Thyroid-Stimulating Hormone Levels within the Reference Range Are Associated with Serum Lipid Profiles Independent of Thyroid Hormones

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Context and Objective: Dyslipidemia in thyroid dysfunction has always been attributed to changes in thyroid hormone (TH) levels. We hypothesized that TSH plays an important role in lipid metabolism independent of TH.

Design and Setting: We conducted a cross-sectional study to investigate the relationship between serum TSH levels and lipid profiles after controlling for free T_3, free T_4, total T_3, total T_4 and nonthyroid factors relevant to lipid metabolism in euthyroid Chinese subjects.

Main Outcome Measures: General linear analysis was performed to determine whether the impact of TSH on serum lipid levels is independent of the TH levels. Moreover, path analysis, an evolutionary multivariable regression technique, was conducted to test whether there is a direct and/or indirect effect between serum TSH and total cholesterol (TC) levels. Additionally, the odds ratios (95% confidence interval) for hypercholesterolemia in relation to TSH categories were calculated.

Results: A total of 3664 euthyroid subjects were finally analyzed. There was a significant linear trend toward higher log TC ($P = 0.021$) and log triglyceride ($P = 0.001$) levels with increasing serum TSH levels within the reference range, which remained significant after adjusting for factors such as TH levels, age, and smoking. Most importantly, the total effect of TSH on TC levels (total effect$_{TC, TSH} = 0.05253$) includes a direct effect (direct effect$_{TC, TSH} = 0.05979$) and an indirect effect via TH. Compared with subjects in the lower part of the reference range (TSH level, 0.27–0.61 mIU/liter), the adjusted odds ratio for hypercholesterolemia was 3.239 (95% confidence interval, 1.392–7.538; $P = 0.007$) for those in the upper category (TSH level, 4.61–5.5 mIU/liter).

Conclusions: The variation in normal TSH levels is partially related to the lipid components and hypercholesterolemia in euthyroid subjects and includes both TH-dependent and TH-independent effects. Our study suggests the importance of controlling TSH in hypothyroid subjects. (***J Clin Endocrinol Metab*** **97: 2724–2731, 2012)**

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CI, confidence interval; CV, coefficient of variation; FPG, fasting plasma glucose; FT_3, free T_3; FT_4, free T_4; GFI, goodness-of-fit index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OR, odds ratio; RMSEA, root mean square error of approximation; TC, total cholesterol; TG, triglyceride; TT_3, total T_3; TT_4, total T_4.

Recently, a large number of clinical studies have indicated that TSH is associated with lipid metabolism and a cluster of cardiovascular diseases (1–11). In these studies, the influence of TSH on serum lipids has always been attributed to thyroid hormone levels. However, we speculate that the effects of TSH on lipid panels may be thyroid hormone-independent. This possibility has not been previously addressed. Our hypothesis is derived from the following primary idea: subclinical hypothyroidism is characterized by normal free T_4 (FT_4) and free T_3 (FT_3) serum levels as well as slightly elevated serum TSH. In patients with subclinical hypothyroidism, although not consistently (12), the following conditions have been reported in a large number of studies: elevated total cholesterol (TC) (1) and low-density lipoprotein-cholesterol (LDL-C) levels (2); decreased high-density lipoprotein-cholesterol (HDL-C) levels (3); and an increased incidence of hypertriglyceridemia (4), coronary heart disease (CHD) events, and mortality from CHD (5, 6). Recent studies have extended these associations to euthyroidism (normal TSH and thyroid hormone levels). As TSH increases within the reference range, serum TC, LDL-C, and triglycerides (TG) all increase, and HDL-C decreases (1, 7, 8); thus, TSH levels are positively and linearly associated with risk factors for CHD (9, 10) and CHD mortality (11). In a more detailed analysis, Ruhla *et al.* (13) found that euthyroid subjects with a TSH in the upper normal range (2.5–4.5 mU/liter) have higher TG levels and an increased incidence of metabolic syndrome. Similarly, Boggio *et al.* (14) suggested that TSH in the upper limits of the reference range (above 2.1 μU/ml) is associated with a less favorable cardiometabolic profile and, consequently, with a higher risk of developing cardiovascular diseases. Thus, serum lipids change along with TSH levels, even when the thyroid hormone levels are normal.

