Gender and Age Impact on the Association Between Thyroid-Stimulating Hormone and Serum Lipids

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Abstract: The relationship between thyroid-stimulating hormone (TSH) and hyperlipidemia is still a topic of debate. We aimed to explore the impact of gender and age on the association between serum TSH and lipid profile in a large cohort of Chinese.

This cross-sectional study enrolled 13,915 participants (8565 male, 5350 female), who self-reported as healthy without any known previous diseases. Clinical data including anthropometric measurements, thyroid function, and other serum parameters were collected.

The associations between TSH and hyperlipidemia of males and females were analyzed separately after dividing TSH and age into subgroups. Odds ratio for hyperlipidemia was calculated by binary logistic regression models.

Young males had significantly higher prevalence of hypercholesterolemia, hypertriglycerideremia, and high serum low-density lipoprotein-cholesterol than females, yet after menopause, females had higher risks of developing hypertriglyceridemia than the reference TSH risks ($P < 0.05$), yet, men did not demonstrate such significances.

Our results showed thyroid hormone independent positive associations between serum TSH and lipids, which were substantially influenced by gender and age. Males demonstrated more protective effects of low TSH against hyperlipidemia, while females showed more detrimental effects of high TSH on hyperlipidemia.

INTRODUCTION

The world faces a burden of thyroid disease that has reached epidemic proportions. It is estimated that around 200 million individuals worldwide have various kinds of thyroid dysfunctions. The association between thyroid function and serum lipid status has become a popular area of research in recent years. It is well recognized that thyroid function can influence the synthesis, mobilization, and degradation of lipids. Recent studies have indicated that thyroid-stimulating hormone (TSH) is associated with adverse changes of lipid dysfunctions. The association between thyroid function and serum lipids, which were substantially influenced by gender and age.

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Gender and age can influence the relationship between thyroid function and lipid profiles. Yet, on the one hand, this aspect has not been thoroughly investigated; on the other, the available literature is still controversial. For example, by using stepwise regression analysis, Tognini et al revealed that age was the most crucial factor influencing serum cholesterol levels, and TSH was the second important factor following age. Furthermore, this research also found that both age and TSH could influence either TC or low-density lipoprotein-cholesterol (LDL) significantly in females. Yet, in males, TSH only strongly affected TC. Nevertheless, in males, both TSH and body mass index (BMI) greatly affected triglycerides (TG) concentrations independently of age, while in women, TSH did not show any obvious influence on TG. The Tromso study, which recruited 5143 participants, displayed a significantly higher risks of developing hypertriglyceridemia than the reference TSH risks ($P < 0.05$), yet, men did not demonstrate such significances.

Our results showed thyroid hormone independent positive associations between serum TSH and lipids, which were substantially influenced by gender and age. Males demonstrated more protective effects of low TSH against hyperlipidemia, while females showed more detrimental effects of high TSH on hyperlipidemia.

Abbreviations: BMI = body mass index, Cr = creatinine, FT3 = free triiodothyronine, FT4 = free thyroxine, LDL = low-density lipoprotein-cholesterol, TC = total cholesterol, TG = triglycerides, TSH = thyroid-stimulating hormone.
positive correlation between TC and TSH, as well as LDL and TSH, in both sex. However, in women, if adjustment was made by age and BMI, these relationships became not significant. Therefore, these discordant results warrant a large-scale investigation with the emphasis on both age and gender.

The aim of the current study was to evaluate the impact of gender and age on the association between TSH and lipid profile and the burden of dyslipidemia in a large cross-sectional Han Chinese population sample.

METHODS

Design

This cross-sectional study was conducted in Tianjin Medical University General Hospital in China, under collaboration from the departments of Health Management, Endocrinology & Metabolism, and Nuclear Medicine. During the period from September 2011 to April 2014, a total of 13,915 eligible subjects (8565 male, 5350 female) participated in this mainly community-based health check program. This work was a part of our continuous project for the general public health of Tianjin Municipality, and the protocol was developed and executed previously by our group.19–21 All participants were asked to complete a self-reported questionnaire and provide an overnight fasting blood sample. All participants were self-reported as healthy without any known previous diseases. In order to avoid the influence of confounding factors, the following criteria were used for exclusion: subjects with thyroid, hepatic, renal, gastro-intestinal diseases, or oncology; subjects with any diseases or taking any medicine that might affect their thyroid status or lipid metabolism (eg, antithyroid drugs, thyroid hormone, amiodarone, iodine, estrogen, androgen, statins, steroid hormones, etc.); and pregnancy. Written consents were obtained, and the institutional review board and ethic committee of Tianjin Medical University General Hospital approved this study.

