Association between high normal-range thyrotropin concentration and carotid intima-media thickness in euthyroid premenopausal, perimenopausal and postmenopausal women

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ARTICLE INFO

ABSTRACT

Objective: There are currently no established cutoff levels for thyrotropin (TSH) within the reference intervals associated with carotid atherosclerosis to prevent the onset of cardiovascular diseases. The present study aimed to determine the TSH cutoff level associated with carotid maximum intima-media thickness (max IMT) in euthyroid premenopausal, perimenopausal and postmenopausal women.

Study design: We conducted a cross-sectional study of 468 euthyroid women who had not been treated for or diagnosed with cardiovascular diseases and/or metabolic disorders among 1221 Japanese women who participated in a comprehensive medical examination at the Hidaka Hospital, Japan. Participants' weight, blood pressure, plasma glucose, serum lipoprotein, free thyroxine and TSH were measured and an interview about menstruation was conducted. Carotid ultrasonography was performed to determine max IMT.

Results: Max IMT significantly increased stepwise as menopausal status progressed ($p < 0.001$). Serum TSH levels were significantly higher in participants with carotid plaques, defined as max IMT ≥ 1.1 mm ($p = 0.038$), and were independently associated with the presence of carotid plaque using multivariate logistic regression analysis ($\beta = 1.218$, $p = 0.036$). In postmenopausal women, significantly higher carotid max IMT values were observed in women with serum TSH ≥ 2.5 μIU/mL compared with women with concentrations < 2.5 μIU/mL ($p = 0.018$) without elevated total cholesterol and low-density lipoprotein cholesterol concentrations. These differences were not observed in premenopausal women.

Conclusions: Laboratory finding of serum TSH concentration ≥ 2.5 μIU/mL may be useful to assess risk of atherosclerosis, especially in postmenopausal women.

1. Introduction

Cardiovascular disease (CVD) is one of the most common causes of death worldwide, and its prevention requires early identification of atherosclerotic risk factors. Women are generally at increased risk for CVD after the menopause [1,2]. The carotid intima–media thickness (IMT), which is a well-known predictor of future cardiovascular events, is clinically significant in postmenopausal women compared with age-matched premenopausal women [3]. Altered metabolism in perimenopausal and postmenopausal status accelerates atherosclerosis due to various metabolic disorders [4].

Thyroid hormone plays a crucial role in promoting systemic

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metabolism and has various effects on the cardiovascular system [5]. Overt hypothyroidism is associated with increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output, and accelerated atherosclerosis and coronary artery disease due to hypercholesterolemia and diastolic hypertension [6]. Subclinical hypothyroidism, diagnosed based on elevated levels of thyrotropin (TSH) despite free 3,5,3'-triiodothyronine (FT_3) and free thyroxine (FT_4) within the reference intervals, is also an indicator of risk for atherosclerosis and myocardial infarction in elderly women [7]. The basal carotid mean IMT is higher in hypothyroid patients compared with euthyroid patients and decreases after normalization of thyroid functions following levothyroxine therapy [8]. Furthermore, carotid mean IMT is positively correlated with TSH and inversely correlated with FT_4 even in euthyroid patients [9]. Although the carotid maximum (max) IMT is more predictive of coronary artery stenosis than mean IMT [10, 11], few studies have reported an association between carotid max IMT and thyroid function. Moreover, differences in the effects of thyroid function on carotid atherosclerosis among premenopausal, perimenopausal and postmenopausal women remain to be elucidated.

It was previously reported that the upper limit of the reference interval of serum TSH should be lowered to 2.5 μIU/mL based on accumulating evidence [12]. Guidelines for thyroid function have been applied for management during pregnancy. Previous studies have described that maternal hypothyroidism during pregnancy caused reduced intelligence quotient scores in children [13]. In addition, the pregnancy loss rate was increased in thyroid antibody-negative euthyroid women with serum TSH levels between 2.5 and 5.0 μIU/mL in the first trimester [14]. Based on these findings, the guidelines of the Endocrine Society and American Thyroid Association recently recommended TSH reference intervals of 0.1–2.5 μIU/mL for the first trimester and 0.2–3.0 μIU/mL for the second trimester [15,16]. In relation to CVD, a previous study reported that the pulse wave velocity (PWV), an indicator of early phase arterial stiffness, was significantly higher in postmenopausal women with serum TSH levels ≥2.5 μIU/mL than that in those with serum TSH levels <2.5 μIU/mL [17]. However, cutoff levels for serum TSH associated with carotid atherosclerosis to prevent future onset of CVD have not been established.

The association between carotid atherosclerosis and a high normal-range TSH concentration remains unknown, and the change in this association before and after menopause remains to be elucidated. Understanding this association may enable the use of a high normal-range TSH to identify risk factors for CVD in women at each status of menopause. Furthermore, setting cutoff points for serum TSH concentration associated with carotid IMT, such as the guidelines for management during pregnancy, may lead to the setting of targets for management to prevent atherosclerosis in its early phase. The present study aimed to determine the TSH cutoff level associated with carotid max IMT in euthyroid premenopausal, perimenopausal, and postmenopausal women.