In addition, evidence from experimental studies strongly supports the hypothesis that TSH directly influences lipid components. Increased TSH levels in subclinical hypothyroidism are associated with a decrease in the activity of hepatic lipase (15), which is a multifunctional protein that modulates lipoprotein metabolism and facilitates cholesterol uptake by the liver. Our previous studies found that TSH increases cholesterol levels in the hepatocytes of several origins and serum in thyroidectomized rats (16, 17). These data indicate that in addition to the classical pathway via thyroid hormone, the influence of TSH on lipid metabolism may involve direct and thyroid hormone-independent effects, thus motivating our current study.

In this study, we aimed to clarify whether the association between serum TSH levels and lipid profiles is independent of thyroid hormones in euthyroid Han Chinese subjects. Our study may help to reveal wider physiological roles of TSH and to characterize the risk factors for hypercholesterolemia more thoroughly to enable prevention and early treatment.

Subjects and Methods

Subjects

We retrospectively reviewed 4848 subjects who were self-referred for a routine health check-up at Provincial Hospital, affiliated to Shandong University (Jinan, China) from January 2004 to December 2009. All participants were asked to complete a self-reported questionnaire and provided an overnight fasting blood sample. Because a previous review identified the time of day of blood TSH sampling as a potential source of misclassification (18), the blood samples were obtained between 0900 and 1000 h. The Ethics Committee of Provincial Hospital affiliated to Shandong University approved this study and exempted the informed consent requirement (19).

Euthyroidism was defined as an FT_4 level between 11.5 and 22.7 pmol/liter and a TSH level between 0.27 and 5.5 mIU/liter. We excluded patients with abnormal thyroid function and those using thyroid medications to obtain a euthyroid population. Moreover, to avoid the influence of confounding factors, the following subjects were also excluded: pregnant women, those with chronic liver diseases or chronic renal diseases, and subjects with any diseases or taking any medicine that might affect their thyroid status and lipid metabolism (for example, thyroid hormones, antithyroid drugs, iodine, amiodarone, estrogens, androgens, steroid hormones, β-adrenoceptor blockers, antiepileptic drugs, statins, and fibrates).

Inclusion and exclusion criteria were used to select a study population of 3709 subjects. After regression analysis involving two variables by one factor, we excluded subjects for whom the absolute value of the residual SD was less than 3. Finally, 3664 euthyroid subjects from the general population were evaluated.

Anthropometric measurements and laboratory methods

Weight and height were measured in kilograms and centimeters, respectively, and body mass index (BMI) was calculated by dividing weight (kilograms) by the square of the height (meters^2). Gender, age, smoking status, and other essential information was obtained from the self-reported questionnaire.

Serum levels of TSH, FT_3, FT_4, total T_3 (TT_3), and total T_4 (TT_4) were assayed using the Advia Centaur XP (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) and its associated kits. The intraassay coefficients of variation (CV) for TSH, FT_3, FT_4, TT_3, and TT_4 were 1.9, 2.2, 3.1, 3.3, and 2.4%, respectively, and the corresponding interassay CV were 3.1, 3.7, 2.8, 3.5, and 4.8%, respectively. Serum levels of fasting plasma glucose (FPG), TC, TG, LDL-C, and HDL-C were measured using enzymatic methods with Olympus reagents and automated spectrophotometry performed on an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). The intraassay and interassay CV were always below 4% for these lipid parameters. All measurements were performed at the clinical laboratory of Provincial Hospital affiliated to Shandong University to minimize interassay variation.

