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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 5,815 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,

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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.

Keywords

subclinical thyroid disorders; carotid intima-media thickness; carotid plaques; atherosclerosis; arterial remodeling

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 lumenintima 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 ≥ 140 mmHg and/or DBP ≥ 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 test, Kruskal-Wallis test and Spearman's correlation) were used for the univariate analysis. For the same reason, median and interquartile range were utilized as summary measures.

Thyroid function was evaluated considering 3 categories: euthyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism. Pearson χ^2 was used to analyse the differences among proportions.

To assess the relationship between dependent variables (either IMT --evaluated as a continuous trait-- or carotid plaques --considered as a dummy, yes/no variable--) and thyroid hormones (TSH and FT4) or function (3 categories), adjusting for confounders, multivariate analysis was run. In particular, multiple regression was used for IMT and logistic regression for carotid plaques.

At first, a 'full model' including anthropometric data, variables associated in the univariate analysis or in the literature, was analysed. Second, variables not associated with the outcome were removed and the remaining were added. The final, 'best model' contained only the covariates which led to a statistically significant increase in R^2 (purposeful selection). Polynomial and interaction terms were tested as well. Collinearity was declared when values of variance inflation factor (VIF) were greater than 10.

Tests of significance were two-sided, and a $p<0.05$ was assumed as statistically significant. In case of multiple comparisons the critical p-value was calculated as 0.05 divided by the number of comparisons, i.e. 0.017 (post-hoc analysis). Stata 11.1 for Windows was used for the analysis.

Results

Table 1 shows the baseline characteristics of our sample divided according to the thyroid function. Compared with euthyroid and with subclinical hypothyroid subjects, individuals with subclinical hyperthyroidism were older and less healthy, showing greater BMI and higher levels of glycaemia and blood pressure.

Analysis of IMT

a) Thyroid hormones (univariate analysis)—In the univariate analysis, age, BMI, glycaemia, SBP, DBP, PP, total cholesterol, LDL, and triglycerides showed a positive association with IMT; by contrast, TSH, and FT4 were negatively correlated with IMT (Table 2). In addition, IMT was higher among males, non-smokers, statin treated patient, and in subjects with hypertension, diabetes, or previous cardiovascular events.

b) Thyroid function (univariate analysis)—Figure 1 depicts IMT values according to thyroid function: the difference among medians was statistically significant ($p<0.001$). The post-hoc analysis revealed that subclinical hyperthyroid patients showed greater IMT compared with euthyroid and with subclinical hypothyroid subjects (Figure 1).

c) Multivariate analysis—Table 3 shows the results of the multiple regression analysis, where either TSH and FT4 as continuous variables (model 1) or thyroid function as categorical variable (model 2) were tested. After adjusting for confounders, IMT remained associated with age, sex, smoking, LDL, HDL, PP, and the history of cardiovascular events, diabetes and hypertension. Specifically, IMT was directly related to age and PP, while it was inversely associated with LDL and HDL levels. Moreover, IMT was greater among males, smokers and in subjects with hypertension, diabetes or previous cardiovascular events. The final model explained 47% of the variability of IMT. Interactions and collinearity were excluded (VIF= 1.93 or lower). The inclusion of thyroid hormones as continuous traits (model 1) or of thyroid function as qualitative trait (model 2) did not lead to a significant increase in R^2, as shown in Table 3. Results were not modified substantially when data were stratified by sex or age.

Carotid plaques

a) Thyroid hormones (univariate analysis)—The same variables associated with IMT were also associated with the presence of plaques in the univariate analysis (Table 4).

b) Thyroid function (univariate analysis)—The frequency of carotid plaques varied according to the thyroid function ($\chi^2=11.7$, $p=0.003$), as it was higher among subclinical hyperthyroid patients compared with euthyroid subjects and with subclinical hypothyroid patients (post-hoc analysis).

c) Multivariate analysis—When we adjusted for confounders (logistic regression, Table 5), only age, sex, LDL, PP, previous cardiovascular events, history of diabetes, and the use of statins significantly predicted the presence of carotid plaques. In particular, holding the covariates at a fixed value, the odds of developing carotid plaques for males and subjects with cardiovascular events were over twice greater than those for females or individuals without cardiovascular history, and almost twice greater among diabetics and statin users. Odds were also slightly but significantly higher as age, LDL and PP increased. Again, the inclusion of thyroid hormones or thyroid function categories to the model did not lead to a significant increase in R^2; age or sex stratification did not produce significant variation of the results (data not shown).

