Introduction

Obesity is associated with numerous co-morbidities such as diabetes, cardiovascular diseases (CVD), hypertension, all-cause mortality and cancers. Over the past 20 years, obesity has become a global epidemic. Increase in caloric intake, decline in physical activity and smoking cessation, in addition to socioeconomic and genetic factors have been considered as predictors for obesity.

Thyroid hormones effect bodyweight through modification of the basal metabolic rate. It is well-recognized that overt hypothyroidism is associated with weight gain; weight loss is a common symptom in patients with overt hyperthyroidism. Some studies have revealed that low thyroid hormone levels, even within normal ranges, are associated with overweight and obesity. Other studies have found no association in this regard. In a study from an iodine sufficient area in Norway (HUNT), out of 27097 subjects, low thyroid function was associated with high body mass index (BMI) in both current smokers and those who have never smoked. In 1853 euthyroid subjects in Australia, small differences in free T4 were associated with differences in BMI in nonsmokers; however, no significant relationship was found between BMI and TSH in both smokers and nonsmokers. In a study in Northern Norway on 10419 subjects, a positive association between TSH and BMI was found only in nonsmokers. In consideration of the conflicting published data, this study was designed to evaluate the association between serum TSH concentrations within the normal reference range and BMI.

Subjects and Methods

This 2006 cross-sectional survey was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), a community-based epidemiological survey conducted since 1999 to identify the prevalence and incidence of risk factors of CVD among residents of Tehran, an area of iodine sufficiency. Of 15005 participants, 1999 subjects (aged ≥ 20 years) were randomly selected for this study. Each individual completed a self-administered health questionnaire that included personal details, family history of goiter, hyperthyroidism or hypothyroidism, use of thyroid hormones, symptoms and signs consistent with hyper- or hypothyroidism, current medication usage, smoking habits, and physical activity status. People with previously known thyroid disorders, those on thyroid medications, and patients with missing information on height, weight, smoking status, and physical activity were excluded. Thus, a total of 1581 subjects (79%) were eligible for the analysis and entered the study. Weight (kg) and height (m) were measured with the subjects barefooted, in light clothes, using standardized instruments. BMI was calculated as dividing the body weight (kg) by height in m². Physical activity level was assessed using a modifiable activity questionnaire (MAQ) in two categories; the active category was based on MET*-minutes per week that equaled or exceeded 600; the inactive category was based on MET of minutes per week less than 600. This level of intensity was previously recommended by the Center for Disease Control and Prevention (CDC) for health benefits. High reliability and moderate validity were found for the Persian translated MAQ.
in Tehran’s adult population. For adjusting measurements smokers were classified as current, non- and ex-smokers.

**Laboratory measurements**

For each participant, a fasting serum sample stored frozen at -70°C, until necessary for measurements of serum TSH and TPOAb. In those with abnormal serum TSH levels, serum total T4 (TT4) and T3 uptake were measured and free T4 index (FTI) was calculated. Normal serum TSH concentrations in this population ranged from 0.3 – 5.8 μU/mL based on the 2.5 and 97.5 TSH percentiles in the previous study.14 Serum TSH concentrations were measured by IRMA (Isotope Kit, Budapest, Majarestan) and TT4 was measured by RIA (Isotope Kit, Budapest, Majarestan). The inter- and intra-assay coefficients of variations for all measured parameters were 3.1% and 3.8%, respectively, T3 uptake was measured by Elisa (Elisa Kit, Pishat Tebe Co., Tehran, Iran). Free thyroxin index (FTI) was calculated by multiplying T4 by T3 uptake. The FTI normal range was 1.13 – 4.6. Inter- and intra-assay coefficients of variations were 4.1 and 5.5, respectively. TPOAb was measured by Elisa (Orgentec Co., Germany) and levels ≥ 40 IU/mL were considered positive.

