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Clinical Investigations

Thyroid Function Is Associated with Presence and Severity of Coronary Atherosclerosis

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Summary

Background: Overt hypothyroidism has been found to be associated with cardiovascular disease. Moreover, subclinical hypothyroidism is a strong indicator of risk for aortic atherosclerosis and myocardial infarction.

Hypothesis: We hypothesized that variation of thyroid function within the normal range may influence the presence and severity of coronary atherosclerosis.

Methods: We studied a total of 100 consecutive men and women (59 men, 41 women, age 63.7 ± 11.0 years) who underwent coronary angiography. Blood was tested for serum thyrotropin concentrations and for free tri-iodothyronine and free thyroxine concentrations. In addition to the assessment of thyroid function, conventional risk factors for coronary artery disease (CAD), clinical characteristics, serum lipid levels, fasting total homocysteine, and angiographic results of coronary artery assessment were obtained. Two experienced cardiologists blinded to clinical and laboratory data reviewed the cinefilms. The severity of CAD was scored as 0 for those with smooth normal epicardial coronary arteries, 0.5 for plaquing (< 50% diameter stenosis), and 1, 2, or 3 for those with single-, double-, or triple-vessel epicardial coronary artery stenosis of > 50%, respectively.

Results: The severity of CAD was scored as 0, 0.5, 1, 2, and 3 in 14, 26, 25, 22, and 13 patients, respectively. Higher levels of serum-free thyroid hormone concentrations were associated with decreased severity of coronary atherosclerosis. Serum-free tri-iodothyronine was 2.99 ± 0.33 pg/ml in patients with a CAD severity score of 0 to 1 and 2.74 ± 0.49 pg/ml in patients with CAD severity scores of 2 and 3 ($p < 0.01$). Moreover, serum-free thyroxine concentrations showed a trend toward higher levels in patients with CAD severity score 0 to 1 compared with patients with CAD severity scores 2 and 3 (11.65 ± 1.87 pg/ml vs. 10.9 ± 2.3 pg/ml; $p = 0.09$). Higher levels of serum thyrotropin concentrations were associated with increased severity of coronary atherosclerosis (1.37 ± 1.02 mU/l vs. 1.98 ± 2.13 mU/l in patients with CAD severity score 0 to 1 versus CAD severity scores 2 and 3; $p = 0.049$). When grouped into three subsets according to their serum free tri-iodothyronine levels (< 2.79, 2.8 to 3.09, and ± 3.1 pg/ml), the prevalence of CAD scores 2 and 3 was significantly higher in the subset of patients with low serum free tri-iodothyronine levels (48.5%) than in the subsets of patients with medium or high tri-iodothyronine concentrations (32.25 and 25%, respectively, p for trend < 0.05).

Conclusion: These data in patients referred for coronary angiography suggest that variation of thyroid function within the statistical normal range may influence the presence and severity of coronary atherosclerosis.

Key words: thyroid function, thyrotropin, coronary artery disease, hypothyroidism, hyperthyroidism

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Introduction

Thyroid hormone (TH) exerts multiple effects on the heart and vascular system.[1–4] Overt hypothyroidism, with its accompanying hypercholesterolemia and hypertension, has been found to be associated with cardiovascular disease.[5, 6] Moreover, subclinical hypothyroidism, defined as an asymptomatic state characterized by normal serum concentrations of free thyroxine and elevated serum concentrations of thyroid-

stimulating hormone (TSH), is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.[7]

No data are available in humans regarding the effects of variation of thyroid function within the normal range on presence and severity of coronary atherosclerosis. In particular, there is no convincing evidence that variation of thyroid function within the statistical normal range for pooled individuals can lead to adverse outcome with respect to coronary artery disease (CAD).

In this investigation, we determined whether there is a relationship between the variation of thyroid function and the presence and severity of coronary atherosclerosis that may be secondary to alteration of vascular endothelial function.

