Association between thyroid hormones, thyroid antibodies and insulin resistance in euthyroid individuals: A population-based cohort

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Abstract

Aim. – The association between insulin resistance and thyroid function in euthyroid subjects has not yet been clarified. This study aimed to investigate the association between thyroid function within the normal reference range and insulin resistance in participants of the Tehran Thyroid Study (TTS).

Methods. – This cross-sectional study was conducted within the framework of the TTS. Of 5786 subjects aged ≥ 20 years, 2758 euthyroid subjects free of thyroid disorders, diabetes, chronic kidney disease and cardiovascular disease, and not taking steroids and lipid-lowering agents, were included. Serum concentrations of free thyroxine (FT4) and TSH were measured. The homoeostasis model assessment index for insulin resistance (HOMA-IR) was used to evaluate IR.

Results. – On linear regression analysis, a negative association was found between serum FT4 levels and HOMA-IR in the model with age, smoking and physical activity (B = −0.09, P < 0.001) and in the WC-adjusted model with age, smoking and physical activity for men (B = −0.06, P < 0.01). In addition, there was a positive association between serum TSH levels and HOMA-IR in both models [with age, smoking and physical activity (B = 0.07, P = 0.006), and age, smoking, physical activity and adjusted for WC (B = 0.05, P = 0.01)] that was not more significant on logistic regression analysis. In women, neither serum FT4 nor TSH levels were associated with HOMA-IR; the prevalence of IR decreased from 27.2 to 19.1 with increasing tertiles of FT4 only in men (P < 0.01). No significant differences were observed in HOMA-IR and its components between thyroid peroxidase antibody (TPOAb)-negative and -positive groups. Also, it was found that metabolically healthy but obese (MHO) subjects had higher levels of TSH than individuals who were MONW (metabolically obese but normal weight; P < 0.01).

Conclusion. – Low FT4 was independently associated with IR in healthy euthyroid Iranian men.
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Keywords: Free thyroxine; Insulin resistance; Thyroid; TSH

1. Introduction

The relationship between thyroid hormones (T4 and T3) and glucose homoeostasis was first suggested in 1947 [1]. Since then, it has been documented that basal energy expenditure, glucose and lipid metabolism, and blood pressure could be affected by thyroid hormones [2,3].

Thyroid dysfunction has been associated with various cardiovascular risk factors similar to components of the metabolic syndrome (MetS) [4–6]. Insulin resistance, which is
accompanied by mild inflammation, is suggested to be the key predictive factor of hypertension, hypertriglyceridaemia, abdominal obesity and impaired glucose metabolism [7,8] and is, therefore, assumed to be the fundamental pathophysiological phenomenon underlying this clustering [9]. However, studies addressing the relationship between thyroid function and insulin resistance have been controversial. Although the presence of insulin resistance in hypothyroidism has been reported in a few studies [10,11], others have failed to show such a relationship [12,13]. However, the association between insulin resistance and hyperthyroidism has been documented in previous research [14]. Furthermore, little is known of the association between thyroid function within reference ranges and insulin resistance. In some previous studies conducted with healthy euthyroid subjects, significant positive correlations were found between free T3 (FT3) and hyperinsulinaemia [15,16], and a negative association was observed between free T4 (FT4) and the homoeostasis model assessment of insulin resistance (HOMA-IR) index [17–19]. In addition, the results of research conducted by Ambrosi et al. [19] implied that thyroid-stimulating hormone (TSH) was positively correlated with the HOMA-IR, while another study showed that insulin resistance interferes with the relationship between TSH levels and low-density lipoprotein cholesterol (LDL-C). Many previous studies focused mainly on serum TSH, whereas free thyroxine levels and the presence of thyroid autoimmunity might represent more accurate markers of thyroid physiology, and facilitate evidence of potential subtle interactions between thyroid function and insulin [18]. Therefore, the present study aimed to investigate the association between thyroid function within the normal reference range and insulin resistance among participants of the Tehran Thyroid Study (TTS).