**Definitions**

Hyper- and hypothyroidism were defined based on the normal values of serum TSH (derived from the results of the reference population in the present survey) and FT4I. Subclinical hypothyroidism was defined as: FT4I = 1.13 – 4.6 with TSH > 5.8 μU/mL; clinical hypothyroidism was considered to be TSH > 5.8μU/mL and FT4I < 1.13. Subclinical hyperthyroidism was defined as TSH < 0.3 μU/mL and FT4I = 1.13 – 4.6; clinical hyperthyroidism was defined as TSH < 0.3 μU/mL with FT4I > 4.6.14 Subjects with serum TSH values within the reference range (0.3 – 5.8 μU/mL) were considered to be euthyroid. In our study we did not separately analyze subclinical and overt types due to the small sample size within each group. Therefore, the subclinical and overt types were combined under one category of thyroid dysfunction.

**Statistics**

The linear regression model was applied to assess the association between TSH as an independent variable and BMI as a dependent variable. In this model, age, sex, physical activity and smoking were added as covariates. BMI was considered to have normal distribution with visual inspection of the histograms. Analysis was performed for subjects with TSH within the normal reference range and a subgroup of negative TPOAb subjects within this population. The study population was divided into 3 groups of euthyroid, hypo- and hyperthyroid. Euthyroid subjects with serum TSH values within the normal reference range were divided by tertile (0.3 – 1.3, 1.3 – 2.2, 2.2 – 5.8). Analysis of covariance (ANCOVA) was applied to compare the mean values of BMI among 5 groups of thyroid functions. Considering the lowest tertile range as the reference group, logistic regression analysis was used to compare the odds ratio for obesity for each category of thyroid function. All measurements were adjusted for age, sex, and smoking status (current, ex- and nonsmokers) and physical activity. Stratified analysis was performed for smokers and nonsmokers. P < 0.05 was statistically significant.

**Results**

The study population (1581 subjects) was comprised of 701 (44.3%) males and 880 (55.7%) females with a mean age of 52 ± 13 years. Of these, 1250 (79.1%) were nonsmokers, while 186 (11.8%) were current smokers, and 140 (8.9%) were ex-smokers. There were 1455 (92%) euthyroid subjects, 85 (5.4%) hypothyroid, and 41 (2.6%) hyperthyroid. Current smokers comprised 24.1% of men and 1.9% of women.

There was a significant positive association between TSH and BMI in euthyroid subjects, both overall and in nonsmokers. In model 1 (age adjusted) each unit increase of 1 μU/mL TSH was associated with an increase in mean BMI of 0.31 kg/m² (95% CI: 0.2 – 0.6, P = 0.002; Table 1). In the same subgroup, after further adjustments for age and sex in model 2, and marginally significant in the multivariate model (adjusted for age, sex, physical activity, and smoking; P = 0.01; Table 1). In the strata for negative TPOAb euthyroid subjects, each unit increase of 1 μU/mL TSH was associated with an increase in mean BMI of 0.4 kg/m² (95% CI: 0.2 – 0.6, P < 0.001, R² = 0.03). In the same subgroup, after further adjustments for sex, smoking and physical activity, the association remained significant (P = 0.03).

Stratified analysis for smokers and nonsmokers showed a significant association between BMI and TSH only in nonsmokers (P < 0.004) after an adjustment for age, whereas in smokers no association was found between TSH and BMI (P < 0.1). In nonsmokers, each unit increase of 1 μU/mL TSH was associated with an increase in mean BMI of 0.36 kg/m² (95% CI: 0.1 – 0.6, P = 0.003). After further adjustments for age, sex and physical activity, the association remained marginally significant in nonsmokers (P = 0.07).

There was upward trend in mean BMI in 3 categories of thyroid function (tertile of TSH within the normal range; P = 0.02; Table 2), which remained significant only in nonsmokers.

Linear regression analysis showed no association between serum TSH values and waist circumferences, except in women, in whom each increase in TSH was associated with a 0.8 mm increase in waist circumference (P < 0.04).

