Subclinical Hypothyroidism with TSH > 7 mIU/l and ≤ 10 mIU/l and Coronary Artery Disease

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ABSTRACT

The association of subclinical hypothyroidism (SCH) with increased cardiovascular risk is controversial when thyroid-stimulating hormone (TSH) concentration is < 10 mIU/l, as well as its association with a higher coronary artery calcium score (CACS) in individuals with low cardiovascular risk. This study evaluated coronary artery disease (CAD) by CACS in asymptomatic, low-cardiovascular risk women with SCH and TSH > 7 mIU/l and ≤ 10 mIU/l untreated for 5 years after diagnosis. The CACS was obtained for two groups of women with low cardiovascular risk. Group A consisted of 32 women with mild SCH (TSH > 7 mIU/l and ≤ 10 mIU/l) who remained untreated for 5 years, and group B consisted of 32 euthyroid women matched for age and body mass index to group A. The CACS ranged from 0 to 350 (median 0, 25–75 % interval: 0–10) in group A and from 0 to 280 (median 0, 25–75 % interval: 0–0) in group B. Scores > 0 and ≥ 10 were significantly more frequent in group A (40.6 vs. 12.5 % and 25 vs. 3.1 %, respectively). A CACS ≥ 100 was also more frequent in group A (18.75 vs. 3.1 %), but the difference was not significant (p = 0.1). The results of the study suggest that long-term SCH with TSH > 7 mIU/l and ≤ 10 mIU/l is associated with a higher risk of CAD in individuals ≤ 65 years, even in those with low cardiovascular risk.

Introduction

Subclinical hypothyroidism (SCH) is a common condition in adults, particularly in women. A major concern is the possible association of SCH with a higher risk of cardiovascular events. This association is more consistent in patients with thyroid-stimulating hormone (TSH) > 10 mIU/l [1]. In individuals with TSH < 10 mIU/l, which account for about 80 % of cases of SCH [2, 3], an increase in cardiovascular outcomes is less convincing and might be possible if TSH > 7 mIU/l [1, 4].

The coronary artery calcium score (CACS) is considered an excellent noninvasive method for the detection of coronary artery disease (CAD) [5]. In addition, the CACS is a predictor of the occurrence of cardiovascular events even in asymptomatic patients without classical risk factors [6]. Some studies have evaluated the association between SCH and high CACS [7–10]. Whereas an association has been demonstrated in patients with intermediate or high cardiovascular risk [7, 8], the data for low-risk patients are conflicting [8–10]. Accordingly, current guidelines suggest levothyroxine (L-T4) therapy of SCH with TSH ≤ 10 mIU/l based on cardiovascular risk only in patients less than 65–70 years of age who are at moderate/high risk, such as patients with dyslipidemia or diabetes mellitus [2, 3, 11–13].

The objective of this study was to evaluate CAD by CACS in women without classical cardiovascular risk factors who have SCH and TSH > 7 mIU/l and ≤ 10 mIU/l. Since the duration of thyroid dysfunction is important for the possible occurrence of repercussions

[11], only patients with persistent SCH for 5 years after diagnosis were evaluated.

Patients and Methods

The study was approved by the Research Ethics Committee of our Institution and informed consent was obtained from each patient.

Patients

CACS was performed in the following two groups:

Group A

This group was derived from a prospective study that evaluated the natural history of SCH with TSH ≤ 10 mIU/l and whose results have been previously published [14]. In summary, 252 women with SCH (serum TSH between 4.5 and 10 mIU/l and normal free T4 concentrations in two measurements obtained at an interval of 12 weeks and after exclusion of other causes of hyperthyrotropinemia) were followed up for a period of 5 years [14]. Among the 241 patients followed up until completion of the study (at the end of 5 years), 46 required L-T4, 55 had spontaneous normalization of serum TSH, and 140 continued to meet the criteria for mild SCH [14]. Among the last patients, 32 who met the selection criteria below were selected.

