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Diabetes & Metabolism 41 (2015) 480–488

Original article

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

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Received 2 December 2014; received in revised form 26 April 2015; accepted 27 April 2015
Available online 3 June 2015

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.

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

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http://dx.doi.org/10.1016/j.diabet.2015.04.004
1262-3636/

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 $mL.kg^{-1}.min^{-1}$ 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 immunoassay (ECLIA) method, using kits (Roche Diagnostics) and a Roche/Hitachi cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The intra- and interassay coefficients