-HbA1c group (r=0.259, p=0.048, Figure 1). Fisher Z-transformation showed a statistical significance of r coefficient between the non-DM and DM groups (Z=–2.912, 95%CI –0.493~–0.096) and between the low-HbA1c and high-HbA1c groups (Z=–1.962, 95%CI –0.87~–0.001). Multiple regression model showed that TSH (β coefficient=0.620, 95%CI 0.482~0.758, p<0.001) and BMI (β coefficient=0.147, 95%CI 0.111~0.184, p<0.001) were significantly associated with HOMA-IR in the high-HbA1c group after adjustment for confounding factors; TSH levels were also independently associated with HOMA-IR in the non-DM group and low-HbA1c group (β coefficient=0.284, 95%CI 0.001~0.586, p=0.034, and β coefficient=0.333, 95%CI 0.001~0.665, p=0.049, respectively).

Discussion

Previous studies demonstrated interactions among TSH, insulin resistance, and serum lipid levels in non-DM adults and type 2 DM females [8,9], suggesting that TSH levels might be related to insulin resistance. Our data showed that TSH levels within the reference range were positively associated with HOMA-IR in subjects with or without type 2 DM. Moreover, there was a better correlation between TSH levels and HOMA-IR in patients with diabetes and in DM patients with poor glucose control (HbA1c ≥7%) when compared with non-DM patients and DM patients with adequate glucose control (HbA1c <7%), respectively.

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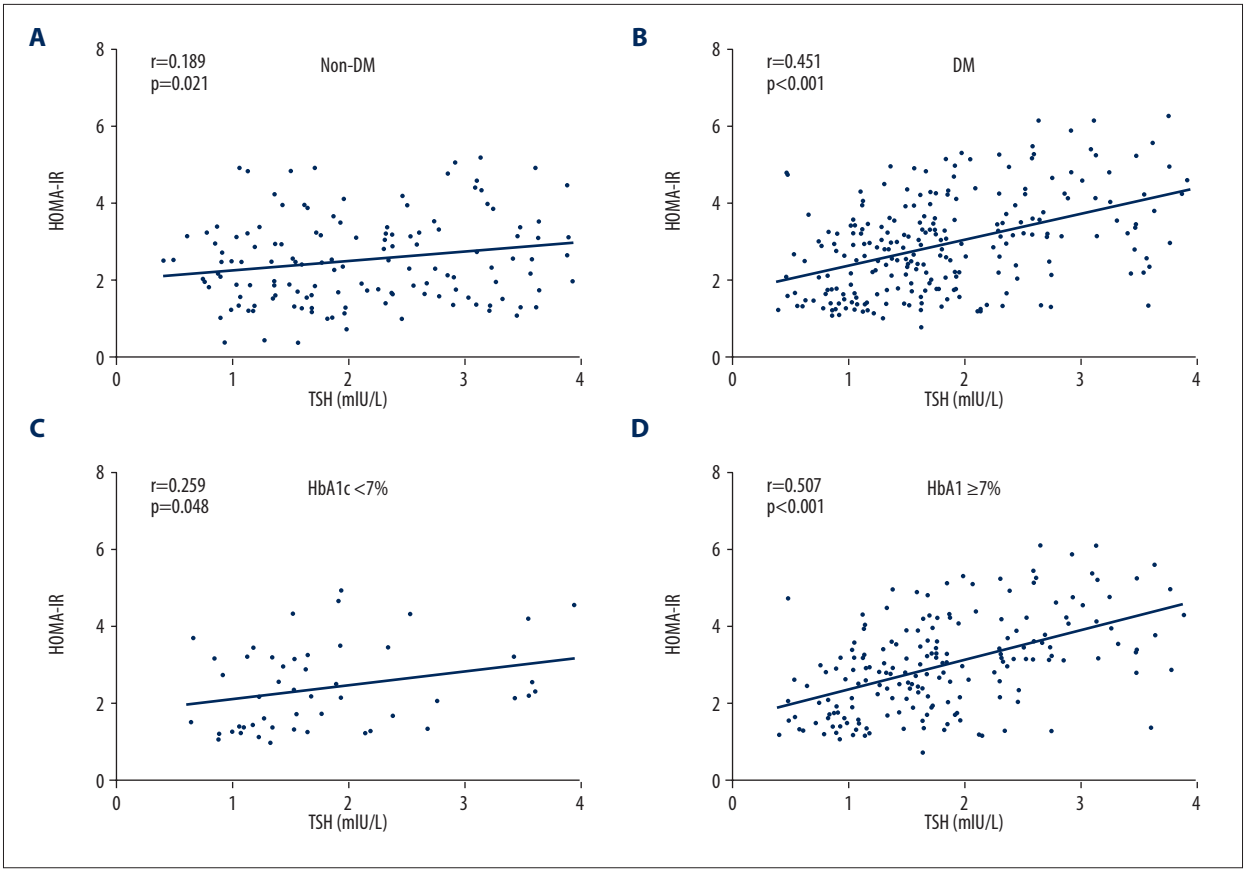

Figure 1. (**A–D**) Associations between thyroid stimulated hormone (TSH) levels and homeostasis model of assessment for insulin resistance index (HOMA-IR).

