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Brief Report

Relationship between Body Mass Index, Waist-to-Hip Ratio, and Serum Lipid Concentrations and Thyroid-Stimulating Hormone in the Euthyroid Adult Population

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What's Known

- The normal range for TSH (0.2-5.5 mIU/L) is used in many laboratories to document normal thyroid function. TSH level beyond normal range correlate significantly with obesity indices and dyslipidemia in subclinical hypothyroid (elevated TSH, Normal T3, T4) and overt hypothyroid (elevated TSH, Decreased T3, T4) individuals.

What's New

- In healthy euthyroid individuals without overt or subclinical hypothyroidism, BMI and LDL-C were significantly higher in the high-TSH group than in the low-TSH group after adjustment for age, sex, calorie intake, total fat and carbohydrate intakes, and physical activity.

Abstract

The aim of this cross-sectional study was to investigate the relationship between body mass index (BMI), waist-to-hip ratio, and lipid parameters and serum thyroid-stimulating hormone (TSH) levels in healthy euthyroid individuals.

This cross-sectional study was conducted between June 1st and July 20th, 2013, at Bushehr University of Medical Sciences. One hundred forty euthyroid individuals were divided into 2 groups: a high-TSH group (TSH between 2.0 and 5.5 mIU/L, n=67) and a low-TSH group (TSH between 0.3 and 2.0 mIU/L, n=73). After overnight fast, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TSH, thyroxine (T4), and triiodothyronine (T3) were measured. Height and weight were measured with a stadiometer, and BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to-hip ratio was determined as waist circumference divided by hip circumference. The simple independent *t*-test and a general linear model were used for statistical analysis. All statistical analyses were done using the SPSS, version 15, statistical software package.

BMI and LDL-C were significantly higher in the high-TSH group than in the low-TSH group after adjustment for age, sex, calorie intake, total fat and carbohydrate intakes, and physical activity. No significant differences were found between the groups in TG, cholesterol, and HDL-C. The association between TSH levels andT4 was significant.

Individuals with TSH levels at the upper limit of normality might be at risk of hypercholesterolemia and obesity.

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Introduction

Recently, public health researchers have shown increased interest in the role of obesity in health and disease. Obesity is a complicated process that depends on signals of satiety and hunger, genetics, endocrine abnormalities, and other factors.[1] Among these potential contributing factors, hypothyroidism is

one of the main causes. The activity of the thyroid gland is regulated by thyrotropin or thyroid-stimulating hormone (TSH), which is secreted by the pituitary gland.[2] However, the association between TSH levels per se and obesity has remained controversial. The normal range for TSH (0.2–5.5 mIU/L)[3] is used in many laboratories to document normal thyroid function; however, individuals with TSH levels >2.0 mIU/L have been found to be at increased risk of dyslipidemia, obesity, and overt hypothyroidism.[3] The relationship between TSH levels and obesity or dyslipidemia in subclinical and overt hypothyroidism has been proven.[4] Nonetheless, the relationship between TSH and obesity or dyslipidemia in individuals with normal TSH and without overt or subclinical hypothyroidism is obscure and few studies to date have focused on this relationship in euthyroid individuals. The novelty and the goal of this study was to investigate the relationship between TSH levels in healthy euthyroid individuals and their obesity indices (body mass index [BMI] and waist-to-hip ratio [WHR]) and lipid parameters.

Patients and Methods

Study Participants

This cross-sectional study was conducted between June 1st and July 20th, 2013, at Bushehr University of Medical Sciences, in Bushehr, Iran. Eligible patients willing to participate in the study were selected from the population of individuals referred to the medical offices in Bushehr.

