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Original Article

Elevated thyroid stimulating hormone levels are associated with metabolic syndrome in a Chinese community-based population of euthyroid people aged 40 years and older

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Abstract

This study investigated whether high-normal thyrotropin (TSH) levels are associated with metabolic syndrome in euthyroid Chinese people ≥ 40 years old. Clinical and metabolic factors were assessed in 2,356 subjects (40–77 years old) with TSH levels in the normal range (0.35–5.00 mU/L). Using 2.50 mU/L as the cut-off point of TSH level within the normal range, we divided subjects into the high-TSH (2.50–5.00 mU/L; $n = 1,064$) and low-TSH (0.35–2.50 mU/L; $n = 1,292$) group. The results showed that the mean levels of body mass index (BMI), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and fasting plasma glucose (FPG) were higher in the high-TSH group and TSH levels were significantly positively correlated with BMI, LDL-C, TC, and FPG. The prevalence of central obesity, hypertriglyceridemia, low high density lipoprotein cholesterol (HDL-C), and high FPG (>5.60 mmol/L) was significantly higher in females and subjects with high-TSH levels. Metabolic syndrome was also more prevalent in the high-TSH group. People over the age of 40 years with high-normal TSH levels had a 1.2-fold increased risk of metabolic syndrome, compared with those with low-normal TSH levels, after adjusting for age and gender. In conclusion, high normal TSH is a risk factor for metabolic syndrome in people ≥ 40 years old.

Keywords: thyroid stimulating hormone, euthyroid, metabolic syndrome, central obesity, dyslipidemia

Introduction

Metabolic syndrome (MS) is a constellation of metabolic abnormalities, including central obesity, glucose intolerance, hypertension, and dyslipidemia. The incidence of MS continues to increase and is becoming a major public health concern worldwide[1]. Mounting evidence suggests that MS is associated with an increased risk of cardiovascular disease (CVD)[2], type 2 diabetes[3] and all-cause mortality[4].

The hypothalamic-pituitary-thyroid (HPT) axis orchestrates a variety of metabolic processes, including thermogenesis and energy expenditure, growth promotion and lipid metabolism, which affect energy balance[5–6]. Thyroid dysfunction presents a risk of CVD due to disruptions in blood pressure and lipid metabolism[7–8]; this is valid for both overt and subclinical hypothyroidism[9–10]. However, whether high-normal thyroid-stimulating hormone (TSH) levels are associated with metabolic derangement remains

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controversial. Studies have reported an association between subclinical hypothyroidism and MS in post-menopausal women[11] and young women of reproductive age[12]; however, few studies have examined this association with subjects that include elderly men.

In 2003, the National Academy of Clinical Biochemistry (NACB) recommended lowering the upper reference limit of TSH to 2.50 mU/L based on the findings of a large-scale epidemiological survey which revealed that ≥95% of normal individuals have TSH levels < 2.50 mU/L and those with higher TSH levels were likely to have various thyroid disorders[13–14]. In this study, we used 2.50 mU/L as the cut-off point of TSH level within normal range to examine the association between high normal TSH levels and MS in a Chinese community-based population aged ≥40 years in Nanjing, Jiangsu Province, China.

Subjects and methods

Subjects

The study was part of the baseline survey from the REACTION study, which investigated the association of diabetes and cancer, and was conducted among 259,657 adults aged 40 years and older in 25 communities across mainland China from 2011 to 2012[15–16]. The sampling survey method was used to collect the baseline thyroid function data of 3,000 subjects from 10,000 subjects aged 40 years and older, who participated in the REACTION study in the Gulou district of Nanjing, Jiangsu Province. After exclusion of 644 individuals with abnormal thyroid function, 2,356 subjects were included in the final analysis. Local ethics committees (the First Affiliated Hospital of Nanjing Medical University, No. 2011-SR-071) approved the study protocol. Written informed consent was obtained from each participant before data collection.