Measurements

Anthropometric measurements and fasting blood tests of the participants were performed during their visits to our institution. Body height and body weight were measured in centimeters and kilograms. BMI was calculated by dividing body weight (kg) by the square of body height (m).2 Fasting blood samples were obtained between 7 AM and 10 AM. TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were analyzed on a fully automated ADVIA Centaur analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) by chemiluminescent reaction principle. TC, TG, LDL, HDL, alanine aminotransferase, total bilirubin, blood urea nitrogen, uric acid, creatinine (Cr), and fasting glucose were determined enzymatically by an auto-analyzer (Hitachi Model 7600 analyzer, Hitachi, Tokyo, Japan).

Definition

The diagnostic criteria for dyslipidemia were in accordance with the National Cholesterol Education Program Adult Treatment Panel III criteria as follows: TC ≥ 5.18 mmol/L, TG ≥ 1.70 mmol/L, LDL ≥ 3.37 mmol/L, and HDL < 0.84 mmol/L.22 Participants were divided into subgroup 1 to 8 according to TSH levels: TSH < 0.3 μIU/mL, 0.3–1.0 μIU/mL < TSH < 1.0 μIU/mL, 1.0–2.0 μIU/mL ≤ TSH < 2.0 μIU/mL, 2.0–3.0 μIU/mL < TSH < 3.0 μIU/mL, 3.0–4.0 μIU/mL < TSH < 4.0 μIU/mL, 4.0–5.0 μIU/mL ≤ TSH < 5.0 μIU/mL, 5.0–10.0 μIU/mL ≤ TSH < 10.0 μIU/mL, and TSH ≥ 10.0 μIU/mL. Participants were also divided into subgroup 1 to 7 based on ages: age < 25 years, 25 years ≤ age < 35 years, 35 years ≤ age < 45 years, 45 years ≤ age < 55 years, 55 years ≤ age < 65 years, 65 years ≤ age < 75 years, and age ≥ 75 years.

Statistical Analysis

Statistics were done as our prior protocols.19–21 All data were presented as mean ± standard deviation. Differences of

### TABLE 1. Population Characteristics Based on Different Genders

|                | Total        | Male         | Female       | T Value/P Value |
|----------------|--------------|--------------|--------------|----------------|
| Case number    | 13,915       | 8565         | 5350         |                |
| Age, years     | 48.65 ± 10.80 | 48.49 ± 10.49 | 48.92 ± 11.29 | −2.28/0.023    |
| BMI, kg/m²     | 25.54 ± 3.47  | 26.29 ± 3.24  | 24.34 ± 3.49  | 33.43/1.028E-235 |
| TSH, μIU/mL    | 2.51 ± 3.58   | 2.17 ± 2.92   | 3.06 ± 4.38   | −14.25/9.216E-46 |
| FT3, pmol/L    | 5.24 ± 0.86   | 5.43 ± 0.83   | 4.93 ± 0.81   | 35.23/2.133E-257 |
| FT4, pmol/L    | 16.27 ± 2.76  | 16.77 ± 2.58  | 15.48 ± 2.84  | 27.50/4.308E-162 |
| TC, mmol/L     | 5.15 ± 0.99   | 5.13 ± 0.97   | 5.18 ± 1.03   | −2.86/0.004    |
| TG, mmol/L     | 1.74 ± 1.34   | 1.98 ± 1.47   | 1.36 ± 0.99   | 27.44/1.890E-161 |
| LDL, mmol/L    | 3.09 ± 0.88   | 3.11 ± 0.86   | 3.06 ± 0.92   | 2.71/0.007    |
| HDL, mmol/L    | 1.34 ± 0.36   | 1.23 ± 0.31   | 1.53 ± 0.37   | −51.78/0.000 |
| ALT, U/L       | 23.67 ± 20.77 | 27.44 ± 23.64 | 17.64 ± 12.96 | 27.82/8.674E-166 |
| TBIL, μmol/L   | 11.99 ± 5.41  | 13.16 ± 5.71  | 10.10 ± 4.27  | 33.81/6.189E-241 |
| BUN, mmol/L    | 2.72 ± 1.34   | 4.95 ± 1.31   | 4.35 ± 1.31   | 26.03/7.063E-146 |
| UA, μmol/L     | 329.97 ± 87.41 | 370.61 ± 76.66 | 264.90 ± 59.87 | 85.83/0.000 |
| Cr, μmol/L     | 73.46 ± 15.00 | 81.04 ± 12.02 | 61.31 ± 10.69 | 98.23/0.000 |
| FG, mmol/L     | 5.43 ± 1.21   | 5.56 ± 1.30   | 5.21 ± 1.01   | 16.90/1.915E-63 |