The participants were invited to come to the Persian Gulf Tropical Medicine Research Center in Bushehr University of Medical Sciences on the following morning in a letter that explained the objectives of the study and was delivered to their homes by the research team. Signed informed consent was obtained from each participant. The criteria for inclusion in the study were TSH levels between 0.4 and 5.5 mIU/L.[3] Potential participants were interviewed and examined by an endocrinologist and excluded if they were using cigarettes, thyroid drugs, estrogen, or medications for hypertension or had any clinical signs of dyslipidemia, diabetes mellitus, or hypothyroidism such as feeling cold, hoarse voice, dry skin, malaise, puffy eyes, poor memory, constipation, muscle weakness or cramps, and slow thinking. Of 950 persons who were willing to participate in the study, 140 were eligible. This sample size was based on the results of a previous study[5] and was calculated by using G*Power (version 3.1, Informer Technologies, Inc.). With a population of 140 individuals, the power of the study will be 90%. We divided the participants into 2 groups: a high-TSH group with TSH between 2.0 and 5.5 mIU/L[3] (n=67) and a low-TSH group with TSH between 0.3 and 2.0 mIU/L[3] (n=73).

Then a blood sample was obtained from each participant and transferred to the laboratory of the Persian Gulf Tropical Medicine Research Center, where plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TSH, thyroxine (T4), and triiodothyronine (T3) levels were determined.

Anthropometric Measurements

Height and weight in the participants were measured with a stadiometer. Heavy outer garments and shoes were removed before height and weight were measured. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured with a non-stretchable measuring tape at the midpoint between the lower edge of the rib cage and the iliac crests. WHR was determined as waist circumference divided by hip circumference. For this parameter, waist circumference was defined as the smallest circumference measured at the navel, and hip circumference was defined as the largest circumference measured at the hips and buttocks.

Physical Activity

Physical activity in the participants was evaluated using a validated questionnaire based on the International Physical Activity Questionnaire, 2005, Epic-Norfolk.[6]

Dietary Intake Analysis

Dietary intake at the time of the study was recorded in an interview conducted by trained dietitian using a food frequency questionnaire (FFQ). In addition, all men and women completed a 24-hour dietary recall for 3 nonconsecutive days. The FFQ showed a correlation coefficient of 0.85 with 24-hourdietary recall. The reproducibility and relative validity of the 168-item FFQ had been tested previously in the Tehran Lipid and Glucose Study.[7] Each food and beverage was analyzed for the content of energy and other nutrients with Nutritionist III software (version 7.0; N-Squared Computing, Salem, OR, USA), which was adapted for Iranian foods. All statistical analyses were done with an IBM computer using the SPSS, version 15, statistical software package (SPSS Inc., Chicago, IL, USA).

The experimental protocol of the study was approved by the Research Deputyship

of Bushehr University of Medical Sciences (DP/8703277/176, 14/4/2013). The ethical aspects of the study were also approved by the Ethics Committee of Bushehr University of Medical Sciences (May 2013), and the research reported here was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Measurement of Serum Parameters

Venous blood samples were obtained between 8.00 and 9.00 hours and centrifuged at 3,000 g for 15 minutes at 4 °C. Immediately after centrifugation, the serum samples were frozen and stored at –80 °C for a period no longer than 6 weeks. To detect TSHin the serum samples, we used a commercially available ELISA kit (Autobio, Zhengzhou, China 450016, Catalog #E1003) according to the manufacturer's instructions. The limit of the detection of the assay was 0.05 mIU/L, and the intra- and inter-assay coefficients of variance were 5.19%–6.54% and 7.36%–8.23%, respectively. Total plasma T4 was determined with a commercially available ELISA kit (Pishtaz Teb CO. LTD., Arak, Iran). Total plasma T3 was also measured with a commercially available ELISA kit (Pishtaz Teb CO. LTD., Arak, Iran). Serum TG was measured with an enzymatic technique for oxidation by glycerol-3 phosphate and detection with phenol aminoantipyrine in an automated Technicon Axon Analyzer. HDL-C concentrations (after precipitation with magnesium chloride) were measured with enzymatic techniques (Pars Azmoon Co., Tehran, Iran). LDL-C concentrations were calculated with the Friedewald formula.[8]