2. Methods

2.1. Study population

Enrollment of the study participants is shown in Fig. 1. In the six years from 2011 to 2016, 1221 Japanese women from the general population underwent carotid ultrasonography and an interview about menstruation during a comprehensive medical examination at the Hidaka Hospital, Takasaki, Japan. To identify euthyroid women without CVD and/or metabolic diseases associated with risk of atherosclerosis, the following participants were excluded: 50 taking current medication for thyroid disorders, 40 taking current medication for diabetes mellitus, 170 taking current medication for dyslipidemia, 172 taking current medication for hypertension, 12 with history of cerebral infarction or hemorrhage, 39 taking current medication and/or past history of CVD, five undergoing hemodialysis, 215 with unconfirmed current and history of medication, and 36 with unconfirmed menopause. Among 486 women who underwent measurement of serum FT_4 and TSH concentration, 11 women with subclinical hypothyroidism, six with subclinical thyrotoxicosis, and one with thyrotoxicosis were excluded. A total of 468 women were included for further analysis. Menopause status was determined by gynecologists based on the interview of last menstrual date and menstrual cycle. Premenopausal status was defined by the presence of regular menstruations in the previous 12 months. Postmenopausal status was defined by a complete absence of menstruation
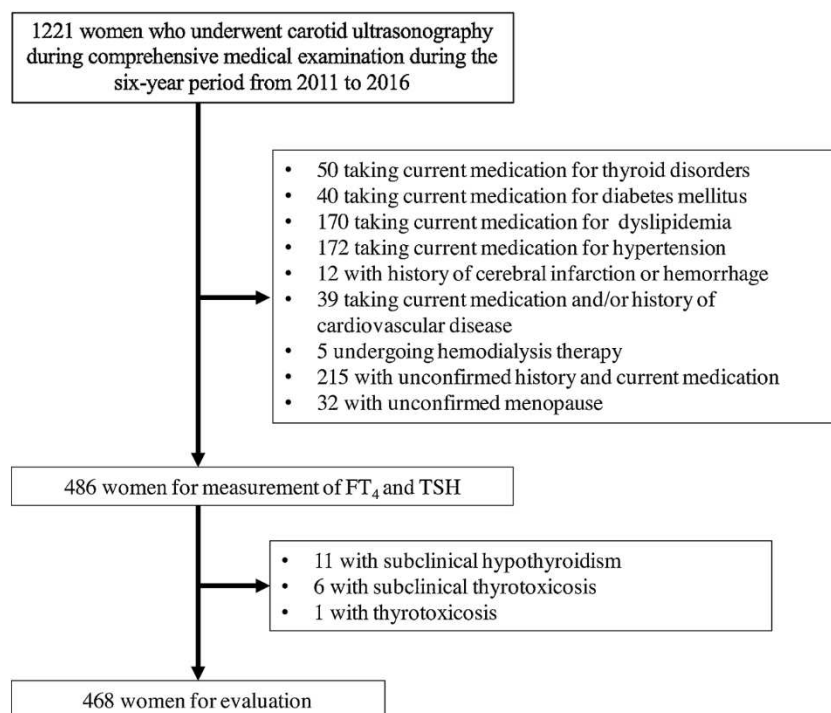


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│ 1221 women who underwent carotid ultrasonography     │
│ during comprehensive medical examination during the  │
│ six-year period from 2011 to 2016                     │
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                        │   ┌──────────────────────────────────────────────────────────┐
                        ├──▶│ • 50 taking current medication for thyroid disorders       │
                        │   │ • 40 taking current medication for diabetes mellitus       │
                        │   │ • 170 taking current medication for dyslipidemia           │
                        │   │ • 172 taking current medication for hypertension           │
                        │   │ • 12 with history of cerebral infarction or hemorrhage     │
                        │   │ • 39 taking current medication and/or history of           │
                        │   │   cardiovascular disease                                   │
                        │   │ • 5 undergoing hemodialysis therapy                        │
                        │   │ • 215 with unconfirmed history and current medication      │
                        │   │ • 32 with unconfirmed menopause                            │
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┌─────────────────────────────────────────────────────┐
│ 486 women for measurement of FT4 and TSH             │
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                        ├──▶│ • 11 with subclinical hypothyroidism                       │
                        │   │ • 6 with subclinical thyrotoxicosis                        │
                        │   │ • 1 with thyrotoxicosis                                    │
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│ 468 women for evaluation                             │
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Fig. 1. Enrollment of the study participants. FT_4, free thyroxine; TSH, thyrotropin.

in the previous 12 months. Perimenopausal status was defined as some menstrual bleeding with some change in cycle regularity in the last 12 months. The study was approved by the ethics committee of Hidaka Hospital (approval no. 186).

2.2. Physical examination and laboratory analyses

Height and weight were measured, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and recorded, and blood samples were obtained from an antecubital vein while the participant was in a seated position after an overnight fast. Serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) were measured by enzymatic assays using an automatic analyzer (TBA-c8000; Canon Medical Systems Corporation). Plasma glucose (PG) concentrations were measured by the glucose oxidase method, and hemoglobin A1c (HbA1c) levels were measured by high-performance liquid chromatography using automatic analyzers (GA 08 II; A&T and HLC-723G9; Tosoh). Serum FT$_4$ and TSH concentrations were measured by chemiluminescence immunoassay using an automatic analyzer (ARCHITECTi2000SR; Abbott). Euthyroid state was defined as serum FT$_4$ concentrations of 0.70–1.48 ng/dL and serum TSH concentrations of 0.35–4.94 μIU/mL.

2.3. Measurement of carotid artery max IMT

Measurement of max IMT of the left or right carotid arteries was performed using ultrasonography (Aplio 300; Canon Medical Systems Corporation) with a 7.5-MHz linear array transducer. Max IMT was determined as the greatest thickness measured on both sides of the common carotid artery, bulbus, and internal carotid artery, excluding the external carotid artery. Carotid plaque was defined as max IMT ≥1.1 mm. All scans were conducted by experienced three well-trained medical technologists without any information on clinical information of the participants. The intra-observer coefficient of variation for IMT measurement was 5.2 % ± 0.8 %.

2.4. Statistical analysis

Data are expressed as median with a 25th–75th percentile. Kruskal-Wallis tests were performed to compare the three groups divided by menopausal status or four groups divided by serum TSH concentrations. Mann–Whitney U test or chi-squared test were used, as appropriate, to identify statistically significant differences between the two groups. Multivariate logistic regression analysis was performed to evaluate the

factors contributing to carotid plaque independently. Serum TG and TSH concentrations were not normally distributed; therefore, logarithmic transformation was performed for multivariate logistic regression analysis. Differences and correlations were considered significant for p-values < 0.05. SPSS Statistics version 25.0 (SPSS, Inc, Chicago, Illinois) was used to perform all statistical analyses.

3. Results

3.1. Comparison of the clinical variables among the participants in premenopausal, perimenopausal, and postmenopausal status

Table 1 shows the clinical variables among premenopausal women (n = 114), perimenopausal women (n = 93), and postmenopausal women (n = 261). There were significant differences in age ($p < 0.001$), weight ($p = 0.009$), SBP ($p < 0.001$), DBP ($p = 0.001$), HbA1c ($p < 0.001$), serum concentrations of TC ($p < 0.001$), TG ($p = 0.001$), LDL-C ($p < 0.001$), and FT$_4$ ($p = 0.006$), PG concentration ($p < 0.001$), and max IMT ($p < 0.001$) among the women in each status. Especially, max IMT, similar to SBP, DBP, serum concentrations of TC, TG, LDL-C, PG concentration and HbA1c, gradually increased with the progression of menopausal status, and was significantly higher in postmenopausal women than in premenopausal and perimenopausal women ($p < 0.001$) (data not shown). There were no significant differences in BMI and serum concentrations of HDL-C and TSH among three groups.