Data presented as mean ± standard deviation, and analyzed by independent sample’s t-test. ALT = alanine aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, Cr = creatinine, FG = fasting glucose, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL = high-density lipoprotein-cholesterol, LDL = low-density lipoprotein-cholesterol, TBIL = total bilirubin, TC = total cholesterol, TG = triglycerides, TSH = thyroid stimulation hormone, UA = uric acid.
indices between groups were analyzed by independent sample’s t-test or one-way analysis of variance. For multiple comparisons among different subgroups, the least significant difference test was applied. In order to compare differences of intergroup prevalence, Chi-square test was performed. Pearson bivariate correlation was conducted between TSH and other variables. After data stratification according to different thyroid functional states, binary logistic regression models were executed to calculate odds ratio for hyperlipidemia with 95% confidence interval (CI). Statistical Package for Social Sciences (SPSS version 17.0, Chicago, IL) was used for statistics. And a P value of <0.05 was defined as significance.

RESULTS

The Characteristics of the Participants in Different Gender

The characteristics of the participants were summarized (Table 1). There were significant differences in all parameters with respect to opposite gender. Males were younger than females, yet BMI in males was higher than in females. TSH was lower in males than in females, while FT3 and FT4 were higher in males than in females. Serum lipids, hepatic, and renal functions were also different between genders.

Age cast differences among the participants (Fig. 1). For males, TC, TG, and LDL showed the tendency of increase from...
the youngest to the age range of 65 to 75, and then decreased in the eldest participants. Inversely, HDL demonstrated a decrease trend. For females, TC, TG, and LDL showed constant trend of increase from the youngest till the eldest, and HDL displayed constant decrease trend.

The differences of serum lipids based on TSH levels were demonstrated in Figure 2. TC in both sex, TG in female, as well as LDL in male, showed consistent increase from the lowest TSH level to the highest TSH level. The differences of HDL levels among the TSH subgroups were relatively subtler in both genders.

Prevalence of Hyperlipidemia in Different Gender

The prevalence of hypercholesterolemia and high serum LDL showed the same increasing tendency in males from the
youngest to the age range of 65 to 75, and then decreased in the eldest participants. Yet, in females, this prevalence tendency increased from the youngest to the eldest (Figure 3). Young males (younger than 45) had significantly higher prevalence than females. However, after menopause (older than 55), females had significantly higher prevalence than males. This crisscross pattern was also discovered in hypertriglyceridemia, yet the converging point was around 65 to 75 years of age. For low-serum HDL, males always showed higher prevalence than females indiscriminate of age.

Prevalence of hyperlipidemia rose when TSH concentration rose, yet no crisscross pattern was found (Figure 4). The prevalence of hypercholesterolemia was higher in females if TSH was less than 0.3 mIU/mL, or between 4.0 and 10.0 mIU/mL, otherwise no significant differences existed. The prevalence of high serum LDL was higher in females if TSH was between 5.0 and 10.0 mIU/mL, this prevalence was higher in males if TSH was between 1.0 and 4.0 mIU/mL. For the prevalence of hypertriglyceridemia and low-serum HDL, males always showed higher prevalence than females.