Methods

Study Subjects and Clinical Examination

In a cross-sectional study, we allocated 100 patients clinically referred for coronary angiography to evaluate chest pain. We excluded patients who took amiodarone, which may alter TSH and free TH levels.[8] The study was approved by the Ethical Committee (Human Subjects Institutional Review Board) of the General Hospital Wels, and informed consent for the collection of 10 ml of blood for laboratory tests was obtained from all study subjects. Patients were interviewed according to a standard questionnaire about clinical characteristics and conventional risk factors for CAD such as smoking, hypertension, hypercholesteremia (total cholesterol level > 200 mg/dl or lipid-lowering therapy), diabetes mellitus (DM), and obesity. Hypertension and DM were defined as a previous medical diagnosis or the use of diet or tablets for their treatment, or blood pressure > 140/90 mmHg and fasting venous glucose levels > 126 mg/dl in previously untreated patients. A trained nurse measured sitting systolic and diastolic blood pressure with a random-zero sphygmomanometer after 5 min of rest. Body mass index was computed as weight divided by height squared. Obesity was defined as a body mass index (BMI) of ≥ 30 kg/m^2, as proposed by the World Health Organization.[9] Elevated values of total cholesterol and low-density lipoprotein (LDL) cholesterol were considered to be > 200 and 130 mg/dl, respectively.

Study Variables

Coronary atherosclerosis assessment: Coronary arteriography studies were performed according to the technique of Judkins[10] after a 12-h fasting period. Two experienced cardiologists blinded to clinical and laboratory data reviewed the cinefilms. The severity of CAD was scored as 0 for patients with smooth normal epicardial coronary arteries, 0.5 for those with plaquing (< 50% diameter stenosis), and 1, 2, or 3 for those with single-, double-, or triple-vessel epicardial coronary artery stenosis of > 50%, respectively. This grading system is simple and informative and was able to give clinicians a "clinically reliable" impression of coronary atherosclerosis assessment.

Laboratory methods: Venipuncture was performed and fasting serum samples were collected. Laboratory testing was done immediately after blood sampling. Total cholesterol[11] and LDL cholesterol were measured with standard laboratory equipment (Hitachi, Roche, Germany).

We assayed levels of TSH by using TSH Dynotest (Brahms, Berlin, Germany); values between 0.4 and 3.5 mU/l were considered normal. Serum free thyroxine levels were measured with an in vitro chemoluminescence-based test (Bayer Diagnostics, Leverkusen, Germany); values between 9 and 18 pg/ml were considered normal. Serum free tri-iodothyronine levels were measured with an in vitro chemoluminescence-based test (Bayer Diagnostics); values between 2.3 and 4.0 pg/ml were considered normal. Limits of detection were 0.01mU/l, 1 pg/ml, and 0.5 pg/ml for TSH, serum free thyroxine levels, and serum free tri-iodothyronine levels, respectively.

Patients were grouped into three subsets according to their serum free tri-iodothyronine levels (< 2.79, 2.8–3.09, and ≥ 3.1 pg/ml), and prevalence of CAD scores was assessed for each subgroup. We defined the range of free tri-iodothyronine levels for each group with the aim to create groups with almost equal numbers of patients.

Statistical Analysis

Results for normally distributed continuous variables are expressed as mean (± standard deviation [SD]).

Differences between means were compared by paired or unpaired Student's *t*-test, as appropriate. All probability values are two-tailed, and statistical significance was considered as rejection of the null hypothesis with > 95% confidence (p values < 0.05 were considered significant). Univariate correlations were performed using the Pearson's correlation coefficient. Multivariate analyses included the use of stepwise regression and the general linear models procedure to identify significant relationships. Thyroid data were included in the analyses. This procedure was used to test whether the presence of CAD in the total population was related to age, gender, BMI, hypertension, diabetes, cigarette use, hypercholesterolemia, fibrinogen levels, total homocysteine levels, TSH concentration, or free tri-iodothyronine or free thyroxine level.