Discussion

Age is the most important risk factor for the development of cardiovascular disease, and a challenge to cardiovascular researchers is to discover and modify cardiovascular risk factors that might increase the risk conferred by aging [2]. As a relevant measure, IMT is directly correlated with the risk of myocardial infarction and stroke [1], and has been construed as a marker of pre-atherosclerosis. However, current evidence suggests that the thickening of intima-media may instead be considered as physiological remodelling accompanying aging,

because IMT increases linearly with age even in subjects who do not develop atherosclerotic plaques [15]. IMT increase is a marker of age-associated inflammation and not atherosclerosis, per se [2]. Although they are distinct entities, atherosclerosis and aging-related arterial remodelling respond to the same biochemical, inflammatory and metabolic factors and should be considered closely linked [2].

The cardiovascular system is a specific target for thyroid hormones and thyroid dysfunction often interferes with cardiovascular hemodynamics [5–8,16,17]. Thyroid failure is associated with worsening of classical cardiovascular risk factors, including elevation of LDL, homocysteine [18] and the development of a procoagulant state [19].

In this study we evaluated whether subclinical thyroid dysfunction is associated with accelerated arterial remodelling, by examining common carotid IMT and the presence of plaques in an extensively characterized population. In agreement with general consensus [20], in our cohort IMT was associated with age, PP, LDL, and HDL, and it was greater among males, smokers, hypertensives, patients with diabetes and previous cardiovascular events. Similarly, the prevalence of carotid plaques increased with age, LDL, and PP, and differed according to sex, the use of statins, diabetes and previous cardiovascular events. In both analyses, there was no association with subclinical thyroid disorders, supporting the inference that accelerated arterial remodelling and development of atherosclerosis are independent of mild variations in thyroid hormone levels. Results in other population surveys that addressed this topic, are controversial. Recent studies did not find a significant relationship between IMT and TSH [9,21]. Conversely, Volzke et al. observed an independent and direct association between hyperthyroidism and IMT [10]. Other studies showed that low-normal thyroid function was associated with an increased IMT [22,23]. Inconsistent results on the association between thyroid hormones and atherosclerotic plaques have been reported. Chiche et al. showed that the prevalence of carotid plaques was significantly lower in patients with overt hypothyroidism than in those having subclinical hypothyroidism and that TSH and FT4 values were not associated with the prevalence of carotid plaques, regardless of thyroid status [24]. Conversely, Dörr et al. reported an association between subclinical hyperthyroidism and carotid plaques and stroke, with an odds ratio of 1.67 and 1.98 respectively [25], consistent with their previous finding [10]. Differences in methodological approaches used in the various studies might, in part, account for the contrasting results: i.e. differences in IMT measurement, evaluation of different carotid segments, small sample sizes, the different ranges of normality of thyroid hormones are possible reasons underlying this discrepancy. In addition, it must be taken into account that the development of atherosclerotic lesions may be promoted by long–standing thyroid dysfunction more than its presence per se, but the duration of the disease is not always assessable.

We acknowledge that the cross-sectional design precluded temporality ascertainment. In addition, a single measurment of TSH and FT4 together with the identification of plaque based on sonographer’s subjective criteria could be futher limitations of our analysis. However, our study is one of the largest studies published so far on the relation of IMT with thyroid function. In addition, the value of our study is strengthened by the relative homogeneity of the population studied and by the statistical approach. Indeed, our

preliminary results (univariate analysis, Figure 1 and Table 1 showed that subclinical hyperthyroid patients had higher IMT values and a higher prevalence of carotid plaques compared with euthyroid subjects). Nevertheless, a more detailed analysis revealed that subclinical hyperthyroid patients were older and less healthy that euthyroid individuals, and thus more prone to develop atherosclerosis. Age and other risk factors overwhelmed the role of thyroid function, as clearly documented by the fact that thyroid function did not predict carotid atherosclerosis after adjusting for confounders.

Although not universally accepted, both subclinical hypothyroidism and hyperthyroidism have been reported to affect the risk of ischemic heart disease [26,27], suggesting the opportunity of treating these patients. Albeit that no long-term prospective analyses are available in literature, some case-control studies focused on the effect of thyroxine supplement therapy in subjects with subclinical hypothyroidism, with divergent results based on small groups of patients [28–30]. A common perception prevalent among medical experts is that the treatment of subclinical disorders should be individualized in elderly patients [3,4].

In conclusion, the lack of an association of subclinical thyroid dysfunctions with increased IMT or the presence of carotid plaques in a large community dwelling, suggests that the accelerated arterial remodelling and atherosclerosis are not affected by mild variations in thyroid hormone. The result of our study may be clinically relevant, as they do not support the idea that treating subclinical thyroid disorders might prevent arterial remodelling; large randomized controlled studies, however, are required to definitively assess the extent to which treatment might benefit patients with subclinical thyroid disorders.