**Discussion**

The main finding of this study was the correlation between a lower serum TSH concentration and higher BMI in all euthyroid subjects. This correlation was significant only in nonsmokers, which indicated that smoking possibly modified the relationship between TSH and BMI. Although this observational study has not estab-

---

**Table 1.** Linear regression analysis for BMI as dependent variable in the euthyroid group and subgroup of negative TPOAb subjects.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Euthyroid subjects</th>
<th>Negative TPOAb euthyroid subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β’</td>
<td>95% CI</td>
</tr>
<tr>
<td>TSH</td>
<td>0.31</td>
<td>0.116–0.505</td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>0.001–0.036</td>
</tr>
</tbody>
</table>

* Unstandardized regression coefficient; † P < 0.05: statistically significant.
Table 2. Mean BMI in 5 categories of thyroid function in the study population (smokers and nonsmokers).

<table>
<thead>
<tr>
<th>TSH (μU/mL)</th>
<th>Hyperthyroid* (&lt;0.3)</th>
<th>Lower tertile (0.3–1.3)</th>
<th>Middle tertile (1.3–2.2)</th>
<th>Upper tertile (2.2–5.8)</th>
<th>Hypothyroid* (&gt;5.8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>41</td>
<td>468</td>
<td>467</td>
<td>515</td>
<td>85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0</td>
<td>28.2</td>
<td>28.8</td>
<td>29.0</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>73</td>
<td>47</td>
<td>54</td>
<td>7</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5</td>
<td>27.2</td>
<td>26.9</td>
<td>27.6</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>395</td>
<td>420</td>
<td>461</td>
<td>78</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4</td>
<td>28.4</td>
<td>29.0</td>
<td>29.1</td>
<td>30.1</td>
<td></td>
</tr>
</tbody>
</table>

*Hyper- and hypothyroid in this study included both clinical and subclinical types of thyroid dysfunction.

lished any casual relationship between TSH and BMI, there are some plausible explanations and study results that have supported this hypothesis. Data on the association between normal range thyroid function and BMI are controversial, thus it is not clear whether this relationship is modified by smoking.

In agreement with our findings, Nymes et al. have investigated 6164 subjects in Northern Norway and found a significant positive correlation between serum TSH and BMI only in nonsmokers. In contrast, in the HUNT study of 27097 individuals, the association of low thyroid function with high BMI was at least as strong in current smokers as it was in those who had never smoked.

In a study by Knudsen et al. conducted on 4082 iodine deficient Danish subjects, a significant positive association was found between TSH categories and both BMI and obesity. They observed a negative association between BMI and free T4. In this study however, the results were not separately analyzed for smokers and nonsmokers.

In the Busselton Health Study of 2108 euthyroid subjects, small differences in free T4 were associated with differences in BMI in nonsmokers, but no relationship was found between TSH and BMI.

In our study the relationship between BMI and TSH persisted following smoking cessation. Tobacco smoking has complex effects on thyroid function; some studies report lower serum TSH concentrations in smokers than in nonsmokers.

We have found a positive relation between TSH and BMI in only nonsmokers. Smokers exhibit a negative association in this regard which implies that smoking could mask or reverse this relationship.

The strengths of this study include a community-based design with a large sample size, careful adjustments for age, gender, smoking and physical activity status, in addition to exclusion of those with TSH values outside the reference interval and those with positive thyroid autoimmunity. Limitations of this study include the following: free thyroxine levels were not measured which could supply us with more information, and we were unable to include a few covariates such as diet energy intake, education and life style which could have affected BMI.

In conclusion, our data support the idea that a small difference in thyroid function, even within the normal reference interval of TSH, may contribute to alterations in BMI among nonsmokers.

Acknowledgement

This work was supported by financial grant from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. There is no conflict of interest in this research study. We sincerely acknowledge all those who assisted with this study and Ms. Niloofar Shiva for language editing of the manuscript.
References

29. Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, Valeria-