Subclinical hypothyroidism represents an additional risk factor for coronary artery calcification, especially in subjects with intermediate and high cardiovascular risk scores

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Abstract

Objective: Several studies have suggested an association between subclinical hypothyroidism (SCH) and increased cardiovascular risk. The aim of this study was to evaluate the presence of coronary artery disease (CAD) in asymptomatic patients with SCH by measuring the coronary artery calcium score (CACS).

Design: A total of 222 asymptomatic subjects (103 SCH and 119 euthyroid (EU)), who were between the ages of 35 and 65 years and had no previous history of CAD, were enrolled for this cross-sectional analysis.

Methods: The criteria for SCH included a confirmed normal serum free thyroxine and high TSH levels. Lipid profile, Framingham risk score (FRS) and CACS analyses were performed for all subjects.

Results: The SCH and EU groups were comparable with respect to age, gender, BMI and frequency of diabetes, systemic arterial hypertension, hypercholesterolaemia and smoking. There was no difference in the median CACS between the SCH and EU groups. However, in the subgroup of subjects with intermediate/high FRS ($AR_{10y} \geq 10\%$), CACS was higher in the SCH subjects compared with EU subjects (EU vs SCH, 0.0 (57.0) vs 23.0 (161.5); $P=0.045$). Multivariate analysis revealed that the risk for CACS > 100 was independently associated with male gender, age > 55 years, and the presence of simultaneous SCH and $AR_{10y} \geq 10\%$ (OR=87.5 (CI=2.1–3500); $P=0.001$). Serum TSH was positively correlated with CACS, especially in intermediate/high FRS subjects ($r_s=0.301$, $P=0.045$).

Conclusions: It was demonstrated that SCH represents an additional risk factor for CAD, notably in intermediate and high FRS subjects.

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Introduction

Subclinical hypothyroidism (SCH), which affects 4–20% of the general population, is defined by an increased serum thyrotropin (TSH) concentration with a normal serum free thyroxine (FT₄) level (1, 2, 3, 4). SCH may be graded as mild (serum TSH, 4.5–9 mU/l) or moderate/severe (serum

TSH, ≥ 10 mU/l) (5), but its clinical significance remains controversial (6). One unanswered question is whether individuals with SCH have only biochemical abnormalities or whether there are significant effects of mild thyroid failure and perhaps the need for levothyroxine (L-T₄)

replacement (7, 8, 9, 10). Previous studies have also suggested an association between SCH and coronary artery disease (CAD) (11, 12, 13, 14). However, whether this association is related to SCH-induced changes in the serum lipid profile or other classical cardiovascular (CV) risk factors remains unclear (15, 16). Some studies have found that subjects with SCH have higher serum total cholesterol (TC) and LDL cholesterol (LDL-C) levels compared with euthyroid (EU) subjects (17, 18). Despite these findings, the impact of L-T₄ replacement on this endpoint, especially in the setting of mild thyroid dysfunction, has been somewhat conflicting in several studies (19, 20, 21, 22). To determine a causative effect between SCH and CV risk factors and possible CV events or mortality, several small clinical trials have assessed the impact of SCH treatment on different adverse endpoints such as dyslipidaemia and blood pressure. Although no clinical trials have assessed the impact of L-T₄ replacement on CV events or mortality, indirect evidence from cohorts have suggested that part of the benefit of treating patients with SCH seems to be derived from a possible reduction in CV morbidity and mortality (23, 24, 25).

Coronary calcification is extremely specific for atherosclerosis, and the amount of coronary calcium is a marker of the total atherosclerotic burden. As a result, the coronary artery calcium score (CACS) has been shown to be the best noninvasive method for CV event prediction in asymptomatic subjects (26, 27, 28, 29). The aim of this study was to evaluate the association between SCH and CACS and to correlate these findings with clinical and biochemical data.

Subjects and methods

Study population

This cross-sectional study was approved (protocol number 069/10) by the Ethical Committee of Clementino Fraga Filho University Hospital (HUCFF) in Rio de Janeiro, Brazil. Written informed consent was obtained from each patient.

A total of 103 SCH outpatients and 119 individuals without thyroid dysfunction (EU subjects) were enrolled from September 2010 to April 2013. All participants were aged between 35 and 65 years at the time of enrolment.

SCH patients were recruited from the endocrine outpatient clinic of HUCFF. The controls were recruited among the patient escorts, hospital staff and volunteers without known CAD disease.