The reference ranges for different parameters were as follows: FPG, 3.9–6.3 mmol/liter; TC, 3.6–6.2 mmol/liter; LDL-C, 0.5–3.36 mmol/liter; HDL-C, 0.8–1.5 mmol/liter; TG, 0.4–1.8

mmol/liter; TSH, 0.27–5.5 mIU/liter; FT_3, 3.5–6.5 pmol/liter; FT_4, 11.5–22.7; TT_3, 0.92–2.79 ng/ml; and TT_4, 58.1–140.6 ng/ml. Hypercholesterolemia was defined in accordance with the National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP/ATPIII) as TC above 6.2 mmol/liter.

Statistical analysis

Due to the significant correlation between thyroid hormones and serum lipids (20–22) and the close relationship among thyroid hormones, principal component analysis was used to overcome the multicolinearity among FT_3, FT_4, TT_3, and TT_4 and to improve the predictive ability of the model (23). Before investigating the correlation of TSH with lipid parameters, three uncorrelated principal components (factor 1, factor 2, and factor 3) were extracted to replace the original predictive variables, with little loss of information in the original variables. These principal components accounted for a large proportion (87.729%) of the variance, but they were correlated with the dependent variables as well. The equations are as follows:

$$\text{Factor1} = 0.192 \times \frac{FT_3 - 4.9869}{0.65884} + 0.392 \times \frac{FT_4 - 17.4741}{2.66429} + 0.464 \times \frac{TT_3 - 1.3610}{0.45369} + 0.468 \times \frac{TT_4 - 98.3905}{25.94527}$$

$$\text{Factor2} = 0.701 \times \frac{FT_3 - 4.9869}{0.65884} + 0.402 \times \frac{FT_4 - 17.4741}{2.66429} - 0.253 \times \frac{TT_3 - 1.3610}{0.45369} - 0.375 \times \frac{TT_4 - 98.3905}{25.94527}$$

$$\text{Factor3} = 0.552 \times \frac{FT_3 - 4.9869}{0.65884} - 0.766 \times \frac{FT_4 - 17.4741}{2.66429} + 0.641 \times \frac{TT_3 - 1.3610}{0.45369} - 0.221 \times \frac{TT_4 - 98.3905}{25.94527}$$

The subjects were divided into six groups according to serum TSH levels within the reference range, including below the 2.5 percentile, above the 97.5 percentile, and quartiles within the 2.5–97.5 percentile range (5).

All data are expressed as the mean ± SD for continuous variables and as numbers or percentages for categorical variables. The non-normally distributed data (FPG, TC, LDL-C, HDL-C, and TG) were log-transformed.

To explore the relationship of TSH with TC, LDL-C, HDL-C, and TG, we performed a general linear analysis in which TSH was a categorical variable using SPSS version 17.0 (SPSS Inc., Chicago, IL). The associations were adjusted for the potential confounding effects of gender, age, smoking status, glucose levels, and the levels of thyroid hormones (FT_3, TT_3, FT_4, and TT_4). Importantly, due to the relatively low influence of TSH on serum lipids under physical conditions, we then conducted a path analysis to validate the results of the general linear analysis. Analytical methods in clinical research often rely on multiple regression models with one main outcome variable and a set of explanatory variables treated equally. Path analysis, in contrast, is a multivariable method based on a model with several linked regression equations (24). Within this system of equations, some of the variables can be considered as outcome variables and as explanatory variables simultaneously. Thus, path analysis is able to simultaneously assess the direct and indirect effects (and thus the total effects) of each variable on other study variables and on TC levels (24). This technique allowed us to test theoretical propositions about cause and effect without manipulating the variables; therefore, it was suitable for our study. The path coefficients were estimated using maximum-likelihood methods with the CALIS procedure and SAS 9.0 software (SAS Institute Inc., Cary, NC).

We further assessed whether the association between TSH and TC levels differed according to age group (below 29 yr of age and 30–39, 40–49, 50–59, 60–69, and 70 yr of age and above) with corrected partial correlation analysis. The odds ratios (OR) and the 95% confidence interval (CI) for hypercholesterolemia in relation to TSH were calculated using an adjusted logistic regression model with TSH 0.27–0.62 mIU/liter as the reference category.