2. Materials and methods

2.1. Study design

This cross-sectional study was conducted within the framework of the TTS [20], a cohort study that itself was within the framework of the Tehran Lipid and Glucose Study (TLGS). The TLGS, an ongoing, integrated, community-based survey with follow-ups at 3-year intervals was initiated in 1997 for the identification and prevention of non-communicable disorders (NCD) [21].

2.2. Study population

For the TLGS initially, 15,005 individuals, aged ≥ 3 years and covered by three medical health centres in Tehran, were selected by multistage stratified cluster sampling with a crude response rate of 57.5%; there were no significant differences in age and gender distributions between responders and non-responders. Of the participants aged ≥ 20 years (n = 10,368), 5786 were randomly selected between March 1997 and December 2004 to participate in the TTS. Following implementation of exclusion criteria (Fig. 1), 2758 euthyroid subjects were ultimately included in the study.

2.3. Medical history and clinical examination

At the first visit, the study was explained to subjects, and their demographic data were obtained. All participants were invited to the TTS unit following clinical examination, and referred to trained physicians after giving their written informed consent to participate.

Participants were interviewed to obtain a past medical history, a detailed personal and family history regarding possible thyroid diseases such as goitre, hyperthyroidism and hypothyroidism, and current medications. Also, information on radioiodine intake, cardiovascular diseases, smoking habits, physical activity levels and any medication that could interfere with thyroid function test results were also obtained. A brief physical examination including anthropometric measurements was performed.

Participants remained seated for 15 min while a qualified physician measured their blood pressure twice with a standard mercury sphygmomanometer, calibrated by the Institute of Standards and Industrial Research of Iran. Anthropometric measurements were taken with shoes removed and participants wearing light clothing. Weight and height were measured according to the standard protocol. Waist circumference (WC) was measured at the level of the umbilicus, and hip circumference was measured at the widest girth of the hip (both in cm). Body mass index (BMI) was calculated by dividing weight (in kg) by the square of height (in m). Information on physical activity was collected using the Modifiable Activity Questionnaire (MAQ) [22], the reliability and convergent validity of which had already been investigated [23]. Each activity was weighted by its relative intensity; the metabolic equivalent (MET) as h/week was calculated as the MET value multiplied by the duration of activity (h) multiplied by the frequency of activity per week, with each MET representing the energy expenditure of an individual at rest (1 MET = 3.5 mL·kg<sup>−1</sup>·min<sup>−1</sup> of oxygen consumption).

The study was approved by the National Research Council of the Islamic Republic of Iran (No. 121), and was performed in accordance with the principles of the Declaration of Helsinki and the human research ethics committee of Shahid Beheshti University.

2.4. Laboratory measurements

All biochemical analyses were done at the TLGS research laboratory. Fasting blood samples were drawn from all participants between 7:00 and 9:00 AM. Fasting and 2-h glucose concentrations, serum total cholesterol (TC), triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C) were measured, and LDL-C was calculated from the serum TC, TG and HDL-C concentrations [23].

FT4 and TSH were determined from serum samples (stored at −70°C) by an electrochemiluminescence immunoasay (ECLIA) method, using kits (Roche Diagnostics) and a Roche/Hitachi cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The intra- and interassay coefficients...
Total participants of Tehran Thyroid Study (5783) assessed for eligibility

3662 subjects excluded from the study:
- 438 had hypothyroidism (subclinical/clinical)
- 340 had hyperthyroidism (subclinical/clinical)
- 651 used lipid lowering agent, glucose lowering agent, corticosteroids, thyroid drugs, anti-thyroid drugs, radio
- 65 had thyroid surgery
- 22 had thyroid cancer
- 297 had thyroid nodule
- 97 were pregnant
- 197 were lactating
- 834 had chronic kidney disease (CKD)
- 212 had cardio vascular disease
- 563 had diabetes

2758 included in study

1531 male
1172 female

Fig. 1. The sampling algorithm used for the study.