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Highlights

1. Mild variations of thyroid hormone are not not associated with increased IMT
2. Subclinical thyroid disorders are not related with an higher frequency of carotid plaques
3. Age is the most important variable associated with an increased IMT

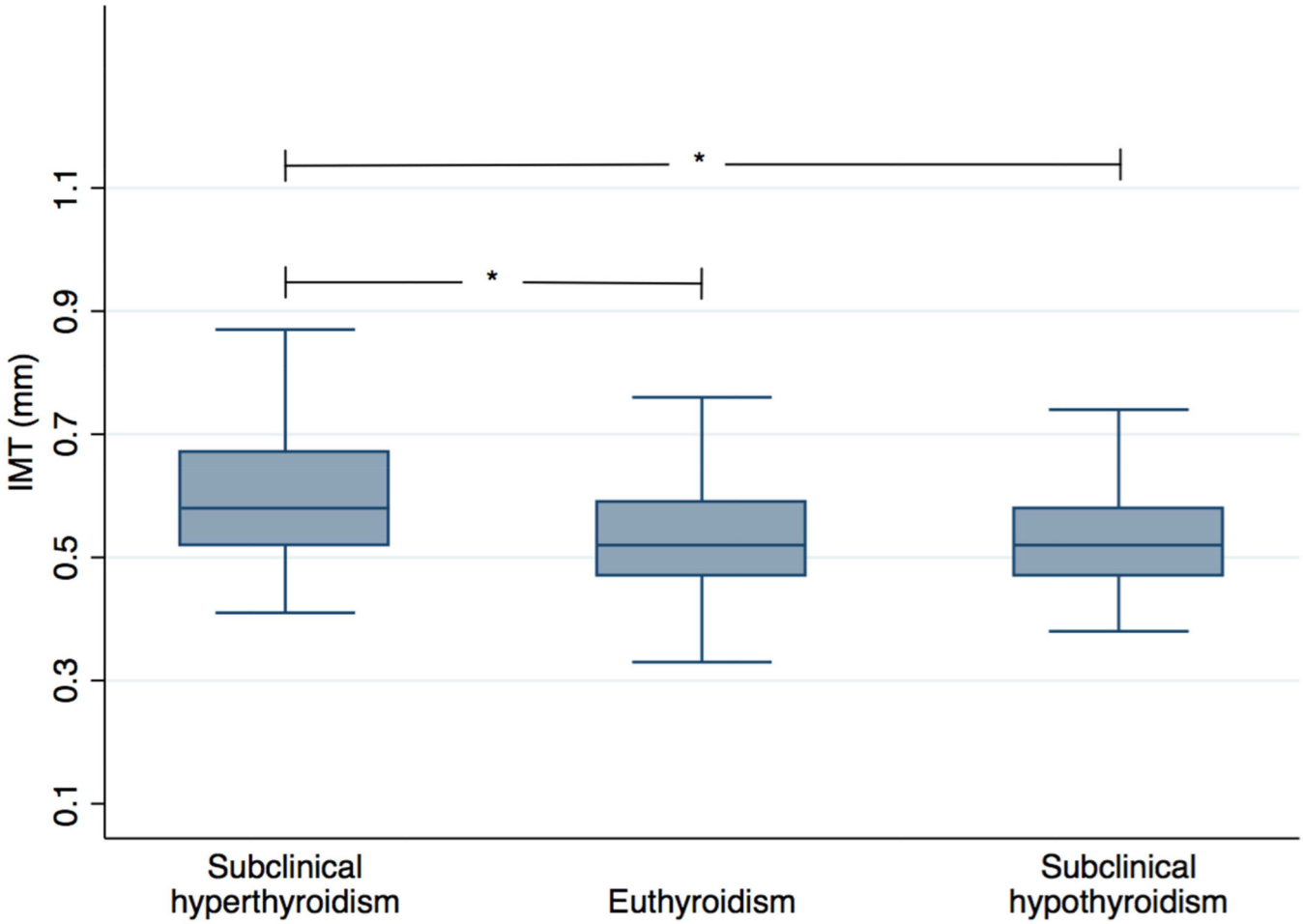

Figure 1.

Table 1

Clinical characteristics of the cohort (n=5815) divided according to thyroid function.