Before the evaluation, all missing data were processed using the expectation-maximization algorithm (25) available in the SPSS 17.0 software. A two-sided P value of <0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics of the study subjects, who were divided into six groups according to their TSH levels. There were significant differences in the composition of the six groups with respect to gender, smoking status, mean age, and the levels of FPG, HDL-C, FT_3, FT_4, TT_3, and TT_4. The imbalance among these multiple confounding factors validated the necessity of the adjustment.

Correlation between TSH and serum lipid levels

Table 2 shows the association between TSH levels within the reference range and the log-transformed concentrations of serum lipids. There was a consistent and significant increase in the log TC and log TG values with increasing levels of TSH within the reference range of 0.27–5.5 mIU/liter. These estimates were adjusted for gender, age, BMI, smoking status, glucose levels, and thyroid hormone levels. Table 2 shows the significant linear trend between TSH and log TC levels (linear coefficient = 0.017; $P = 0.021$) and TSH and log TG levels (linear coefficient = 0.074; $P = 0.001$). Thus, subjects with high serum TSH levels within the reference range had slightly higher adjusted TC and TG levels compared with those with low serum TSH levels within the reference range (Fig. 1). These results clearly indicate the significant positive correlation between TSH and TC levels and TSH and TG levels that are independent of thyroid hormone levels.

In addition, the general linear analysis revealed an impact of age on TC levels that was greater than the other confounding factors, which led to a subgroup analysis. Using corrected partial correlation analysis, the coefficients in subjects below 29 yr of age and 30–39, 40–49, 50–59, 60–69, and 70 yr of age and above are 0.053,

TABLE 1. Population characteristics of 3664 euthyroid subjects from the general population, including a statistical comparison of the characteristics across TSH categories within the reference range (0.27–5.5 mIU/liter)

Characteristic	TSH (mIU/liter)						P^a
	0.27–0.61	0.62–1.35	1.36–1.92	1.93–2.65	2.66–4.60	4.61–5.50	
Gender (n)							
Male	62	513	447	389	315	21	
Female	50	362	421	495	535	54	
All	112	875	868	884	850	75	0.000
Smoking status (n)							
None	77	595	630	708	720	67	
Occasional	5	62	52	47	40	2	
Often	30	218	186	129	90	6	0.000
Hypercholesterolemia							
n	12	136	140	130	138	17	
Prevalence rate (%)	10.71	15.54	16.13	14.71	16.24	26.67	0.322
BMI (kg/m^2)	25.01 (3.56)	25.28 (3.72)	25.09 (3.50)	24.85 (3.71)	24.89 (3.67)	25.13 (3.11)	0.162
Age (yr)	51.30 (13.38)	48.82 (13.22)	47.84 (14.06)	46.16 (13.93)	47.01 (13.71)	49.17 (14.09)	0.000
FPG (mmol/liter)	5.73 (1.57)	5.50 (1.43)	5.41 (1.41)	5.35 (1.30)	5.31 (1.32)	5.15 (0.90)	0.002
TC (mmol/liter)	4.98 (0.91)	5.21 (0.98)	5.24 (0.97)	5.24 (0.99)	5.25 (1.03)	5.32 (1.08)	0.131
LDL-C (mmol/liter)	2.94 (0.74)	3.04 (0.77)	3.07 (0.76)	3.05 (0.78)	3.06 (0.81)	3.01 (0.76)	0.665
HDL-C (mmol/liter)	1.43 (0.35)	1.42 (0.35)	1.44 (0.35)	1.48 (0.35)	1.48 (0.35)	1.44 (0.34)	0.000
TG (mmol/liter)	1.38 (0.88)	1.67 (1.53)	1.57 (1.29)	1.56 (1.37)	1.55 (1.42)	1.90 (2.60)	0.080
FT_3 (mmol/liter)	5.22 (0.75)	5.08 (0.72)	4.98 (0.65)	4.97 (0.60)	4.89 (0.64)	5.00 (0.65)	0.003
FT_4 (mmol/liter)	18.03 (2.87)	17.97 (2.66)	17.57 (2.66)	17.40 (2.54)	16.78 (2.63)	16.90 (2.69)	0.000
TT_3 (mmol/liter)	1.63 (0.50)	1.45 (0.48)	1.33 (0.41)	1.35 (0.50)	1.28 (0.39)	1.21 (0.37)	0.000
TT_4 (mmol/liter)	120.39 (35.42)	100.70 (29.18)	98.33 (24.04)	98.95 (24.36)	94.10 (23.91)	88.27 (12.20)	0.000

Data are expressed as mean (SD) unless otherwise specified.