2.5. Definitions

TSH and FT4 reference ranges were defined based on reference ranges for the general population [24]. Euthyroidism was defined as a TSH within the reference range of 0.32–5.06 mIU/L while taking no thyroid medications or agents that might interfere with thyroid function test results.
Levels of TSH>5.06 mIU/L with FT4 0.91–1.55 ng/dL, TSH>5.06 mIU/L with FT4<0.91 ng/dL, TSH<0.32 mIU/L with FT4 0.91–1.55 ng/dL, and TSH<0.32 mIU/L with FT4>1.55 ng/dL were considered subclinical hypothyroidism, clinical hypothyroidism, subclinical hyperthyroidism and clinical hyperthyroidism, respectively [24]. Physical activity (PA) levels were categorized as slight (MET<600 min/week), moderate (MET≥600 but<1500 min/week) and vigorous (MET≥1500 min/week) [25]. Subjects with current and past histories of smoking were deemed current and ex-smokers, respectively, while those who had never smoked were considered non-smokers.

The HOMA-IR was used to evaluate insulin resistance (IR), as calculated by the following formula: Fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5 [26]. The highest quartile of HOMA-IR was considered the cutoff point for IR, and subjects with a HOMA-IR index ≥ 2.28 (highest quartile) were regarded as insulin-resistant. In addition, those with TPOAb levels >40 IU/mL were regarded as TPOAb-positive.

Metabolically obese but normal-weight (MONW) subjects were defined as having a BMI < 25 kg/m² while meeting criteria for MetS (having at least three abnormal metabolic components), while the metabolically healthy but obese (MHO) phenotype was defined as a BMI ≥ 25 kg/m² but metabolically healthy (having no more than two metabolic abnormalities).

In the present study, the following criteria from the Joint Interim Statement (JIS) [27] for the Iranian population were used to define abnormal metabolic components [28]: 1) WC > 95 cm for both genders; 2) serum TG ≥ 150 mg/dL or taking specific treatment; 3) HDL-C < 40 mg/dL in men and <50 mg/dL in women, or taking specific treatment; 4) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or taking specific treatment for previously diagnosed hypertension; and 5) fasting blood glucose (FBG) ≥ 100 mg/dL or taking treatment for diabetes.

2.6. Statistical analysis

Baseline characteristics of the study subjects were based on FT4 tertiles and categorized as: T1 < 1.21, T2 ≥ 1.21 but <1.35, and T3 ≥ 1.35 ng/dL for men; and T1 < 1.08, T2 ≥ 1.08 but <1.21, and T3 ≥ 1.21 ng/dL for women. Data across the three groups were compared using analysis of variation (ANOVA) and Kruskal–Wallis tests based on distribution of the variables. Because TSH, insulin, TPOAb and TG had skewed distributions, they were expressed as medians and interquartile range (IQR).

On multivariate analysis, the modification effect of gender on the relationship between thyroid function testing (TFT) and IR outcome was tested by entering interaction terms (interaction = TFT*gender) into the model; given the significant modifying effect of gender on FT4 and TSH (both P<0.05), our analysis was stratified by gender.

Linear regression analyses were performed using HOMA-IR with different levels of adjustment. Because insulin sensitivity and thyroid function can be affected by age, obesity, PA levels and smoking, these confounding variables were included in different models. Both WC and BMI were evaluated in regression models, and minor differences were found between the results of the adjusted model for each variable. However, as WC has been reported to be a clinically more important predictor of IR than BMI, it was also evaluated in an adjusted model. The association of FT4 and TSH with HOMA-IR was presented as a standardized correlation coefficient (β). As serum TSH values were non-normally distributed, they were log-transformed.

Comparisons of FBG, insulin and HOMA-IR between TPOAb-negative and -positive groups were performed with Student’s t test for continuous variables and the Mann–Whitney test for skewed variables.

Our study population was categorized into two groups, the MONW and MHO, to compare thyroid hormones, thyroid antibodies, HOMA-IR and its components, using Student’s t test for continuous variables and the Mann–Whitney test for skewed variables.

All P values were two-tailed, with P<0.05 considered statistically significant. Statistical analyses were performed using Stata version 12 software (StataCorp LP, College Station, TX, USA).

The highest quartile of the HOMA-IR was considered the cutoff point for IR, and subjects with a HOMA-IR score ≥ 2.28 (highest quartile) were regarded as insulin-resistant.

