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Serum Thyrotropin Concentrations Are Not Associated with the Ankle-Brachial Index: Results from Three Population-Based Studies

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Key Words

Epidemiology · Population-based study · Thyrotropin · Thyroid · Peripheral arterial disease · Ankle-brachial index

Abstract

Background: There is only limited data on the potential association between thyroid dysfunction and peripheral arterial disease (PAD). ***Objective:*** The aim of our study was to investigate the potential association of thyroid function, as defined by serum concentrations of the clinically used primary thyroid function marker thyrotropin [i.e. thyroid-stimulating hormone (TSH)] and 3,5-diiodothyronine (3,5-T_2), with the ankle-brachial index (ABI) as a marker of PAD. ***Methods:*** We used data from 5,818 individuals from three cross-sectional population-based studies conducted in Northeast (SHIP-2 and SHIP-TREND) and Central Germany (CARLA). Measurement of serum TSH concentrations was conducted in one central laboratory for all three studies. In a randomly selected subpopulation of 750 individuals of SHIP-TREND, serum 3,5-T_2 concentrations were measured with a recently developed immunoassay. ABI was measured either by a hand-held Doppler ultrasound using the Huntleigh Dopplex D900 or palpatorily by the OMRON HEM-705CP device. ***Results:*** Serum TSH concentrations were not significantly associated with ABI values in any of the three studies. Likewise, groups of individuals with a TSH <0.3 mIU/l or with a TSH ≥3.0 mIU/l had no significantly different ABI values in comparison with individuals with a TSH in the reference range. Analyses regarding TSH within the reference range or serum 3,5-T_2 concentrations did not reveal consistent significant associations with the ABI. No sex-specific associations were detected. ***Conclusions:*** The results of our study do not substantiate evidence for an association between thyroid function and PAD, but further studies are needed to investigate the associations of overt forms of thyroid dysfunction with PAD.

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Background

Peripheral arterial disease (PAD) is characterized by a narrowing of the arterial blood vessels in the lower limb, which is caused by atherosclerotic processes. PAD is associated with a higher risk for cardiovascular mortality [1, 2] and cardiovascular events [1, 3, 4]. A link between thyroid dysfunction and atherosclerotic processes has been previously described, pointing towards an association between hypothyroidism and atherosclerosis [5–7].

However, there is only limited data on the potential linkage between thyroid dysfunction and PAD as one of the major atherosclerotic diseases. One study reported a significantly higher prevalence of increased serum thyroid-stimulating hormone (TSH) concentrations in 30 elderly women with PAD in comparison to a control group without PAD [8]. In contrast, a population-based study detected no significant association between subclinical hypothyroidism and PAD-related hospitalization or procedures among 2,730 elderly individuals aged 70–79 years [9]. In that study, however, the direct association between thyroid function and ankle-brachial index (ABI) was not investigated.

ABI assessed by Doppler ultrasound is the gold standard method to determine PAD [10]. Population-based data on the association between thyroid dysfunction and PAD determined by ABI is lacking. In addition to TSH, 3,5-diiodothyronine (3,5-T_2) concentrations may also be related to PAD, since 3,5-T_2 concentrations have been shown to be associated with leptin [11], an adipokine which has an impact on atherosclerotic events [12]. Furthermore, previous studies, mainly assessed in animals, demonstrated associations of 3,5-T_2 with lipid [13, 14] and glucose metabolism [11, 15], which are both risk factors in the pathogenesis of atherosclerosis. Therefore, the aim of our research was to investigate the potential association of thyroid function, as defined by two independent markers of systemic and metabolic thyroid hormone status, i.e. the serum concentrations of TSH and 3,5-T_2, with ABI assessed by Doppler ultrasound in three population-based studies with 5,718 individuals in total covering an age range of 20–90 years.