Results

Patient characteristics are summarized in Table I. The severity of CAD was scored as 0, 0.5, 1, 2, and 3 in 14, 26, 25, 22, and 13 patients, respectively (Fig. 1).

Among conventional risk factors, univariate correlates of angiographic CAD prevalence were patient age ($p = 0.048$), male gender ($p < 0.01$), high LDL cholesterol levels ($p = 0.02$), low high-density lipoprotein (HDL)-cholesterol levels ($p = 0.02$), high plasma fibrinogen levels ($p < 0.01$), and high fasting total homocysteine levels ($p = 0.04$). After multivariate adjustment, age (odds ratio [OR] 1.11), male gender (OR 2.1), hypercholesterolemia (OR 1.9), remained independent predictors of CAD prevalence (all $p < 0.05$).

TABLE I Characteristics of all patients

Variables	All patients	FT3 (< 2.79 pg/ml)	FT3 (2.8 to 3.09 pg/ml)	FT3 (≥ 3.1 pg/ml)
No.	100	33	31	36
Male, n (%)	59 (59)	16 (48.5)	21 (67.4)	22 (61.1)
Age, years (range)	63.7 (38-80)	66.5 (48–84)	64.8 (47–81)	60.2 (38–80)
Total cholesterol, mg/dl	209 ± 43.5	206.8 ± 45.7	209.2 ± 47.3	210.8 ± 37.4
LDL, mg/dl	125 ± 40.3	117.5 ± 43.9	128.8 ± 41.4	127.3 ± 34.3
HDL, mg/dl	49.8 ± 13.3	47.7 ± 11.7	51.5 ± 14.9	50.4 ± 13.3
Hypertension, n (%)	55 (55)	18 (54.5)	15 (48.4)	22 (61.1)
Diabetes, n (%)	15 (15)	5 (15.2)	4 (12.9)	6 (16.7)
Smokers, n (%)	23 (23)	7 (21.2)	7 (22.6)	9 (25)
1-VD CAD, n ~(%)	26 (26)	8 (24.2)	9 (29)	8 (22.2)
2- or 3-VD CAD, n ~(%)	35 (35)	16 (48.5)	10 (32.3)	9 (25)
Total homocysteine, µmol/l	12.6 (4.2)	13.7 (5)	12.9 (4.9)	11.5 (2.3)
Fibrinogen, g/l	3.58 ± 0.82	3.79 ± 0.89	3.59 ± 0.64	3.39 ± 0.86

Values are mean (± standard deviation) when not otherwise specified.
Abbreviations: FT = free tri-iodothyronine level, CAD = coronary artery disease, VD = vessel disease, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

Coronary Artery Disease Prevalence/Severity and Thyroid Function

Higher levels of serum free TH concentrations were associated with decreased severity of coronary atherosclerosis. Serum free tri-iodothyronine was 2.99 ± 0.33 pg/ml in patients with a CAD severity score of 0 to 1 and 2.74 ± 0.49 pg/ml in those with a CAD severity score of 2 and 3 ($p < 0.01$).

Serum free thyroxine concentrations showed a trend toward higher levels in patients with CAD severity score 0 to 1 compared with patients with CAD severity score 2 and 3 (11.65 ± 1.87 pg/ml vs. 10.9 ± 2.3 pg/ml; $p = 0.09$).

Higher levels of serum thyrotropin concentrations were associated with increased severity of coronary atherosclerosis (1.37 ± 1.02 mU/l vs. 1.98 ± 2.13 mU/l in patients with CAD severity score 0 to 1 vs. those with CAD severity score 2 and 3; $p = 0.049$).

After adjustment for conventional risk factors, both decreased free THs and increased serum thyrotropin levels remained significant predictors of advanced CAD.