3.2. Comparison of the clinical variables between the participants according to absence or presence of plaque

The 468 women were divided into two groups according to the absence (non-plaque group, n = 356) or presence (plaque group, n = 112) of carotid plaque defined as max IMT ≥1.1 mm. Table 2 shows the comparison of the clinical variables between the two groups. Compared with the women in the non-plaque group, those in the plaque group were significantly older ($p < 0.001$) and had a significantly higher percentage of postmenopausal women ($p < 0.001$). Similarly, women in the plaque group had significantly higher SBP ($p = 0.002$), HbA1c ($p < 0.001$), serum concentrations of TC ($p < 0.001$), LDL-C ($p = 0.001$), and TSH ($p = 0.038$), and max IMT ($p < 0.001$) than women in the non-plaque group. There were no significant differences in weight, BMI, DBP, PG concentration, and serum concentrations of HDL-C, TG, and FT$_4$ between the two groups.

Table 1
Comparison of clinical variables among each participant divided by premenopausal, perimenopausal, and postmenopausal status.

	Premenopausal (n = 114)	Perimenopausal (n = 93)	Postmenopausal (n = 261)	p-value
Age (year)	42 (40–45)	49 (47–51)	59 (55–65)	<0.001
Weight (kg)	53.8 (48.2–59.2)	53.5 (48.9–60.0)	51.1 (47.4–56.5)	0.009
BMI (kg/m^2)	21.2 (19.2–22.9)	21.3 (19.8–24.0)	21.1 (19.4–23.0)	0.721
SBP (mmHg)	107 (101–117)	113 (105–123)	115 (106–128)	<0.001
DBP (mmHg)	66 (62–74)	71 (64–80)	71 (65–78)	0.001
TC (mg/dL)	198 (180–215)	217 (199–242)	233 (214–258)	<0.001
HDL-C (mg/dL)	69 (60–81)	72 (60–82)	72 (62–85)	0.347
TG (mg/dL)	66 (49–93)	70 (57–92)	82 (60–111)	0.001
LDL-C (mg/dL)	107 (90–123)	126 (105–151)	132 (114–154)	<0.001
PG (mg/dL)	94 (90–99)	95 (91–100)	98 (93–104)	<0.001
HbA1c (%)	5.5 (5.3–5.7)	5.6 (5.3–5.8)	5.8 (5.6–6.0)	<0.001
FT$_4$ (ng/dL)	1.03 (0.97–1.09)	1.01 (0.95–1.08)	1.05 (0.99–1.12)	0.006
TSH (μIU/mL)	1.43 (1.03–2.14)	1.28 (1.08–1.89)	1.49 (1.08–2.07)	0.438
max IMT (mm)	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.8 (0.6–1.3)	<0.001

Data are expressed as median (25th–75th percentile). The groups divided by menopausal status were compared using Kruskal–Wallis test.
BMI, body mass index; DBP, diastolic blood pressure; FT$_4$, free thyroxine; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima–media thickness; PG, plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyrotropin.

Table 2
Comparison of clinical variables between two groups according to absence or presence of carotid plaque.

	Non-plaque group (n = 356)	Plaque group (n = 112)	*p*-value
Age (year)	50 (45–58)	61 (55–66)	<0.001
Postmenopausal (%)	46.9	83.9	<0.001
Weight (kg)	52.7 (47.8–58.1)	51.2 (47.8–55.7)	0.090
BMI (kg/m²)	21.1 (19.4–23.3)	21.1 (19.4–22.5)	0.444
SBP (mmHg)	111 (104–122)	118 (106–130)	0.002
DBP (mmHg)	69 (63–77)	71 (65–79)	0.102
TC (mg/dL)	218 (198–244)	233 (215–256)	<0.001
HDL-C (mg/dL)	71 (60–83)	69 (62–84)	0.864
TG (mg/dL)	71 (57–104)	80 (59–110)	0.167
LDL-C (mg/dL)	121 (101–147)	135 (116–154)	0.001
PG (mg/dL)	96 (92–102)	98 (92–104)	0.116
HbA1c (%)	5.7 (5.4–5.9)	5.8 (5.6–6.0)	<0.001
FT$_4$ (ng/dL)	1.04 (0.98–1.11)	1.04 (0.97–1.12)	0.721
TSH (µIU/mL)	1.41 (1.02–2.05)	1.57 (1.16–2.31)	0.038
max IMT (mm)	0.6 (0.5–0.7)	1.5 (1.3–1.7)	<0.001

Data are expressed as median (25th–75th percentile). Carotid plaque was defined as max IMT ≥1.1 mm. The plaque group was compared with the non-plaque group using chi-squared test or Mann–Whitney *U* test as appropriate. BMI, body mass index; DBP, diastolic blood pressure; FT$_4$, free thyroxine; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima–media thickness; PG, plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyrotropin.

3.3. Multivariate logistic regression analysis for factors contributing to carotid artery plaque

Table 3 shows the potential independent risk factors of carotid artery plaque by multivariate logistic regression analysis based on the results of the comparison between the plaque and non-plaque groups. Age (β = 0.080, *p* < 0.001) and logarithmic TSH (β = 1.218, *p* = 0.036) were independently associated with carotid artery plaque. However, postmenopausal status, weight, SBP, DBP, TC, logarithmic TG, LDL-C, PG, and HbA1c were not independently associated with carotid artery plaque.

3.4. Comparisons of max IMT among four groups of serum TSH concentrations

Fig. 2 presents the comparisons of max IMT among four groups of serum TSH concentrations divided as follows, <2.0 µIU/mL, 2.0–2.5 µIU/mL, 2.5–3.0 µIU/mL, and ≥3.0 µIU/mL in all participants (A), premenopausal women (B), perimenopausal women (C), and

Table 3
Multivariate logistic regression analysis for factors contributing to carotid artery plaque.