3. Results

Out of 5783 TTS participants, 3662 were excluded from the present study, which finally included 2758 healthy euthyroid subjects (Fig. 1). Their baseline characteristics based on gender-specific FT4 tertiles are presented in Table 1. There were significant differences in age, BMI, WC, TC, LDL-C and TG in both men and women based on FT4 tertiles. However, significant differences were observed for DBP, SBP, FBG and HOMA-IR across FT4 tertiles only in men.

In the linear regression analysis after adjusting for age, smoking and PA (Table 2), serum TSH, entered as a continuous variable, was positively associated with HOMA-IR (β=0.07, P=0.006) in male subjects, an association that remained significant even after adding WC to the previous model (β=0.05, P=0.01). Moreover, a negative association was found between serum FT4 as a continuous variable and HOMA-IR in one model with age, smoking and PA (β=−0.09, P<0.001), and in the age, smoking, PA and WC-adjusted model in men (β=−0.06, P<0.01). For women, neither serum FT4 nor TSH levels were associated with HOMA-IR in either model. In addition, our results also revealed that FT4 was negatively associated with fasting insulin (model 1: β=−0.09, P<0.001; model 2: β=−0.06, P=0.005), while TSH was positively correlated with fasting insulin only in men (model 1: β=0.08, P=0.003; model 2: β=0.06, P=0.008), with no association found between TFT and FBG in either men or women. It should be noted that the same results were found after including individuals with chronic kidney disease (CKD) and cardiovascular disease (CVD).

As shown in Fig. S1 (see supplementary material associated with this article online), based on TSH tertiles, the prevalence of IR differed significantly among men (P=0.04), but not among women; in men, it decreased from 27.2 to 19.1% with
### Table 1
Baseline characteristics of the study population based on serum free thyroxine (FT4) tertiles.

<table>
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<th></th>
<th>Serum FT4 tertiles (ng/dL)</th>
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<tbody>
<tr>
<td></td>
<td>Lowest (≤1.21)</td>
<td>Middle (≥1.21 but &lt;1.35)</td>
<td>Highest (≥1.35)</td>
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<td></td>
<td>(n = 508)</td>
<td>(n = 512)</td>
<td>(n = 510)</td>
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<tr>
<td>Age (years)</td>
<td>42.6 ± 13.0</td>
<td>38.2 ± 12.4</td>
<td>33.9 ± 11.5</td>
<td>&lt;0.01</td>
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<td>BMI (kg/m²)</td>
<td>26.1 ± 3.9</td>
<td>25.3 ± 3.4</td>
<td>25.0 ± 4.3</td>
<td>&lt;0.01</td>
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<td>WC (cm)</td>
<td>89.9 ± 10.8</td>
<td>87.9 ± 10.7</td>
<td>86.8 ± 11.2</td>
<td>&lt;0.01</td>
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<td>SBP (mmHg)</td>
<td>118.2 ± 16.0</td>
<td>115.6 ± 14.3</td>
<td>116.1 ± 15.5</td>
<td>0.01</td>
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<td>DBP (mmHg)</td>
<td>76.8 ± 11.0</td>
<td>75.1 ± 10.1</td>
<td>75.5 ± 10.3</td>
<td>0.02</td>
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<td>TC (mg/dL)</td>
<td>200.9 ± 41.0</td>
<td>194.9 ± 39.3</td>
<td>186.0 ± 41.1</td>
<td>&lt;0.01</td>
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<tr>
<td>LDL-C (mg/dL)</td>
<td>129.1 ± 35.0</td>
<td>124.9 ± 32.4</td>
<td>118.5 ± 35.0</td>
<td>&lt;0.01</td>
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<tr>
<td>HDL-C (mg/dL)</td>
<td>37.6 ± 9.0</td>
<td>37.1 ± 8.9</td>
<td>38.1 ± 9.6</td>
<td>0.23</td>
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<tr>
<td>TG (mg/dL)</td>
<td>153 (105–213)</td>
<td>146 (102–208)</td>
<td>126 (86–191)</td>
<td>&lt;0.01</td>
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<tr>
<td>FBG (mg/dL)</td>
<td>90.9 ± 8.9</td>
<td>88.8 ± 8.9</td>
<td>88.8 ± 8.5</td>
<td>&lt;0.01</td>
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<tr>
<td>Fasting insulin (mU/L)*</td>
<td>7.07 (5.07–10.43)</td>
<td>6.79 (4.69–9.10)</td>
<td>6.92 (4.72–9.56)</td>
<td>0.06</td>
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<tr>
<td>TSH (mIU/L)</td>
<td>1.47 (0.96–2.08)</td>
<td>1.42 (0.90–2.06)</td>
<td>1.40 (0.92–2.01)</td>
<td>0.56</td>
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<td>TPOAb (IU/mL)</td>
<td>5.04 (3.09–8.40)</td>
<td>4.69 (2.97–9.07)</td>
<td>4.90 (2.96–9.26)</td>
<td>0.68</td>
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<td>HOMA-IR</td>
<td>1.58 (1.08–2.39)</td>
<td>1.46 (1.00–2.03)</td>
<td>1.51 (1.00–2.09)</td>
<td>0.01</td>
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<tr>
<td>Current smoker [n (%)]</td>
<td>98 (19.7)</td>
<td>118 (23.2)</td>
<td>125 (24.7)</td>
<td>0.19</td>
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<td>Physical activity [n (%)]</td>
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<tr>
<td>Light</td>
<td>312 (62.9)</td>
<td>324 (63.7)</td>
<td>323 (63.8)</td>
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<tr>
<td>Moderate</td>
<td>80 (30.9)</td>
<td>79 (15.0)</td>
<td>100 (19.8)</td>
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<tr>
<td>Heavy</td>
<td>104 (21.0)</td>
<td>106 (20.8)</td>
<td>83 (16.4)</td>
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</table>

