The relation between changes in thyroid function and anthropometric indices during long-term follow-up of euthyroid subjects: the Tehran Thyroid Study (TTS)

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Clinical Study

Abstract

Objective: Uncertainties exist regarding the causal relationship between thyroid function tests (TFT) within the euthyroid range and anthropometric measures. This longitudinal cohort is aimed to examine the relationship between the two conditions.

Subjects and methods: Euthyroid participants of Tehran Thyroid Study (TTS) attending phase I (1999–2001) were included in this study and were followed up to phase IV (2008–2011). TSH and free T₄ (fT₄) levels as well as weight (Wt), waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR) were measured at both phases.

Results: 971 women and 784 men were included in the analysis. During 9.7 years of follow-up, increases in TSH levels, Wt and WHR as well as a decrease in fT₄ level were observed. Multivariable regression analysis showed a significant relationship between TSH changes and alterations in WC in women (β=0.69, P=0.021) and men (β=0.61, P=0.038). Moreover, a significant negative association of ΔfT₄ with changes in weight was documented (β=−0.49, P=0.001 in women and β=−0.56, P<0.001 in men). Additionally, we found a negative relationship between ΔfT₄ and ΔHC in men (β=−0.36, P=0.001).

Conclusion: In both genders, there was a positive relationship between changes in TSH and waist circumference and conversely a negative association of changes of fT₄ levels with weight over time.

Introduction

Thyroid hormones are known to affect the resting energy expenditure (REE) (1). While overt thyroid dysfunctions are known to be associated with some degrees of weight change, whether small changes in thyroid function – within the normal laboratory range – would lead to alterations in anthropometric indices or not is still a matter of debate (2).

Some cross-sectional studies have shown an association between high body mass index (BMI) and low levels of free T₄ or high levels of TSH within the euthyroid range (3, 4, 5). Others have documented the relationship only in certain subgroups, including smokers (6, 7). There are also reports indicating an association between slight alterations in thyroid function and subcutaneous fat accumulation (8) or insulin resistance (9). However, these results are not agreed upon by all investigators, especially in elderly subgroups (10). Moreover, the presence of thyroid autoimmunity seems to affect this...
relationship (11). To overcome the potential flaw of cross-sectional studies, few cohorts have examined the effect of variation in thyroid function on measures of body mass. These longitudinal studies showed that an increase in TSH concentration within the reference range was positively associated with increases in weight (12), waist circumference (WC), waist-to-hip ratio (WHR) (13) and BMI (13, 14). Moreover, the Dan Thyr longitudinal study recently concluded that, while there was an association between weight alteration and TSH change, TSH level was not a determinant of future weight change (15).

Considering the above-mentioned uncertainties regarding the causal relationship between thyroid function and anthropometric indices and the paucity of longitudinal studies addressing the issue, we conducted the present cohort to assess the association between TSH and free T₄ changes within the reference range and alterations in weight and other anthropometric measures in participants of the Tehran Thyroid Study (TTS).

Subjects and methods

Subjects

Participants of the Tehran Thyroid Study (TTS) were recruited for this study. Initiated in 1999, the TTS is an ongoing cohort being conducted within the context of the Tehran Lipid and Glucose Study (TLGS), a large population-based study for identification and prevention of noncommunicable diseases; profiles of both are fully described elsewhere (16, 17).

In brief, individuals aged ≥20 years, residents of district No. 13 of Tehran, were selected using multistage cluster random sampling. Baseline measurement including weight, height, waist and hip circumference, and body mass index (BMI) were recorded and fasting blood samples were obtained. All participants were invited for follow-up studies at 3 years intervals.

Participants in phase I (1999–2001) and IV (2008–2011) of the TTS were included in our study if they had (i) available required data in both phases I and IV, including weight; waist and hip circumference; TSH, fT₄ and TPO Ab levels; and (ii) TSH and fT₄ levels within the national reference ranges in both phases I and IV.

Our exclusion criteria consisted of (i) history of overt or subclinical thyroid diseases (hyperthyroidism, hypothyroidism, thyroid nodules and goiter); (ii) current use or history of thyroid treatments (thyroid hormones/antithyroid medications, corticosteroids, Iodine ablation and surgery); and (iii) pregnancy.

Reference levels for normal TSH and free T₄ levels were drawn from a study of Tehranian population (18) aimed to determine reference intervals for TSH and fT₄ based on the criteria of the National Academy of Clinical Biochemistry (NACB). According to this study, the national reference range for TSH level was set as 0.32–5.96 U/L, and normal range for fT₄ level was defined as 11.84–19.95 pmol/L.

