Subclinical hyperthyroidism and sport eligibility: An exploratory study on cardiovascular pre-participation screening in subjects treated with levothyroxine for multinodular goiter

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ABSTRACT. Background: Subclinical hyperthyroidism (sHT) affects cardiovascular (CV) morphology and function; whether such changes can impact on sport eligibility is unclear. Aim: This exploratory study evaluated the CV system and sport eligibility in athletes with levothyroxine-induced sHT, in the setting of mandatory pre-participation screening. Subjects and methods: A full, non-invasive CV screening (history and physical examination, 12-lead ECG, echocardiography, 24-hour Holter ECG, exercise stress test) was performed in two groups of untrained female athletes affected by non-toxic multinodular goiter. One group was taking levothyroxine at mildly suppressive doses (TG) whereas the other was untreated (UG). There was also a group of healthy controls (HC). Results: In TG the following characteristics were observed: a) a higher resting heart rate (HR; \( p < 0.01 \) and \( p < 0.05 \), vs HC and UG respectively), b) a thicker left ventricular posterior wall (\( p < 0.05 \) vs HC, and \( p < 0.05 \) vs HC and UG, respectively), c) a higher mean HR during the 24-hour Holter ECG (\( p < 0.01 \) and \( p < 0.05 \), vs HC and UG respectively), and d) a lower achieved maximum work load (\( p < 0.05 \), vs HC). No differences in the prevalence of cardiac arrhythmias among groups were observed. Sport eligibility was granted to all except one subject in the TG. Conclusions: Although some alterations were found in athletes with levothyroxine-induced mild sHT, these are probably of limited clinical relevance and they did not contraindicate sport participation in the majority of cases. Future research to address both health risks and the need for specific evaluations (e.g. free thyroxine, TSH, echocardiography) during the pre-participation screening of athletes with sHT is warranted. (J. Endocrinol. Invest. 32: 825-831, 2009)

INTRODUCTION

The aim of pre-participation screening of trained or untrained athletes is to identify subjects with underlying diseases that would expose them to health risks during sport (e.g. a worsening of clinical condition or the occurrence of cardiac events) (1-4). While great attention has been given so far to cardiovascular (CV) disorders (5, 6), interest is growing in other disorders that influence sport eligibility, especially as some of these may affect the CV system, such as endocrine diseases (7). It would be of great importance for the health of athletes to identify sport eligibility criteria according to different types of endocrine pathology. This would also underline the responsibility of sport-medicine physicians, particularly in those countries where it is mandatory for athletes to undergo pre-participation screening and to obtain an eligibility certificate before taking part in competitive sports. This study investigated sport eligibility in subjects affected by subclinical hyperthyroidism (sHT). This condition is characterized by very low or undetectable levels of circulating TSH, while the serum free thyroxine (\( FT_4 \)) and free triiodothyronine (\( FT_3 \)) remain within the normal limits, often in the absence of clinically evident symptoms and signs of hyperthyroidism (8). It is known that sHT can affect cardiac morphology and function (9-12) and represents a risk factor for CV complications (13), such as inappropriate sinus tachycardia, atrial tachyarrhythmia (including paroxysmal atrial fibrillation), impaired left ventricular (LV) diastolic function and systolic dysfunction during effort (10, 14). Indeed, even TSH suppressive therapy with levothyroxine (\( LT_4 \); i.e. exogenous sHT) has been shown to influence the CV system (8, 9, 15), impair exercise capacity (16, 17) and possibly increase mortality due to cardiac arrhythmias (14, 18).

Currently, despite great clinical interest, there are no evidence-based criteria to indicate how to guarantee safe sport participation or to lay down guidelines on granting sport eligibility certificates for subjects taking \( LT_4 \) for TSH suppression. Naturally, this would be particularly important in sports where the CV system is placed under severe strain (19). In addition, apart from the strain put on the CV system during sport training and competition, the CV risk in athletes may also be heightened by the many prohibited products taken in various disciplines; these “doping” substances can influence both CV morphology and function (i.e. stimulants, androgenic anabolic steroids, growth hormone, erythropoietin).

On this basis, the aim of this first, small-scale study was to obtain a preliminary idea of how mildly TSH suppressive therapy with \( LT_4 \) (20) might influence both CV parameters and individual sport eligibility, as assessed in the setting of mandatory pre-participation screening. To this

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end, we performed a more detailed pre-participation screening, including further CV examinations beyond the mandatory 12-lead ECG, in female subjects affected by not compressive non-toxic multinodular goiter, taking LT₄. These subjects were compared with a similar group of untreated patients and with matched healthy controls. To our knowledge, no studies concerning pre-participation CV screening and sport eligibility in subjects with LT₄-induced sHT exist in the literature.