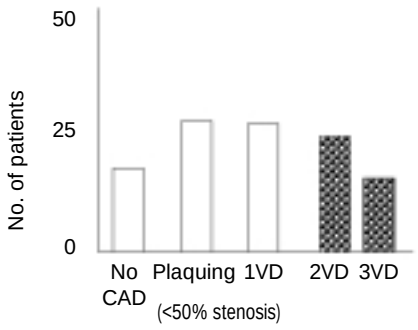

FIG. 1 Severity of coronary artery disease (CAD) in the overall patient population. 1VD = single-vessel disease, 2VD = double-vessel disease, 3VD = triple-vessel disease.

No patient had overt hyperthyroidism or overt hypothyroidism. We found six patients with subclinical hyperthyroidism defined as a TSH level < 4.0 mU/l in the presence of a normal free thyroxine level. This subgroup comprised one patient without CAD, three patients with CAD score of 0.5, and two patients with single-vessel disease (VD). Three patients had subclinical hypothyroidism (defined as a TSH level > 4.0 mU/l in the presence of a normal free thyroxine level. This subgroup comprised one patient with no CAD, one patient with double VD, and one patient with triple VD.

Because of a strong association between subclinical hypothyroidism and risk for atherosclerosis, we reanalyzed the relationship between serum free tri-iodothyronine and CAD severity after excluding these three patients. Decreased free tri-iodothyronine remained a significant predictor of advanced CAD ($p < 0.05$) and increased serum thyrotropin levels showed a strong trend toward predicting severity of CAD ($p = 0.07$).

Coronary Artery Disease Prevalence/Severity and Subsets According to Free Tri-Iodothyronine Levels

A significant correlation was observed between the serum free tri-iodothyronine levels and presence of CAD ($r = -0.29$, $p < 0.01$). When grouped into three subsets according to their serum free tri-iodothyronine levels (< 2.79, 2.8–3.09, and ≥ 3.1 pg/ml) the prevalence of CAD score 2 and 3 was significantly higher in patients with low serum free tri-iodothyronine levels (48.5%) than in patients with medium or high tri-iodothyronine concentrations (32.25 and 25%, respectively, p for trend < 0.05; Fig. 2).

Discussion

Our data show that variation of TH concentrations within the statistical normal range may influence the presence and severi-

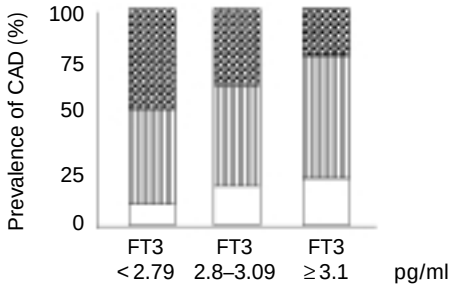

FIG. 2 Relation between percent prevalence of absent, mild (plaquing or single-vessel disease), or multivessel (double- or triple-vessel) coronary artery disease (CAD) and subsets of free tri-iodothyronine levels (FT). Trend achieves significance at $p < 0.01$. □ = No CAD, ▥ = ≤ single vessel disease, ▩ = double and triple vessel disease.

ty of coronary atherosclerosis. We could clearly demonstrate that higher levels of serum free TH concentrations are associated with decreased severity of coronary atherosclerosis. Decreased free tri-iodothyronine remained a significant predictor of advanced CAD even after exclusion of patients with subclinical hypothyroidism, indicating that variations of tri-iodothyronine concentrations (within the statistical normal range) influence the presence and severity of coronary atherosclerosis.

Moreover, higher levels of serum thyrotropin concentrations were associated with increased severity of CAD, but the association between tri-iodothyronine concentrations and CAD was slightly stronger.

High-density lipoprotein, LDL, total homocysteine, and fibrinogen levels provided no pathophysiologic explanation for the association of TH concentrations and severity of CAD.