Data collection

The sociodemographic characteristics of all study participants were assessed by a questionnaire. Lifestyle factors, such as smoking status, alcohol intake and exercise, were also assessed. Waist circumference was measured in centimeters using the minimum circumference between the lower rib margin and the iliac crest in the standing position. Blood pressure was measured three times in all patients with at least a 5-minute interval between measurements. The average value was used to define systolic blood pressure (SBP) and diastolic blood pressure (DBP). Levels of fasting plasma glucose (FPG), TSH, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured after at least 12 hours of fasting in all subjects. The reference range of TSH was 0.35–5.00 mU/L. Based on the recommended cut-off
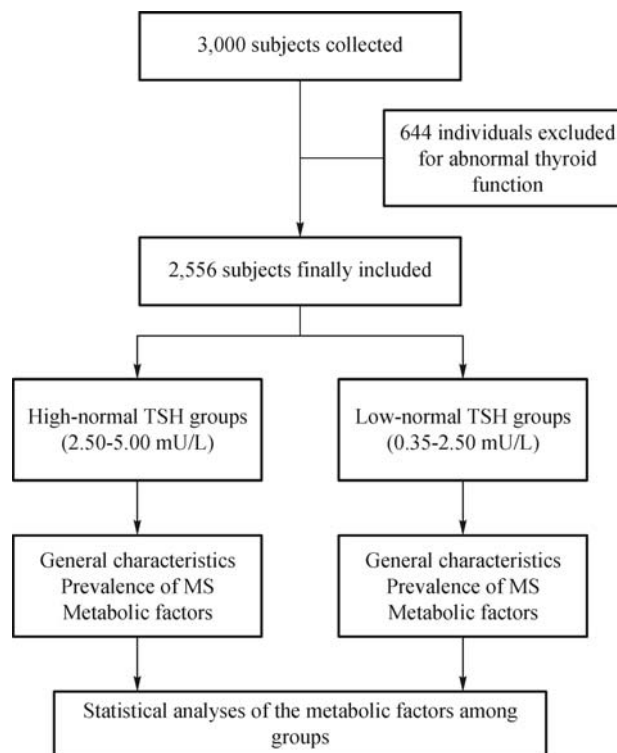

Fig. 1 **Flowchart of the progress of the cross-sectional study**

value of TSH from the NACB guidelines[14], subjects were divided into the high-TSH (2.50–5.00 mU/L) and low-TSH (0.35–2.50 mU/L) groups.

Definitions

Euthyroidism was defined as FT3, FT4 and TSH levels within normal reference ranges (3.50–6.50 pmol/L, 8.50–22.50 pmol/L, and 0.35–5.00 mU/L, respectively), without taking any thyroid medication. Body mass index (BMI) was defined as body weight in kilograms divided by the square of body height in meters. The presence of MS was ascertained according to the following criteria suggested by the International Diabetes Federation[17]: (I) central obesity (defined as waist circumference, males $\geq$ 90 cm and females $\geq$ 80 cm; when BMI is $\geq$ 30 kg/m^2, central obesity can be assumed with no need for waist circumference measurement); (II) triglycerides levels $\geq$ 150 mg/dL or specific treatment for this lipid abnormality; (III) low HDL-C: HDL-C $\leq$ 40 mg/dL (0.9 mmol/L) in males and $\leq$ 50 mg/dL (1.1 mmol/L) in females; (IV) SBP/DBP $\geq$ 130/85 mmHg or treatment for previously diagnosed hypertension; (V) high FPG: FPG $\geq$ 5.60 mmol/L. When central obesity plus two of the four above criteria were met, a diagnosis of MS was made.

Statistical analyses

Data analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). All data were expressed as mean $\pm$ standard deviation (SD) or as percentages, where appropriate. Statistical comparisons were performed using independent-samples t tests for data with a normal distribution and χ^2 tests for data with a skewed distribution. Pearson or Spearman correlation was used to determine the relationship between TSH and other parameters. Logistic regression analysis was performed to evaluate the odds ratio that predicts the presence of MS in two groups. For all analyses, a probability (P) value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study subjects