[a] Statistical comparison of the characteristics of the subjects by TSH category.

0.018, 0.035, 0.032, 0.072, and 0.133, respectively. The results of the stratification by age showed that the association between TSH levels and log TC was consistent in all age groups, although this association was stronger among the older group than among the younger groups.

The direct effect of TSH on TC levels

The relationships between TSH and TC levels were further elaborated by path analysis, which is an extension of multiple regression approaches. The χ^2 test, the root mean square error of approximation (RMSEA), and the goodness-of-fit index (GFI) were used to judge the goodness-of-fit of the models. An RMSEA value less than 0.06, a GFI value greater than 0.90, and an insignificant χ^2 test ($P > 0.05$) indicate an acceptable model (26). The path model diagram with standardized estimates is displayed in Fig. 3, which shows an excellent fit between the model and the data across a number of model fit indices: χ^2 (2616.6219) = insignificant; RMSEA = 0.0589; GFI = 0.9926. All individual path model coefficients were statistically significant ($P < 0.05$). The total effects of FT_3, FT_4, gender, age, FPG, BMI, and smoking status on TC levels were found to be the direct effects of those independent variables, as displayed in Fig. 2. In addition, the total effects of TT_3 and TT_4 on TC levels were found to be solely due to indirect effects via FT_3 and FT_4, respectively. Most importantly, as predicted, the significant total effect of TSH on TC levels (total effect $_{TC,\ TSH} = 0.05253$) includes a significant direct effect on TC (direct effect $_{TC,\ TSH}$ =

TABLE 2. Mean of log-transformed serum lipids and geometric mean of serum lipids (mmol/liter) according to TSH category in 3664 euthyroid subjects

TSH (mIU/liter)	logTC	logLDL-C	logHDL-C	logTG
0.27–0.61	0.716	0.482	0.148	0.163
0.62–1.35	0.734	0.494	0.142	0.208
1.36–1.92	0.739	0.502	0.145	0.207
1.93–2.65	0.742	0.505	0.151	0.214
2.66–4.60	0.740	0.505	0.147	0.222
4.61–5.50	0.740	0.494	0.134	0.277
P	0.020	0.113	0.445	0.031
Linear coefficient	0.017	0.011	−0.006	0.074
P for linear trend	0.021	0.281	0.529	0.001

Values shown were adjusted for gender, age, BMI, smoking status, FPG, and thyroid hormones (FT_3, FT_4, TT_3, and TT_4).