To be eligible for inclusion, SCH patients had to show slightly increased serum TSH levels ($4.0 < \text{TSH} < 10.0$ mU/l) and normal serum FT₄ levels ($0.8\text{--}1.9$ ng/dl) in at least two measurements taken no < 2 months apart. All SCH patients had autoimmune primary hypothyroidism. The control group had no history of thyroid disease and had normal values for serum TSH, FT₄ and anti-thyroid peroxidase antibody (TPO-Ab). The exclusion criteria for this study included known CAD, use of drugs that could interfere with thyroid function or the lipid profile (e.g. statins), use of anti-platelet drugs, hospitalisation within the last 2 months, pregnancy and a history of any disease known to interfere with circulating thyroid hormone levels (e.g. nephrotic syndrome, renal failure, liver failure and AIDS).

Clinical and biochemical parameters

Specific anamnesis and general physical examinations were done. The Framingham risk score (FRS) was calculated according to the data obtained, including gender, age, serum TC, serum HDL-C, systolic blood pressure and smoking status (30). According to the FRS, all diabetic patients were classified as high risk (>20%). Height and weight were measured with participants barefoot and wearing light clothing. Systolic and diastolic blood pressures were measured in each arm with the patients at rest for at least 10 min, with a 5 min interval between measurements, using a pneumatic sphygmomanometer. BMI was calculated as weight (kg) divided by height squared (m²).

The blood samples were collected from patients after 12 h of fasting. This analysis was performed at a maximum interval of 4 months before cardiac computed tomography (CT) imaging. Serum measurements of TSH, FT₄, TPO-Ab, TC, triglycerides (TGs), HDL-C, LDL-C, non-HDL-C and glucose were carried out. The samples were centrifuged and analysed immediately after collection. The serum TSH, FT₄ and TPO-Ab levels were measured by immunochemiluminescence (Immulite 2000; DPC (Diagnostic Products Corporation, Los Angeles, CA, USA)). The reference ranges for TSH and FT₄ were $0.4\text{--}4.0$ mU/ml and $0.8\text{--}1.9$ ng/dl, respectively, and a TPO-Ab level >35 IU/ml was considered positive. Intra-assay coefficients of variation (CV) were 3.8–12.5, 4.4–7.5, and 4.3–5.6%, and inter-assay CV were 4.6–12.5, 4.8–9.0 and 7.8–10.5% for TSH, FT₄ and TPO-Ab respectively.

The levels of TC, TG and HDL-C were measured with an immunoenzymatic assay kit (Dimension Flex, Siemens, Erlangen, Germany). LDL-C was calculated using the

Friedewald equation, where $LDL = (TC - HDL) - (TG/5)$. Non-HDL-C was calculated using the following formula: $non-HDL-C = TC - HDL-C$. Reference ranges for TC, HDL-C, TG and LDL-C were based on the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) (30). Glucose was measured using the kinetic u.v. hexokinase method with a Dade Behring Dimension RXL analyser. The reference range for glucose was 70–99 mg/dl. The sensitivity of the method was 0.80 mg/dl, with inter- and intra-assay CV being 1.4 and 2.82% respectively.

Cardiac CT imaging: CACS

CACS scans were performed using 64-slice (Somatom Sensation, Siemens) and 256-slice (Brilliance iCT, Philips, Best, The Netherlands) scanners with the following standard parameters: axial acquisition with collimation, 32×3 mm and no gap, and 65% (for Siemens) or 75% (for Philips) cardiac phases. The tube voltage was 120 kVp, and the amperage was adjusted according to body habitus. The Agatston calcium score was calculated for all exams in offline remote workstations (Leonardo for Siemens and Philips Portal) (31). We carefully followed the calcium scoring protocol recommended in current guidelines (32). The inter scanner variability for the calcium score between a 64 multi-slice scanner and Electron Beam CT was previously studied by Mao *et al.* (33), who demonstrated an inter scanner agreement of 99% for the presence of coronary calcium and a strong linear relationship between the two scanners (33).

According to their CACS values, the participants were classified as follows: $CACS = 0$, no calcification; $0.1 \leq CACS \leq 100$, mild calcification and $CACS > 100$, moderate to severe calcification (34).

Statistical analysis

Statistical analysis was performed using the SPSS for Windows programme, version 13.0. Continuous variables were reported as median values (interquartile range) and compared between two groups using the Mann–Whitney *U* test because the majority of variables were not uniformly distributed. Comparisons among three or more groups were assessed with the Kruskal–Wallis test. Categorical variables were expressed as percentages and compared with the χ^2 test or Fisher's exact test. Analysis of the correlation between two variables was performed using Spearman's correlation coefficient (r_s). A *P* value < 0.05 was considered to be statistically significant.