Incidence of Thyroid Dysfunction in Different Gender

Females had significantly higher thyroid dysfunction incidence than males (Table 2), hypothyroidism and hyperthyroidism were defined as TSH > 5.0 mIU/mL and TSH < 0.3 mIU/mL, respectively. Most age subgroups demonstrated the same pattern of differences in opposite sex, except for the youngest and the eldest. There existed a significant increasing tendency of hypothyroidism incidence with aging (except for the youngest) for both gender (Chi value for male, 86.911, \( P = 1.326 \times 10^{-16} \); Chi value for female 58.561; \( P = 8.818 \times 10^{-11} \)).

Correlations Between TSH and Serum Lipid Levels in Different Gender

Significant negative relationships were demonstrated for FT3 and FT4 for both genders. In males, positive relationships were demonstrated for age, TC, LDL, and Cr. In females, positive relationships were demonstrated for age, BMI, TC, TG, LDL, alanine aminotransferase, blood urea nitrogen, uric acid, and Cr (Table 3).

Risks of Developing Hyperlipidemia in Different TSH Concentrations in Opposite Gender

Binary logistic regression models were utilized on different thyroid functional state. Thyroid functional states were designated as the categorical variables, and the mid-normal TSH group of \( "2.0 \text{ mIU/mL} \leq \text{TSH} < 3.0 \text{ mIU/mL}" \) was set as the reference. Model 1 had FT3 and FT4 as covariates. Model 2 had all parameters as covariates (Tables 4 and 5). In males, we demonstrated significantly reduced risks of hyperlipidemia while TSH decreased from the reference level, indicating protective effects of low TSH against hyperlipidemia. For instance, in Model 2, the risks of hypercholesterolemia, hypertriglyceridemia, and high serum level of LDL in TSH subgroup 1 were only 0.198 (\( P < 0.01 \)), 0.425 (\( P < 0.05 \)), and 0.219
In females, the reduced risks of hyperlipidemia along with the decreasing TSH level did not reach such significance as in males. For example, in Model 2, the risks of hypercholesterolemia, hypertriglyceridemia, and high serum level of LDL were just 0.553 ($P < 0.05$), 0.642 ($P > 0.05$), and 0.635 ($P > 0.05$) of the reference risks. On the other hand, our results displayed that if TSH level rose, the risks of hyperlipidemia generally increased, especially in the subgroup of TSH < 10.0 mIU/mL, indicating detrimental effects of high TSH levels on dyslipidemia.

![FIGURE 4. Prevalence of dyslipidemia in different TSH subgroups. Definition of dyslipidemia: hypercholesterolemia (HyperTC), TC ≥ 5.18 mmol/L; hypertriglyceridemia (HyperTG), TG ≥ 1.70 mmol/L; high serum level of low-density lipoprotein-cholesterol (HyperLDL), LDL ≥ 3.37 mmol/L; low serum level of high-density lipoprotein-cholesterol (LowHDL), HDL < 1.04 mmol/L. TSH subgroups 1 to 8 referred to the followings: TSH < 0.3 mIU/mL, 0.3 mIU/mL ≤ TSH < 1.0 mIU/mL, 1.0 mIU/mL ≤ TSH < 2.0 mIU/mL, 2.0 μIU/mL ≤ TSH < 3.0 μIU/mL, 3.0 μIU/mL ≤ TSH < 4.0 μIU/mL, 4.0 μIU/mL ≤ TSH < 5.0 μIU/mL, 5.0 μIU/mL ≤ TSH < 10.0 μIU/mL, TSH ≥ 10.0 μIU/mL. HDL = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein-cholesterol, TC = total cholesterol, TG = triglycerides, TSH = thyroid stimulating hormone. #Difference of prevalence between genders was significant at 0.05; * difference of prevalence between gender was significant at 0.01.](image)