Tunbridge *et al.* found a weak association between minor electrocardiographic changes and minor degrees of increased TSH in women. No cross-sectional association with ischemic heart disease was observed in their study.[12]

Our data support and expand previous case-control studies that also showed an association between some degree of elevated TSH and CHD at least in elderly women.[7, 13, 14] Data from Powell *et al.* suggest an association between elevated thyrotropin concentrations and peripheral arterial disease.[15]

Our data are in contrast to findings reported by Heinonen *et al.*, who presented results of men and women together and provided no evidence that latent thyroid failure is associated with CAD;[16] they mainly included patients with thyroiditis. In contrast, we did not systematically investigate thyroid autoimmunity. Therefore, comparison of the two study populations has to be made with caution.

Overt as well as subclinical hypothyroidism, with its accompanying disorders of metabolism and hemodynamics, has been found to be associated with cardiovascular disease, in particular with CAD.[5–7] Our findings expand on these data and raise the question of what values for thyroid function could be associated with higher risk for coronary atherosclerosis and possibly adverse outcome.

The hypothesis that variation of TH concentrations within the statistical normal range may influence disease and outcome is not entirely new. Additional evidence includes impaired fetal neurodevelopment in mothers with a free thyroxine concentration below the 10th percentile (< 10·4 pmol/l) at 12 weeks' gestation,[17] and apparently impaired psychological well being in patients on thyroxine replacement who have TSH values in the laboratory normal range.[18] It has been shown that thyroxine administration to individuals with TSH values in the range 2·0 to 4·0 mU/l lowered cholesterol, whereas no effect was detected with initial TSH in the range 0.4 to 1.99 mU/l.[19] Finally, Bunevicius *et al.* could demonstrate that tri-iodothyronine administration may improve psychological well being while maintaining thyroid function broadly within the reference range.[20]

Recent data suggest narrow individual variation in thyroid function compared with the reference range.[21] Hence, keeping in mind such common conditions as subclinical hyperthyroidism, it may be important to derive statistical reference ranges from truly healthy individuals, not just from the population at large.[22] Such stratification tightens the normal range to around 0.5 to 3.5 mU/l. Emerging epidemiologic data suggest that higher TSH concentrations (maybe > 2.0 mU/l) may be associated with adverse effects.

The underlying mechanisms that may be involved in the association between variation of thyroid function and cardiovascular disease may include effects on endothelial function, relaxation of smooth muscle cells,[23] hypercoagulability,[24] blood rheology,[25] and inhibition of collagen-induced platelet aggregation.[26] Overt hypothyroidism may result in accelerated atherosclerosis and CAD presumably because of the associated hypertension, hypercholesterolemia, and hyperhomocysteinemia. Subclinical hypothyroidism may be associated with hypertension, hypertriglyceridemia, and elevated total cholesterol/HDL cholesterol ratio.[27] The data of the present study showed that lower tri-iodothyronine concentrations (within the statistical normal range) were not associated with higher total cholesterol levels. In contrast, total cholesterol levels showed a trend toward higher values in the group with the highest tri-iodothyronine concentrations. Thus, total cholesterol levels did not change the association of TH concentrations with coronary atherosclerosis.

Limitations

Our study has certain limitations. First, it is a cross-sectional study of patients referred for coronary angiography. The study design of this investigation cannot establish causality; it can only establish an association. Hence, any conclusion derived from such a study must be considered preliminary and hypothesis generating rather than hypothesis proving. Second, this study includes a relatively small number of patients. Furthermore, the study population represents an inhomogeneous cohort with respect to age, gender, and concomitant illness (that may cause changes in thyroid function), a fact that could be considered as a shortcoming of this work, but it re-

flects clinical reality of cross-sectional research and does not invalidate data.

Conclusion

We found that variation of thyroid function even within the normal range may influence the presence and severity of coronary atherosclerosis. Additional research should be undertaken to determine whether this association can be confirmed in a large-scaled prospective study.

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