Of the 2,356 participants (mean age, 58.19±8.16 years; range, 40-87 years) included for analysis, 1,064 (45.16%) were allocated to the high-TSH group and 1,292 (54.84%) to the low-TSH group (***Fig. 1***). The general characteristics of the two groups are presented in ***Table 1***. As shown in ***Table 1***, gender distribution was different between the two groups (P < 0.05), and the mean levels of BMI, TC, LDL-C, and FPG were all significantly higher in the high-TSH group than those in the low-TSH group (24.95±3.47 *vs*. 24.59±3.13, 5.10±1.00 *vs*. 4.98±0.99, 2.94±0.81 *vs*. 2.86±0.77, and 6.41±1.76 *vs*. 6.27±1.59, respectively; all P < 0.05). Among all of the subjects, TSH levels were significantly positively correlated with BMI, LDL-C, TC, and FPG (all P < 0.05).

Table 1 **Physical and metabolic characteristics of the study participants (mean±SD)**

Parameters	Overall	TSH 0.35–2.50 mU/L	TSH 2.50–5.00 mU/L	$P^\dagger$	γ	$P^\ddagger$
Number(*n*)	2,356	1,292	1,064	–	–	–
Gender(male/female)	969/1,387	618/674	351/713	< 0.001*	–	–
Age(years)	58.19±8.56	58.23±8.08	58.14±8.16	0.805	−0.003	0.901
WC(cm)	86.00±9.28	85.96±9.18	86.04±9.41	0.825	−0.003	0.882
BMI(kg/ m^2)	24.75±3.30	24.59±3.13	24.95±3.47	0.010*	0.061	0.003*
TC(mmol/L)	5.03±1.00	4.98±0.99	5.10±1.00	0.004*	0.059	0.004*
TG(mmol/L)	1.71±1.27	1.66±1.32	1.76±1.20	0.058	0.036	0.081
LDL−C(mmol/L)	2.90±0.79	2.86±0.77	2.94±0.81	0.012*	0.050	0.015*
HDL−C(mmol/L)	1.35±0.32	1.35±0.33	1.35±0.32	0.943	0.014	0.505
SBP(mmHg)	132.21±17.71	132.27±17.71	132.15±17.12	0.864	0.007	0.724
DBP(mmHg)	79.48±10.58	79.68±10.68	79.22±10.47	0.292	−0.024	0.237
FPG(mmol/L)	6.35±1.69	6.27±1.59	6.41±1.76	0.046*	0.042	0.040*
PPG(mmol/L)	9.44±3.86	9.32±3.75	9.55±3.94	0.143	0.032	0.116
TSH(mU/L)	2.44±1.17	1.54±0.55	3.54±0.72	< 0.001*	–	–

Values are presented as mean $\pm$ SD; *P < 0.05; $P^\dagger$: derived from a comparison of the mean level of physical and metabolic characteristics between two groups; *r*: correlation coefficient; $P^\ddagger$: derived from correlation analysis. BMI: body mass index, kg/m^2; SBP: systolic blood pressure, mmHg; DBP: diastolic blood pressure, mmHg; HDL-C: high density lipoprotein cholesterol, mmol/L; LDL-C: low density lipoprotein cholesterol, mmol/L; TG: triglycerides, mmol/L; TC: total cholesterol, mmol/L; FPG: fasting plasma glucose, mmol/L; PPG: postprandial plasma glucose, mmol/L; TSH: thyroid-stimulating hormone,mU/L

Table 2 Prevalence of metabolic syndrome and its components in different subgroups

Parameters	Overall TSH (mU/L)		$P^\dagger$	Male TSH (mU/L)		$P^\ddagger$	Female TSH (mU/L)		$P^\#$
	0.35–2.50	2.50–5.00		0.35–2.50	2.50–5.00		0.35–2.50	2.50–5.00	
MS	38.5	42.9	0.035*	30.6	33.6	0.351	45.8	47.4	0.590
Central obesity	57.8	65.5	< 0.001*	48.2	50.4	0.547	66.6	72.9	0.012*
Hypertension	31.6	32.2	0.774	32.2	32.3	1.000	31.1	32.2	0.708
High FPG	59.6	64.9	0.008*	68.6	70.4	0.621	54.3	61.6	0.007*
Low HDL-C	11.1	13.6	0.077	8.3	9.1	0.635	13.8	15.8	0.291
High TG	32.6	37.8	0.009*	35.8	38.5	0.406	29.7	37.4	0.003*