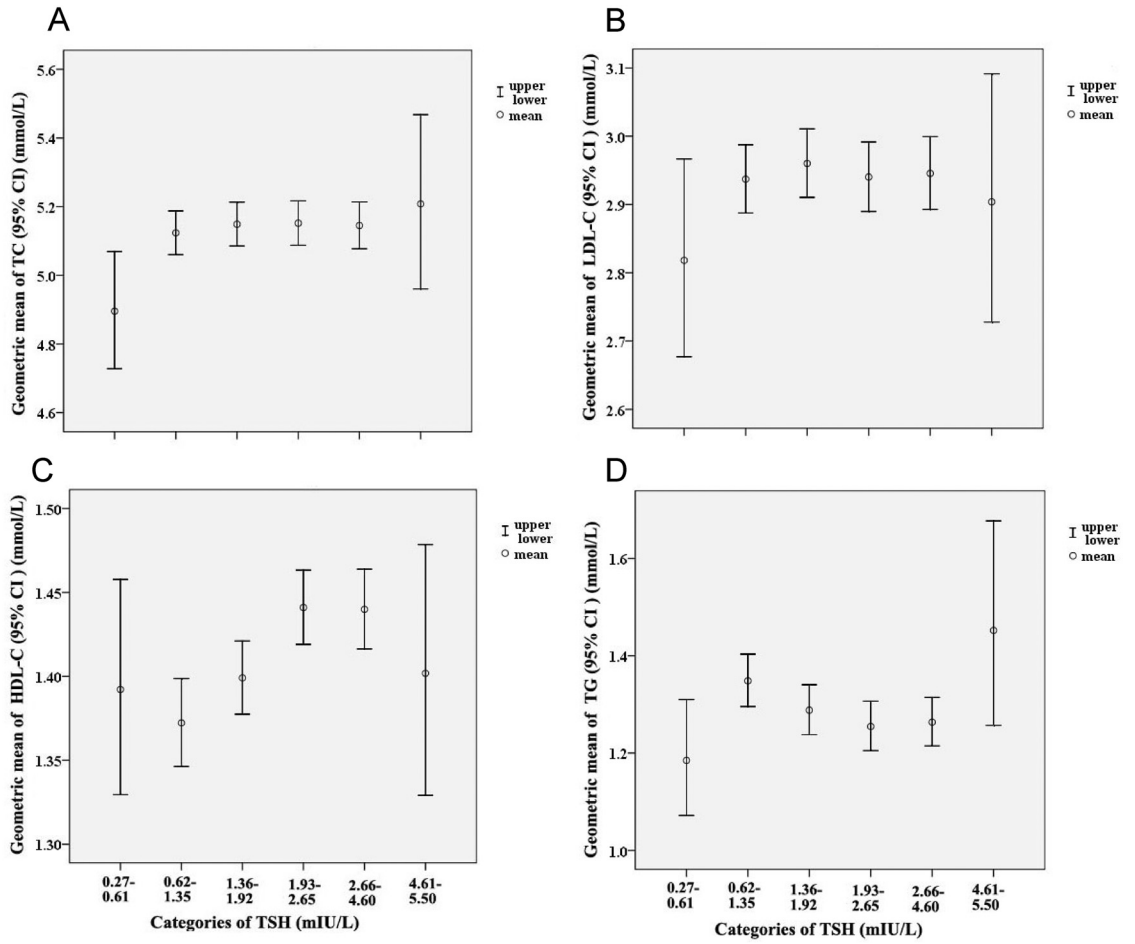

FIG. 1. Correlation of TSH with TC, LDL-C, HDL-C, and TG.

0.05979) and an indirect effect via thyroid hormones as intermediary variables. This finding is in close agreement with the data obtained from the general linear analysis.

The relationship between TSH and the prevalence of hypercholesterolemia

Multivariate logistic regression analysis revealed that increased TSH levels were associated with an increased risk of hypercholesterolemia. The OR for hypercholesterolemia adjusted by TSH categories were calculated as described in *Subjects and Methods*. Compared with the low normal TSH group (TSH = 0.27–0.62 mIU/liter), the adjusted OR (95% CI) for hypercholesterolemia were found to be 1.824 (0.951–3.496), 2.037 (1.064–3.901), 1.925 (1.003–3.695), 2.105 (1.097–4.040), and 3.239 (1.392–7.538) in the five increasingly higher normal TSH groups. Overall, the prevalence of hypercholesterolemia was 15.64% in this study population. Subjects with high normal TSH levels (TSH = 4.61–5.5 mIU/liter) displayed a significantly higher prevalence of hypercholesterolemia than those with low normal TSH levels at a rate of 26.67 *vs.* 10.71% ($P = 0.006$). The prevalence of hypercholesterolemia increased gradually with increasing TSH category (Fig. 3).

