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Regression of the Increased Common Carotid Artery-intima Media Thickness in Subclinical Hypothyroidism after Thyroid Hormone Replacement

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Abstract. The association between subclinical hypothyroidism and cardiovascular disease and the beneficial effect of levothyroxine replacement in subclinical hypothyroidism are still under debate. The present study was designed to determine whether subclinical hypothyroidism is associated with an increase in the intima-media thickness of the common carotid artery (C-IMT) and whether thyroid hormone replacement can reverse this change in the C-IMT. Patients with newly-diagnosed subclinical (n=36) and overt (n=40) hypothyroidism and healthy euthyroid individuals (n=32) participated in this study. All the patients were examined for clinical characteristics, and the serum lipid levels and the C-IMT were measured. Patients with subclinical hypothyroidism had a C-IMT measurement after 18 months of levothyroxine replacement. There were meaningful differences in total cholesterol and LDL-cholesterol levels between patients with subclinical hypothyroidism and euthyroidism. The subjects with subclinical and overt hypothyroidism had a greater C-IMT compared with euthyroid controls (0.66±0.10 and 0.70±0.11 *vs.* 0.57±0.08 mm, respectively; $P < 0.05$). After 12 months of euthyroidism, 28 of 36 patients with subclinical hypothyroidism completed the follow-up study. Thyroid hormone replacement significantly decreased the C-IMT (0.67±0.11 to 0.60±0.10 mm; $P = 0.021$) and improved the lipid profile. Based on multiple regression analysis, the decrement in LDL-cholesterol was independently associated with the regression of the C-IMT. Subclinical hypothyroidism was closely related to an increased C-IMT. Thyroid hormone replacement resulted in regression of the increased C-IMT, which was attributed to the improvement in the lipid profile.

Key words: Atherosclerosis, Cardiovascular disease, Intima-media thickness, Subclinical hypothyroidism

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THYROID hormone has profound effects on the cardiovascular system [1]. In particular, overt hypothyroidism is known to be a risk factor for atherosclerosis and cardiovascular disease [2]. Subclinical hypothyroidism (i.e., increased serum thyrotropin concentration and normal serum thyroxine levels) is a common condition affecting 4% of the general population and 10% to 15% of the elderly [3]. Subclinical hypothyroidism, like over hypothyroidism, may be a risk factor for cardiovascular disease; however, it is controversial whether subclinical hypothyroidism results in an increased risk of atherosclerotic disease and whether the replacement of thyroid hormone reverses or prevents the risk of cardiovascular disease.

Several studies have reported no association between cardiovascular risk and subclinical hypothyroidism [4, 5]. Contrary to these results, a recent meta-analysis concluded that subclinical hypothyroidism was associated with atherosclerosis and coronary artery disease [6], and some placebo-controlled studies have shown the beneficial effect of levothyroxine replacement on cardiovascular risk and early atherosclerotic changes in patients with subclinical hypothyroidism [7, 8].

The intima-media thickness of the common carotid artery (C-IMT) is an established measure of subclinical atherosclerotic changes and is increasing used as a surrogate end points of vascular outcomes in clinical trials

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aimed at determining the success of interventions that lower risk factors for atherosclerosis and associated disease [9, 10]. Nagasaki *et al*. [11] recently described the reverse of thickened C-IMT in patients with overt hypothyroidism by thyroid hormone replacement therapy.

The present study was designed to determine whether subclinical hypothyroidism is associated with an increase in the C-IMT, and whether thyroid hormone replacement improves the lipid profile and causes regression of the C-IMT in subjects with subclinical hypothyroidism.

Methods

Subjects

Thirty-six patients with newly diagnosed subclinical hypothyroidism and 40 patients with overt hypothyroidism were consecutively recruited from the outpatient clinic. All patients had documented subclinical or overt hypothyroidism after they had had at least two thyroid function tests measured at least 2 months apart, were positive for anti-thyroid peroxidase (TPO) antibodies, and had findings compatible with Hashimoto's thyroiditis on thyroid ultrasound. Thirty-two euthyroid subjects matched to the patients group for gender, age, and body mass index (BMI) were recruited as the control group. Thyroid autoimmunity was not detected in any of the controls. Exclusion criteria included previous thyroid disease and its treatment (anti-thyroid medications, thyroid hormone, thyroidectomy, or radioiodine therapy), diabetes mellitus, hypertension, a serum creatinine > 1.3 mg/dL, smoking, medications known to affect the lipid profile (e.g., statin), and in cases of females, current or previous pregnancy in the last 1 year and a postmenopausal state. Patients with subclinical hypothyroidism were instructed to maintain their normal dietary or physical habits throughout the study. All participants signed consent forms, and the Institutional Review Board of CHA University approved this study.