Group B

After the formation of group A, a second group was obtained for comparison. Among women consecutively evaluated by us, euthyroid patients (TSH 0.5–3.5 mIU/l) who also met the selection criteria were recruited. Women who matched those of group A for age and body mass index (BMI) were selected intentionally. Group B was complete when the same number of participants as in group A was reached.

Selection criteria

Exclusion criteria: history of myocardial infarction or stable or unstable angina; stroke or transient ischemic attack; non-traumatic amputation; revascularization surgery, angioplasty or stent placement in any vascular territory; heart failure; known atherosclerotic disease in any vascular territory detected by previous imaging; smoking; history of coronary events in a first-degree relative less than 55 years if male or less than 65 years if female; use of antihypertensive, statin, antihyperglycemic, or antiplatelet agents.

Inclusion criteria: TSH > 7 mIU/l and ≤ 10 mIU/l in two measurements obtained for the diagnosis of SCH and in the last assessment of group A; fasting glucose < 100 mg/dl and HbA1c 39 mmol/mol (< 5.7 %); blood pressure < 140/90 mmHg; HDL cholesterol > 50 mg/dl; LDL cholesterol < 160 mg/dl; glomerular filtration rate (GFR), calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, > 60 ml/min/1.73 m^2.

Assays

TSH and free T4 were measured with a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA), with reference values of 0.4–4 mIU/l and 10.3–23 pmol/l, respectively.

CACS

Computed tomography for CACS followed the recommendations of international protocols [15]. The CACS was expressed as Agatston units. There is consensus that a CACS ≥ 300 indicates very high risk [5, 16], but a score ≥ 100 is already considered to be associated with high cardiovascular risk [5, 16, 17]. Finally, even asymptomatic individuals with a CACS between 1 and 10 are already at an increases risk of cardiovascular events when compared to those with a score of 0 [5, 17]. We therefore analyzed the following cut offs: 0, 10, 100, and 300.

Statistics

Fisher's exact test, Mann–Whitney U-test (comparison between the two groups), and logistic regression were used for statistical analysis. The two-tailed Pearson correlation coefficient test was used to analyze the correlation of CACS with TSH values. A p-value < 0.05 was considered significant.

Results

▶ **Table 1** shows the characteristics of the women on the occasion of computed tomography for CACS. In addition to age and BMI, groups A and B were similar in terms of blood pressure, glucose, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and GFR.

The CACS ranged from 0 to 350 (median 0, 25–75 % interval: 0–10) in group A and from 0 to 280 (median 0, 25–75 % interval: 0–0) in group B. The frequency of a high CACS, considering the different cut offs (see Methods), is shown in ▶ **Table 1**. CACS > 0 and ≥ 10 were significantly more frequent in group A (untreated SCH), even after adjusting for the parameters of ▶ **Table 1**. Although the frequency of a CACS ≥ 100 was apparently also higher in group A, the difference did not reach statistical significance. In our study, only one patient (from group A) had a CACS > 300. Finally, no correlation was found between TSH values and CACS (p = 0.2).

Discussion

This study evaluated patients with TSH ≤ 10 mIU/l because this group accounts for approximately 80 % of cases of SCH [2, 3], because greater controversy regarding the association of SCH with CAD exists for these TSH concentrations [1], and because of the greater debate about the need for treatment of SCH [2, 3, 11–13]. Patients > 65–70 years of age were not evaluated because L-T4 therapy in SCH with TSH ≤ 10 mIU/l does not seem to provide any benefit in this group [18–20] or might be even deleterious [21], and because there is consensus that treatment would not be indicated [2, 3, 11–13]. Patients with low cardiovascular risk were selected since the association of SCH with high CACS is more controversial in this population [8–10], while it is more consistent in intermediate/high-risk patients [7, 8]. In individuals < 65–70 years of age with high cardiovascular risk or classical risk factors such as diabetes and dyslipidemia, treatment of SCH is already recommended, especially if TSH > 7 mIU/l [2, 3, 11–13]. Finally, CACS were obtained after persistence of SCH for 5 years since repercussions depend on the duration of the disease [11] and may not be detected at the time of diagnosis.

