CLINICAL STUDY

Impact of subclinical hypothyroidism on the coronary artery disease in apparently healthy subjects

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Abstract

Objective: Cardiovascular disease (CVD) occurs frequently and may progress more rapidly in overt hypothyroidism (OVH). However, the role of mild thyroid failure as a risk factor for CVD is not clear. This study is aimed at exploring the association between subclinical hypothyroidism (SCH) and coronary artery disease (CAD), as detected by cardiac computed tomography (CT), in apparently healthy subjects.

Subjects and methods: We retrospectively enrolled 2404 asymptomatic subjects who underwent cardiac CT with an intermediate to high risk (Framingham 10-year risk $\geq 10\%$) of developing CAD but with no known CAD or thyroid disease. Coronary artery calcium score (CACS) was assessed by calcium scan, and the presence of the plaques (CAD), with $\geq 50\%$ stenosis being indicative of obstructive CAD, was assessed by coronary CT angiography.

Results: Of the 2404 subjects, 2355 subjects were euthyroid (Eu; 53 ± 9 years, 83 females) and 49 had SCH (58 ± 12 years, seven females). CAD and CACS > 100 were more prevalent in SCH subjects than in Eu subjects (Eu vs SCH: CAD, 948 (40.6%) vs 31 (63.3%), $P = 0.002$; CACS > 100, 239 (10.3%) vs 10 (20.4%), $P = 0.031$). SCH was also an independent risk factor for CAD after a multivariate analysis (odds ratio: 2.125, 95% confidence interval: 1.049–4.307, $P = 0.036$).

Conclusions: SCH subjects who were at an intermediate-to-high risk of developing CAD were significantly more likely to exhibit occult CAD than Eu subjects, especially in men with SCH. These findings suggest that mild thyroid failure also independently contributes to the development of CAD.

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Introduction

The cardiovascular system is a major target of thyroid hormone action (1, 2). Changes in thyroid function result in several alterations in cardiac hemodynamics. Overt hypothyroidism (OVH) has been known to accelerate the development of coronary atherosclerosis. Small-scaled case–control and cohort studies have shown that coronary atherosclerosis in subjects with hypothyroidism is more frequent and severe than in normal subjects (3). There is substantial evidence that OVH alters the traditional risk factors for cardiovascular disease (CVD) by increasing the circulating levels of atherogenic low-density lipoprotein cholesterol (LDL-C) particles, inducing systolic/diastolic hypertension and abnormalities in coagulation and increasing plasma homocysteine and C-reactive protein levels (1–8).

Subclinical hypothyroidism (SCH) is characterized by elevated serum TSH levels with normal concentrations of free thyroxine (fT_4) (9). The rate of detection of SCH is

markedly increasing due to the rise in routine screening procedures. However, the contribution of SCH to the future development of atherosclerosis is still being debated.

X-ray coronary angiography is still the gold standard for the diagnosis of coronary artery disease (CAD), but it has some limitations due to its invasive nature. Recent advancements in the multidetector technology of computed tomography (CT) have allowed physicians to explore coronary artery anatomy in a noninvasive manner (10, 11). Coronary artery calcium score (CACS) has already been accepted as an effective prognostic indicator of CAD that is independent of traditional risk factors (12–14). Coronary CT angiography (cCTA) can provide comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaques.

Bachar *et al.* (15) reported that occult CAD is common in asymptomatic patients with a risk profile for CAD and that in about 5% of patients at clinical risk, cCTA can detect obstructive CAD that mandates further investigation. Hadamitzky *et al.* (16) demonstrated the

ability of cCTA to predict further cardiac events, including unstable angina and late revascularization (>90 days after the index visit), in asymptomatic patients who had high cardiovascular risk profiles.

In this study, we, therefore, investigated the incidence of atherosclerotic CAD, as detected by cardiac CT, in asymptomatic subjects with intermediate-to-high risk profiles according to the thyroid function and explored the relationship between mild thyroid failure and occult CAD.

Subjects and methods

Study population

The medical records of consecutive asymptomatic subjects without known CAD who underwent a cardiac CT evaluation as part of his or her self-referred health checkup at the Seoul National University Bundang Hospital (SNUBH) Health Promotion Center between December 2005 and November 2008 were reviewed. Among these, 2404 who met the inclusion criteria (i) euthyroidism (Eu) or SCH and ii) intermediate-to-high risk of developing CVD based on the Framingham risk predictor model (Framingham 10-year risk $\geq 10\%$)) were included in our analysis; 2355 subjects were Eu (2272 males and 83 females) and 49 were SCH (42 males and seven females).