Material and Methods

Study Populations

Analyses are based on data from three population-based studies. The first two studies are separate cohorts of the Study of Health in Pomerania (SHIP), conducted in the same population of Northeast Germany [16]. Initially 6,267 individuals were invited for the first cohort, of whom 2,333 individuals aged 30–90 years participated at the second follow-up (SHIP-2). Parallel to SHIP-2 a new cohort was established (SHIP-TREND) in which 8,826 individuals were invited and 4,420 individuals aged 20–80 years participated. In both studies, individuals were selected from population registries. The third study comprised data from the baseline examinations of the Cardiovascular Disease, Living and Ageing in Halle (CARLA) study, a population-based cohort study conducted in Central Germany, in which 5,000 individuals were invited to participate. Of those, 1,779 individuals aged 45–80 years were examined between 2002 and 2005 [17]. In all studies, participants gave informed written consent and all studies were approved by the local ethics committees and followed the Declaration of Helsinki.

In the two SHIP studies, all probands were invited to participate in the ABI examinations and subsamples of 1,430 (SHIP-2) and 2,697 individuals (SHIP-TREND) responded. To account for the possible selection bias according to nonparticipation in the ABI examination, inverse probability weights using education, equivalence income, blood pressure (BP), diabetes, lipids and BMI as explanatory variables were applied [18]. In SHIP-2, analyses were additionally weighted for dropout from the baseline examination (SHIP-0) to SHIP-2. In CARLA, individuals with missing data in any of the considered variables (n = 106) were excluded, resulting in a study population of 1,691 individuals.

Assessments

Blood samples were taken between 7 a.m. and 1 p.m. in the SHIP studies and between 7 a.m. and 7 p.m. in CARLA. All blood samples of the three studies were analyzed at the central laboratory of the University Medicine Greifswald. Serum TSH concentrations were measured by immunochemiluminescent procedures (Dimension Vista; Siemens, Eschborn, Germany) for all three studies. Low and high serum TSH concentrations were defined by the cutoffs 0.3 mIU/l and 3.0 mIU/l according to Baskin et al. [19]. In a randomly selected subpopulation of 750 individuals of SHIP-TREND, serum 3,5-T_2 concentrations were measured as a potential parameter of peripheral thyroid hormone status [20] with a recently developed chemiluminescent immunoassay based on monoclonal anti-3,5-T_2 antibodies produced in mice at the Charité Institute for Experimental Endocrinology [21]. The functional sensitivity of the assay is specified as 0.2 nM. The interassay coefficient of variation was between 12.9 and 5.6% of the linear working range of the assay.

For ABI assessment in SHIP, systolic BP was measured with a 'Dopplex D900' (Huntleigh Healthcare Ltd.) Doppler ultrasound probe and a BP cuff (Welch Allyn) in both arms (brachial artery) and both ankles (anterior and posterior tibial artery). Measurements were taken in the supine position after at least 10 min of rest. ABI was calculated using the lower of the right and left tibial pressures divided by the higher of the two brachial artery pressures.

For ABI measurement in CARLA, the supine systolic BP at the arm and ankle was measured after 5 min of rest using the OMRON HEM-705CP device. First, a simultaneous measurement of BP at both arms was performed. For the BP measurements used for the calculation of ankle-arm index, the OMRON HEM-705CP device remains on the arm with the higher systolic BP. The circumference of both calves was determined at the midpoint of the BP cuff to select the adequate cuff size. The cuff was positioned approximately 5 cm above the inner ankle over the posterior tibial artery using the contour wrap technique. Measurement of BP was started si-

multaneously on the arm and ankle at the same time. First, two measurements were performed on the right ankle, followed by two measurements on the left ankle. Between each pair of measurements, there was a 1-min delay. To calculate ABI, the mean systolic BP of that ankle side which was lowest was divided by the brachial systolic BP which was the highest.

Age, sex, smoking status, and history of myocardial infarction, stroke, and atrial fibrillation were assessed by computer-assisted personal interviews. Smokers were categorized into three categories (lifetime nonsmokers, former smokers, and current smokers).