Factor	β	OR (95 % CI)	*p*-value
Age	0.080	1.083 (1.040–1.129)	<0.001
Postmenopausal status	0.494	1.639 (0.736–3.649)	0.227
Weight	−0.015	0.985 (0.954–1.016)	0.336
SBP	0.019	1.019 (0.994–1.046)	0.141
DBP	0.000	1.000 (0.965–1.036)	0.997
TC	−0.005	0.995 (0.983–1.007)	0.387
logTG	−0.933	0.393 (0.090–1.723)	0.216
LDL-C	0.012	1.012 (0.998–1.026)	0.105
PG	−0.032	0.968 (0.937–1.001)	0.059
HbA1c	0.894	2.445 (0.976–6.124)	0.056
logTSH	1.218	3.381 (1.084–10.547)	0.036

CI, confidence interval; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; logTG, logarithmic triglyceride; OR, odds ratio; PG, plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; logTSH, logarithmic thyrotropin.

postmenopausal women (D). Although a significant difference in max IMT was not observed among the four groups in all participants by Kruskal–Wallis test (*p* = 0.057), max IMT were tended to be high in group 2.5–3.0 µIU/mL and group ≥3.0 µIU/mL (Fig. 2A). There was no significant difference in max IMT among the four groups in premenopausal women (*p* = 0.937) (Fig. 2B) and perimenopausal women (*p* = 0.080) (Fig. 2C). In contrast, a significant difference in max IMT was observed among the four groups in postmenopausal women (*p* = 0.029) (Fig. 2D).

3.5. Comparison of max IMT and other clinical variables using serum TSH cutoff values of 2.0, 2.5, or 3.0 µIU/mL in premenopausal, perimenopausal, and postmenopausal women

The premenopausal, perimenopausal, and postmenopausal women were divided into two groups (less than and greater than the cutoff value) according to serum TSH concentration cutoff values of 2.0, 2.5, or 3.0 µIU/mL. Fig. 3 shows the comparison of the max IMT between the two groups for each cutoff point of serum TSH concentration in premenopausal (A), perimenopausal (B), and postmenopausal women (C). There were no significant differences in max IMT between the bisected groups at each cutoff value for serum TSH concentrations in premenopausal women (Fig. 3A) and perimenopausal women (Fig. 3B). Similarly, significant differences were not observed in max IMT between two groups using a cutoff point of 2.0 µIU/mL of serum TSH concentrations in postmenopausal women (Fig. 3C). In contrast, max IMT were significantly higher in women with values ≥2.5 µIU/mL than in those with values <2.5 µIU/mL using a cutoff value of 2.5 µIU/mL serum TSH in postmenopausal women (*p* = 0.018) (Fig. 3C). Using a cutoff value of 3.0 µIU/mL serum TSH, max IMT were also higher in women with values ≥3.0 µIU/mL compared with those with values <3.0 µIU/mL in postmenopausal women (*p* = 0.012) (Fig. 3C).

In postmenopausal women, Table 4 demonstrated the comparison of max IMT and other clinical variables between bisected groups at each cutoff value for serum TSH concentrations. There were no significant differences in clinical variables including max IMT in the two groups divided using a cutoff value of 2.0 µIU/mL serum TSH. Using a cutoff value of 2.5 µIU/mL serum TSH, there were no significant differences in clinical values, except for max IMT, between the two groups. In contrast, TC (*p* = 0.004) and LDL-C (*p* = 0.003), in addition to max IMT, were higher in women with values ≥3.0 µIU/mL compared with those with values <3.0 µIU/mL, using a cutoff value of 3.0 µIU/mL serum TSH. In premenopausal women, women with values ≥2.0 had significantly lower serum concentrations of TC and higher concentrations of PG than those with values <2.0, and women with greater TSH concentrations than each cutoff value had significantly higher serum TG concentrations (Supplementary Table 1). In perimenopausal women, women with values ≥3.0 had significantly lower serum TC concentrations (Supplementary Table 2).