	Subclinical hyperthyroidism (n=143)	Euthyroidism (n=5385)	Subclinical hypothyroidism (n=287)	p value§
Age (yrs)	58 (46–68)*#	41 (29–57)	39 (26–53)	<0.001
Female (n, [%])	88, 62%	2964, 55%	202, 70%*	<0.001
BMI (Kg/m^2)	26.6 (23.7–29.2)*#	24.7 (21.8–28.0)	23.8 (20.9–27.7)	<0.001
Glycaemia (mg/dl)	90 (83–103)*#	85 (78–93)	82 (76–90)*	<0.001
SBP (mmHg)	130 (120–145)*#	122 (112–136)	120 (110–132)*	<0.001
DBP (mmHg)	80 (73–86)*#	75 (70–83)	75 (70–81)	0.001
PP (mmHg)	50 (41–61)*#	47 (40–55)	46 (39–52)	<0.001
TSH (μUI/ml)	0.24 (0.11–0.33)*#	1.59 (1.06–2.20)	5.09 (4.41–6.84)*	<0.001
FT4 (ng/dl)	1.32 (1.17–1.47)#	1.29 (1.18–1.41)	1.22 (1.08–1.36)*	<0.001
Total cholesterol (mg/dl)	212 (186–243)	206 (178–235)	206 (179–242)	0.112
LDL (mg/dl)	130 (109–153)	125 (101–149)	127 (103–152)	0.108
HDL (mg/dl)	64 (56–74)	63 (53–73)	62 (53–73)	0.115
Triglycerides (mg/dl)	63 (48–88)#	71 (50–105)	74 (53–105)	0.030
Smoking (n, [%])	17 (12%)*	1112 (21%)	50 (17%)	0.017
Hypertension (n, [%])	64 (45%)*#	1559 (29%)	69 (24%)	<0.001
Diabetes (n, [%])	16 (11%)*#	242 (5%)	12 (4%)	0.001
CV events (n, [%])	2 (2.1%)	91 (1.7%)	2 (0.7%)	0.400
Plaque (n, [%])	16 (11.2%)*#	264 (4.9%)	13 (4.5%)	0.003

Continuous data are given as median and interquartile range; categorical data are expressed as absolute and relative frequencies.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TSH, thyroid-stimulating hormone; FT4, free thyroxine; LDL, low density lipoprotein; HDL, high density lipoprotein; CV, cardiovascular.

§ Kruskal-Wallis test or Pearson $\chi 2$ test as indicated.

* vs euthyroidism ($p<0.017$)

vs subclinical hypothyroidism ($p<0.017$).

Table 2

Association of clinical parameters with IMT: results of the univariate analysis.

Panel A (Continuous variables)		
Variable	**rho**	**p value**
Age	0.68	<0.001
BMI[a]	0.41	<0.001
Glycaemia	0.33	<0.001
SBP	0.45	<0.001
DBP	0.39	<0.001
PP[b]	0.30	<0.001
TSH	−0.21	<0.001
FT4	−0.13	<0.001
Total cholesterol	0.27	<0.001
LDL	0.25	<0.001
HDL	0.01	0.31
Triglycerides	0.22	<0.001

Panel B (Categorical variables. IMT is expressed as mm)		
Variable	**median (IQR)**	**p value**
Sex (M/F)	0.53 (0.48–0.62) / 0.52 (0.47–0.57)	<0.001
Smoking (n/y)	0.53 (0.48–0.60) / 0.51 (0.46–0.57)	<0.001
Hypertension (n/y)	0.50 (0.46–0.55) / 0.60 (0.53–0.70)	<0.001
Diabetes (n/y)	0.52 (0.47–0.59) / 0.63 (0.55–0.74)	<0.001
Statins (n/y)	0.52 (0.47–0.58) / 0.71 (0.62–0.82)	<0.001
CV events (n/y)	0.52 (0.47–0.59) / 0.68 (0.62–0.77)	<0.001

Abbreviations: IMT, intima-media thickness; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TSH, thyroid-stimulating hormone; FT4, free thyroxine; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; CV, cardiovascular; IQR, interquartile range.

[a] Calculated as weight in kilograms divided by height in meters squared

[b] Calculated as SBP – DBP.

