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Does TSH Directly Affect Serum Lipid Levels in Euthyroid Patients Whose TSH Levels Are in the Normal Range? A Review of Two Retrospective Studies Advocated in Support of this Concept

SUMMARY

Background

TSH regulates serum thyroid hormone levels, which in turn affect lipid synthesis, uptake, release, and degradation. However, can TSH affect lipid metabolism directly, independently of its effect on thyroid hormone levels? Clinically, one does sometimes see a patient with hypercholesterolemia whose TSH level is high, yet whose thyroid hormone levels are within the normal range, but many factors other than TSH could be involved. The TSH receptor can be detected in many cell types besides thyrocytes, and TSH does affect growth and functions in these cells in vitro. Several recent papers from Shandong University have been interpreted as showing that TSH directly affects serum lipid levels, even in patients with normal T_3 and T_4 levels. This group previously reported thought-provoking studies on rats, which showed that thyroidectomy raises the level of hepatic cholesterol and of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis. By giving L-T_4 to those rats, the serum cholesterol level was normalized, and the hepatic HMGCR level fell. However, if they also gave the rats TSH, hepatic HMGCR rose, indicating that TSH itself affects the expression of this protein in the liver (1). I review two recent retrospective clinical studies from the Shandong group that contend that TSH levels directly influence lipid levels in euthyroid patients.

STUDY 1

Wanjia X, Chenggang W, Aihong W, Xiaomei Y, Jiajun Z, Chunxiao Y, Jin X, Yinglong H, Ling G. A high normal TSH level is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease. Lipids Health Dis 2012;11:44.

Methods

Based on abnormalities noted on electrocardiograms (EKGs) and then confirmed by angiography, about 1000 asymptomatic patients (45 to 88 years old) were newly diagnosed to have coronary heart disease (CHD) between 2004 and 2010 in the Qianfoshan or Shandong Provincial Hospitals. Only patients who were clinically stable were candidates for study. Any patients taking medications that might affect thyroid or lipid metabolism; who had ever smoked; who were missing thyroid tests; who had renal, hepatic, or neurologic disease; or who had evidence of euthyroid sick syndrome (with a low reverse T_3) were excluded. This left 521 potential subjects, of whom 406 were used for the study. Thyroid-function tests were measured using an electrochemiluminescence detection assay (Roche Elecsys 2010). The laboratory reference range for TSH was given as 0.27 to 4.2 mIU/L, however the authors defined patients as euthyroid if their T_4 and T_3 levels were normal and their TSH was between 0.3 and 4.8 mIU/L. The patients were segregated into four (unequal) groups based on their TSH levels: 0.3 to 0.99 mU/L (79 patients); 1.0 to 1.89 (135), 1.9 to 2.49 (78), and 2.5 to 4.8 (114). Multiple linear regression and logistic-regression analyses were used to establish whether TSH levels within the euthyroid range were associated with total cholesterol, non–high density lipoprotein (HDL) cholesterol, and triglycerides.

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Results

The FT_3 and FT_4 levels (all within the normal range) did not correlate significantly with log-transformed lipid levels in these asymptomatic patients with CHD, whereas the patients' TSH levels did correlate significantly with log-transformed total cholesterol, non–HDL cholesterol and triglyceride levels. The levels of FT_4, FT_3, uric acid, fasting blood glucose, diastolic or systolic blood pressure, and antibody positivity did not differ among the four TSH groups. Analysis of variance indicated that after adjusting for these potential confounding factors, each of the three groups with the higher TSH levels had significantly higher log-transformed cholesterol, triglyceride, and non–HDL cholesterol levels than those in the group with the lowest TSH levels. (One might note that the major rise occurred between the first and second TSH groups: the levels in the third and fourth groups were not much higher than in the second group. This was also true for the prevalence of cholesterol or triglyceride levels above 200 mg/dl).

Conclusions

After adjusting for sex, age, history of diabetes, fasting blood glucose, hypertension, alcohol intake, and uric acid (but not body-mass index), a logistic-regression analysis indicated that the TSH level was an independent factor predictive of increased lipid abnormality in these euthyroid nonsmokers with asymptomatic CHD. In some parts of the world, patients with a TSH level at the high end of the "normal range" cited in this paper would probably be categorized as having mild subclinical hypothyroidism; but even if this was the true diagnosis, the results do suggest that TSH levels are correlated with total cholesterol and triglyceride levels in a collection of euthyroid and almost-euthyroid patients with CHD. Obviously, lipid levels are only one of many actors, since even the patients in the group with the lowest TSH and lipid levels did have CHD, although they didn't have an "atherogenic lipid profile."