4. Discussion

The present study demonstrated an association between carotid atherosclerosis and detailed thyroid function in euthyroid Japanese women at each menopausal status. Carotid max IMT gradually increased with the progression of menopausal status, although significant difference was not observed in serum TSH concentrations among the women in premenopausal, perimenopausal, and postmenopausal status. Serum TSH concentrations were significantly higher in women with carotid plaques, and were independently associated with carotid plaque by multivariate logistic regression analysis. Moreover, in postmenopausal women, max IMT were significantly differed among the four groups of <2.0 µIU/mL, 2.0–2.5 µIU/mL, 2.5–3.0 µIU/mL, and ≥3.0 µIU/mL serum TSH concentration, and a significantly higher max IMT values were observed in women with ≥2.5 µIU/mL serum TSH than in those with <2.5 µIU/mL serum TSH without elevated TC and LDL-C
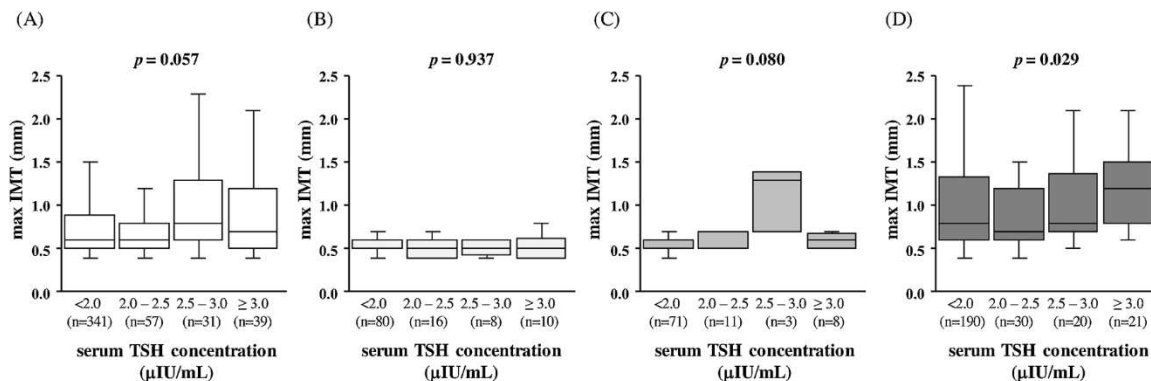
Fig. 2. Comparisons of max intima-media thickness (max IMT) among four groups of the serum thyrotropin (TSH) concentrations divided as follows: <2.0 μIU/mL, 2.0–2.5 μIU/mL, 2.5–3.0 μIU/mL, and ≥3.0 μIU/mL. The groups were compared using Kruskal–Wallis test in all participants (A), premenopausal women (B), perimenopausal women (C), and postmenopausal women (D).
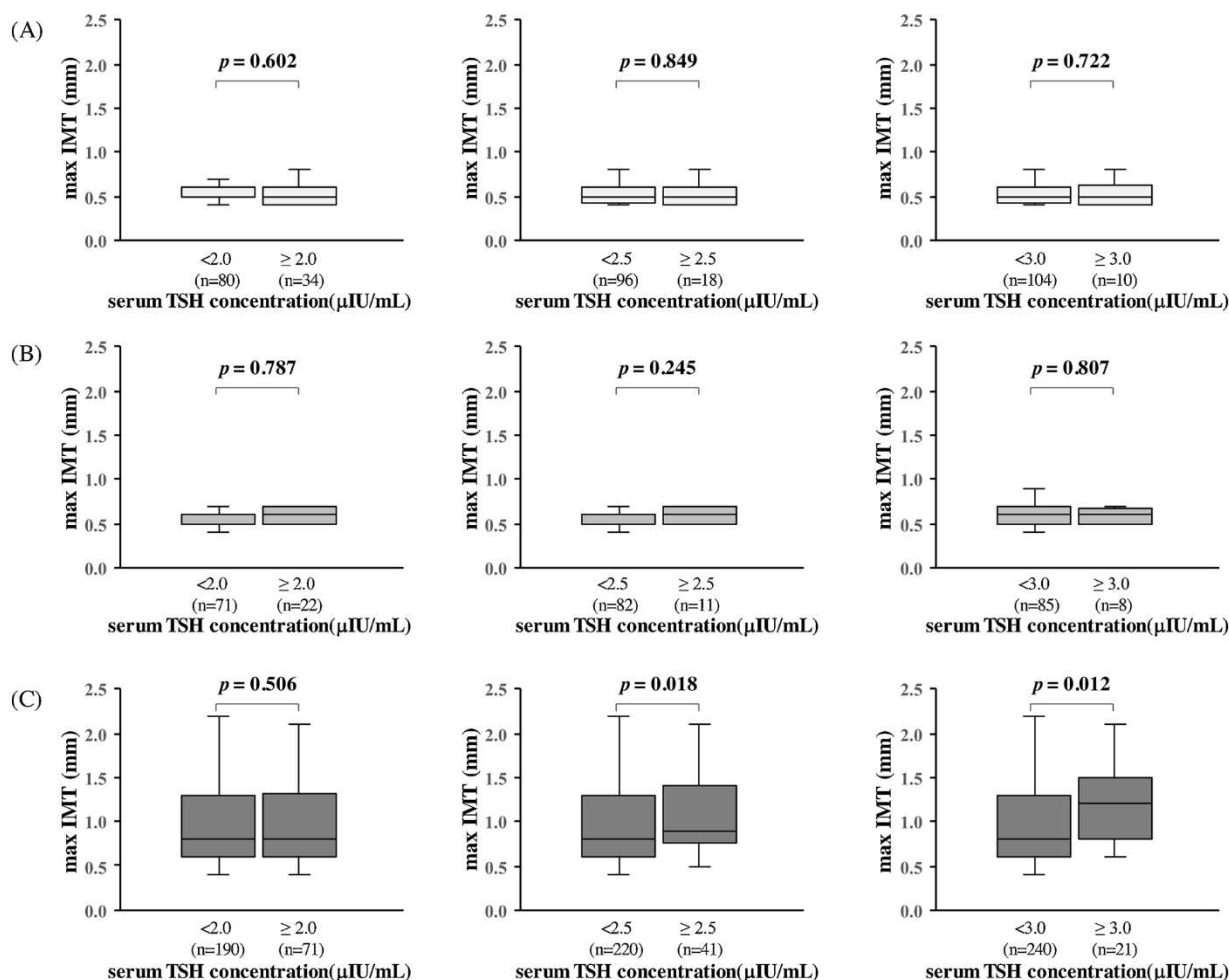

Fig. 3. Comparisons of max intima-media thickness (max IMT) between bisected groups using cutoff values of 2.0, 2.5 or 3.0 μIU/mL in premenopausal women (A), perimenopausal women (B), and postmenopausal women (C). The two groups were compared using Mann–Whitney *U* tests.

concentrations. These differences were not observed in premenopausal and perimenopausal women.

Serum TSH concentrations detect slight changes in thyroid function more sensitive than serum FT_4 concentrations, because a slight drop in FT_4 results in an amplified response in TSH secretion [12]. Serum TSH concentrations increased with age among women in the National Health and Nutrition Examination Survey (NHANES III) [18] and the Thyroid Epidemiology, Audit, and Research Study (TEARS) [19]. In this study,

although postmenopausal women had higher serum concentration of FT_4 than premenopausal and perimenopausal women, max IMT were significantly correlated with serum TSH concentration by Spearman's correlation analysis and multiple linear regression analysis, but not FT_4. Therefore, we used serum TSH concentration for cutoff value analysis in the association between max IMT and detailed thyroid function. Previously, serum TSH concentrations ≥2.5 μIU/mL in euthyroid state were associated with the development of metabolic syndrome, which was as

Table 4

Comparison of clinical variables between bisected groups using cutoff values of 2.0, 2.5 or 3.0 µIU/mL serum TSH in postmenopausal women.