Statistical Analyses

Continuous variables were expressed as medians and 25th and 75th percentiles; categorical variables were expressed as absolute numbers and percentages. Serum TSH concentrations were associated with ABI by linear regression adjusted for age, sex, and smoking status, and in the SHIP studies additionally for time between core and ABI examination in each of the three studies separately. For these analyses, TSH was power-transformed to reduce the impact of outliers in the TSH variable on the results [22]. To account for possible nonlinear relationships between serum TSH concentrations or any of the confounders with the respective outcome, fractional polynomials were tested [22]. In this analysis no nonlinear relationships between serum TSH concentrations and ABI were detected. In SHIP, all analyses were additionally weighted for nonparticipation at the ABI examination. Inverse probability weights were therefore calculated by taking the inverse of the individual probabilities derived from a logistic regression with participation at the ABI examination as the outcome and per capita income, highest school degree, hypertension, age, sex, diabetes mellitus type 2, BMI, cholesterol, and smoking status as explanatory variables. To account for a potential bias according to high ABI values due to medial arteriosclerosis, we repeated all multivariable analyses under exclusion of individuals with ABI values >1.3 (n = 102 in SHIP-2, n = 122 in SHIP-TREND, and n = 174 in CARLA) [23]. $p < 0.05$ was considered statistically significant. All analyses were carried out using Stata 13.1 (Stata Corporation, College Station, Tex., USA).

Results

Description of the Study Populations

Individuals from CARLA were older than individuals from the SHIP studies (table 1). In all three studies individuals with a TSH <0.3 mIU/l were in the median older than individuals with a TSH in the reference range. This difference was more pronounced in the SHIP studies than in CARLA. In the SHIP studies, individuals with a TSH ≥3.0 mIU/l were in the median younger than individuals with a TSH in the reference range, while these two groups did not differ according to age in the CARLA study. In the SHIP studies, ABI values did not differ among groups of TSH, whereas in CARLA ABI values were in the median lower in individuals with a TSH ≥3.0 mIU/l than in individuals with a TSH within the reference range. The frequency of ABI <0.9 was highest in CARLA.

Multivariable Analyses

Power-transformed TSH was not significantly associated with ABI in either the SHIP studies or in CARLA (table 2). Likewise, groups of individuals with a TSH <0.3 mIU/l or with a TSH ≥3.0 mIU/l had no significantly different ABI values compared to individuals with a TSH in the reference range in any of the studies. After exclusion of individuals with a TSH <0.3 mIU/l or with a TSH ≥3.0 mIU/l, serum TSH concentrations within the reference range were not significantly associated with ABI in any of the studies. Likewise, serum 3,5-T_2 concentrations were not significantly associated with ABI in SHIP-TREND ($\beta = 0.007$; 95% CI = –0.039, 0.053). We repeated these analyses in individuals without evidence of cardiovascular diseases (i.e. pacemaker, cardiac surgery, or history of myocardial infarction, stroke, or atrial fibrillation) with similar results compared to those among the whole populations of the single studies (table 2).

With one exception we did not detect any significant association between power-transformed TSH, categorized TSH, or serum TSH within the reference range and ABI in sex-stratified analyses in SHIP-2, SHIP-TREND, and CARLA (table 2). In males, individuals with a TSH ≥3.0 mIU/l had significantly lower ABI than individuals with a TSH within the reference range in SHIP-TREND. In CARLA the effect size of this association was comparable to the effect size in SHIP-TREND, but missed statistical significance. In SHIP-2, however, the effect size for this association pointed towards another direction and was also not statistically significant.

In the population excluding individuals with ABI values >1.3, no substantially different results in comparison to those presented in table 2 were observed.

