

ORIGINAL ARTICLE

A cross-sectional survey of relationship between serum TSH level and blood pressure

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It is still controversial whether subclinical hypothyroidism and euthyroidism affect blood pressure. The study aimed to explore the relationship between different levels of thyroid-stimulating hormone (TSH) and blood pressure in the participants with subclinical hypothyroidism and euthyroidism. A total of 1319 participants were administered a questionnaire survey, and their blood pressure, height and body weight measurements were taken. Blood samples were taken to test serum TSH. FT3 and FT4 were further examined if TSH was abnormal. Participants were divided into euthyroid group and subclinical hypothyroidism group. Euthyroid group was further divided into three groups: group A (TSH 0.3–0.99 mIU l⁻¹), group B (TSH 1.0–1.9 mIU l⁻¹) and group C (TSH 1.91–4.8 mIU l⁻¹). Results showed that different levels of serum TSH had no relation with systolic blood pressure (SBP) and diastolic blood pressure (DBP). The prevalence of hypertension in subclinical hypothyroidism group was significantly

higher than euthyroid group in females (41.3 vs 25.6%, $P < 0.05$). The risk of hypertension in subclinical hypothyroidism group was significantly higher than that in the euthyroid group after adjusted for age, gender, smoking status, HOMA-IR (homoeostasis model assessment of insulin resistance) and body mass index (odds ratio (OR) = 1.753, 95% confidence interval (CI) 1.067–2.879, $P = 0.027$). This association was stronger in females (OR = 3.545, 95% CI 1.576–7.975, $P = 0.004$), but there was no statistical significance in males. Within normal range of TSH, both SBP and DBP were similar among the three groups. The prevalence and risk of hypertension were also similar among the three groups. In conclusion, the prevalence of hypertension in subclinical hypothyroidism group was significantly higher than in euthyroid group in females. Change of TSH in normal range did not affect blood pressure.

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Keywords: TSH; subclinical hypothyroidism; blood pressure

Introduction

Thyroid dysfunction, both hypo- and hyperthyroidism, may increase the risk of hypertension.^{1,2} However, it is still controversial whether mild thyroid dysfunction, such as subclinical hypothyroidism and also euthyroidism, affect blood pressure. Previous studies have found that hypertension had existed in the patients with subclinical hypothyroidism who are characterized as having high serum thyroid-stimulating hormone (TSH) level and normal thyroid hormones.³ Subclinical hypothyroidism was an independent risk factor for atherosclerosis and myocardial infarction in elderly women.⁴

Recently, some researches^{5–8} had investigated cross-sectionally the relation between thyroid function and blood pressure. Some found that there was a modest, but significant positive association between serum TSH and blood pressure within the normal serum TSH range,^{5,6} but the Framingham Heart Study investigators reported no correlation between serum TSH and any of the thyroid hormone levels in euthyroid participants.⁸ This epidemiological study explored the relation between different levels of serum TSH and blood pressure in the participants with subclinical hypothyroidism and euthyroidism on the basis of cross-sectional epidemiological survey.

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Patients and methods

Participants

In 2007, a total of 1534 inhabitants, aged 18–85 years, of three communities in DaDong district,

Shenyang city, participated in a stratified sample survey on thyroid diseases and type 2 diabetes.

Exclusion criteria were (i) participants having a personal history of thyroid disease or taking medication affecting thyroid function, such as thyroxine, antithyroid drugs, glucocorticoid, antiepileptic and contraceptive drugs etc.; (ii) pregnant women or within the first year of postpartum period; (iii) participants without important relevant information; (iv) participants with diabetes, and treated with oral hypoglycaemic drugs or with insulin; (v) participants who were recently diagnosed with hypothyroidism or hyperthyroidism in this investigation; (vi) participants with hypertension who had taken oral antihypertensive drugs in the past 4 weeks. Moreover, 14 participants with subclinical hyperthyroidism were also excluded from the study. Finally, 1319 participants were enrolled and evaluated.