Binary logistic regression was applied to detect, in multivariate analysis, the specific covariates that were independently associated with a CACS > 100 . Those covariates were included in three steps (method=enter), with the following variables included in the first step: high blood pressure, diabetes, dyslipidaemia, obesity, male gender, age > 55 years, smoking habits and isolated SCH. In the second step, absolute risk of a CV event in 10 years ($AR_{10y} \geq 10\%$) was added to the analysis, and the presence of simultaneous or combined SCH + $AR_{10y} \geq 10\%$ was added to the third step. Stratified analysis was also performed to detect differences in specific comparisons according to specific groups ($AR_{10y} \geq 10$ or $< 10\%$).

Results

The clinical and biochemical analysis results for all 222 enrolled subjects (103 SCH and 119 EU) are summarised in Table 1. The SCH and EU groups were similar in terms of gender distribution, age, BMI and frequencies of diabetes,

Table 1 Comparison of clinical and biochemical characteristics according to thyroid function. Continuous variables: median (interquartile range).

	Total		
	SCH (<i>n</i> = 103)	EU (<i>n</i> = 119)	<i>P</i> value
Age (years)	54.0 (12.3)	52.3 (12.0)	0.990
Female (%)	82.6	78.1	0.214
TSH (mU/ml)	5.8 (2.6)	1.7 (1.2)	< 0.001
FT ₄ (ng/dl)	1.0 (0.2)	1.2 (0.3)	< 0.001
Smoking (%)	6.9	9	0.145
Diabetes (%)	11.7	7.9	0.240
Hypertension (%)	41.4	33.7	0.288
Obesity (%)	40.4	30.3	0.361
BMI (kg/m ²)	28.4 (7.8)	27.3 (6.9)	0.580
SBP (mmHg)	130.0 (27.0)	120.0 (20.0)	0.480
DBP (mmHg)	80.0 (20)	80.0 (20)	0.740
FBG (mg/dl)	93.0 (14.0)	93 (13.0)	0.570
TC (mg/dl)	201.5 (48.5)	211.0 (57.0)	0.308
HDL-C (mg/dl)	47.0 (15.2)	58.0 (21.0)	< 0.001
LDL-C (mg/dl)	125.5 (22.0)	128.0 (48.0)	0.896
TG (mg/dl)	116.0 (82.5)	98.0 (73.0)	0.010
Non-HDL-C (mg/dl)	153.0 (54.0)	154.0 (56.0)	0.392
FRS	12.0 (5.0)	11.0 (5.0)	0.002
AR _{10y} (%)	4.9 ± 6 (2.2)	3.8 ± 5.4 (2.2)	0.048
Low AR _{10y} (%)	84.3	85.2	
Intermediate AR _{10y} (%)	4.9	7.0	0.628
High AR _{10y} (%)	10.8	7.8	

SCH, subclinical hypothyroidism; EU, euthyroid; TSH, thyrotropin; FT₄, free thyroxine; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FRS, Framingham risk score; AR_{10y}, absolute risk of cardiovascular event in 10 years by FRS.

systemic arterial hypertension, hypercholesterolaemia and smoking. Higher TG ($P=0.01$) and lower HDL-C levels ($P=0.001$) were found in the SCH group. The serum TSH level in the SCH group ranged from 4.1 to 10.0 mU/l, and those in the control group ranged from 0.5 to 3.9 mU/l. The serum FT₄ level in the SCH and control group ranged from 0.8 to 1.8 ng/dl.

The absolute risk of a CV event in 10 years (AR_{10y}) was analysed by splitting the results into three FRS categories: low risk (<10%), intermediate risk (10–20%) and high risk (>20%). The SCH and EU groups were comparable with respect to the frequencies of FRS categories, with most subjects showing a low risk (Table 1). However, the mean AR_{10y} (2.2 (5.0) vs 2.2 (3.0); $P=0.048$) and mean FRS ($P=0.002$) values were higher in the SCH group in each category.

There were no differences in the mean CACS between the SCH and EU groups in a global analysis, and the frequency of CACS >100 was not higher in the SCH group.

After evaluating all participants, SCH was not associated with a high risk for moderate to severe calcification in the bivariate analysis (OR=1.448 (CI=0.575–0.364); $P=0.430$) or multivariate analysis (Table 2). Logistic binary regression detected that the risk for a CACS >100 was independently associated with male gender, age >55 years and the presence of simultaneous SCH and AR_{10y} ≥ 10% (OR=87.5 (CI=2.1–3500); $P=0.001$), as given in Table 2.