Written informed consent was obtained from all participants. Following approval by the Research Ethics Committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, the study was conducted in accordance with the principles of the Declaration of Helsinki.

Measurements

The participants were interviewed by trained staff to obtain demographic data, medical history, detailed personal and family history regarding possible thyroid disease such as goiter, hyperthyroidism or hypothyroidism and current medication as well as history of iodine ablation, smoking habits and taking any medication that could interfere with thyroid function test results. According to smoking status, participants were categorized as (i) never-smokers or (ii) current smokers or quitters. Physical activity was assessed by the Lipid Research Clinics (LRC) questionnaire (19). Additionally, female subjects were classified into two groups regarding their menstrual status: (i) nonmenstruating for at least the past 1 year or (ii) currently menstruating women.

For all participants, a brief physical examination including anthropometric measurements was performed by trained physicians at baseline and every 3 years thereafter. Anthropometric measurements were taken with shoes removed and having the participant wearing light clothes. Using digital scales, weight was recorded in kilograms, and was documented to the nearest 100 g. Height was measured with participants in a standing position, using a tape meter, with the shoulders in normal alignment. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus using an unstretched tape meter, without any pressure to the body surface, and was recorded to the nearest 0.1 cm. Hip circumference was measured at the widest girth of the hip and was rounded to the nearest 0.1 cm. All measurements were taken by the same person.

Fasting blood samples were drawn between 07:00 and 09:00 h after an overnight fast into Vacutainer tubes at each assessment. Blood centrifugation was performed
within 30 min of drawing. Free thyroxine (fT4) and TSH levels were determined on −70°C stored serum samples by the electrochemiluminescence immunoassay (ECLIA) method in both phases I and IV, using Roche Diagnostics kits and Roche/Hitachi Cobas e411 analyzer (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay Plus Control, Bio-Rad Laboratories) was used to monitor the accuracy of assay; the intra- and interassay CVs were 1.3 and 3.7% for fT4 and 1.5 and 4.5% for TSH determinations respectively. Thyroid peroxidase antibody (TPO Ab) was assayed by immunoenzymometric assay (IEMA) using related kit (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co, Salzburg, Austria); intra- and interassay CVs were 3.9 and 4.7% respectively.

**Statistical analysis**

TSH levels and fT4 concentrations were analyzed as continuous variables. Categorical variables are shown as percent/numbers and continuous variables are presented as mean ± s.d. or median (IQR 25–75). The t-test, Mann–Whitney or χ2 tests were employed to compare means, medians or categorical data respectively. Univariate analysis and multivariable regression models were run to examine the relationship between changes in TSH and fT4 and alterations in weight, waist circumference and waist-to-hip ratio. Multivariable analyses were adjusted for age, smoking status (in men; ref, nonsmoker), physical activity (ref, light and moderate activity), menstrual status and baseline measurements (including weight, WC, HC and WHR). Statistical analyses were conducted by SPSS 16.0 statistical software package (SPSS). A threshold of P<0.05 was set as significance level.

**Results**

From among 6217 participants attended the TTS phases I and IV, blood samples from 4161 individuals were available, from whom and based on inclusion and exclusion criteria, 1755 individuals (55.3% female) entered the study. Median length of follow-up was 9.7 years (IQR 9.1–10.3 years). The mean age of the participants was 43.5 ± 13.8 years at the baseline and 53.3 ± 13.7 years at follow-up. Among the individuals recruited, 9.5% of women and 5.2% of men had positive antiperoxidase antibodies at phase I. The corresponding numbers for smokers were 4 and 38.4% respectively. Median baseline serum TSH level was 1.58 U/L (1.05–2.31) and 1.33 U/L (0.89–1.86) for women and men, correspondingly. At baseline, 303 women had reached menopause by definition (Table 1).

There were significant differences between women and men in age, weight, WC, HC, WHR, TSH level and fT4 level in both phases. Weight, HC, WHR and fT4 were also significantly different between the two genders (Table 1).

At follow-up, we observed an increase in TSH levels (0.52 ± 0.91 U/L in women; 0.51 ± 0.73 U/L in men) as well as weight (2.96 ± 7.02 kg in women; 3.98 ± 7.29 kg in men), WC (8.15 ± 9.14 cm in women; 8.58 ± 7.18 cm in men) and WHR (0.10 ± 0.07 in women; 0.06 ± 0.05 in men). Also, a slight decrease in free T4 level was recorded.