Methods

- 1. The questionnaire:** The questionnaire included general information, such as name, gender, ethnicity, date of birth, address, identification card number, educational qualification, profession, family income, telephone number, duration of time living in DaDong district, history of childbearing, status of medical insurance, involvement in sports and their diet intake (including state of iodine intake), history of smoking and drinking, family history and personal history of thyroid disorders and other diseases.
- 2. Measurement of blood pressure, height and body weight:** All the participants were made to rest for at least 30 min and then blood pressure of their right arm was measured twice with a desk-model sphygmomanometer with the participants in a sitting position. There was a 3-min interval between the two measurements for each participant, and then the mean value of the two measurements was used. Height and body weight were measured to calculate body mass index (BMI). $BMI = \text{body weight (kg)}/\text{height (m)}^2$.
- 3. Blood sample collection:** Fasting blood samples were drawn for serum TSH, fasting plasma glucose and insulin tests. Serum FT3 and FT4 were further examined if TSH was abnormal. The Homoeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: $HOMA-IR = \text{fasting plasma glucose (mmol l}^{-1}) \times \text{insulin (mIU l}^{-1})/22.5$.
- 4. Assay:** Serum TSH, FT3 and FT4 were tested with super-sensitive chemiluminescence immunoassay (IMMULITE, Diagnostic Products Corporation, Los Angeles, CA, USA), plasma glucose was tested with hexokinase law (the first Japanese pharmaceutical kit, Kyoto, Japan), and insulin with radioimmunoassay (Biotechnology Research Institute of the North Port, Beijing, China). The

intra-assay coefficients of variation were $<8\%$ and the inter-assay coefficients of variation were $<10\%$. The reference ranges of TSH, FT4 and FT3 were $0.3\text{--}4.8\text{ mIU l}^{-1}$, $10.3\text{--}24.5$ and $2.3\text{--}6.3\text{ pmol l}^{-1}$, respectively.

- 5. Diagnostic Criteria:** (1) Hypertension: $SBP \geq 140\text{ mmHg}$ and/or $DBP \geq 90\text{ mmHg}$ under quiescent condition, or with previous history of hypertension. (2) Hyperthyroidism: $TSH < 0.3\text{ mIU l}^{-1}$, $FT3 > 6.3$ and/or $FT4 > 24.5\text{ pmol l}^{-1}$. Subclinical hyperthyroidism: $TSH < 0.3\text{ mIU l}^{-1}$, FT3 and FT4 within the reference range. (3) Hypothyroidism: $TSH > 4.8\text{ mIU l}^{-1}$, $FT4 < 10.3\text{ pmol l}^{-1}$. Subclinical hypothyroidism: $TSH > 4.8\text{ mIU l}^{-1}$, FT4 within the reference range.

Statistical analyses

Data processing and statistical analysis were performed by SPSS 11.5 software. χ^2 -test was used for the analysis of counting data. The *t*-test and analysis of variance were used for the analysis of quantitative data. TSH and HOMA-IR were analysed after log transformation was performed. Spearman's rank-related analysis and linear regression analysis were used to evaluate the correlation of the factors. Risk factors were analysed using logistic regression. Level of significance was set to 5%.

Ethical aspects

Research protocols were approved by the medical ethics committee of The First Affiliated Hospital, China Medical University. All participants provided a written informed consent after the research protocols were carefully explained to them.

Results

The relationship between different serum TSH levels and mean blood pressure

The baseline characteristics of 1319 participants are shown in Table 1. After 115 patients who had taken hypotensive drugs in the past 4 weeks were excluded, using the Spearman's rank-related correlation analysis among the remaining 1204 persons, we found that the levels of serum TSH were not associated with either mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) ($P > 0.05$), whereas age, gender, smoking status, HOMA-IR, BMI were associated with both SBP and DBP ($P = 0.000$). The multiple linear regression analysis showed that levels of serum TSH still had no relation with mean SBP and DBP, even after adjustment for above factors (Table 2).

The previous findings of our research group showed that the incidence of thyroid dysfunction between serum TSH level of 1.0 and 1.9 mIU l^{-1} was the lowest.⁹ There were 1226 participants whose serum TSH levels were within the reference range ($0.3\text{--}4.8\text{ mIU l}^{-1}$); after excluding 102 patients who had taken hypotensive drugs in past 4 weeks, the

Table 1 Baseline characteristics of participants

| | All | Euthyroid | Subclinical hypothyroidism |
|----------------------------|--------------|--------------|----------------------------|
| Number | 1319 | 1226 | 93 |
| Age (year) | 44.8 ± 13.5 | 44.7 ± 13.6 | 46.2 ± 12.8 |
| Gender (female %) | 60.6% | 59.1% | 80.6% ^a |
| Smoking status (smoking %) | 23.8% | 25% | 7.5% ^a |
| HBP (%) | 32.8% | 32.3% | 39.8% |
| SBP (mm Hg) | 126.9 ± 21.1 | 126.7 ± 20.9 | 130.2 ± 23.9 |
| DBP (mm Hg) | 80.7 ± 12.0 | 80.7 ± 11.9 | 80.4 ± 12.6 |
| TSH (mIU ⁻¹) | 2.3 ± 1.7 | 2.0 ± 1.0 | 6.8 ± 2.4 ^a |
| BMI (kg m ⁻²) | 24.3 ± 3.7 | 24.3 ± 3.7 | 24.4 ± 3.2 |
| HOMA-IR | 2.8 ± 5.1 | 2.8 ± 5.3 | 2.4 ± 1.2 ^a |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homoeostasis model assessment of insulin resistance; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

^aCompared with euthyroid group $P < 0.05$.