Statistical Analysis

The distribution of the variables was studied with probability plots and the Shapiro–Wilk test. To identify differences between the 2 groups in BMI, WHR, and serum lipid parameters, we used the simple independent Student *t*-test. The general linear model was employed to adjust the differences between the 2 groups for age, sex, physical activity, total calorie intake, total dietary fat, and total dietary carbohydrates. The relationship between TSH and T4 or T3 was determined by calculating the Pearson correlation coefficient. Multiple linear regression models were utilized to determine the association between TSH and circulating T3 or T4 levels with adjustment for age and sex. A value of $P<0.05$ was accepted as significant.

All statistical analyses were done with an IBM computer and the SPSS, version 15, statistical software package (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the participants in the 2 groups are shown in table 1. Overall, the prevalence of overweight and obesity (BMI>25) was 53.2% and mean±SD age was 29±14 years.

The independent Student *t* test showed no significant differences between the 2groups in age, sex, T3, T4, calorie intake, and carbohydrate or total fat intake (table 1). Table 2 shows that BMI and LDL-C were significantly higher in the high-TSH group than in the low-TSH group before and after adjustment for age, sex, calorie intake, total fat, total carbohydrates, and physical activity. No significant differences between the groups were found for TG, cholesterol, and HDL-C.

The bivariate correlation analysis showed a correlation between serum TSH levels and T4 levels (r=-0. 3, P=0.01). The association between TSH levels and T4 was determined with the multiple linear regression analysis. There was a significant negative association between TSH and T4 levels. This significant relationship persisted after adjustment for age and sex (table 3). There was no association between TSH and T3 levels.

Discussion

Our findings showed that the euthyroid individuals whose TSH concentrations were>2.0 mIU/L had a higher BMI than those with lower TSH levels. This finding is consistent with a large population study that found a significant positive association between TSH and BMI, although in this study the participants' TSH levels were within the normal range.[9] The ligand of TSH and the TSH receptors, located on adipose cell membranes, mediates adipocyte proliferation.[10] In fact, one possible explanation for the increased TSH levels in

Table 1: Characteristics of the individuals (N=140)

Characteristics	Low-TSH Group	High-TSH Group	P value
Age (y)	34.61±15.43	31.39±16.38	0.15
Sex			
Female	48	45	0.23
Male	25	22	0.34
TSH	1.2±0.31	3.65±0,45	0.03
T4 (µg/dL)	9.13±2.63	8.44±2.07	0.08
T3(ng/dL)	70.28±19.52	60.80±27.17	0.93
Calorie intake (Kc)	3205±811	3165±690	0.56
Carbohydrate (g/d)	394±197	382±151	0.93
Total fat (g/d)	121±41	126±76	0.56

Data are presented as means±SD.
TSH:Thyroid -stimulating hormone; T3: Triiodothyronine; T4: Thyroxine

Table 2: Differences of variables between the groups analyze with the t-test (unadjusted) and general linear model, univariate (adjusted for age, sex, physical activity, total calorie intake, total dietary fat, and total dietary carbohydrates)

Group Characteristics	Low-TSH Group	High-TSH Group	P value (adjusted)	P value (unadjusted)
BMI (kg/m^2)	25.29±5.15	27.82±16.24	0.03	0.01
WHR	0.92±0.08	0.90±0.07	0.09	0.07
Chol (mg/dL)	178.63±42.19	179.56±41.37	0.80	0.87
LDL-C (mg/dL)	99.62±34.16	123.35±48.97	0.05	0.03
HDL-C (mg/dL)	47.50±12.20	48.18±22.07	0.89	0.98
TG (mg/dL)	153.86±81.29	163.92±123.56	0.72	0.83
T4 (µg/dL)	9.13±2.63	8.44±2.07	0.08	0.04
T3 (ng/dL)	70.28±19.52	60.80±27.17	0.93	0.98