STUDY 2

Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, Zhang B, Guan Q, Xu J, Zhang J, Zhang D, Lin H, Yu C, Zhao J. Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. J Clin Endocrinol Metab 2012;97:2724-31. Epub June 22, 2012.

Methods

From 2004 to 2009, a total of 4848 patients came to the Shandong Provincial hospital for a routine health checkup. Thyroid-function tests were performed on blood obtained between 9 and 10 a.m., using an Advia Centaur Xp system (which others have found to give TSH results that closely agree with the results obtained with the Elecsys 2010 system used in the previous article). Patients were excluded if their TSH was outside the reference range (given as 0.27 to 5.5 mU/L); if FT_4, FT_3, total T_4, or total T_3 was outside its reference range; or if they were pregnant, had chronic liver or renal disease, or were taking medicine that might affect thyroid or lipid status. A total of 3709 subjects met these criteria; missing data were projected using expectation-maximization software, but the numbers for missing data were not provided. To offset the well-known correlations among FT_4, FT_3, total T_4 and total T_3, three "uncorrelated principal components" were derived from these four hormone determinations and accounted for almost 88% of variance, but they still correlated with the dependent variables. After the data were subjected to regression analysis involving two variables by one factor, 45 patients were excluded because the absolute value of their residual standard deviation was less than 3, leaving 3664 subjects in

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the study. The authors grouped the patients into six categories according to their TSH levels: in 3% of patients, the TSH was between 0.27 and 0.61 mU/L, in the next 24%, it was between 0.62 and 1.35, in the next 24% between 1.36 and 1.92, in the next 24% between 1.93 and 2.65, in the next 23% between 2.66 and 4.60, and in the last 2% between 4.61 and 5.50. Associations of TSH as a categorical variable with total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were assessed using general linear analysis, after correcting for sex, age, body-mass index (BMI), smoking status, glucose levels, and thyroid-hormone levels. To validate results obtained with general linear analysis, a multivariable path analysis was also performed, which provided an assessment of both direct and indirect effects of each variable on total cholesterol levels.

Results

In the 95% of subjects comprising the four groups with TSH levels between 0.62 and 4.60 mU/L, the mean prevalence of hypercholesterolemia was about 15%. In the 2% with the highest TSH (4.6 to 5.5 mU/L), the prevalence of hypercholesterolemia was 26.7%, whereas in the 3% with the lowest TSH (0.27 to 0.61 mU/L), the prevalence was 10.7%. After adjusting for age, sex, BMI, smoking status, glucose levels, and thyroid-hormone levels, there was a slight but significant linear relation between the TSH levels and the log-transformed cholesterol ($P = 0.021$) and also the log-transformed triglyceride levels ($P<0.001$), independent of thyroid hormone levels. Multivariable path analysis to assess both direct and indirect effects of each variable indicated that FT_3, FT_4, sex, age, glucose level, BMI, and smoking had direct effects on total cholesterol levels. Total T_4 and T_3 had only indirect effects on the total cholesterol level (via FT_4 and FT_3). TSH had both a small direct effect on the total cholesterol level, as well as indirect components mediated via FT_3 and FT_4.

Conclusions

The complex multivariable pathway analysis indicates that a part of the effect of TSH on the cholesterol level in euthyroid patients is direct, which would support the contention that TSH can play an independent role in lipid metabolism, even when thyroid hormone levels are within the normal range.

ANALYSIS AND COMMENTARY

In the first clinical study, it is not clear why obesity was not included as a confounding variable, since it does appear to be associated with the TSH level in normal euthyroid individuals (2). In both studies, the ranges for normal TSH seem a bit wide, and thus the data obtained from patients whose TSH levels were near the outer limits could have influenced the results of the statistical analyses.

Several of the pathways involved in regulating the metabolism of intracellular and circulating lipids have been found to respond to TSH. Various cell types, including adipocytes, fibroblasts, monocytes, and vascular cells are also known to be TSH-responsive, so TSH could also be acting on lipid metabolism in many tissues in addition to the liver. One reason for studying hepatic HMGCR is that its gene's promoter does not contain a canonical thyroid-hormone response element, and the level of HMGCR messenger RNA in the liver takes 48 hours to respond to T_3. The HMGCR promoter does contain other response elements, including one for the cAMP response element (CRE) binding protein. The authors showed that a nuclear extract from hepatocytes treated with TSH used in an electrophoretic mobility assay caused

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