**Table 1** Characteristics of participants attending both phases I (1999–2001) and IV (2008–2011) of Tehran Thyroid Study. All data are presented as mean ± s.d. unless otherwise specified. Smoking and menstrual statuses are presented as n (%). TSH levels are presented by median (IQR: 25–75).

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
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<th>Phase IV</th>
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<tbody>
<tr>
<td></td>
<td>Women (n=971)</td>
<td>Men (n=784)</td>
<td>Women (n=971)</td>
<td>Men (n=784)</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>42.2 ± 13.3</td>
<td>45.1 ± 14.3</td>
<td>52.0 ± 13.2</td>
<td>54.8 ± 14.1</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never smoked</td>
<td>928 (95.6)</td>
<td>479 (61.1)</td>
<td>924 (95.2)</td>
<td>458 (58.4)</td>
</tr>
<tr>
<td>Quit/current smoker</td>
<td>39 (4.0)</td>
<td>301 (38.4)</td>
<td>44 (4.5)</td>
<td>324 (41.3)</td>
</tr>
<tr>
<td>Menstrual status (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Menstruating</td>
<td>653 (67.3)</td>
<td>–</td>
<td>437 (45.0)</td>
<td>–</td>
</tr>
<tr>
<td>Nonmenstruating</td>
<td>303 (31.2)</td>
<td>–</td>
<td>475 (48.9)</td>
<td>–</td>
</tr>
<tr>
<td>Weight* (kg)</td>
<td>68.1 ± 11.8</td>
<td>75.7 ± 12.7</td>
<td>71.1 ± 12.4</td>
<td>79.7 ± 13.7</td>
</tr>
<tr>
<td>Waist circumference* (cm)</td>
<td>88.5 ± 12.2</td>
<td>89.9 ± 11.2</td>
<td>96.6 ± 11.9</td>
<td>98.5 ± 10.4</td>
</tr>
<tr>
<td>Hip circumference* (cm)</td>
<td>104.5 ± 9.5</td>
<td>97.1 ± 7.0</td>
<td>102.6 ± 9.1</td>
<td>100.2 ± 7.2</td>
</tr>
<tr>
<td>Waist-to-hip ratio*</td>
<td>0.85 ± 0.08</td>
<td>0.92 ± 0.07</td>
<td>0.94 ± 0.08</td>
<td>0.98 ± 0.06</td>
</tr>
<tr>
<td>TSH level* (U/L)</td>
<td>1.58 (1.05–2.31)</td>
<td>1.33 (0.89–1.86)</td>
<td>2.1 (1.49–2.98)</td>
<td>1.8 (1.29–2.53)</td>
</tr>
<tr>
<td>fT4 level* (pmol/L)</td>
<td>15.06 ± 1.67</td>
<td>15.83 ± 1.67</td>
<td>14.80 ± 1.67</td>
<td>15.32 ± 1.67</td>
</tr>
<tr>
<td>Anti-TPO Ab positive (%)</td>
<td>92 (9.5)</td>
<td>41 (5.2)</td>
<td>101 (10.4)</td>
<td>50 (6.4)</td>
</tr>
</tbody>
</table>

*P value for differences between genders in each phase was <0.01.
Table 2 Changes in TSH and fT₄ levels and anthropometric measures in participants across phase I (1999–2001) through phase IV (2008–2011) of Tehran Thyroid Study. All data are presented as mean±s.d.

<table>
<thead>
<tr>
<th></th>
<th>Women (n=971)</th>
<th>Men (n=784)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Weight* (kg)</td>
<td>2.96±0.14</td>
<td>3.94±0.29</td>
</tr>
<tr>
<td>Δ Waist circumference** (cm)</td>
<td>8.15±0.14</td>
<td>8.58±0.18</td>
</tr>
<tr>
<td>Δ Hip circumference* (cm)</td>
<td>−1.87±0.14</td>
<td>3.12±0.63</td>
</tr>
<tr>
<td>Δ Waist-to-hip ratio*</td>
<td>0.10±0.07</td>
<td>0.06±0.05</td>
</tr>
<tr>
<td>Δ TSH** (U/L)</td>
<td>0.52±0.91</td>
<td>0.51±0.73</td>
</tr>
<tr>
<td>Δ Free T₄* (pmol/L)</td>
<td>−0.25±1.51</td>
<td>−0.56±1.41</td>
</tr>
</tbody>
</table>

*P value for differences between genders was <0.01; **P value for differences between genders was not significant.