Values are presented as percentage.*$P < 0.05$. $P^\dagger$: derived from a comparison of the overall prevalence of metabolic syndrome and its components between the two groups; $P^\ddagger$: derived from a comparison of the prevalence of metabolic syndrome and its components between the two groups in male; $P^\#$: derived from a comparison of the prevalence of metabolic syndrome and its components between the two groups in female. TSH: thyroid-stimulating hormone, mU/L; MS: metabolic syndrome; TG: triglycerides, mmol/L; HDL-C: high density lipoprotein cholesterol, mmol/L; FPG: fasting plasma glucose, mmol/L.

Prevalence of MS

Table 2 shows the prevalence of MS and its components. The prevalence of MS was significantly higher in the high-TSH group than in the low-TSH group (42.9% *vs.* 38.5%, $P = 0.035$). Central obesity (65.5% *vs.* 57.8%, $P < 0.001$), hypertriglyceridemia (37.8% *vs.* 32.6%, $P = 0.009$), and high FPG (>5.6 mmol/L) (64.9% *vs.* 59.6%, $P = 0.008$) were significantly more frequent in the high-TSH group than in the low-TSH group, respectively. Moreover, the prevalence of central obesity, hypertriglyceridemia, and high FPG (>5.60 mmol/L) in the female subgroup were also significantly higher in the high-TSH group than in the low-TSH group (all $P < 0.05$).

Multivariable risk assessment

The association of TSH level with MS and its components was assessed using binary logistical regression analysis adjusted for age and gender. Metabolic syndrome, central obesity, hypertension, high FPG, low HDL-C and high TG were applied as dependent variables and TSH as an independent variable (**Table 3**). The odds ratio (95% confidence intervals) that predicts the presence of MS, central obesity, high FPG, low HDL-C, and hypertriglyceridemia were 1.21 (1.02–1.43), 1.23 (1.03–1.46), 1.26 (1.06–1.49), 1.31 (1.03–1.67), and 1.31 (1.10–1.55), respectively (all $P < 0.05$) in the high-TSH group compared with the low-TSH group.

Discussion

In this study, we observed that TSH levels at the upper range of reference value were correlated with various MS parameters in 2,356 euthyroid persons aged ⩾ 40 years. The prevalence of MS was significantly greater among subjects in the high-TSH group (2.50–5.00 mU/L) than in the low-TSH group (0.35–2.50 mU/L). Regarding the components of MS, central obesity, high FPG, and hypertriglyceridemia were significantly frequent in the high-TSH group. These findings are consistent with a previous study of young women[12]. Our results indicate that high-normal TSH levels also act as a predictor of MS.

Table 3 Association of thyroid stimulating hormone as an independent variable with metabolic parameters by logistic regression analyses adjusted for age and gender.

Parameters	B	SE	OR(95%CI)	P
MS	0.19	0.09	1.21 (1.02–1.43)	0.025*
Central obesity	0.21	0.09	1.23 (1.03–1.46)	0.020*
Hypertension	−0.03	0.09	0.97 (0.82–1.16)	0.763
High FPG	0.23	0.09	1.26 (1.06–1.49)	0.008*
Low HDL-C	0.27	0.12	1.31 (1.03–1.67)	0.029*
High TG	0.27	0.09	1.31 (1.10–1.55)	0.002*

The summary of the regression models were performed using metabolic syndrome, central obesity, hypertension, high FPG, low HDL-C and high TG as dependent variables and TSH as an independent variable adjusted by age and gender. *$P < 0.05$. OR: odds ratio, was computed with the use of binary logistic regression model. B: unstandardized regression coefficients; SE: standard error.
BMI: body mass index, kg/m^2; SBP: systolic blood pressure, mmHg; DBP: diastolic blood pressure, mmHg; HDL-C: high density lipoprotein cholesterol, mmol/L; LDL-C: low density lipoprotein cholesterol, mmol/L; TG: triglycerides, mmol/L; TC: total cholesterol, mmol/L; FPG: fasting plasma glucose, mmol/L; TSH: thyroid-stimulating hormone, mU/L.