Discussion

In three population-based studies, we did not find consistent associations between thyroid function defined by serum concentrations of TSH and 3,5-T_2 and ABI. This finding is in agreement with a population-based study in which serum TSH concentrations were not associated with PAD-related hospitalization and procedures in individuals aged 70–79 years [9], but in contrast to a small patient study [8] in which prevalence of increased TSH was higher in elderly women with PAD than in those without. The major drawback of that study is that individuals were not randomly selected, which might have given rise to bias [8]. Furthermore, no T_4 or T_3 values were determined and only 130 individuals were in-

Table 1. Description of the study populations stratified by serum TSH concentrations

	TSH 0.3–3.0 mIU/l	TSH <0.3 mIU/l	TSH ≥3.0 mIU/l
SHIP-2			
n	1,332	52	46
TSH, mIU/l	1.07 (0.75, 1.46)	0.16 (0.08, 0.22)	3.66 (3.25, 4.98)
Age, years	57 (46, 66)	64 (49, 72)	51 (45, 64)
Men	658 (49.4)	23 (44.2)	17 (37.0)
Smoking status			
Former	570 (42.8)	25 (48.1)	18 (39.1)
Current	232 (17.4)	9 (17.3)	14 (30.4)
BMI	27.5 (24.8, 30.6)	27.5 (25.1, 30.7)	25.6 (23.5, 29.1)
Total cholesterol, mM	5.5 (4.8, 6.2)	5.0 (4.4, 5.7)	5.5 (4.9, 6.3)
ABI	1.13 (1.08, 1.20)	1.12 (1.07, 1.20)	1.14 (1.09, 1.20)
ABI <0.9	27 (2.0)	2 (3.9)	2 (4.4)
Systolic BP, mm Hg	132 (120, 144)	134 (114, 145)	126 (117, 143)
Diastolic BP, mm Hg	80 (74, 86)	77 (70, 85)	79 (73, 85)
SHIP-TREND			
n	2,501	80	98
TSH, mIU/l	1.14 (0.79, 1.57)	0.23 (0.15, 0.27)	3.76 (3.26, 4.80)
Age, years	53 (42, 64)	59 (50, 71)	49 (37, 58)
Men	1,278 (51.1)	28 (35.0)	35 (35.7)
Smoking status			
Former	973 (38.9)	39 (48.8)	13 (16.3)
Current	564 (22.6)	13 (16.3)	24 (24.5)
BMI	27.5 (24.7, 30.8)	27.7 (24.4, 31.4)	27.0 (24.2, 30.1)
Total cholesterol, mM	5.4 (4.7, 6.2)	5.5 (4.5, 6.3)	5.5 (4.8, 6.2)
ABI	1.12 (1.07, 1.18)	1.12 (1.08, 1.20)	1.11 (1.08, 1.17)
ABI <0.9	32 (1.8)	0	0
Systolic BP, mm Hg	127 (115, 139)	123 (111, 137)	122 (113, 136)
Diastolic BP, mm Hg	77 (71, 83)	74 (67, 81)	75 (70, 82)
Diiodothyronine, nM	0.24 (0.20, 0.37)	0.38 (0.20, 0.55)	0.30 (0.21, 0.39)
CARLA			
n	1,446	216	29
TSH, mIU/l	0.77 (0.56, 1.09)	0.19 (0.11, 0.25)	4.01 (3.34, 6.53)
Age, years	64 (55, 73)	65 (59, 72)	65 (55, 78)
Men	807 (55.8)	103 (47.7)	10 (34.5)
Smoking status			
Former	521 (36.0)	73 (33.8)	12 (41.4)
Current	639 (44.2)	108 (50.0)	13 (44.8)
BMI	27.9 (25.1, 30.9)	27.8 (25.0, 30.8)	28.6 (25.1, 30.6)
Total cholesterol, mM	5.4 (4.8, 6.2)	5.4 (4.8, 5.9)	5.5 (5.0, 6.3)
ABI	1.16 (1.08, 1.24)	1.16 (1.07, 1.23)	1.09 (1.04, 1.16)
ABI <0.9	78 (5.4)	19 (8.8)	1 (3.5)
Systolic BP, mm Hg	143 (129, 156)	141 (128, 160)	142 (134, 164)
Diastolic BP, mm Hg	85 (78, 92)	84 (77, 93)	90 (83, 94)