After adjusting for age, smoking status (in men), physical activity, menstrual status in women and baseline anthropometric measures, multivariable regression model consisting of weight, WC, HC and WHR was conducted to examine the association of ΔTSH and ΔfT₄ with anthropometric indices. Our analysis showed that there was a positive relationship between TSH changes and alterations in WC in women (β=0.69, P=0.021) (Table 4). Similarly, in men, we found a significant association between TSH changes and ΔWC (β=0.61, P=0.038) (Table 4). Moreover, our analysis revealed a significant negative association of ΔfT₄ with changes in weight (β=−0.49, P=0.001 in women and β=−0.56, P<0.001 in men). Additionally, there was a negative relationship between ΔfT₄ and ΔHC in men (β=−0.36, P=0.001) (Table 4). Notably, no significant relationship between ΔfT₄ and anthropometric measures was observed in anti-TPO Ab positive subjects in multivariable analysis (data not shown).

**Discussion**

In this longitudinal study, we observed TSH changes within laboratory ranges to be positively associated with slight increase in waist circumference in both genders. Moreover, alterations in fT₄ were also found to have significant negative relationship with changes in weight and hip circumference during 9.7 years of follow-up.

Not many longitudinal studies have focused on the association between thyroid function test within the

Table 3 Univariate analysis showing the relationship between changes in TSH and fT₄ levels and anthropometric changes in the participants across phase I (1999–2001) through phase IV (2008–2011) of Tehran Thyroid Study (TTS). P<0.05 was set as a significant level.

<table>
<thead>
<tr>
<th></th>
<th>Δ TSH (U/L)</th>
<th>P</th>
<th>Δ free T₄ (pmol/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔWt (kg)</td>
<td>0.003</td>
<td>0.42 (−0.06, 0.91)</td>
<td>0.084</td>
<td>0.028</td>
</tr>
<tr>
<td>ΔWC (cm)</td>
<td>0.007</td>
<td>0.81 (0.18, 1.43)</td>
<td><strong>0.01</strong></td>
<td>0.009</td>
</tr>
<tr>
<td>ΔHC (cm)</td>
<td>0.001</td>
<td>0.21 (−0.21, 0.63)</td>
<td>0.326</td>
<td>0.014</td>
</tr>
<tr>
<td>ΔWHR</td>
<td>0.005</td>
<td>0.01 (0.00, 0.01)</td>
<td><strong>0.032</strong></td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔWt (kg)</td>
<td>0.004</td>
<td>0.61 (−0.08, 1.31)</td>
<td>0.085</td>
<td>0.033</td>
</tr>
<tr>
<td>ΔWC (cm)</td>
<td>0.008</td>
<td>0.89 (0.21, 1.57)</td>
<td><strong>0.011</strong></td>
<td>0.011</td>
</tr>
<tr>
<td>ΔHC (cm)</td>
<td>0.004</td>
<td>0.39 (−0.05, 0.83)</td>
<td>0.082</td>
<td>0.026</td>
</tr>
<tr>
<td>ΔWHR</td>
<td>0.006</td>
<td>0.01 (0.00, 0.01)</td>
<td><strong>0.028</strong></td>
<td>0.000</td>
</tr>
</tbody>
</table>

HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; Wt, weight.
reference range and weight alterations. However, they have documented conflicting results on the role of gender and smoking. Examining the effect of increased TSH on BMI in 6164 euthyroid individuals (54% female, mean age 59.7 ± 14.0) between years 1994 and 2001, the fifth Tromsø study showed a significant positive relationship between TSH changes and BMI alterations only in nonsmoker subjects (14). Also, Fox and coworkers revealed that in a 3.5-year follow-up of 2407 persons (46% female, mean age 48 ± 10), increases in TSH level were associated with statistically significant weight gain in both genders (12), although, they reported a smaller effect size in men. Accordingly, in a longitudinal study of 15 020 healthy individuals (66% female, median age 52 years (IQR 46–60)), the Hunt study showed that within normal laboratory range, there was a positive association between TSH raise and increase in weight, WC and BMI in both genders (13). On the other hand, another study by Gopinath and coworkers reported a strong positive relationship between TSH changes over a 5-year period and incident weight gain only in women (20). While insufficient study power in certain subgroups might provide some clarification about differences in observed effects sizes, the differences between our findings on anthropometric indices and above observations might best be explained by differences in number of studied individuals, length of follow-up and baseline characteristics (baseline weight, WC, etc.).