MATERIALS AND METHODS

Study population

All the volunteers, affected by non-toxic multinodular goiter (no.=20) and controls (no.=12), were recruited in our Department and were included in one of the three study groups based on the following arbitrary criteria:

- treated group (TG; no.=10), made up of untrained Caucasian women, 30-45 years of age, who had been on LT₄-suppressive treatment for non-toxic multinodular goiter for at least 4 years and had had serum TSH concentration consistently between 0.1 and 0.4 mIU/l for at least 6-12 months, as assessed during, at least, two prior measurements and at the beginning of the study;
- untreated group (UG; no.=10), made up of untrained Caucasian women, 30-45 years of age, with multinodular non-toxic goiter diagnosed at least 4 years before the study. They were not taking any drugs and had had serum TSH concentration in the normal range for at least 6-12 months, at two prior measurements (minimum) and at the beginning of the study;
- healthy control (HC) group (no.=12), which included matched healthy Caucasian women, comparable for age, body size and level of habitual physical activity and with normal TSH and thyroid hormone profiles.

In order to eliminate the possible effects of exercise training on the CV system, we selected only subjects with a history of sport participation (e.g. team sports, track and field, running), but not trained at a competitive level for at least 4 years prior to the study. They practised physical activity at a low to moderate level, as evaluated by the International Physical Activity Questionnaire (IPAQ) (21). The selection criteria also included: a normal menstruation pattern; no smoking during the previous 5 years; no history or symptoms of thyroid or CV diseases, or other illnesses that could influence the results of this study; no taking of substances (e.g. drugs and/or nutritional supplements) known to alter endocrine function or the CV system.

We progressively included and evaluated our volunteers in the setting of mandatory pre-participation physical examinations performed to obtain an official sport eligibility certificate, before starting a specific training program for competitive sports. The study was approved by the local Scientific/Ethics Committee and written informed consent was obtained.

Endocrine evaluations

A single morning blood sample was collected from all volunteers between 07:30 and 08:30 h, taken from a forearm vein after an overnight fast. Treated volunteers were given LT₄ immediately after blood sample collection. Blood samples were placed on ice until centrifugation and serum separation. Serum samples were frozen at –40 C until analyzed for FT₃, FT₄ and TSH. All healthy volunteers underwent a thyroid ultrasonography (MyLab25, Esaote, Genova, Italy) evaluation before inclusion.

Serum FT₃ and FT₄ concentrations were measured by using the radioimmunometric method (Immunotech, Prague, Czech Republic). Serum TSH concentration was evaluated by an ultra-sensitive immunoradiometric method (Immunotech, Prague, Czech Republic), with a sensitivity of 0.025 mIU/l. The inter- and intra-assay coefficients of variation for FT₃, FT₄ and TSH were 5.5 and 6.4%, 7.5 and 8.3%, and 5.7 and 3.7%, respectively. The reference ranges were: 2.5-5.8 pmol/l for FT₃, 11.5-23.0 pmol/l for FT₄ and 0.45-4.5 mIU/l for TSH.

Cardiovascular evaluations

All the subjects were interviewed to evaluate the occurrence of symptoms of CV and/or thyroid origin, in particular, symptoms related to β-adrenergic hyper-activity (e.g. palpitations, muscle tremors, heat intolerance, sweating, anxiety) (17, 22, 23). The symptom rating scale (SRS) for sHT was also evaluated (24). Then, after familiarization with the medical environment and bicycle ergometer, all the subjects underwent a full physical examination, arterial blood pressure evaluation, 12-lead ECG, two-dimensional and Doppler-echocardiography, maximal exercise stress test and 24-hour Holter-ECG.

12-lead ECG

Standard 12-lead ECG was performed with an X-scribe II system (Mortara Instruments, Milwaukee, WI, USA) with the subject in supine position and recorded at 25 mm/sec. ECG patterns were evaluated according to the commonly adopted criteria (25). We focused our attention on ECG parameters described as an index for high CV risk in patients affected by sHT [i.e. increased P-R interval, P-wave maximum voltage (P max), P-wave dispersion (PWD), corrected QT interval duration (QTc)] (8,26-29).

Echocardiography

Two dimensional B-mode and M-mode study and Doppler-echocardiography evaluations were performed by using an ultrasound mechanical system equipped with 3.5 MHz transducer (Terason T-3000, Mortara Instruments, Milwaukee, WI, USA). All evaluations were performed by a single experienced cardiologist, blinded to the volunteer group, with the subject in the left lateral decubitus position using conventional parasternal and apical views, according to the American Society of Echocardiography standardization (30).

LV end-diastolic (LVEDD) and end-systolic (LVESD) dimension, interventricular septal thickness (IVST), LV posterior free wall thickness (LVPWT), transverse left systolic atrial diameter (LAD), aortic diameter (AoD) were measured, and LV mass index (LVMi) was calculated in all volunteers according to the formula of Devereux et al. (31). LV ejection fraction (LVEF) was calculated from end-diastolic and end-systolic volumes in the apical 4-chamber view. In patients with normal sinus rhythm, the early diastolic peak flow velocity (VE), late diastolic peak flow velocity (VA) and respective VE/VA ratio were also evaluated.

Maximal exercise stress test

Maximal exercise stress test was performed with a bicycle ergometer (Ergocard II, Ote Biomedica, Genova, Italy). The exercise load was increased 25 Watt every 2 min until exhaustion or when severe fatigue, weakness, dyspnea or severe ECG alter-