The Institutional Review Board of the SNUBH approved the study protocol. All of the subjects were fully informed regarding our study protocol and participation, and either the subjects or their legal guardians provided written informed consent.

Measurement of anthropometric and biochemical parameters

A medical history of CAD, including myocardial infarction or angina, hypertension, diabetes mellitus, dyslipidemia, stroke, a family history of premature CAD, a current medication profile, and smoking status, was systematically acquired. Height (cm) and body weight (kg) were measured to the nearest 0.1 cm and 0.1 kg respectively. During the height and weight measurements, the subjects were barefoot and wearing light clothing. Body mass index was calculated by dividing weight by the height squared (kg/m^2). Waist circumference was measured to the nearest 0.1 cm at the narrowest point between the lower limit of the ribcage and the iliac crest. Blood pressure was recorded three times after subjects had been in a relaxed state for at least 10 min and with 5 min of rest between measurements. The subjects were asked to refrain from smoking for 24 h and from consuming alcohol for 7 days before blood sampling. After a 14 h overnight fasting, venous blood samples were drawn from the antecubital vein. Plasma was separated immediately by centrifugation (538 **g**, 20 min, at 4 °C), and biochemical analyses were conducted immediately. The fasting plasma concentrations of glucose, HbA1c, total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol (HDL-C), and LDL-C were measured enzymatically using the Hitachi 747 chemistry analyzer (Hitachi).

The serum fT$_4$ and TSH levels were determined by a chemiluminescence immunoassay using a commercially available kit (Architect, Abbott). The reference ranges of fT$_4$ and TSH were 0.7–1.5 ng/dl and 0.4–4.9 mU/l respectively. The 10-year Framingham risk score (FRS), a point system based on age, sex, systolic blood pressure, TC, HDL-C, and smoking, was calculated according to the NCEP guidelines (17, 18).

Cardiac CT: CACS and cCTA

Patients with heart rates >70 beats per minute received 10–30 mg of intravenous esmolol (Jeil Pharm. Co., Ltd, Seoul, Korea) prior to cardiac CT imaging. Cardiac CT was performed using a 64-slice multidetector CT scanner (Brilliance 64; Philips Medical Systems, Best, The Netherlands).

Before cCTA, a nonenhanced prospective ECG-gated sequential scan was performed to measure CACS with the following parameters: section collimation, 40×0.625 mm; rotation time, 420 msec; tube voltage, 120 kV; and tube current, 55 mA. cCTA was thereafter performed on the patients using retrospective ECG gating with ECG-based tube current modulation and the following parameters: rotating time, 420 msec; tube voltage, 120 kV; effective tube current–time product, 800 mAs; table feed per scan, 3.8 mm; and pitch, 0.2. A bolus of 80 ml of iomeprol (Iomeron 400; Bracco, Milan, Italy) was injected i.v. (4 ml/s) followed by a 50 ml saline chaser. A region of interest was placed on the descending thoracic aorta, and image acquisition was automatically initiated once a selected threshold (150 Hounsfield units) had been reached using bolus tracking. Each patient's ECG was simultaneously recorded to allow for retrospective, segmental data reconstruction. The images were initially reconstructed during the mid-diastolic phase (75% of R–R interval) of the cardiac cycle. Additional reconstructions were performed if motion artifacts were present. The mean radiation exposure from the cardiac CT was 13.21 ± 0.82 mSv (13.21 ± 0.83 for men and 13.33 ± 0.79 for women).

All of the scans were independently analyzed using the 3D workstation (Brilliance; Philips Medical Systems) by two experienced investigators who were blinded to the clinical information. After making independent evaluations, a consensus interpretation was used to make a final diagnosis.

CACS were measured using a scoring system previously described by Agatston *et al.* (19). Based on the CACS, participants were categorized in the following manner: no plaques, 0; mild plaques, 0.1–100; and moderate to severe plaques, >100 (19, 20).