As the FRS findings differed significantly between the SCH and EU groups, we performed a stratified analysis of the CACS to compare more homogeneous groups. Specifically, the participants of both groups were divided

according to their FRS AR_{10y} into two categories: low risk (AR_{10y} <10%) and intermediate/high risk (AR_{10y} ≥ 10%). These comparisons between SCH and EU subjects in the two categories of FRS AR_{10y} (low risk and intermediate/high risk) showed that all subjects were comparable in terms of age, gender, BMI, smoking, hypertension and diabetes frequency (Table 3).

When only the intermediate/high risk subgroup was considered, the mean CACS and the frequency of a CACS >100 were higher among SCH subjects compared with EU subjects (Table 4).

Serum TSH was positively correlated with CACS in the intermediate/high risk subgroup ($r_s=0.301$, $P=0.045$) but not in the entire group ($r_s=0.088$, $P=0.098$). In addition, SCH was associated with a high risk for a CACS >100 in the intermediate/high risk group (OR=11.2 (CI=1.19–105); $P=0.02$), although this association was reduced when smoking was included in the multivariate analysis (OR=11.2 (CI=1.00–125); $P=0.050$). However, smoking was not an independent risk factor for a CACS >100 in this subgroup of subjects, when other factors such as EFR category or SCH presence were considered (OR=11.2 (CI=0.99–128); $P=0.852$).

Discussion

To our knowledge, this is the second published study to evaluate the association between coronary disease and SCH using CACS evaluation. We observed that the CACS was higher and more severe in SCH patients when an intermediate/high risk for CV disease development was present (AR_{10y} ≥ 10%). This result is in accordance with the hypothesis that SCH leads to atherosclerosis by

Table 2 Logistic binary regression analysis of the analysed parameters associated with the risk of CACS > 100.

Variables	Block 1 ^a		Block 2 ^b		Block 3 ^c	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Hypertension	0.87 (0.20–3.9)	0.85				
Diabetes	3.29 (0.56–19.30)	0.18				
Dyslipidaemia	2.41 (0.40–14.74)	0.34				
Obesity (BMI ≥ 30)	0.99 (0.22–4.59)	0.99				
Gender (male)	7.47 (1.34–41.6)	0.02	14.00 (1.92–102.11)	0.01	12.96 (1.70–95.88)	0.01
> 55 years old	3.41 (0.63–18.5)	0.15			7.47 (1.10–52.20)	0.04
Smoking	0.01 (0.00–2.8)	0.79				
SCH	1.9 (0.35–10.45)	0.46				
Isolated AR _{10y} ≥ 10%			6.26 (0.44–87.7)	0.173		
SCH + AR _{10y} ≥ 10%					87.5 (2.1–3500)	0.02

SCH, subclinical hypothyroidism.

^aMethod = enter.

^bIncluding isolated AR_{10y} ≥ 10%.

^cAdding combined or simultaneous SCH + AR_{10y} ≥ 10% in the analysis.

Table 3 Comparison of clinical and biochemical characteristics according to AR_{10y} by FRS. Continuous variables: median (interquartile range).

	Low risk			Intermediate/high risk		
	SCH (87)	EU (102)	P value	SCH (16)	EU (17)	P value
Age (years)	53.0 (13.1)	51.2 (11.5)	0.230	57.0 (8.7)	56.7 (9.3)	0.191
female (%)	92.0	84.7	0.135	37.5	35.3	0.895
TSH (mU/l)	6.2 (2.4)	1.7 (1.2)	<0.001	5.1 (2.1)	1.6 (1.4)	<0.001
FT ₄ (ng/dl)	1.0 (0.2)	1.1 (0.3)	<0.001	1.0 (0.3)	1.2 (0.3)	<0.001
Smoking (%)	5.3	10.0	0.270	16.7	0	0.060
Diabetes (%)	1.2	0	0.294	68.8	52.9	0.356
Hypertension (%)	37.3	29.2	0.294	66.7	56.3	0.576
Obesity (%)	40.0	33.0	0.300	42.9	37.5	0.400
BMI (kg/m ²)	28.0 (8.4)	28.8 ± 6.0 (28.0)	0.943	28.7 (6.6)	26.0 (6.8)	0.682
SBP (mmHg)	124.0 (23.5)	120.0 (30.0)	0.976	144.5 (30.0)	120.0 (56.7)	0.352
DBP (mmHg)	80.0 (10.0)	80.0 (10.0)	0.965	90.0 (27.0)	75.0 (45.0)	0.476
FBG (mg/dl)	92.0 (14.0)	91.0 (11.0)	0.552	110.0 (44.0)	109.0 (16.8)	0.520
TC (mg/dl)	203.0 (47.0)	211.0 (53.3)	0.313	190.0 (93)	201.0 (59.5)	0.892
HDL-C (mg/dl)	48.0 (17.0)	59.0 (22.0)	<0.001	39 (12)	46 (23.5)	0.160
LDL-C (mg/dl)	127.0 (145)	130.0 (51.7)	0.955	108.0 (23.5)	117.0 (54.5)	0.892
TG (mg/dl)	113.0 (64.0)	97.0 (59.7)	0.021	175.0 (152.0)	122 (12.0)	0.322
Non-HDL-C (mg/dl)	154.0 (50.0)	154.5 (57.5)	0.557	153.0 (153)	155.0 (46.5)	0.892