Data are expressed as medians (25th and 75th percentiles) for continuous data or as absolute numbers (percentages) for categorical data.

cluded in that study [8], which also hampers the generalizability of the findings. The fact that there is only one small study reporting an association between thyroid function and PAD might argue for a lack of an association between thyroid hormones and PAD.

Similarly to the results in the whole study population, we did not find any consistent association between serum TSH concentrations and ABI values when we compared males and females. We detected a significant association between increased TSH and ABI in SHIP-TREND males.

Table 2. Association between serum TSH concentrations and ABI

	ABI – total population			ABI – population without prevalent cardiovascular events		
	SHIP-2	SHIP-TREND	CARLA	SHIP-2	SHIP-TREND	CARLA
Males and females						
PTSH	–0.044 (–0.105, 0.017)	–0.014 (–0.048, 0.019)	0.018 (–0.024, 0.059)	–0.031 (–0.087, 0.026)	–0.014 (–0.048, 0.021)	0.007 (–0.034, 0.048)
TSH <0.3 mIU/l[a]	–0.005 (–0.043, 0.034)	0.010 (–0.013, 0.034)	–0.006 (–0.024, 0.012)	0.006 (–0.027, 0.039)	0.002 (–0.022, 0.026)	–0.003 (–0.021, 0.016)
TSH ≥3 mIU/l[a]	–0.010 (–0.058, 0.038)	–0.005 (–0.021, 0.011)	–0.021 (–0.068, 0.025)	–0.003 (–0.049, 0.042)	–0.008 (–0.025, 0.009)	–0.025 (–0.071, 0.021)
TSH within the reference range	–0.013 (–0.027, 0.002)	–0.001 (–0.009, 0.007)	0.010 (–0.003, 0.023)	–0.008 (–0.022, 0.006)	–0.001 (–0.008, 0.007)	0.008 (–0.005, 0.021)
Males						
PTSH	–0.018 (–0.098, 0.062)	–0.036 (–0.097, 0.025)	0.037 (–0.029, 0.104)	0.006 (–0.071, 0.083)	–0.032 (–0.094, 0.031)	0.018 (–0.048, 0.084)
TSH <0.3 mIU/l[a]	0.007 (–0.039, 0.054)	0.026 (–0.016, 0.067)	–0.027 (–0.056, 0.001)	0.006 (–0.043, 0.056)	0.015 (–0.032, 0.061)	–0.022 (–0.051, 0.007)
TSH ≥3 mIU/l[a]	0.030 (–0.018, 0.079)	–0.024 (–0.052, 0.003)	–0.009 (–0.095, 0.077)	0.038 (–0.010, 0.086)	–0.029 (–0.058, –0.001)*	–0.022 (–0.108, 0.064)
TSH within the reference range	–0.011 (–0.033, 0.011)	0.001 (–0.014, 0.012)	0.006 (–0.014, 0.026)	–0.007 (–0.028, 0.014)	0.002 (–0.012, 0.015)	0.003 (–0.016, 0.023)
Females						
PTSH	–0.059 (–0.146, 0.029)	–0.005 (–0.042, 0.031)	0.002 (–0.049, 0.052)	–0.058 (–0.137, 0.022)	–0.006 (–0.045, 0.032)	–0.006 (–0.058, 0.045)
TSH <0.3 mIU/l[a]	–0.017 (–0.073, 0.040)	0.005 (–0.023, 0.033)	0.015 (–0.007, 0.038)	0.006 (–0.038, 0.050)	–0.002 (–0.030, 0.026)	0.017 (–0.006, 0.040)
TSH ≥3 mIU/l[a]	–0.035 (–0.104, 0.036)	0.003 (–0.015, 0.022)	–0.024 (–0.076, 0.027)	–0.031 (–0.099, 0.036)	0.001 (–0.019, 0.021)	–0.026 (–0.077, 0.025)
TSH within the reference range	–0.012 (–0.031, 0.007)	–0.002 (–0.011, 0.006)	0.015 (–0.002, 0.033)	–0.010 (–0.029, 0.008)	–0.003 (–0.012, 0.006)	0.013 (–0.005, 0.031)