	Cutoff value = 2.0 µIU/mL		Cutoff value = 2.5 µIU/mL		Cutoff value = 3.0 µIU/mL	
	<2.0 (n = 190)	≥2.0 (n = 71)	<2.5 (n = 220)	≥2.5 (n = 41)	<3.0 (n = 240)	≥3.0 (n = 21)
Age (years)	59 (55–64)	61 (56–66)	59 (55–64)	63 (57–67)	59 (55–65)	63 (58–68)
Weight (kg)	50.8 (47.1–56.3)	51.6 (47.9–57.3)	51.0 (47.4–56.4)	51.5 (48.6–57.1)	50.9 (47.4–56.5)	52.4 (49.9–57.5)
BMI (kg/m^2)	21.0 (19.2–23.0)	21.3 (19.7–23.1)	21.1 (19.4–23.0)	21.5 (19.1–23.0)	21.0 (19.2–23.0)	21.6 (19.8–23.7)
SBP (mmHg)	115 (106–129)	115 (107–127)	115 (106–128)	116 (109–127)	115 (106–128)	116 (108–127)
DBP (mmHg)	72 (64–79)	71 (66–76)	72 (64–79)	71 (66–76)	72 (65–78)	69 (65–76)
TC (mg/dL)	233 (213–257)	238 (218–261)	233 (213–256)	243 (219–264)	232 (213–256)	249 (235–274)*
HDL-C (mg/dL)	72 (62–85)	72 (62–85)	72 (62–86)	69 (63–82)	72 (62–85)	69 (63–83)
TG (mg/dL)	82 (60–110)	83 (62–120)	82 (60–110)	83 (68–128)	82 (60–111)	86 (71–116)
LDL-C (mg/dL)	132 (114–152)	134 (111–155)	131 (113–151)	143 (117–158)	131 (113–151)	155 (136–159)*
PG (mg/dL)	98 (93–104)	99 (93–104)	98 (93–104)	100 (93–105)	98 (93–104)	99 (90–104)
HbA1c (%)	5.8 (5.6–6.0)	5.8 (5.6–6.0)	5.8 (5.6–6.0)	5.8 (5.7–6.1)	5.8 (5.6–6.0)	5.8 (5.7–6.1)
FT$_4$ (ng/dL)	1.06 (0.99–1.12)	1.01 (0.96–1.09)*	1.06 (0.99–1.13)	0.99 (0.95–1.06)*	1.05 (0.99–1.12)	1.01 (0.95–1.07)*
TSH (µIU/mL)	1.27 (0.91–1.57)	2.63 (2.28–3.16)*	1.35 (0.98–1.73)	3.03 (2.72–3.47)*	1.43 (1.01–1.87)	3.47 (3.17–3.81)*
max IMT (mm)	0.8 (0.6–1.3)	0.8 (0.6–1.3)	0.8 (0.6–1.3)	0.9 (0.8–1.4)*	0.8 (0.6–1.3)	1.2 (0.8–1.5)*

Data are expressed as median (25th–75th quartile). * $p < 0.05$ comparing variables between two groups divided by each cutoff value for TSH concentration using Mann–Whitney U test.

BMI, body mass index; DBP, diastolic blood pressure; FT$_4$, free thyroxine; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima–media thickness; PG, plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyrotropin.

high as 1.7-fold in the general population [20] and 1.95-fold in postmenopausal women [21]. The Tromsø Study demonstrated that the carotid mean IMT was not significantly associated with serum TSH level divided into three groups, < 0.48 µIU/mL, 0.48–4.16 µIU/mL, and >4.16 µIU/mL [22]. In contrast, the carotid mean IMT was independently associated with low normal thyroid function in euthyroid individuals [9]. Postmenopausal women with serum TSH concentrations ≥2.5 µIU/mL showed significantly higher PWV values compared with those with serum TSH levels <2.5 µIU/mL, although there was no significant difference in carotid mean IMT between the two groups [17]. While the association between detailed thyroid function and carotid atherosclerosis remains controversial, the present study demonstrates for the first time that the significant association between max IMT of carotid artery and serum TSH concentration ≥2.5 µIU/mL was observed only in postmenopausal women, and not in premenopausal and perimenopausal women. Furthermore, the significance of a cutoff point of serum TSH 2.5 µIU/mL in atherosclerosis may further support the findings from previous studies.

Overt and subclinical hypothyroidism reportedly promotes atherosclerosis based on the direct effect of thyroid hormone on blood vessels, in addition to the mechanism mediating hypercholesterolemia. Thyroid hormones act directly on vascular smooth muscle cells to relax coronary arteries [23]. We previously reported that type 2 iodothyronine deiodinase (D2), a thyroid hormone activating enzyme that converts T$_4$ to T$_3$, is expressed in human coronary artery smooth muscle cells (hCASMCs) and human aortic smooth muscle cells (hASMCs) [24]. Intracellular thyroid hormone activation by D2 suppresses the DNA synthesis and migration activity of hCASMCs [25], suggesting a direct inhibitory effect of thyroid hormone against atherosclerosis. Vasodilatation is lower in patients with overt and subclinical hypothyroidism, indicating effects on endothelial cells [26]. In addition, thyroid hormone induces rapid activation of phosphoinositide 3-kinase (PI3K)/Akt/endothelial nitric oxide synthase in endothelial cells. We recently reported that the conversion of T$_4$ to T$_3$ by D2 is involved in the thyroid receptor α1/PI3K-mediated nongenomic actions of T$_4$ in human umbilical vein endothelial cells, including stimulation of Akt phosphorylation and Rac activation [27]. These findings suggested that thyroid hormones induce endothelial cell migration, which is important for vessel repair and angiogenesis against the progression of atherosclerosis. Moreover, TSH itself stimulates the proliferation of vascular smooth muscle cells, resulting in the promotion of atherosclerosis [28]. In the present study, serum TSH concentrations ≥2.5 µIU/mL were significantly associated with carotid max IMT in postmenopausal women, suggesting a direct effect of thyroid hormone, and possibly TSH, on arterial walls associated with progress of atherosclerosis.

The present study has some limitations. First, this study used a relatively small sample size to assess the association between detailed thyroid function and carotid atherosclerosis. The reason for the small sample size was that only euthyroid women without CVD and/or metabolic disorders at risk for atherosclerosis were enrolled. Second, FT$_3$ and anti-thyroid antibodies, including anti-thyroglobulin antibody and anti-thyroid peroxidase antibody, were not measured. Thyroid autoimmunity is reportedly associated with an increase in carotid IMT independent of thyroid function [29]. It is necessary to evaluate the effect of serum TSH cutoff values on carotid atherosclerosis with or without anti-thyroid antibodies in premenopausal and postmenopausal women in future studies. Third, although menopausal status was determined based on the interview of previous menstrual date and menstrual cycle, we were not able to measure serum concentrations of estrogen and follicular stimulating hormone (FSH), and to evaluate the detailed menopausal symptoms. Because of the difficulty of perimenopausal status determination, especially, further study needs to analyze the association between the atherosclerosis and detailed thyroid function, with or without the menopausal symptoms, in detailed menopausal classifications. Another limitation is that age may have been directly associated with thyroid functions and carotid max IMT. In our study, there was no difference in age comparing the two groups bisected by any serum TSH at each menopausal status, and there were no significant correlations between age and serum TSH concentration by Spearman's correlation analysis and multiple linear regression analysis (data not shown). These results suggest that age and serum TSH concentration are independently associated with carotid IMT, and highlight the potential usefulness of measuring serum TSH concentration to assess the risk of atherosclerosis, especially in postmenopausal women, even if age is relevant. We expect that further studies in a large number of women at each menopausal status for assessment the association between carotid IMT and detailed thyroid function independent with the effect of age will validate our hypothesis.

