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No evidence of association between subclinical thyroid disorders and common carotid intima medial thickness or atherosclerotic plaque

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Abstract *Background and aims:* Increased carotid artery intima-media thickness (IMT) and the presence of plaques have been shown to be predictors of cardiovascular disease. The cardiovascular risk in patients with overt thyroid diseases is related to increased risk of atherosclerosis, but there has been no clear evidence about subclinical disorders. We have assessed whether subclinical thyroid dysfunction is associated with arterial thickening and plaque.
Methods and results: The SardiNIA study is a population-based survey on the Italian island of Sardinia. We reviewed data from 5815 subjects (aged 14–102 years), none of whom had overt hyperthyroidism or hypothyroidism or was taking thyroid medication. Serum thyrotropin (TSH), free thyroxine, together with carotid ultrasound IMT and the presence of common carotid plaques were analysed in all subjects. Possible association of IMT and carotid plaques with thyroid parameters was evaluated by univariate and multivariate analyses. IMT was significantly associated with age, sex, smoking, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol, pulse pressure (PP), history of arterial hypertension, diabetes, and previous cardiovascular events ($p = 0.001$ or lower, $R^2 = 0.47$). Carotid plaques were predicted by age, sex, LDL, PP, history of diabetes, previous cardiovascular events, and the use of statins ($p = 0.029$ or lower). Thyroid hormone was not predictive of carotid atherosclerosis when adjusted for confounders.
Conclusion: Thyroid hormone is not associated with increased IMT or with the presence of carotid artery plaque. Our data do not support the idea that treating subclinical disorders might help to prevent arterial remodelling or carotid atherosclerosis.

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Introduction

Atherosclerosis is a multifactorial disease involving the interplay of genetic and environmental factors, and is a leading cause of death and morbidity worldwide. Thickening of the common carotid intima-media is a typical sign of arterial aging in rodents, non-human primates and humans and is closely linked to atherosclerosis. Its measurement has been proposed as adding value to cardiovascular risk prediction [1,2].

Thyroid hormones exert relevant effects on the cardiovascular system, as clearly documented in overt thyroid dysfunctions. International guidelines suggest specific treatment for overt thyroid disorders [3,4] because the chronic exposure to clinically relevant abnormal concentrations of thyroid hormone may worsen some cardiovascular risk factors. In particular, hypothyroidism is associated with increased low density lipoprotein cholesterol (LDL) circulating levels [5], higher diastolic blood pressure (DBP), low-grade inflammation, and hypercoagulability [6]. On the other hand, hyperthyroidism is associated with increased heart rate, pulse pressure (PP), and pulse wave velocity [7,8] compared to euthyroid subjects. The relation between subclinical thyroid dysfunctions and atherosclerosis is less clear. Recent cross sectional studies analysing the association of thyrotropin (TSH) levels with intima-media thickness (IMT) in the general population reached varying conclusions [9,10].

In the present study we aimed to examine whether subclinical thyroid dysfunctions are associated with accelerated arterial remodelling, thereby increasing the risk for atherosclerosis.

Methods

The SardiNIA study investigates more than 300 genotypic and phenotypic aging-related traits in a longitudinal survey [11]. From the initial sample of 6148 individuals, subjects who reported taking thyroid medications (thyroid hormone replacement or thyrostatics) or drugs that alter thyroid function tests (amiodarone, lithium, and corticosteroids) were excluded. For the present study, we also excluded subjects with overt thyroid dysfunction (both hypothyroidism and hyperthyroidism), yielding a final sample of 5815 (aged 14–102 years). All had routine medical examinations including i) measurements of height, weight, systolic blood pressure (SBP) and DBP; ii) medical history, including therapy; iii) blood sampling (see below); and iv) carotid ultrasound (see below).

Each participant signed an informed consent form. All study methods were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the governing Ethics Committee, Azienda Sanitaria Locale 4 (ASL4).

Biochemical and hormone assays

Venous blood samples were drawn between 7 and 8 a.m. after an overnight fast. Serum samples were stored at −80 °C until use. Plasma triglycerides and total cholesterol were determined by an enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, TX, USA). High density lipoprotein cholesterol (HDL) was determined by dextran sulphate–magnesium precipitation. LDL concentrations were estimated by the Friedewald formula. Fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments Inc., Fullerton, CA, USA).

TSH and free thyroxine (FT4) were assessed with a two-site, solid-phase chemiluminescent immunometric assay, as described elsewhere [8]. Normal values for TSH are 0.4–4.0 μIU/ml and for FT4: 0.89–1.76 ng/dl.

We defined subclinical thyroid dysfunction as the presence of serum FT4 level in the normal reference range together with high serum TSH (subclinical hypothyroidism) or low serum TSH (subclinical hyperthyroidism). Euthyroidism was defined as the presence of TSH concentration within the reference range.

Arterial structure

Carotid ultrasound was performed with a linear-array, 5- to 10-MHz transducer (Ultramark 9 HDI, Advanced Technology Laboratories, Inc., Seattle, Washington), as previously described [12]. Briefly, the subject was placed in the supine position with his/her neck in extension and rolled contralaterally by about 45°. The right common carotid artery was examined at 1.5 cm proximal to the carotid bifurcation. IMT was evaluated as the distance between the lumen-intima interface and the media-adventitia interface. A single sonographer manually measured the IMT on the frozen frame of a suitable longitudinal image off-line. He was blinded to the identity of the subject. IMT value was calculated by averaging 5 consecutive measurement points (in 1-mm steps).

Carotid plaques were identified on the basis of subjective criteria of the sonographer and defined as a focal encroachment of the arterial wall [13].

Definition of cardiovascular risk factors

Hypertension was defined as SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg, and/or self-reported use of antihypertensive drugs. PP was defined as SBP − DBP. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Diabetes mellitus was defined as self-reported diagnosis of diabetes and/or self-reported use of antidiabetic drugs or elevated fasting glycated haemoglobin or fasting glycaemia, according to the American Diabetes Association guidelines [14]. Smokers were defined as current consumers of at least one cigarette per day. We defined the term “cardiovascular event” as the documented history of myocardial infarction or stroke.

Statistical analysis

Since continuous variables were not distributed normally (Shapiro–Wilk test), nonparametric tests (Wilcoxon rank-sum