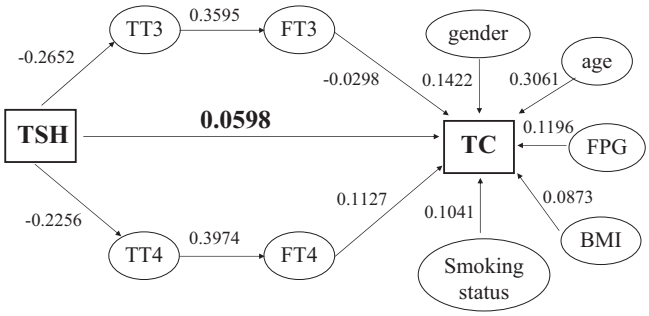

FIG. 2. Effects of TSH, thyroid hormones, gender, age, FPG, BMI and smoking status on TC levels.

Discussion

In this study, we explored the relationship between serum lipid levels and TSH in 3664 euthyroid Han Chinese subjects. We found positive correlations between TSH and TC levels and TSH and TG levels. The association between TSH and TC became stronger with increased age, and the prevalence of hypercholesterolemia increased as TSH

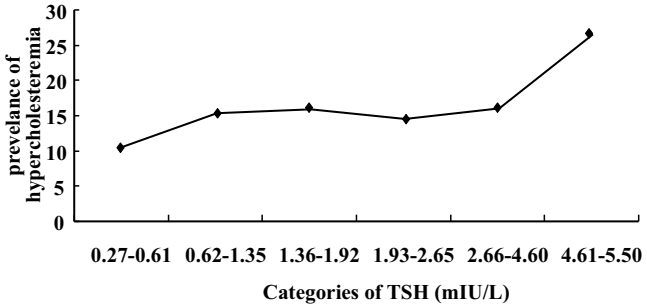

FIG. 3. Correlation of TSH with prevalence of hypercholesterolemia.

showed a gradual increase. Moreover, these relationships remained significant after further adjusting for thyroid hormone levels. Our results showed that even within its reference range, TSH was positively correlated with lipid components independent of FT_3, TT_3, FT_4, and TT_4. These associations indicate that subtle variations in TSH alone may contribute to increased lipid levels and the prevalence of hypercholesterolemia even in clinically euthyroid individuals. To the best of our knowledge, this study is the first to address the independent contribution of TSH to lipid parameters and hypercholesterolemia.

Several studies have searched for an association between TSH and serum lipids in euthyroid subjects, and they have obtained results similar to ours. The HUNT study performed in Norway showed a linear and significant increase in serum TC, LDL-C, and TG levels with increasing TSH within the reference range (7). Similarly, positive correlations were found between TSH and lipid profiles in euthyroid Chinese (3), Korean (27), Latin American (1), and Spanish (8) populations. However, in these studies, the estimates were adjusted for only traditional serum lipid confounding factors, such as age, gender, BMI, and smoking status. It is known that serum lipid levels are always higher in overtly hypothyroid subjects than in healthy controls (28). Subclinical hypothyroidism is associated with increased levels of TC and LDL-C (2), even accompanied by increased TG (4) and decreased HDL-C levels (3) in some, of course not all studies (12). More recent studies have shown significant correlations in euthyroid subjects between FT_3 and TG and HDL-C (20); TT_3 and TC, LDL-C and TG (21); and FT_4 and TC, LDL-C, HDL-C and TG (1, 22, 27). Consistent with these results, our study found significant negative correlations between thyroid hormone levels and both TC and LDL-C levels through multiple linear regression analysis (data not shown). These results point toward the same conclusion: that lipid levels in the serum are obviously affected by the blood thyroid hormone levels, even when they are within the normal range. Thus, except for gender, age, BMI, and other classical confounding variables, thyroid hormones may be an important contributor when considering the relationship between TSH and lipid parameters. It is essential to evaluate the thyroid hormone level-independent effects of TSH on lipid profiles. If these important variables determining lipid levels are not corrected for, the association between TSH and the lipid profile is questionable. In the present study, we were able to identify a significant correlation between TSH and lipid parameters even when we adjusted for the effects of thyroid hormones. Our results clearly indicate an independent relationship between TSH and lipid levels.