During the cCTA, each of the identified lesions was examined using maximum intensity projection and multiplanar reconstruction techniques on the short axis and along multiple longitudinal axes. The lesions were classified according to the maximal luminal diameter of a stenosis observed on any plane. The image quality was evaluated on a per-segment basis and classified as good (no artifacts), adequate (the presence of image-degrading artifacts, but feasible for evaluation with moderate confidence), or poor (the presence of image-degrading artifacts and feasible for evaluation only with low confidence). The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the maximal stenotic site and compared with the mean values of the proximal and distal reference sites. If the image was of adequate or poor quality, the coronary segments were visually scored for the grading of coronary artery stenosis.

We used the presence of any plaques (CAD), obstructive CAD (stenosis $\geq 50\%$), and CACS >100 as surrogate markers of CAD.

Statistical analysis

The continuous variables are expressed as the mean $\pm$ S.D., whereas the categorical variables are presented as absolute values and percentages. The unpaired Student's t-test was used to test for differences in normally distributed continuous variables and Mann–Whitney U test was used for comparisons involving variables that were not normally distributed. Categorical variables were compared with the χ^2 test or Fisher's exact test as appropriate. Multivariate and logistic regression analysis was employed to identify independent predictors of CAD, obstructive CAD, and CACS >100. A P value <0.05 was considered statistically significant, and all analyses were performed using the SPSS 15.0 statistical package (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics according to thyroid functional status

Among the 2404 subjects, the numbers of Eu and SCH subjects were 2355 and 49 respectively. The comparison of their clinical and biochemical characteristics is shown in Table 1.

The SCH group included more females and older subjects than the Eu group (the number of female, Eu versus SCH, 83 (3.5%) vs 7 (14.3%), $P<0.005$; age, Eu versus SCH, 53 ± 9 vs 58 ± 12, $P<0.005$). The subjects' history of diabetes, hypertension, hypercholesterolemia, and smoking was similar. There were no differences in clinical and biochemical characteristics between the Eu and the SCH groups. There were also no differences in 10-year FRS between the two groups (14.5 ± 4.7 vs 15.6 ± 6.2, $P=0.373$).

Because the male gender is a very strong coronary risk factor, we also compared the characteristics of the subjects according to gender. The basal characteristics of the two groups were more similar when analyzed

Table 1 Comparison of clinical and biochemical characteristics according to the thyroid function and sex.

	Total		Male		Female	
	Eu (*n*=2355)	SCHypo (*n*=49)	Eu (*n*=2272)	SCHypo (*n*=42)	Eu (*n*=83)	SCHypo (*n*=7)
TSH (mIU/l)	1.62±0.87	7.52±3.12*	1.60±0.86	7.70±3.30*	2.05±0.94	6.44±1.30*
Free T4 (ng/dl)	1.09±0.14	1.02±0.14*	1.09±0.14	1.02±0.14*	1.07±0.15	0.98±0.13
Age (years)	53±9	58±12*	53±9	58±12*	57±13	63±14
Female	83 (3.5)	7 (14.3)*	N/A	N/A	N/A	N/A
Smoking	2087 (91.9)	37 (86.0)	2075 (92.6)	36 (90.0)	12 (40.0)	1 (33.3)
Hypertension	764 (32.4)	19 (38.8)	727 (32.0)	17 (40.5)	37 (44.6)	2 (28.6)
Diabetes	314 (13.3)	8 (16.3)	306 (13.5)	7 (16.7)	8 (9.6)	1 (14.3)
Hypercholesterolemia	1661 (70.5)	35 (71.4)	1605 (70.6)	29 (69.0)	56 (67.5)	6 (85.7)
FHx of CAD	283 (17.9)	5 (15.2)	269 (17.9)	5 (17.9)	14 (18.7)	0 (0.0)
Hx of stroke	26 (1.7)	0 (0.0)	26 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
WC (cm)	88.7±7.4	87.6±7.9	88.9±7.2	88.1±7.7	83.6±9.7	84.9±8.6
BMI (kg/m²)	25.8±4.1	25.1±3.7	25.9±4.0	25.8±3.4	21.3±3.9	21.2±3.3
SBP (mmHg)	122±15	124±17	122±15	124±15	125±22	124±28
DBP (mmHg)	77±11	76±10	77±11	77±10	71±11	70±7
FBS (mg/dl)	99±26	98±16	99±26	98±15	96±32	97±19
HbA1c (%)	5.9±0.9	5.9±0.6	5.9±0.9	5.9±0.6	5.9±1.3	6.0±0.5
TC (mg/dl)	214±36	214±36	214±35	211±34	211±44	234±43
LDL-C (mg/dl)	119±27	118±30	119±27	116±30	114±32	127±33
HDL-C (mg/dl)	49±11	52±14	49±11	50±12	57±14	60±19
TG (mg/dl)	164±108	158±76	166±105	159±72	130±165	148±100
10-year FRS (%)	14.5±4.7	15.6±6.2	14.5±4.7	15.6±6.3	12.0±1.8	14.7±6.4