### TABLE 2. Incidence of Hypothyroidism and Hyperthyroidism on Different Genders

| Age (and Case Number Count) in Different Age Subgroups, years | Male | Female |
|---------------------------------------------------------------|------|--------|
| 25 ≤ A < 35                                                   |      |        |
| Euthyroidism                                                 | 94.87% (37) | 89.47% (34) |
| Hypothyroidism                                               | 5.13% (2) | 7.89% (3) |
| Hyperthyroidism                                               | 0.00% (0) | 2.63% (1) |
| 35 ≤ A < 45                                                   |      |        |
| Euthyroidism                                                 | 97.23% (2567) | 91.62% (414) |
| Hypothyroidism                                               | 2.31% (61) | 7.28% (113) |
| Hyperthyroidism                                               | 0.45% (12) | 0.87% (24) |
| 45 ≤ A < 55                                                   |      |        |
| Euthyroidism                                                 | 97.19% (2835) | 87.14% (1497) |
| Hypothyroidism                                               | 2.26% (66) | 11.12% (191) |
| Hyperthyroidism                                               | 0.55% (16) | 1.75% (30) |
| 55 ≤ A < 65                                                   |      |        |
| Euthyroidism                                                 | 95.49% (1692) | 84.17% (925) |
| Hypothyroidism                                               | 4.51% (66) | 14.0% (155) |
| Hyperthyroidism                                               | 0.79% (14) | 1.73% (19) |
| 65 ≤ A < 75                                                   |      |        |
| Euthyroidism                                                 | 91.21% (384) | 82.84% (333) |
| Hypothyroidism                                               | 8.79% (36) | 15.67% (63) |
| Hyperthyroidism                                               | 0.24% (1) | 1.49% (6) |
| A ≥ 75                                                        |      |        |
| Euthyroidism                                                 | 96.42% (9258) | 88.02% (4709) |
| Hypothyroidism                                               | 3.58% (129) | 11.98% (152) |
| Hyperthyroidism                                               | 0.56% (48) | 3.00% (3) |

Chi-square value/P value

- Hypothyroidism: 0.274/0.600
- Hyperthyroidism: 0.274/0.600

Incidence of hypothyroidism and/or hyperthyroidism between males and females compared by Chi-square method.
- Hypothyroidism defined as TSH > 5.0 μIU/mL, hyperthyroidism defined as TSH < 0.3 μIU/mL.
TSH on hyperlipidemia. However, this pattern appeared to be much more significant in females than in males, particularly for hypertriglyceridemia. In females, if TSH was higher than 4.0 µIU/mL, risks of developing hypertriglyceridemia were significantly higher in both models than the reference TSH subgroup risks (all P < 0.05). Nevertheless, in males so such significances existed.

**DISCUSSION**

Clinical and subclinical thyroid dysfunctions are both very common clinical entities, the latter usually denotes the presence of a disease without obvious symptoms. Mild thyroid dysfunction often means the evolution of the disease at an early stage. The incidence of mild hypothyroidism and mild hyperthyroidism were reported to be around 9.5% and 1.8%, respectively. Results of the current study not only were in concord with the above-reported data, we also distinguished incidence disparity between genders. Mild hypothyroidism represents early thyroid failure, which is usually progressive, especially when TSH is higher than 10 µIU/mL, making it an important topic in people’s health.

Recently, a large number of clinical studies have indicated that TSH is associated with a deleterious change of lipid metabolism. And it has been suggested that the proatherogenic influence of TSH on serum lipid profile is in a thyroid hormone independent manner. Abnormal elevation of TC, LDL, and TG, and decrease of HDL have been observed in patients with subclinical hypothyroidism, even in subject with normal TSH (TSH near the upper limit within the normal reference range). The current large population-based study was able to provide evidence to support these findings.

| TABLE 3. Pearson Bivariate Correlations Between TSH and Other Variables Based on Different Genders |
|-----------------------------------------------|-----------------------------------------------|
| **Correlation Coefficients for Males** | **Correlation Coefficients for Females** |
| Age | 0.044** | 0.059** |
| BMI | 0.012 | 0.040** |
| FT3 | −0.103** | −0.149** |
| FT4 | −0.146** | −0.213** |
| TC | 0.027* | 0.074** |
| TG | 0.002 | 0.074** |
| LDL | 0.031** | 0.061** |
| HDL | −0.011 | −0.013 |
| ALT | 0.008 | 0.032* |
| TBIL | −0.003 | −0.034* |
| BUN | 0.015 | 0.048** |
| UA | 0.002 | 0.036** |
| Cr | 0.066** | 0.081*** |
| FG | 0.011 | −0.003 |

ALT = alanine aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, Cr = creatinine, FG = fasting glucose, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL = high-density lipoprotein-cholesterol, LDL = low-density lipoprotein-cholesterol, TC = total cholesterol, TG = triglycerides, TBIL = total bilirubin, TSH = thyroid stimulation hormone, UA = uric acid.