In the present study, the mean BMI value and prevalence of central obesity were greater in the high-TSH group than in the low-TSH group, in accordance with the results of previous reports[12,18]. Moreover, other studies have demonstrated a correlation between TSH and BMI. For example, Nyrnes *et al.*[19] found a positive and significant correlation between serum TSH within the normal range and BMI both in a cross-sectional and longitudinal study, possibly because elevated TSH levels promote weight gain, resulting in obesity. Hypothyroidism results in decreased basal metabolic rate, and together they affect lipid and carbohydrate metabolism, leading to weight gain[20–21]. However, other studies have shown that the prevalence of subclinical hypothyroidism is associated with increased obesity[22]; it has also been suggested that abnormalities in thyroid function may be secondary to weight excess[23]. High-normal or slightly high TSH levels seem to be positively correlated with the degree of obesity[24]. This phenomenon may be due to neuroendocrine dysfunction, especially by inappropriate secretion of leptin, a notable adipocyte-derived hormone, which accelerates excess TSH secretion in obesity[25–26]. Leptin is produced by adipose tissue and may equilibrate the HPT axis by regulating TRH expression in the paraventricular nucleus[27–28], leading to subsequent modification of hypothalamic TSH production[29–30].

Hypercholesterolemia is a well-known feature of hypothyroidism. Classically, hypothyroidism-associated dyslipidemia is characterized by elevated LDL-C levels and has been described both in overt and subclinical disease[31]. In this study, we found a significant positive correlation between circulating TSH and TC, or LDL-C concentrations. These findings are consistent with the well-known association between hypothyroidism and elevated levels of TC and LDL-C[32]. However, the mechanism by which thyroid hormones modulate the blood lipid profile is multi-factorial. Thyroid hormones may stimulate hydroxy-methylglutaryl coenzyme A (HMG CoA), the key enzyme of LDL biosynthesis, and induce its synthesis[33]. Thyroid hormones also decrease LDL catabolism by reducing the number of LDL-C receptors on the membranes of liver cells[32]. In hypothyroidism, there is a decrease in the activity of hepatic lipase and cholesterol 7 alpha hydroxylase[34–36]. In addition, the expression of hepatic LRP1 decreased[37]. These alterations may be associated with elevated circulating remnant lipoproteins.

In our study, we found no linear association between SBP or DBP and TSH level. Moreover, there was no difference in the prevalence of hypertension between the high- and low-TSH groups. This result is not consistent with that of a previous study[12], which identified a positive, linear association between SBP and DBP and TSH level. Although hypothyroidism can cause hypertension, the results of the vast majority of studies did not find a significant association between elevated TSH levels and blood pressure[38–39].

We observed that the prevalence of abnormal fasting glucose was quite high in the high-TSH group and that TSH levels were significantly positively correlated with FPG, which is consistent with the findings of many other investigations[8,12]. Our study had some limitations, however, as we did not measure insulin secretion status. Since, insulin resistance (IR) is the key pathophysiological component of MS, and according to the AUC (area under the curve) and HOMA-IR (homeostasis model assessment of insulin resistance), more information may be revealed about this topic.

Moreover, we found the prevalence of central obesity, hypertriglyceridemia, and high FPG (>5.60 mmol/L) in the female subgroup were also significantly higher in the high-TSH group than in the low-TSH group. The age of our subjects was 40 years and older, and females in this age group were in menopausal transition or postmenopausal. Many studies have indicated that MS is highly prevalent in postmenopausal women[40–41] and our finding adds to the growing body of evidence implicating menopause as a predictor of MS, independent of age[40].

In conclusion, this report extends existing information regarding the association between the components of MS and thyroid function in the euthyroid state. Our data showed that people aged $\geqslant 40$ years with high-normal TSH levels (>2.50 mU/L) had approximately 1.2-fold increased risk of MS compared with those with TSH levels $\leqslant 2.50$ mU/L after adjustment for age and gender. Therefore, high-normal or mildly elevated TSH levels in the elderly is a risk factor of MS and its components, and should be considered when evaluating such patients.

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