BMI: Body mass index; WHR: Waist-to-hip ratio; TSH: Thyroid-stimulating hormone; T3: Triiodothyronine; T4: Thyroxine; TG: Triglyceride; Chol: Cholesterol; LDL-C: Low-density lipoprotein; HDL-C: High-density lipoprotein

Table 3: Multiple linear regression analysis for the association between TSH (independent variable) and T3 and T4 (dependent variables)

		β	P value
T3	Unadjusted	−0.04	0.92
T3	Age-adjusted	−0.05	0.97
T3	Age-sex adjusted	−0.05	0.98
T4	Unadjusted	−0.30	0.01
T4	Age-adjusted	−0.33	0.01
T4	Age-sex adjusted	−0.33	0.02

T3: Triiodothyronine; T4: Thyroxin

obese individuals may be related with the effect of TSH on leptin secretion by adipocytes.[11] In this connection, several epidemiological studies have found a positive relationship between TSH and leptin levels in humans.[2] Antunes et al.[12] suggested that TSH released leptin by acting directly on the adipocytes and that elevated leptin might explain the linkage between TSH and obesity by inducing insulin resistance. It should be noted that obesity is the result of adipocyte hypertrophy and hyperplasia,[13] and insulin controls the volume and number of adipocytes.[13]

The relationship between obesity and TSH may also be involved in the correlation between TSH levels and other thyroid hormone levels. It should be borne in mind that TSH has a very short half-life (<1 h) compared to the half-lives of T4 (7 d) and T3 (1 d).[4] Serum TSH concentrations return rapidly to normal values if serum T4 and T3 remain within normal levels. In contrast, serum TSH remains elevated in the upper normal range if thyroid hormone levels are not stable enough throughout the day to restore physiological secretion rates in the pituitary gland. The elevated serum TSH levels in our apparently euthyroid individuals appeared to be inadequate to sustain tissue euthyroidism. In other words, in euthyroid individuals whose serum TSH concentrations are in the upper normal range, serum thyroid hormones might be not adequate to control metabolism throughout the day even though laboratory results show apparently normal values. Thyroid hormones use several metabolic pathways which are relevant to resting energy expenditure.[14] Therefore, euthyroid individuals with a serum TSH concentration in the upper normal range may in fact have a mild form of tissue hypothyroidism. Resting energy expenditure seems to be very sensitive to small fluctuations in TSH.

In the present study, we found that mean LDL-C concentration was higher in the high-TSH group than the low-TSH group. The activity of enzymes such as cholesterol ester transfer protein, hepatic lipase, lipoprotein lipase, HMG-CoA reductase, and the LDL receptor decreases after thyroid hormone deficiency appears.[4] All individuals in our study had no abnormalities in their thyroid hormone profile; however, mean LDL-C concentration was higher in the high-TSH group than in the low-TSH group. To understand this inconsistency, we note that we also observed a significant inverse association between serum TSH concentrations and T4 levels. This reflects the sensitivity of thyroid hormones to minor changes in the activities of the pituitary gland.[15] When a small change occurs in TSH levels, even within the normal range, it can disrupt the balance in thyroid hormone secretion, which in turn can influence LDL-C metabolism. Therefore, increased LDL-C levels would be anticipated in the participants in our study whose serum TSH concentrations, albeit elevated, were still within the upper limit of normal reference values.

As a potential limitation of our study, we note that the results of cross-sectional studies do not establish causal relationships. However, they do reveal associations among variables that can suggest potential mechanisms of action and that are useful for generating hypotheses that merit further investigation in intervention studies.

Conclusion

We conclude that individuals whose TSH levels are at the upper limit of the normal range might be at risk of hypercholesterolemia and obesity. However, we do not recommend the use of thyroid-modifying drugs to reduce weight or ameliorate LDL-C levels in these individuals.

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Conflict of Interest: None declared.

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