Notably, we observed a more pronounced increase in TSH levels than some other studies with similar length of follow-up. This larger increase might be due to the wider TSH level range in our euthyroid population. While we need to emphasize here that our larger TSH cutoff has been drawn from a study of Tehranian population mentioned earlier (18), however, we believe that this greater increase did not influence our results, since our analyses were run on a per unit basis.

Addressing fT4 changes, we found a significant negative association between ΔfT4 and changes in weight in both genders. However, we observed the relationship between ΔfT4 and HC alterations to be present only in men. The amount of predicted weight change per each unit of fT4 change is rather small (~0.49 kg in women and ~0.56 kg in men). Thereby, any clinical conclusion drawn from these results should take into consideration the actual amounts of weight gain or loss associated with fT4 alterations within the normal references. Our study is the first study that has examined relationship between fT4 changes and alterations in anthropometric indices. Interestingly, our findings are in accordance with previous longitudinal and cross-sectional reports assessing the association between baseline fT4 and weight changes. For instance, in a population-based study, Knudsen and coworkers found a negative association between BMI and categories of baseline serum fT4 levels (2). Likewise, Shon and coworkers demonstrated that in euthyroid women, fT4 was negatively correlated with BMI (21). Moreover, Dvoráková and coworkers observed that the inverse relationship between BMI and fT4 was lost in men (22). On the other hand, another study on healthy individuals found that fT4 was a predictor of abdominal subcutaneous fat, independent of age, sex and smoking (8). In accordance with above reports, recently, the longitudinal Dan Thy study showed that the relationship between ΔTSH and ΔfT4 differed significantly between groups with different weight changes (15).

Our findings could be explained by the pathophysiological mechanism underlying the anthropometric
changes observed in overt thyroid disorders. Resting energy expenditure (REE), which generally reflects obligatory thermogenesis in human, is known to be highly sensitive to thyroid hormone stimulation (23). In hypothyroidism, the obligatory thermogenesis is reduced and stimulation of brown fat tissue is increased (23). In turn, leptin, secreted by adipocytes, might increase thermogenesis by regulating thyrotropin-releasing hormone (TRH) neurons (24). Moreover, the moderate increase in free and total T₃ levels, frequently observed in obese individuals, leads to an increase in energy expenditure (25).

Notably, we found no significant relationship between ΔfT₃ and changes in anthropometric measures in anti-TPO antibody positive (Ab+) subjects in multivariable analysis. These results could not be compared directly with those of the previous studies, since a similar analysis has not been made by related investigations so far. Nevertheless, the rather small size of the anti-TPO Ab+ group might have affected the lack of association we observed.

Compared with the mean weight gain, we observed more increase in the mean WC among our population. Examining the rising trends of obesity and central obesity in the TLGS cohort, a related different pattern of rising between the two entities has been previously reported by our colleagues (26). Along with low physical activity and unhealthy diet, ecological characteristics of Tehran metropolis, which impose further unhealthy changes on life style and eating behavior of its inhabitants, might provide some explanation.

Our findings need to be interpreted in the context of limitations we encountered. We did not have data on fT₃ levels. Considering that little is known about the relation between changes in fT₃ levels and alterations in weight, assessing fT₃ levels would add to the interpretability and robustness of our results. Additionally, we did not have access to the nutritional information of our participants, and thereby no adjustment was made based on their nutritional status. Also, records on physical activity in phase one were collected based on qualitative Lipid Research Clinic (LRC) questionnaire, which has not been validated for Iranian population, and last but not least, due to their small group size, current smokers and ex-smokers were analyzed together.

The strengths of the current survey include its longitudinal population-based design, substantial number of participants and relatively long follow-up duration. Moreover, nation-specified cutoffs for TSH and fT₄ have been used to define normal laboratory ranges. In addition, we have examined a comprehensive list of actually measured anthropometric indices along with an inclusive range of possible confounding factors in our analysis.

In conclusion, we found a significant relationship between changes in TSH and waist circumference over time. Also alterations in fT₄ were negatively associated with changes in weight in both genders. However, role of thyroid autoimmunity as well as causal relationship between the two conditions need to be determined.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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