*P value <0.05 when compared with euthyroid group. Eu, euthyroid; SCH, subclinical hypothyroidism; FHx, family history; CAD, coronary artery disease; Hx, past medical history; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; 10-year FRS, 10-year Framingham risk score; N/A, not applicable.

according to gender and the age differences disappeared in the female group (Eu versus SCH, 57 ± 13 vs 63 ± 14, $P = 0.257$).

A comparison of the incidence of CAD according to thyroid functional status

Table 2 shows the comparison of the subjects' cardiac CT findings. The CACSs (mean (range)) were higher in the SCH group (45.3 (0–2836.7) vs 141.5 (0–4582), $P = 0.015$). The incidences of CAD and CACS > 100 were also higher in males with SCH (CAD, Eu versus SCH, 948 (40.6%) vs 31 (63.3%), $P < 0.005$; CACS > 100, 232 (10.3%) vs 10 (20.4%), $P = 0.031$). The differences in CAD incidences remained after adjusting for age (whole group, odds ratio (OR) 1.935, 95% confidence interval (CI): 1.021–3.668, $P = 0.021$; male, OR 1.086, 95% CI: 1.075–1.097, $P = 0.024$). However, we did not observe a difference in incidence of obstructive CAD between the two groups because of the limited number of SCH subjects ($n = 42$, Table 2) and the low incidence of obstructive CAD itself.

In the female subjects, the incidence of CAD was slightly higher in the SCH group compared with the Eu group (Eu versus SCH: 17 (20.5%) vs 4 (57.1%), $P = 0.049$), but this difference was barely significant and disappeared after adjustment for age. We studied only seven SCH subjects; therefore, a larger sample size is warranted.

When we explored the relationship between CACS and TSH and fT_4, TSH and CACS had significant correlation ($r = 0.053$, $P = 0.009$) but fT_4 was not related to CACS ($r = -0.13$, $P = 0.535$). We could get similar findings in male (CACS and fT_4, $r = -0.021$, $P = 0.320$; CACS and TSH, $r = 0.059$, $P = 0.005$) but could not in female subjects (CACS and fT_4, $r = 0.175$, $P = 0.099$; CACS and TSH, $r = -0.005$, $P = 0.965$), maybe due to limited subject number.

Multivariate analysis of the relative risk of CAD

We performed a multivariate analysis to identify risk factors that relate to SCH. After the multivariate analysis, known cardiovascular risk factors, such as age, male gender, high blood pressure, high fasting blood glucose levels, and hypercholesterolemia, were also significant risk factors for CAD, obstructive CAD, or CACS > 100 (Table 3). SCH was an independent risk factor for CAD (OR 2.125, 95% CI: 1.049–4.307, $P = 0.036$) but not for CACS > 100 and obstructive CAD (CACS > 100, OR 0.821, 95% CI: 0.186–3.614, $P = 0.794$; obstructive CAD, OR 1.162, 95% CI: 0.499–2.703, $P = 0.727$).

We also tried to perform a subgroup analysis because several of the factors, such as age, sex, and TSH levels, could have been confounding. However, further subanalyses showed no significant relationship between

Table 2 Comparison of CTA findings of the subjects according to the thyroid function and sex. Data are presented as mean $\pm$ s.d. or n (%). CACS data are presented as mean (range).