Table 3

Multiple regression analysis of IMT including either TSH and FT4 (model 1) or thyroid function (model 2)

	Model 1		Model 2	
	β (s.e.)*	p value	β (s.e.)*	p value
Age	38.7 (0.8)	<0.001	38.8 (0.8)	<0.001
Sex	150.1 (24.0)	<0.001	149.4 (23.9)	<0.001
Smoking	95.2 (28.0)	0.001	95.1 (28.0)	0.001
LDL	−1.1 (0.3)	0.001	−1.1 (0.3)	0.001
HDL	−3.1 (0.8)	<0.001	−3.2 (0.8)	<0.001
PP	7.3 (1.0)	<0.001	7.2 (1.0)	<0.001
CV events	431.5 (88.3)	<0.001	432.5 (88.3)	<0.001
Hypertension	149.6 (31.5)	<0.001	149.1 (31.5)	<0.001
Diabetes	249.9 (54.5)	<0.001	246.8 (54.5)	<0.001
TSH	2.0 (4.4)	0.653	-	-
FT4	−79.3 (58.7)	0.177	-	-
Subclinical hyperthyroidism	-	-	54.6 (70.7)	0.44
Euthyroidism	-	-	-	Reference
Subclinical hypothyroidism	-	-	44.5 (50.4)	0.377

*Both beta coefficients and standard errors have to be Multiplied by 10^{-4}

Abbreviations: IMT, intima-media thickness; β, beta coefficients; s.e., standard errors of the coefficients; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein; PP, pulse pressure; CV, cardiovascular; TSH, thyrotropin; FT4, free thyroxine.

Table 4

Association of clinical parameters with the presence of carotid plaques: results of the univariate analysis.

Panel A (Continuous variables. Data are expressed as median and IQR)			
Variable	**No plaques**	**Plaques**	**p value**
Age (years)	40.2 (28.3–54.3)	68.6 (61.0–74.1)	<0.001
BMI (Kg/m^2)[a]	24.6 (21.6–27.8)	28.0 (25.0–31.0)	<0.001
Glycaemia (mg/dl)	85 (79–93)	95 (86–109)	<0.001
SBP (mmHg)	121 (111–135)	143 (130–155)	<0.001
DBP (mmHg)	75 (70–83)	81 (74–90)	<0.001
PP[b]	47 (40–54)	59 (50–70)	<0.001
TSH (μUI/ml)	1.63 (1.07–2.33)	1.25 (0.77–1.95)	<0.001
FT4 (ng/dl)	1.29 (1.18–1.41)	1.24 (1.11–1.38)	<0.001
Total cholesterol (mg/dl)	206 (177–235)	225 (198–247)	<0.001
LDL (mg/dl)	124 (101–148)	139 (117–159)	<0.001
HDL (mg/dl)	63 (53–73)	63 (53–72)	0.959
Tryglicerides (mg/dl)	70 (50–103)	88 (63–132)	<0.001

Panel B (Categorical variables)		
Variable	**Presence of plaques (%)**	**χ^2, p value**
Sex (M/F)	7.4 / 3.2	52.4, <0.001
Smoking (n/y)	5.8 / 2.0	29.5, <0.001
Hypertension (n/y)	1.9 / 12.8	297,8 <0.001
Diabetes (n/y)	4.3 / 21.1	152,9 <0.001
Statins (n/y)	4.6 / 22.8	97.6, <0.001
CV events (n/y)	4.6 / 29.2	118,8 <0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure, TSH, thyroid-stimulating hormone; FT4, free thyroxine; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; CV, cardiovascular; IQR, interquartile range.

[a] Calculated as weight in kilograms divided by height in meters squared

[b] Calculated as SBP – DBP.

Table 5

Logistic regression of carotid plaques.

	Model 1		Model 2	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Age	1.09 (1.08–1.11)	<0.001	1.09 (1.08–1.11)	<0.001
Sex	2.38 (1.80–3.13)	<0.001	2.43 (1.84–3.20)	<0.001
LDL	1.01 (1.00–1.01)	0.008	1.00 (1.00–1.01)	0.009
PP	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
CV events	2.06 (1.21–3.51)	0.008	2.07 (1.21–3.53)	0.008
Diabetes	1.87 (1.29–2.70)	0.001	1.83 (1.27–2.64)	0.001
Statins	1.69 (1.06–2.71)	0.029	1.71 (1.06–2.74)	0.027
TSH	1.00 (0.92–1.07)	0.903	-	-
FT4	0.66 (0.33–1.35)	0.258	-	-
Subclinical hyperthyroidism	-	-	1.37 (0.76–2.48)	0.297
Euthyroidism	-	-	-	Reference
Subclinical hypothyroidism	-	-	1.19 (0.62–2.28)	0.595

Abbreviations: OR, odds ratio; CI, confidence interval; LDL, low density lipoprotein cholesterol; PP, pulse pressure; CV, cardiovascular, TSH, thyrotropin; FT4, free thyroxine.

Model 1 included thyroid hormone as continuous variables, model 2 included thyroid hormone categories.