In line with the present study, Mueller et al. reported a significant association between TSH and insulin resistance in women with polycystic ovary syndrome, and the association was independent of age and BMI [5]. We also found that TSH levels were independently associated with HOMA-IR in type 2 DM patients and in non-DM individuals. Moreover, TSH levels within the reference range have been reported to be positively and linearly associated with BMI, blood pressure, and unfavorable serum lipids [10–12], all of which were considered to be risk factors for CHD [13–15]. Moreover, insulin resistance exists in both hyperthyroidism and hypothyroidism [1]. Subclinical hyperthyroidism and hypothyroidism are also associated with insulin resistance [2,3], which might explain the consequently high risk of developing CHD events in patients with mild thyroid dysfunction [16,17]. Therefore, we speculate that thyroid dysfunction aggravates insulin resistance, and thereby increases the risk of CHD. However, our study was retrospective and we did not perform further follow-up analyses of the relationships among TSH, insulin resistance, and CHD events.

Thyroid hormone levels are regulated by TSH, and in turn provide a negative feedback effect. It seems that the results of our study disagree with the findings of Lambadiari et al. Lambadiari et al. selected 17 healthy subjects, 22 first-degree relatives of patients with diabetes, 15 subjects with impaired glucose tolerance, and 24 type 2 DM patients, and concluded that thyroid hormone levels were positively associated with insulin resistance [4]. There are 3 reasons for the inconsistent results. First, patients in the Lambadiari et al. study were at all stages of type 2 DM in a small sample size, while the present study included more DM patients and most of them had poor glucose control (80.54%). Second, only diet-controlled DM patients were included in the Lambadiari et al. study. We also enrolled patients who took oral anti-diabetic drugs. Third, FT3 and FT4 levels increased while HOMA-IR values decreased from the control group to DM group, and all data from the 4 groups together were used to perform the generalized linear analyses, which means that the positive association between thyroid hormone levels and HOMA-IR values might be the result of changing stages of type 2 DM. In the present study, we did the generalized linear analyses in non-DM, low-, and high-HbA1c groups to avoid the effect of changing stages.

TSH receptor has been reported in a variety of cell types, including adipocytes [18]. When TSH binds to the receptor in adipocytes, it stimulates interleukin-6 release from adipocytes,

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and then mediates proliferation, differentiation, and leptin secretion of preadipocytes and adipocytes [19]. Ectopic fat plays a critical role in the development of insulin resistance [20]; therefore, fat cells might be a possible key factor in the association of insulin resistance and TSH. As shown in Table 1, patients with diabetes, especially those with high HbA1c levels, whose HOMA-IR levels were higher than the others, were more likely to develop CHD, hypertension, and dyslipidemia. Shulman et al. reported that insulin resistance promotes dyslipidemia and cardiometabolic disease and HOMA-IR has been considered as a risk factor of cardiovascular events [13,20]. Moreover, Chubb et al. found more complex associations among dyslipidemia, thyroid function, and insulin resistance, showing that serum lipid levels, including TC and TG, were modified by ln(TSH) and ln(HOMA-IR) [9]. Recently, Skoczynska also found positive correlations between TSH and TC, LDL-c and TG [21]. More work is needed to explore the complicated relationships among TSH, insulin resistance, dyslipidemia, and cardiovascular disease.

Our study shows a positive and linear association between TSH and HOMA-IR, suggesting that the screening of thyroid function is important for type 2 DM patients, especially for those with high HbA1c levels. It may help physicians to evaluate the degree of insulin resistance and to guide treatment for glucose control. However, our study has some limitations. First, this study is retrospective and observational and it was difficult to avoid selection and confounding bias. In our data, we found an imbalance of the baseline characteristics, including prevalence of hypertension and coronary heart disease and serum lipid levels, and those variables were adjusted in a regression model to lessen the influence of this limitation. Second, the sample size of this study was relatively small and only patients without use of exogenous insulin were included. Moreover, the control group was not selected from healthy individuals, so our results might not be generalizable to healthy populations. Larger investigations are needed to confirm this association. Third, this study was not prospective and we did not conduct follow-up visits. The causality of TSH and insulin resistance and the relationship between their interactions and CHD events are both unclear. Further studies with more patients and follow-up visits are necessary to answer these questions.

Conclusions

There is a positive and linear association between TSH levels within reference range and HOMA-IR in both non-DM subjects and type 2 DM patients. A better correlation exists in patients with diabetes, especially in patients with high HbA1c levels. These data suggest that thyroid functions may influence the development of insulin resistance and type 2 DM.

Conflict of interest

None.

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