Table 2 Multiple linear regression analysis of the relationship between serum TSH and SBP and DBP

| | SBP | | | DBP | | |
|----------------|---------|-------|--------|--------|-------|--------|
| | B | s.e. | P | B | s.e. | P |
| Gender | -10.304 | 1.149 | 0.000* | -6.605 | 0.724 | 0.000* |
| Age | 1.821 | 0.036 | 0.000* | 0.109 | 0.023 | 0.000* |
| BMI | 0.295 | 0.141 | 0.000* | 0.911 | 0.089 | 0.000* |
| Smoking status | -2.158 | 1.066 | 0.043* | -1.324 | 0.672 | 0.049* |
| Lg(HOMA-IR) | 4.677 | 2.008 | 0.020* | 4.280 | 1.266 | 0.001* |
| Lg(TSH) | 0.295 | 0.838 | 0.576 | 0.859 | 1.030 | 0.404 |

Abbreviations: B, regression coefficient; BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homoeostasis model assessment of insulin resistance; SBP, systolic blood pressure; s.e., standard error; TSH, thyroid-stimulating hormone.

* $P < 0.05$.

remaining 1124 individuals were divided into group A (TSH 0.3–0.99 mIU l⁻¹, 211 individuals), group B (TSH 1.0–1.9 mIU l⁻¹, 430 individuals) and group C (TSH 1.91–4.8 mIU l⁻¹, 483 individuals). Using variance analysis, both mean SBP and DBP were shown to be similar among three groups after adjusting for age, gender, smoking status, HOMA-IR and BMI (Table 3).

Influence of different serum TSH levels on hypertension prevalence

Of the 1319 participants, 433 patients had hypertension and 886 didnot. The prevalence of hypertension in subclinical hypothyroidism group was significantly higher than that in euthyroid group in females (41.3 vs 25.6%, $P < 0.05$).

There were significant differences between hypertensives and non-hypertensives in age (52.2 ± 12.4 vs 41.2 ± 12.5 years old), gender (female: 49.9 vs 68.5%), proportion of smokers (27.5 vs 22%), HOMA-IR (3.0 ± 1.5 vs 2.4 ± 1.2) and BMI (26.1 ± 3.6 vs 23.4 ± 3.4 kg m⁻²) (all $P < 0.05$), which suggested that these factors were associated with hypertension. After adjusting for age, gender, smoking status, HOMA-IR and BMI, logistic regression analysis indicated that different serum TSH levels remained independent risk factors for hypertension

(odds ratio (OR) = 1.324, 95% CI 1.033–1.697, $P = 0.027$). The risk for hypertension in subclinical hypothyroidism group was 1.753 times more than that in euthyroid group (OR = 1.753, 95% CI 1.067–2.879, $P = 0.027$), this association was stronger in females (OR = 3.545, 95% CI 1.576–7.975, $P = 0.004$), but there was no significant difference in males (Table 4).

The prevalence of hypertension was similar among groups A, B and C in euthyroid participants. Logistic regression analysis showed that serum TSH levels in normal range were not associated with hypertension prevalence after adjusting for age, gender, smoking status, HOMA-IR and BMI (OR = 0.990, 95% CI 0.847–1.158, $P = 0.903$).

Discussion

The cross-sectional epidemiological investigation indicated that there was no difference in mean blood pressure between the subclinical hypothyroidism group and euthyroid group. However, the prevalence of hypertension in subclinical hypothyroidism group was significantly higher than that in the euthyroid group. This association was especially stronger in females, and there was no statistical significance in males.

Table 3 The comparisons of SBP and DBP among euthyroid participants

| Group | TSH (mIUl ⁻¹) | Number (individuals) | SBP (mm Hg) | DBP (mm Hg) |
|-------|---------------------------|----------------------|--------------|-------------|
| A | 0.3–0.99 | 211 | 124.7 ± 19.0 | 79.6 ± 11.7 |
| B | 1.0–1.9 | 430 | 123.8 ± 17.7 | 81.0 ± 11.8 |
| C | 1.91–4.8 | 483 | 123.9 ± 19.2 | 79.5 ± 11.4 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.
Both SBP and DBP were adjusted for age, gender, smoking status, HOMA-IR and BMI.