▶ **Table 1** Characteristics of the women included in the study and frequency of a high CACS in groups A and B.

	Group A (n = 32)	Group B (n = 32)	p-Value
Age (years) (median)	27–66 (47)	26–65 (45)	1.0
BMI (kg/m^2) (median)	18.5–33.1 (23.5)	18.8–33 (23.3)	1.0
TSH (mIU/l) (median)	7.1–10 (8.7)[†]	–	
	7.2–10 (8.9)[*]	0.6–3.2 (1.8)[*]	< 0.001
SBP (mmHg) (median)	95–130 (118)	95–135 (116)	0.9
DBP (mmHg) (median)	60–85 (75)	60–85 (73)	0.85
Glucose (mg/dl) (median)	66–99 (81)	68–99 (84)	0.88
Total cholesterol (mg/dl) (median)	135–255 (210)	130–246 (200)	0.2
LDL cholesterol (mg/dl) (median)	65–158 (128)	58–149 (122)	0.3
HDL cholesterol (mg/dl) (median)	51–85 (60)	51–80 (61)	1.0
Triglycerides (mg/dl) (median)	55–148 (105)	60–145 (110)	0.8
eGFR (ml/min/1.73 m^2)	65–135 (106)	68–138 (109)	0.9
CACS			
>0	13 (40.6%)	4 (12.5%)	0.022
≥10	8 (25%)	1 (3.1%)	0.026
≥100	6 (18.75%)	1 (3.1%)	0.1
≥300	1 (3.1%)	0	

Group A: Untreated subclinical hypothyroidism; Group B: Euthyroid; BMI: Body mass index; TSH: Thyrotropin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; eGFR; Estimated glomerular filtration rate calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; CACS: Coronary artery calcium score. [†] In the diagnosis. [*] During the evaluation of CACS.

Our results suggest a higher risk of CAD, evaluated here by CACS, in patients ≤ 65 years with SCH and TSH ≤ 10 mIU/l but > 7 mIU/l, even in those classified as low cardiovascular risk. The difference in the frequency of CACS > 0 and ≥ 10 was significant and there was also a trend towards a higher frequency of a CACS ≥ 100 in patients with untreated SCH. We believe that this finding did not reach statistical significance because of its low frequency and the number of participants in the study. It is important to stress that the results were obtained in patients with TSH > 7 mIU/l. This finding agrees with a previous study that evaluated the association between clinical CAD and SCH [1]. This cut off has also been recommended by many authors for the indication of L-T4 when based on cardiovascular risk [1, 3, 4, 13].

We found no difference between patients and controls for cholesterol concentrations (total, HDL, and LDL) or systolic and diastolic blood pressure levels. We attribute this lack of difference to the selection criteria of the study. First, women with dyslipidemia and arterial hypertension were excluded, a fact that might have minimized differences between groups. Second, only patients with TSH ≤ 10 mIU/l were evaluated and it is known that the impact of SCH on these parameters is lower at these TSH concentrations. The similarity observed between the groups suggests that the possible association of SCH with CAD cannot be fully explained by these parameters (dyslipidemia and blood pressure).

We recognize that our study has some limitations. First, we did not evaluate cardiovascular events but rather CAD by CACS. How-

ever, a CACS > 0 is diagnostic of the presence of CAD and the CACS is directly related to the short- and long-term risk of cardiovascular events [5, 6, 16, 17], even in asymptomatic individuals and those without classical risk factors [6], like the participants in the present study. Second, the effect of SCH treatment on CAD risk was not evaluated in the population studied. Third, the sample may have been insufficient to detect differences in higher CACS between the groups.

In conclusion, the results of the present study indicate a higher risk of CAD (evaluated by CACS) in women ≤ 65 years with persistent SCH (at least 5 years) and with TSH > 7 mIU/l and ≤ 10 mIU/l, even in the population classified as low cardiovascular risk. Randomized studies evaluating the effect of treatment of SCH in this subgroup would be desirable.

Funding

Conflict of Interest

The authors declare that they have no conflict of interest.

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