*Values with normal distribution are presented as means ± SD; values with abnormal distribution are presented as medians (Q1–Q3); categorical variables are presented as n (%); 3% of values were missing for education and 0.8% for physical-activity variables.

BMI: Body Mass Index; WC: waist circumference; SBP/DBP: systolic/diastolic blood pressure; TC: total cholesterol; LDL/HDL-C: low-density/high-density lipoprotein cholesterol; TG: triglyceride; FBG: fasting blood glucose; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibody; HOMA-IR: homeostasis model assessment of insulin resistance.
Table 2
Linear regression analysis of association of serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) concentrations with fasting blood glucose (FBG), fasting insulin and HOMA-IR Index.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Models</th>
<th>FBG (mg/dL)</th>
<th>Fasting insulin (mU/L)*</th>
<th>HOMA-IR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men (n = 1531)</td>
<td>Women (n = 1172)</td>
<td>Men (n = 1531)</td>
</tr>
<tr>
<td>FT4</td>
<td></td>
<td>β</td>
<td>R²</td>
<td>β</td>
</tr>
<tr>
<td>1</td>
<td>0.031</td>
<td>0.06</td>
<td>0.011</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>0.018</td>
<td>0.09</td>
<td>0.032</td>
<td>0.10</td>
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<tr>
<td>TSH*</td>
<td></td>
<td>0.047</td>
<td>0.059</td>
<td>−0.036</td>
</tr>
<tr>
<td>2</td>
<td>0.020</td>
<td>0.09</td>
<td>0.049</td>
<td>0.10</td>
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</table>

β reported as standardized regression coefficients (95% CI); * P<0.05.

* Log-transformed; Model 1: adjusted for age, physical-activity levels and smoking; smoking status excluded from women’s model due to small sample size and large estimated SD; Model 2: adjusted for age, physical-activity levels and waist circumference; smoking status excluded from women’s model due to small sample size and large estimated SE; HOMA-IR (homeostasis model assessment of insulin resistance) was a dependent variable.

increasing tertiles of FT4 (P = 0.01), whereas no such differences were observed across FT4 tertiles in women.