Table 4 Comparison of risk for hypertension prevalence between different TSH level groups

| | TSH (mIUl ⁻¹) | N | Hypertensives (%) | OR | 95% CI | P |
|--------|---------------------------|------|-------------------|-------|-------------|--------|
| All | 0.3–4.8 | 1226 | 396 (32.3) | 1.753 | 1.067–2.879 | 0.027* |
| | >4.8 | 93 | 37 (39.8) | | | |
| Male | 0.3–4.8 | 502 | 211 (42.0) | 0.776 | 0.255–2.361 | 0.655 |
| | >4.8 | 18 | 6 (33.3) | | | |
| Female | 0.3–4.8 | 724 | 185 (25.6) | 3.545 | 1.576–7.975 | 0.004* |
| | >4.8 | 75 | 31 (41.3)* | | | |

Abbreviations: CI, confidence interval; OR, odds ratio; TSH, thyroid-stimulating hormone.
Compared with the participants with TSH between 0.3 and 4.8 mIUl⁻¹, *P<0.05.

Clinical hypothyroidism can raise the levels of blood pressure. The increment of systemic vascular resistance may be the main mechanism in clinical hypothyroidism patients. T3 can directly act on arterial smooth muscle cells of blood vessels to cause vasodilation.¹⁰ When hypothyroidism occurs, declining T3 level increases the vascular resistance and the level of blood pressure. Hypothyroidism can also lead to the abnormality of sodium metabolism, the sympathetic nervous system activity raising, and the glomerular filtration rate decreasing etc., which may be involved in the occurrence of hypertension.^{6,11,12} Blood pressure salt sensitivity was also one of the critical factors for hypertension in hypothyroid patients.¹³ The study of Gumieniak *et al.*⁶ showed that the relationship between FTI and salt sensitivity is, in part, mediated by the vascular action of thyroid hormone.

Recent researches indicated that cardiovascular disorders had existed in the subclinical hypothyroidism stage. Luboshitzky *et al.*³ found that the prevalence of hypertension in the subclinical hypothyroidism group was significantly higher than that in the normal control group, which coincided with our conclusion. Rotterdam's study showed that subclinical hypothyroidism was an independent risk factor for atherosclerosis and myocardial infarction.¹⁴ Blood hypercoagulability, blood viscosity increment, lipid abnormalities presenting in subclinical hypothyroidism patients could increase the risk for atherosclerosis,¹⁴ and these factors may also be involved in pathogenesis, in which the subclinical hypothyroidism affects the blood pressure.

Recently, the fact whether the reference range of serum TSH (0.3–4.8 mIUl⁻¹) is a safe range was doubted. When TSH was in the reference range, there was a linear increase in SBP and DBP with the increasing serum TSH levels, and the prevalence of hypertension also increased.^{5,14,15} The Whickham study indicated that serum TSH 2.0 mIUl⁻¹ was considered as the upper limit of the safe range.¹⁶ A prospective survey of our group found that the incidence of thyroid dysfunction between serum TSH level 1.0 and 1.9 mIUl⁻¹ was the lowest. When the serum TSH level was >1.9 mIUl⁻¹, the incidence of hypothyroidism increased, and when the serum TSH level <1.0 mIUl⁻¹, the incidence of hyperthyroidism increased.⁹ In present study, we divided the participants with euthyroidism into three groups according to the levels of serum TSH, that is, TSH 0.3–0.99, 1.0–1.9 and 1.91–4.8 mIUl⁻¹, and the results showed that there were no association between the serum TSH level within the normal reference range with blood pressure. Roos *et al.*⁷ studied the association between euthyroidism and metabolic syndrome, they also did not find any relationship between serum TSH level and blood pressure. The serum TSH is the most sensitive indicator for the change of thyroid function, so in this study, we only analysed the association between the serum TSH levels and blood pressure.

In conclusion, our investigation confirmed that subclinical hypothyroidism could increase the risk for hypertension prevalence. More prospective studies should be performed to confirm the association between euthyroidism and blood pressure. TSH

within the normal range was not associated with blood pressure.

What is known about topic?

- The prevalence of hypertension in subclinical hypothyroidism group was significantly higher than in euthyroid group in females.
- Change of TSH in normal range did not affect blood pressure.

What this study adds

- This epidemiological study explored the relationship between different levels of serum TSH and blood pressure in the participants with subclinical hypothyroidism and euthyroidism on the basis of cross-sectional epidemiological survey.
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Conflict of interest

The authors declare no conflict of interest.

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