In this large population-based study, we found that after correcting for the effects of thyroid hormones and other confounding factors, serum TC and TG levels increased consistently with increasing TSH. These associations displayed remarkably linear trends. Furthermore, we calculated how much TC and TG would increase with a 1-mIU/liter rise in TSH (data not shown). Importantly, to overcome the defects of the general linear analysis, we performed path analysis, the straightforward extension of multiple linear regression. Path analysis is a powerful analytical tool that permits the simultaneous estimation of both direct and indirect influences on outcomes. This tool allows the explanatory power of competing models to be compared and reveals mediational effects by examining the changes in the strength of the variable relationships across models. With this powerful tool, we found that the action of TSH on TC levels consists of both direct effects and indirect effects via thyroid hormones. Our results clearly indicate that in the association between TSH and lipids, thyroid hormones are important mediators, and TSH might have an independent role as well.

The plausible explanations for the direct effects of TSH on lipids have not been fully elucidated. Our previous *in vivo* and *in vitro* studies demonstrated that liver cells express TSH receptor (16) and that TSH itself up-regulates the expression of hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (a rate-limiting enzyme in cholesterol synthesis) by acting on the TSH receptor in hepatocyte membranes (17). TSH thereby promotes cholesterol synthesis in the liver and elevates cholesterol levels in hepatocytes of several origins and in serum of thyroidectomized rats. More recent study in our lab indicated that the TSH receptor plays an important role in adipocyte differentiation and adipogenesis, resulting in obesity in mice and increasing BMI in humans (29). Other possible explanations for this thyroid hormone-independent association may involve the effects of TSH on adipocyte growth and development (30); the stimulation of lipolysis by TSH in cultured adipocytes and the elevation of serum free fatty acid levels *in vivo* (31); the effects on leptin (32); and the intermediate roles of visceral obesity (33), insulin resistance (34–36), hypoadiponectinemia (37), age, *etc.* Fur-

thermore, certain signaling pathways such as MAPK and the downstream molecules, which are activated by increasing TSH (38) and involved in cholesterol biosynthesis (39), may also be relevant. The detailed mechanism involved requires further investigation. However, these results support the existence of a physiological mechanism through which TSH directly regulates cholesterol metabolism. Taken together with previous results, this study may shed new light on the physiological role of TSH.

The strengths of our study include the relatively large sample size for the detection of the small effects of TSH within the normal range on serum lipids; the consideration of multicolinearity among FT_3, FT_4, TT_3, and TT_4; the utilization of uncorrelated principal components; and the correction for thyroid hormone levels for a rational evaluation of the effects of TSH on serum lipids. However, our study also has potential limitations. First, using a cross-sectional design, cause-and-effect relationships cannot be fully established, although our previous experimental studies may provide a sufficient explanation for this phenomenon. Second, we observed only general and age-related correlations between TSH and serum lipids. We cannot exclude the possibility that a stronger association may exist with different types of stratification, such as gender or BMI. To have a sufficient number of subjects in each classification, we had to select age, the factor most clearly affecting serum in our study, to be the index of categorization. Third, a recent study indicated that the control of TSH secretion by free thyroid hormones may be impaired in obesity (33). Of all the participants in our study, 19.2% were obese (BMI $\geq$ 28), and the mean (SD) BMI was 25.04 (3.62). Moreover, Hoermann *et al.* (40) revealed that the relationship between TSH and FT_4 is complex, but not a simple log-linear model. Thus, in the path analysis, this potential negative regulation of the influence of thyroid hormones on TSH was not considered.

In summary, we found thyroid hormone-independent positive relationships between the serum TSH levels and the levels of TC and TG and the incidence of hypercholesterolemia in euthyroid Han Chinese subjects. Moreover, the association between TSH and TC levels was found to be stronger with increasing age. Our study documents a weak (because the TSH level was under the normal state) but direct effect of the normal range of TSH levels on serum lipids that is independent of the thyroid hormone levels. From a clinical perspective, in hypothyroidism, it may be therapeutically important to keep TSH at a low normal level to maximize the control of cholesterol production. Further prospective study is required to assess the effect of maintaining TSH at a low level on lipid abnormalities.

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