	Total				Male				Female			
	Eu (n=2355)	SCH (n=49)	P	P*	Eu (n=2272)	SCH (n=42)	P	P*	Eu (n=83)	SCHypo (n=7)	P	P*
CACS	45.3 (0–2836.7)	141.5 (0–4582.9)	0.015	0.025	46.0 (0–2836.7)	154.0 (0–4582.9)	0.044	0.195	26.0 (0–720.5)	63.2 (0–328.0)	0.025	0.183
CACS >100	239 (10.3)	10 (20.4)	0.031	0.232	232 (10.3)	9 (21.4)	0.036	0.161	7 (8.4)	1 (14.3)	0.491	0.914
CAD	948 (40.6)	31 (63.3)	0.002	0.021	931 (41.4)	27 (64.3)	0.004	0.024	17 (20.5)	4 (57.1)	0.049	0.089
Obst. CAD	88 (3.8)	2 (4.1)	0.709	0.859	85 (3.8)	2 (4.8)	0.673	0.957	3 (3.7)	0 (0.0)	1.000	0.999

Eu, euthyroid; SCH, subclinical hypothyroidism; CACS, coronary artery calcium score; CAD, coronary artery disease; Obst. CAD, obstructive CAD. P*, P value adjusted for age.

Table 3 Relative risks in the presence of CAD, obstructive CAD, and CACS >100.

	CAD		Obstructive CAD		CACS >100	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.094 (1.081–1.107)	0.000	1.058 (1.032–1.085)	0.000	1.116 (1.097–1.136)	0.000
Male gender	3.724 (1.645–8.429)	0.002	2.498 (0.310–20.162)	0.390	1.989 (0.715–5.528)	0.188
Smoking	1.324 (0.935–1.876)	0.114	1.239 (0.594–2.582)	0.568	1.501 (0.955–2.360)	0.078
SBP	1.009 (1.003–1.015)	0.004	1.000 (0.985–1.015)	0.996	1.002 (0.992–1.011)	0.725
FBS	3.193 (2.046–4.985)	0.000	2.206 (0.864–5.637)	0.098	3.869 (2.118–7.067)	0.000
BMI	1.001 (0.977–1.026)	0.911	0.957 (0.898–1.019)	0.172	1.045 (1.005–1.086)	0.025
LDL-C	1.006 (1.002–1.009)	0.001	1.000 (0.992–1.008)	0.946	0.999 (0.994–1.004)	0.664
HDL-C	0.992 (0.984–1.000)	0.054	0.969 (0.947–0.991)	0.005	1.000 (0.988–1.012)	0.992
SCH	2.125 (1.049–4.307)	0.036	0.821 (0.186–3.614)	0.794	1.162 (0.499–2.703)	0.727

CAD, coronary artery disease; CACS, coronary artery calcium score; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; FBS, fasting blood glucose; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCH, subclinical hypothyroidism.

SCH and the risk of CAD between young (<65 years) or old subjects (≥65 years) (data not shown). We could not analyze the influence of the female gender due to small number.

Discussion

We compared the incidence of CAD in subjects with intermediate-to-high risk profiles according to thyroid function. The incidence of CAD was relatively high in apparently healthy people (40.7%) and significantly higher in the SCH subjects (63.3%) than in the Eu subjects (40.6%).

The relationship between CAD and OVH is well known. In patients with OVH, CAD frequently occurs and may progress more rapidly by several mechanisms. OVH increases arterial stiffness and systemic vascular resistance, which results in higher blood pressure (8). Dyslipidemia, especially a marked increase in LDL-C levels, is a well-known characteristic of OVH (4), and elevated LDL-C levels increase arterial stiffness and atherogenicity (6). Diastolic hypertension can also increase cardiovascular risk (5). In addition, the relatively lower thyroid hormone levels of patients with OVH may amplify the cardiovascular risks associated with insulin resistance, although hypothyroidism itself does not cause insulin resistance directly (21). Through these complex mechanisms, OVH is thought to accelerate the development of coronary atherosclerosis (1).

SCH is a very prevalent condition affecting around 4% of the general population and 10–15% of the older population (22). In our study, the overall incidence of SCH was 2.0% (49/2, 404), which was relatively low because most of our selected subjects were male. The incidence of SCH was 1.8% (42/2, 314) and 7.8% (7/90) in males and females respectively.

However, the association between SCH and CAD is still somewhat controversial (23–27). The Busselton Health Study reported that SCH is an independent risk factor for coronary heart disease (26). Also, several

studies have shown an association between SCH and either specific age ranges or TSH levels. The Rotterdam Study (23) showed a higher prevalence of atherosclerotic CVD in female SCH patients who were 55 years of age or older. However, Ochs *et al.* (27) found in their meta-analysis using population-based cohort studies that the relative risk of SCH for CAD was significantly higher in subjects younger than 65 years, but not in subjects of age 65 years and older. Razvi *et al.* (28) also reported results from a meta-analysis showing that SCH is associated with increased CAD in subjects from younger populations only. The degree of SCH could be another important factor. SCH subjects with a TSH ≥10 mU/l may also have an increased CAD risk, and recent data have shown that SCH is associated with an increased risk of CAD events and CAD mortality (27, 29).