In conclusion, serum TSH concentration was significantly higher in women with carotid plaque and was independent contributor to carotid plaque in euthyroid women. Moreover, postmenopausal women with serum TSH levels ≥2.5 µIU/mL had significantly higher carotid max IMT without hypercholesterolemia. Therefore, laboratory finding of serum TSH concentrations ≥2.5 µIU/mL, as well as measurement of other risk factors, may be useful to prevent atherosclerosis in postmenopausal women.

Contributors

Koji Sakamaki contributed to conceptualization, methodology, data collection and analysis, and writing and revision of the original draft.

Katsuhiko Tsunekawa contributed to conceptualization, methodology, data analysis, and reviewing and editing the manuscript.

Nobuyoshi Ishiyama contributed to data collection.

Mizuho Kudo contributed to data collection.

Kimiko Ando contributed to data collection.

Masako Akuzawa contributed to data collection.

Katsuyuki Nakajima contributed to data collection and reviewing and editing the manuscript.

Yohnosuke Shimomura contributed to data collection and reviewing and editing the manuscript.

Osamu Araki contributed to data collection and reviewing and editing the manuscript.

Takao Kimura contributed to conceptualization and reviewing and editing the manuscript.

Masami Murakami contributed to conceptualization, methodology, supervision, and reviewing and editing the manuscript.

All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

Ethical approval

The study was approved by the ethics committee of Hidaka Hospital (approval no. 186).

Ethical statement

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of Hidaka Hospital (approval no. 186).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2020.10.022.

References

[1] W.B. Kannel, M.C. Hjortland, P.M. McNamara, T. Gordon, Menopause and risk of cardiovascular disease: the Framingham study, Ann. Intern. Med. 85 (4) (1976) 447–452, https://doi.org/10.7326/0003-4819-85-4-447.

[2] J.C.M. Witteman, D.E. Grobbee, F.J. Kok, A. Hofman, H.A. Valkenburg, Increased risk of atherosclerosis in women after the menopause, Br. Med. J. 298 (6674) (1989) 642–644, https://doi.org/10.1136/bmj.298.6674.642.

[3] K. Sutton-Tyrrell, H.C. Lassila, E. Meilahn, C. Bunker, K.A. Matthews, L.H. Kuller, Carotid atherosclerosis in premenopausal and postmenopausal women and its association with risk factors measured after menopause, Stroke 29 (6) (1998) 1116–1121, https://doi.org/10.1161/01.str.29.6.1116.

[4] M.C. Carr, The emergence of the metabolic syndrome with menopause, J. Clin. Endocrinol. Metab. 88 (6) (2003) 2404–2411, https://doi.org/10.1210/jc.2003-030242.

[5] I. Klein, K. Ojamaa, Mechanisms of disease: thyroid hormone and the cardiovascular system, N. Engl. J. Med. 344 (7) (2001) 501–509, https://doi.org/10.1056/NEJM200102153440707.

[6] A.R. Cappola, P.W. Ladenson, Hypothyroidism and atherosclerosis, J. Clin. Endocrinol. Metab. 88 (6) (2003) 2438–2444, https://doi.org/10.1210/jc.2003-030398.

[7] A.E. Hak, H.A.P. Pols, T.J. Visser, H.A, Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study, Ann. Intern. Med. 132 (4) (2000) 270–278, https://doi.org/10.7326/0003-4819-132-4-200002150-00004.

[8] T. Nagasaki, M. Inaba, Y. Henmi, Y. Kumeda, M. Ueda, H. Tahara, S. Sugiguchi, S. Fujiwara, M. Emoto, E. Ishimura, N. Onoda, T. Ishikawa, Y. Nishizawa, Decrease in carotid intima-media thickness in hypothyroid patients after normalization of thyroid function, Clin. Endocrinol. 59 (5) (2003) 607–612, https://doi.org/10.1046/j.1365-2265.2003.01893.x.

[9] N. Takamura, A. Akilzhanova, N. Hayashida, K. Kadota, H. Yamasaki, T. Usa, M. Nakazato, T. Maeda, Y. Ozono, K. Aoyagi, Thyroid function is associated with carotid intima-media thickness in euthyroid subjects, Atherosclerosis 204 (2) (2009) 77–81, https://doi.org/10.1016/j.atherosclerosis.2008.09.022.

[10] Y. Irie, N. Katakami, H. Kaneto, R. Kasami, S. Sumitsuji, K. Yamasaki, K. Tachibana, T. Kuroda, K. Sakamoto, Y. Umayahara, Y. Ueda, K. Kosugi, I. Shimomura, Maximum carotid intima-media thickness improves the prediction ability of coronary artery stenosis in type 2 diabetic patients without history of coronary artery disease, Atherosclerosis 221 (2) (2012) 438–444, https://doi.org/10.1016/j.atherosclerosis.2012.01.022.

[11] K. Fujihara, H. Suzuki, A. Sato, T. Ishizu, S. Kodama, Y. Heianza, K. Saito, H. Iwasaki, K. Kobayashi, S. Yatoh, A. Takahashi, N. Yahagi, H. Sone, H. Shimano, Comparison of the Framingham Risk Score, UK Prospective Diabetes Study (UKPDS) Risk Engine, Comparison of the Framingham risk score, UK Prospective Diabetes Study (UKPDS) Risk Engine, Japanese Atherosclerosis Longitudinal Study-Existing Cohorts combine (JALS-ECC) and maximum carotid intima-media thickness for predicting coronary artery stenosis in patients with asymptomatic type 2 diabetes, J. Atheroscler. Thromb. 21 (8) (2014) 799–815, https://doi.org/10.5551/jat.20487.