SCH, subclinical hypothyroidism; EU, euthyroid; TSH, thyrotropin; FT₄, free thyroxine; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FRS, Framingham risk score; AR_{10y}, absolute risk of cardiovascular event in 10 years by FRS.

augmenting classical CV risk factors such as dyslipidaemia and systemic hypertension (6). Indeed, positive correlations between serum TSH and blood pressure (35, 36) and between TSH and serum lipids (2, 37, 38) have been demonstrated in several studies. In addition, a potential relationship between SCH and metabolic syndrome and a reduction in insulin sensitivity have also been proposed (39, 40), and SCH also seems to be associated with additional CV risk factors.

The results of this study are consistent with the findings of a recent publication (41) showing a higher CACS in male SCH patients. However, this previous study only evaluated subjects with an intermediate/high CV risk, most of them males, which most likely explains the weak association between SCH and an abnormal CACS in females. This previous study also evaluated coronary CT angiography and found no difference in the prevalence of obstructive CAD between the SCH and EU groups.

The population evaluated in this study was mostly female, which is consistent with the higher prevalence of SCH among the female population in general (4). In addition, we performed a subgroup analysis of low and intermediate/high FRS subjects, whereas the previous study only evaluated intermediate to high-risk subjects in a retrospective approach.

The positive correlation between serum TSH levels and CACS also supports recent findings showing that a higher CAD risk has been linked to serum TSH levels > 7.0 mU/l (11). Predicting CAD risk in asymptomatic individuals is challenging in clinical practice, and the CACS is a useful screening tool (27, 42, 43). Coronary calcification is highly specific for atherosclerosis and represents the cumulative effects of risk factors and vascular age (44). In particular, greater numbers of atherosclerotic plaques are associated with increased plaque instability, with an increasing risk of acute coronary events (26). The Multi-Ethnic Study

Table 4 CACS results according to thyroid function and FRS. Continuous variables: median (interquartile range).

	Total			Low risk			Intermediate/high risk		
	SCH	EU	P value	SCH	EU	P value	SCH	EU	P value
CACS	0.0 (11.3)	0.0 (4.0)	0.389	0.0 (0.0)	0.0 (3.2)	0.036	23.0 (161.5)	0.0 (57.0)	0.045
CACS > 100 (n/%)	10/9.7	9/7.6	0.582	3/3.5	8/8.2	0.182	7/43.8	1/5.9	0.01

CACS, coronary artery calcium score; FRS, Framingham risk score; SCH, subclinical hypothyroidism; EU, euthyroid; n, total numbers.

of Atherosclerosis (MESA) demonstrated the usefulness of the CACS as a CAD screening test, notably in the female subgroup where the FRS presents low accuracy (45, 46). The absence of coronary calcification in asymptomatic patients is associated with a good CV prognosis, whereas in symptomatic patients or individuals with risk factors, a negative CACS evaluation should be followed by another diagnostic test, as there is a high risk for non-calcified coronary plaques in such patients (47). CACS may also be used to identify and stratify high-risk patients, such as uremic patients, to implement preventive strategies, as demonstrated by Splendiani *et al.* (48).

The major limitation of this study was the choice of a cross-sectional design, as this approach does not support an analysis of cause or consequence. Another limitation was the lack of information concerning the duration of thyroid disease in all studied individuals and the presence of other CV risk factors that are not assessed in the FRS. For example, alcohol consumption was one such factor not evaluated in this study.

In conclusion, we found that SCH may represent an additional risk factor for CAD, notably among intermediate and high FRS patient subgroups. In this context, it is imperative that randomised, placebo-controlled studies be carried out to explore the impact of L-T₄ in minimising CV risk in this population.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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