**TABLE 4. The Likelihood of Hyperlipidemia Among Different Thyroid Functional States in Logistic Regression Models for Males**

| Model 1 | Model 2 |
|-----------------------------------------------|-----------------------------------------------|
| **OR 95% CI in Different TSH Subgroups, µIU/mL** | **OR 95% CI in Different TSH Subgroups, µIU/mL** |
| TSH < 0.3 | HyperTG | 0.196 (0.103–0.382) | 0.158 (0.084–0.305) |
| TSH < 1.0 | HyperTG | 0.261 (0.113–0.599) | 0.202 (0.084–0.490) |
| TSH < 2.0 | HyperTG | 0.858 (0.392–1.874) | 0.705 (0.311–1.592) |
| TSH < 3.0 | HyperTG | 0.878 (0.392–1.974) | 0.761 (0.322–1.807) |
| TSH < 5.0 | HyperTG | 0.987 (0.449–2.187) | 0.859 (0.373–1.964) |
| TSH < 10.0 | HyperTG | 1.000 (0.449–2.187) | 0.882 (0.373–2.099) |
| TSH ≥ 10.0 | HyperTG | 1.000 (0.449–2.187) | 0.882 (0.373–2.099) |

HyperTC = high serum level of total cholesterol, HyperLDL = high serum level of low-density lipoprotein-cholesterol, HyperTG = hypertriglyceridemia, HyperTC = hypercholesterolemia. LowHDL = low-serum level of high-density lipoprotein-cholesterol, OR = odds ratio, TSH = thyroid stimulation hormone.

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www.md-journal.com | 7
The Likelihood of Hyperlipidemia Among Different Thyroid Functional States in Logistic Regression Models for Females

| TSH Subgroup | Hyperlipidemia OR (95% CI) | HyperLDL OR (95% CI) | LowHDL OR (95% CI) | P-value |
|-------------|---------------------------|----------------------|-------------------|---------|
| TSH < 0.5   | 1.194 (0.921–1.517)       | 1.430 (0.921–2.219)  | 1.517 (1.117–2.011) | < 0.001 |
| 0.5 ≤ TSH < 2.0 | 1.106 (0.899–1.360)       | 1.528 (1.192–1.931)  | 0.810 (0.618–1.061) | 0.051   |
| 2.0 ≤ TSH < 3.0 | 1.036 (0.863–1.243)       | 1.283 (1.028–1.604)  | 0.982 (0.712–1.433) | 0.772   |
| TSH ≥ 3.0   | 1.117 (0.935–1.335)       | 1.400 (1.148–1.708)  | 1.070 (0.816–1.417) | 0.125   |

HyperLDL: high serum level of low-density lipoprotein-cholesterol, HyperTG: hypertriglyceridemia, LowHDL: low serum level of high-density lipoprotein-cholesterol, OR: odds ratio, TSH: thyroid stimulation hormone.

P < 0.05.

Our study might shed some new light on the pathophysiological role of TSH on lipid in clinical perspective.
Limitation of the study deserves comments. First, using a cross-sectional design, causality relationship could not be established. Prospective studies are necessary to truly determine their cause-and-effect relationship. Second, we applied stringent exclusion criteria to rule out their relevant disease histories. However, since the annual health checkup policy is not good enough to cover the majority of Chinese, a number of the participants with various diseases might not be aware of them, which could be a confounding factor for our investigation. Third, the power of the present study could have been stronger if a multicentric population and a much larger number of subjects were recruited.

In conclusion, we found that serum TSH levels were positively associated with the levels of TC, LDL, and TG, and the incidence of hyperlipidemia, these relationships were independent of thyroid hormones. Moreover, these associations were found to be stronger with increasing age. Males demonstrated more protective effects of low TSH against hyperlipidemia, while females showed more detrimental effects of high TSH on hyperlipidemia.

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