The multiple logistic regression analysis based on the presence or absence of IR showed that only higher serum FT4 [odds ratio (OR): 0.27, 95% confidence interval (CI): 0.12–0.61; P<0.01] was associated with lower chances of IR in men (Table S1; see supplementary material associated with this article online). In addition, it was observed that serum TSH levels did not influence the chances of being insulin-resistant in either men or women (Table S2; see supplementary material associated with this article online).

Comparisons of HOMA1-IR and its components based on the presence or absence of thyroid autoimmunity are presented in Table S3 (see supplementary material associated with this article online). There were no significant differences in HOMA-IR, fasting insulin or FBG between the TPOAb-negative and -positive groups.

Comparisons of thyroid hormones, thyroid antibodies, HOMA-IR and its components in the MHO and MONW phenotypes are shown in Table S4 (see supplementary material associated with this article online). MHO subjects had higher levels of TSH than those with the MONW phenotype (P<0.01). There were also statistically significant differences in serum FT4 levels between the two groups (P<0.01). Although no significant differences were found between TPOAb and HOMA-IR in the MHO vs MONW groups, MHO patients had higher levels of fasting insulin and lower levels of FBG compared with MONW patients (P<0.01). Also, as shown in Fig. 2, the prevalence of TPOAb positivity did not differ significantly between the MHO and MONW groups (P = 0.12).

4. Discussion

Findings of the present study revealed that higher serum FT4 levels were associated with lower odds of IR, but only in men; therefore, low serum FT4 levels in male subjects, albeit normal, were associated with an increased risk of IR. In contrast, there was no association between FT4 within the reference range and odds of presenting with IR in women. Moreover, although a significant positive association was observed between serum TSH levels and IR on linear regression analysis, this association was not significant in the logistic regression model.

Although several studies have investigated the possibility of an association between thyroid function and IR in euthyroid subjects, the available data addressing this association are inconsistent. In line with our results, a population-based study by Shin et al. [18] of 6241 subjects to investigate the relationship between thyroid function, as assessed by FT4 and TSH levels, and IR in healthy euthyroid subjects showed that lower FT4 levels, rather than higher TSH levels, were associated with IR. Likewise, a study conducted in an Hispanic population demonstrated that IR was associated with low FT4 concentrations, but not serum TSH levels [17]. Examination of the association of IR with thyroid hormones by Roos et al. [29] revealed a negative correlation between HOMA-IR and FT4 after adjusting for WC, age and gender, whereas the relationship between the HOMA-IR index and TSH levels was no longer significant after further adjustment for obesity.

Our present results are also in agreement with those of Muscogiuri et al. [30], who observed no correlation between TSH levels and insulin sensitivity per se. Also, an investigation of 1333 German subjects found that TSH was weakly correlated with IR, a relationship that lost its significance after excluding subjects with impaired glucose metabolism [31]. In a cohort study of a Korean population, no significant associations were
found between TSH and FT4 concentrations and HOMA-IR at baseline whereas, after a 3-year follow-up, higher levels of TSH were significantly correlated with changes in insulin levels and HOMA-IR after adjusting for age, gender, BMI, baseline TSH, smoking status, alcohol intake and exercise [32]. The study also showed that lower levels of FT4 were significantly associated with changes in HOMA-IR after controlling for age, gender, BMI, baseline FT4 levels and baseline HOMA-IR. However, the loss of significance after further adjustments for smoking status, alcohol intake and exercise showed that the association between FT4 and IR may be modified by other potential confounders [32].

Such discrepancies may have been due to the use of different inclusion criteria such as subjects with impaired glucose tolerance (IGT) and diabetes mellitus, study designs, ethnicity and iodine status of the population in these studies.

Our present findings, however, are not in agreement with those of Farasat et al. [33], who reported that moderately high FT4 and TSH levels were significantly correlated with IR in subjects with IGT, a difference that may be due to differences in exclusion criteria (for example, exclusion of known diabetes in the present study). In addition, the results of that study were not adjusted for gender, abdominal obesity or PA, despite their importance to the aetiology of IR.