In addition, the Wickham survey, a large-scale, long-term follow-up study, found no evidence to suggest that SCH is associated with an increased risk of ischemic heart disease (IHD) (30). These discrepancies may have originated from the heterogeneity of the study subjects with regard to age and sex distribution, number, and the characteristics of the selected subjects, such as inpatient or community setting. In this study, we included only subjects with intermediate-to-high risk profiles (10-year FRS ≥10%) who would have benefitted from further examinations to facilitate risk stratification in our assessment of the relationship between SCH and CAD. We found that SCH increased the risk of occult CAD in the subjects with increased coronary risk.

In our study, we performed cardiac CT evaluations to detect CAD. CACS has already been accepted as an effective prognostic indicator of CAD that is independent of traditional risk factors (12–14). Although the diagnostic accuracy of cCTA has been reported in many studies, its practical value to predict clinical events is less defined (31). However, Russo *et al.* (32) recently reported that CACS and cCTA findings, such as obstructive CAD and presence of noncalcified or mixed plaques, were predictors of a coronary event. In this study, 60% of the study subjects were asymptomatic and about 70% were classified as intermediate risk.

Hulten *et al.* (33) showed that, in patients with normal findings on cCTA, major adverse cardiovascular events (MACE) were extremely rare, and future MACE incrementally increased with increasing CAD in patients with abnormal cCTA findings. Therefore, the presence of CAD on cCTA may be a very sensitive and useful marker for predicting MACE in asymptomatic subjects.

In our study subjects, the presence of CAD, representative of the presence of occult CAD, was significantly associated with SCH (Tables 2 and 3). The fact that, even after adjustment for CVD risk factors (including the male gender, which is the strongest risk factor for CAD), SCH was still significantly associated with the presence of CAD suggests that even mild thyroid failure may influence the occurrence of occult CAD and can be a useful marker to predict future MACE, as reported by Hulten *et al.* (33).

In a recent paper, Razvi *et al.* (34) reported data from a Wickham Reanalysis. They showed that there was an association between IHD and IHD-related mortality in patients with SCH over 20 years of follow-up, which is in contrast to the data from the original Wickham survey report (30). These results could also support our study results showing an association between SCH and occult CAD.

Although this study failed to identify an association between SCH and either obstructive CAD or CACS >100 (Tables 2 and 3), this may be due to the very low prevalence of obstructive CAD itself. Further studies with more subjects are needed to draw any definitive conclusions.

In females, the presence of CAD was not associated with SCH most likely because the number of females included in the study was too small.

Our study included only one individual with TSH levels > 10 mU/l, and there were only four subjects with TSH levels > 7 mU/l. Therefore, we could not compare the group with higher TSH levels with the others because there were not enough patients with SCH to draw any conclusions.

Our study had some limitations including the retrospective design, the lack of information about the duration of the thyroid dysfunction, and the lack of data pertaining to serum autoantibodies and free triiodothyronine. Because patents were self-referred for cardiac CT, selection bias may limit the generalizabilitI of the clinical characteristics of this cohort to the overall SCH population. Also we could not evaluate the association between SCH and CAD risk in subjects with a low-risk profile of CAD, and we, therefore, cannot extend our results to healthy subjects without risk factors at this moment. Furthermore, regarding the radiation exposure and lack of cost-effectiveness and outcome data, we cannot recommend cardiac CT evaluation in asymptomatic subjects even if at intermediate-to-high CAD risk (35). However, our study is the first report examining the association between

SCH and CAD using cardiac CT, which is a very accurate and sensitive method for detecting CAD in a noninvasive manner.

In summary, this study suggests that subclinical hypothyroidism is an independent risk factor for coronary artery disease in apparently healthy subjects. The risk of occult CAD is increased in SCH subjects who have an increased clinical CAD risk. Thus, we can speculate that T_4 replacement may be beneficial for SCH subjects with increased coronary risk, although a further large-scale prospective study is needed to clarify these findings.

Declaration of interest

Funding

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