Data are expressed as linear regression β (95% CI). All analyses were adjusted for age, sex, and smoking status, and in the SHIP studies for the time between core and ABI examinations. PTSH = Power-transformed TSH. * $p < 0.05$. [a] Reference: TSH in the reference range.

However, this association was not statistically significant after correction for multiple testing and was also not confirmed by the two other studies. Thus, the detected significant association might be a false-positive finding.

Previous studies have shown associations of 3,5-T_2 with atherosclerotic risk factors and endpoints [11, 13–15, 24]. Particularly, a linkage of 3,5-T_2 with lipid and glucose metabolism was demonstrated in animal models [13–15], which was confirmed for glucose but not for lipid metabolism in 1,000 humans of the SHIP-TREND study [11]. In these 1,000 subjects, an association between 3,5-T_2 and retinal arteriolar narrowing, a marker of microvascular damage accompanied by media thickening and development of sclerotic plaques [25], was also demonstrated. Thus, there is some evidence for an association between 3,5-T_2 and atherosclerotic processes. However, in our study we could not show an association between 3,5-T_2 and PAD, which in addition to the null finding for serum TSH concentrations argues for a lack of an association between thyroid hormones and PAD.

It has to be stressed that the number of individuals with overt forms of thyroid dysfunction was low in SHIP-2, SHIP-TREND, and CARLA. In CARLA only 13% of all individuals with decreased serum TSH concentrations had increased serum free triiodothyronine (fT_3) or increased free thyroxine concentrations (fT_4), while only 5 of the 29 individuals with increased serum TSH concentrations had decreased concentrations of fT_3 or fT_4. In the

two SHIP studies, fT_3 and fT_4 were not measured, but data from the baseline examination of SHIP-2 points towards a low prevalence of overt thyroid dysfunction in SHIP [26]. Thus, we are not able to draw conclusions from our study about the hypothetical association between overt forms of thyroid dysfunction and PAD. Likewise, the number of individuals with ABI <0.9, which is an accepted clinical cutoff for diagnosis of PAD [27], was low in the three considered studies and, thus, power was not sufficient to investigate the association between serum TSH concentrations and ABI <0.9.

The main strength of our study is that we used data from three population-based studies from two different regions in Germany with 5,718 individuals in total. Thus, our results are generalizable to the background population of Germany. However, in the SHIP studies, only a subsample participated at the ABI examination, but we applied inverse probability weights to minimize potential selection bias. Another drawback of our study was the nonavailability of fT_3 and fT_4 measurements which followed guideline recommendations to determine serum TSH as baseline parameter of thyroid function in healthy individuals. Thus, we were not able to study the potential associations of serum fT_4 and fT_3 concentrations with PAD, which would have given more detailed information on the association between thyroid function and PAD. In SHIP-TREND, however, we detected no significant association between 3,5-T_2, which is at least considered to represent partially a degradation product of T_3 and T_4, and PAD. This may argue for the lack of an association between thyroid function and PAD. A further limitation might be that different methods were used in CARLA and SHIP for the assessment of ABI.

In conclusion, the results of our study do not substantiate evidence for an association between thyroid function and PAD, but further studies are warranted to investigate the associations of overt forms of thyroid dysfunction and PAD.

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Disclosure Statement

The authors disclose no conflict of interest.

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