According to the results of the present study, despite the association of lower FT4 levels with IR, higher TSH levels were not linked with IR. Indeed, the divergent association found between thyroid hormones and paraclinical outcomes is not clear, and serum FT4 might be a more reliable marker of tissue thyroid status, as suggested by previous studies [29,34]. Despite the importance of the hypothalamic–pituitary–thyroid axis in thyroid hormone homoeostasis, functions such as peripheral thyroid activity and local regulatory mechanisms of thyroid hormone, including intracellular transportation, deionization of T4 into active T3 and binding to nuclear receptors, are eventually mediated by circulating FT4 levels [34]. It should also be noted that, in spite of the importance of TSH levels in determining thyroid dysfunction, a study by Hoermann et al. [35] demonstrated the complex nature of the TSH–FT4 relationship, suggesting that the TSH response to a deviating FT4 value may not correlate with an inverse log relationship between TSH and FT4, but may be irregularly related to the extent of the deviation from an optimal set point.

Although the physiological mechanism of the relationship between FT4 levels and insulin sensitivity could not be determined in the present study, there are some possible explanations. First, it has recently been postulated that the expression and activation of uncoupling proteins β3 adrenergic receptor (β2AR) and peroxisome proliferator-activated receptor (PPAR)-γ, which both play a role in the regulation of insulin sensitivity, are triggered by thyroid hormones [36]. Thus, our findings may be explained by the proposed role of thyroid hormones in the modulation of these insulin-sensitivity-related molecules. Second, the mechanism could be related to a collaboration between thyroid hormones and catecholamines, leading to increased lipolysis, decreased visceral fat mass and improved insulin sensitivity [37]. It is worth noting that the stimulation of insulin sensitivity and lipolysis by thyroid hormones, but not abnormally raised thyroxine concentrations, is only observed within the normal reference range [37]. Third, peripheral IR in muscle and adipose tissue due to low leptin levels, a reduced muscle oxidative capacity and impaired glucose transporter type 4 (GLUT4) expression have all been reported in hypothyroidism [38]. Based on the association observed between FT4 and insulin sensitivity in euthyroid men, it has been hypothesized that lower FT4 levels may affect insulin sensitivity to a lesser extent through mechanisms related to hypothyroidism.

Another interesting finding of our present study is that, despite the association of serum FT4 with IR in men, there was no significant association in women. As suggested by a study by Geer and Shen [39], there are substantial gender-specific differences related to insulin sensitivity between men and women: specifically, men have more visceral and hepatic adipose tissue associated with increased IR, while women have greater general adiposity, a phenomenon that may be involved in the greater insulin sensitivity reported in women. In addition, via its advantageous effects on insulin and glucose homeostasis, adipose-tissue distribution and proinflammatory markers, oestrogen could contribute to gender differences; compared with men, women also have higher levels of adiponectin, an insulin-sensitizing hormone and protective element leading to a more insulin-sensitive environment [39]. Thus, these moderating mechanisms associated with a lower prevalence of IR in women may perhaps be the reason that no association between IR and thyroid function in women was observed in our present study.

Our study did find that individuals with the MHO phenotype had elevated serum TSH levels in the normal range compared with MONW subjects. Several population-based studies have shown that BMI is positively correlated with serum leptin as a compensatory mechanism against leptin resistance; indeed, increased leptin levels upregulate thyrotropin-releasing hormone expression in rat hypothalamus, suggesting that elevated leptin might boost TSH output into the upper reference range, which might be reversed after weight reduction in the obese [30,40].

The present study has some limitations that should be mentioned. First, its cross-sectional design does not provide definite information on cause-and-effect relationships; second, total T4 and total or free T3 levels were not measured, and there were contradictory data regarding the free T3/FT4 ratio involvement in metabolic and cardiovascular diseases. On the other hand, the strengths of our study include its large sample size, population-based design, appropriate exclusion criteria, and assessment of FT4, TSH and thyroid autoimmunity.

5. Conclusion

Low levels of FT4, rather than TSH, were independently associated with IR in healthy euthyroid Iranian men. Nevertheless, further population-based cohort studies are now needed to assess whether, in the long term, low FT4 levels in euthyroid ranges are linked to greater IR.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2015.04.004.

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