[12] L. Wartofsky, R.A. Dickey, The evidence for a narrower thyrotropin reference range is compelling, J. Clin. Endocrinol. Metab. 90 (9) (2005) 5483–5488, https://doi.org/10.1210/jc.2005-0455.

[13] J.E. Haddow, G.E. Palomaki, W.C. Allan, J.R. Williams, G.J. Knight, J. Gagnon, C. E. O'Heir, M.L. Mitchell, R.J. Hermos, S.E. Waisbren, J.D. Faix, R.Z. Klein, Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child, N. Engl. J. Med. 341 (8) (1999) 549–555, https://doi.org/10.1056/NEJM199908193410801.

[14] R. Negro, A. Schwartz, R. Gismondi, A. Tinelli, T. Mangieri, A. Stagnaro-Green, Increased Pregnancy Loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy, J. Clin. Endocrinol. Metab. 95 (9) (2010) E44–E48, https://doi.org/10.1210/jc.2010-0340.

[15] L. De Groot, M. Abalovich, E.K. Alexander, N. Amino, L. Barbour, R.H. Cobin, C. J. Eastman, J.H. Lazarus, D. Luton, S.J. Mandel, J. Mestman, J. Rovet, S. Sullivan, Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metab. 97 (8) (2012) 2543–2565, https://doi.org/10.1210/jc.2011-2803.

[16] E.K. Alexander, E.N. Pearce, G.A. Brent, R.S. Brown, H. Chen, C. Dosiou, W. A. Grobman, P. Laurberg, J.H. Lazarus, S.J. Mandel, R.P. Peeters, S. Sullivan, Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum, Thyroid 27 (3) (2017) 315–389, https://doi.org/10.1089/thy.2016.0457.

[17] I. Lambrinoudaki, E. Armeni, D. Rizos, G. Georgiopoulos, M. Kazani, A. Alexandrou, E. Deligeoroglou, A. Livada, C. Psychas, M. Creatsa, G. Bouboulis, M. Alevizaki, K. Stamatelopoulos, High normal thyroid-stimulating hormone is associated with arterial stiffness in healthy postmenopausal women, J. Hypertens. 30 (3) (2012) 592–599, https://doi.org/10.1097/HJH.0b013e32834f5076.

[18] J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E.W. Gunter, C. A. Spencer, L.E. Braverman, T.S.H. Serum, T(4), and thyroid antibodies in the United States population (1988 to 1994): national Health and Nutrition Examination Survey (NHANES III), J. Clin. Endocrinol. Metab. 87 (2) (2002) 489–499, https://doi.org/10.1210/jcem.87.2.8182.

[19] T. Vadiveloo, P.T. Donnan, M.J. Murphy, G.P. Leese, Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS), J. Clin. Endocrinol. Metab. 98 (3) (2013) 1147–1153, https://doi.org/10.1210/jc.2012-3191.

[20] S. Ruhla, M.O. Weickert, A.M. Arafat, M. Osterhoff, F. Isken, J. Spranger, C. Schofl, A.F.H. Pfeiffer, M. Mohlig, A high normal TSH is associated with the metabolic syndrome, Clin. Endocrinol. 72 (5) (2010) 696–701, https://doi.org/10.1111/j.1365-2265.2009.03698.x.

[21] H.T. Park, G.J. Cho, K.H. Ahn, J.H. Shin, S.C. Hong, T. Kim, J.Y. Hur, Y.T. Kim, K. W. Lee, S.H. Kim, Thyroid stimulating hormone is associated with metabolic syndrome in euthyroid postmenopausal women, Maturitas 62 (3) (2009) 301–305, https://doi.org/10.1016/j.maturitas.2009.01.007.

[22] R. Jorde, O. Joakimsen, E. Stensland, E.B. Mathiesen, Lack of significant association between intima-media thickness in the carotid artery and serum TSH level. The Tromsø study, Thyroid 18 (1) (2008) 21–25, https://doi.org/10.1089/thy.2007.0165.

[23] K. Ojamaa, J.D. Klemperer, I. Klein, Acute effects of thyroid hormone on vascular smooth muscle, Thyroid 6 (5) (1996) 505–512, https://doi.org/10.1089/thy.1996.6.505.

[24] H. Mizuma, M. Murakami, M. Mori, Thyroid hormone activation in human vascular smooth muscle cells - Expression of type II iodothyronine deiodinase, Circ. Res. 88 (3) (2001) 313–318, https://doi.org/10.1161/01.res.88.3.313.

[25] T. Kasahara, K. Tsunekawa, K. Seki, M. Mori, M. Murakami, Regulation of iodothyronine deiodinase and roles of thyroid hormones in human coronary artery smooth muscle cells, Atherosclerosis 186 (1) (2006) 207–214, https://doi.org/10.1016/j.atherosclerosis.2005.07.018.

[26] J. Lekakis, C. Papamichael, M. Alevizaki, G. Piperingos, P. Marafelia, J. Mantzos, S. Stamatelopoulos, D.A. Koutras, Flow-mediated, endothelium-dependent vasodilatation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values, Thyroid 7 (3) (1997) 411–414, https://doi.org/10.1089/thy.1997.7.411.

[27] T. Aoki, K. Tsunekawa, O. Araki, T. Ogiwara, M. Nara, H. Sumino, T. Kimura, M. Murakami, Type 2 iodothyronine deiodinase activity is required for rapid stimulation of PI3K by thyroxine in human umbilical vein endothelial cells, Endocrinology 156 (11) (2015) 4312–4324, https://doi.org/10.1210/en.2014-1988.

[28] L.M. Tian, J. Ni, T.K. Guo, J. Liu, Y.M. Dang, Q. Guo, L.Y. Zhang, TSH stimulates the proliferation of vascular smooth muscle cells, Endocrine 46 (3) (2014) 651–658, https://doi.org/10.1007/s12020-013-0135-4.

[29] M.M. Ciccone, G. De Pergola, M.T. Porcelli, P. Scicchitano, P. Caldarola, M. Iacoviello, G. Pietro, F. Giorgino, S. Favale, Increased carotid IMT in overweight and obese women affected by Hashimoto's thyroiditis: an adiposity and autoimmune linkage? BMC Cardiovasc. Disord. 10 (2010) 22, https://doi.org/10.1186/1471-2261-10-22.