Classification of thyroid status

Study participants were classified into one of the following three groups based on their thyroid function tests:

1) Overt hypothyroidism was defined as a thyroid stimulating hormone (TSH) concentration > 5.5 mIU/L with a free thyroxine (FT4) concentration < 11.4 pmol/L.

2) Subclinical hypothyroidism was defined as a TSH concentration > 5.5 mIU/L with a normal FT4 concentration.

3) Euthyroidism was defined as a normal TSH concentration and a normal FT4 concentration.

Study design

Before thyroid hormone replacement, all participants underwent a standard examination which included the followings: a detailed medical history; measurement of fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride; and measurement of blood pressure, height, and weight. Also, the risk of atherosclerosis was assessed by the C-IMT.

Thereafter, all hypothyroid patients received levothyroxine; the dosage was adjusted individually to maintain FT4 and TSH concentrations within the respective reference ranges. The mean maintenance dosages of levothyroxine after 1 year (mean follow-period, 14 months) were 67 μg/d and 115 μg/d in patients with subclinical and overt hypothyroidism, respectively. Normalization of serum TSH levels required about approximately 4.2 and 5.8 months in patients with subclinical and over hypothyroidism, respectively. In the case of subclinical hypothyroidism, previous tests were re-examined after achievement of euthyroidism for 1 year (average, 18 months after thyroid hormone substitution). Of 36 patients with subclinical hypothyroidism, 8 patients were lost to follow-up for the following reasons: the loss of follow-up (3 patients), transfers to other institutions for reasons of being at a distance from their place of residence (4 patients), or the refusal of follow-up assessment for C-IMT (1 patient). Thus, 28 patients completed the follow-up study, and the data of these patients was analyzed for evaluating the effects of thyroid hormone replacement on changes in the lipid profile and the C-IMT.

Analytical measurement

The serum TSH concentration was measured using a chemiluminescent immunometric assay with a functional sensitivity of 0.008 mIU/L (reference range, 0.35~5.50 mIU/L). FT4 concentrations were measured with a direct monoclonal antibody assay and had a reference range of 11.4-22.6 pmol/L.

Table 1. Baseline characteristics of the study population

	Euthyroid control (n=32)	Subclinical hypothyroidism (n=36)	Overt hypothyroidism (n=40)	*P* for trend
Age (yr)	36.1±5.4	36.0±6.2	37.8±6.3	NS
Gender (female, %)	84.4	86.1	90	NS
Body mass index (kg/m^2)	23.3±3.1	23.1±2.8	23.9±3.1	NS
Waist circumference (cm)	80.9±9.7	80.5±8.5	82.9±9.8	NS
Systolic blood pressure (mmHg)	116.3±16.5	126.3±15.1	128.1±14.5	NS
Diastolic blood pressure (mmHg)	76.9±10.5	77.3±10.3	78.7±12.1	NS
Glucose (mmol/L)	5.03±0.48	4.96±0.44	5.14±5.77	NS
Total cholesterol (mmol/L)	4.19±0.75	5.00±0.86*	6.00±1.25*†	< 0.001
LDL-cholesterol (mmol/L)	2.22±0.27	3.07±0.28*	3.75±0.36*†	< 0.001
HDL-cholesterol (mmol/L)	1.47±0.31	1.39±0.38	1.35±0.40	NS
Triglyceride (mmol/L)	1.04±0.37	1.21±0.47	1.77±0.66*	< 0.05
T3 (nmol/L)	2.23±0.52	1.76±0.37	1.20±0.54*	< 0.05
FT4 (pmol/L)	15.9±2.3	12.8±2.3*	7.85±3.7*†	< 0.001
TSH (mIU/L)	1.60±0.60	12.32±5.90*	110.47±65.23*†	< 0.001
Intima-media thickness (mm)	0.57±0.08	0.66±0.10*	0.70±0.11*	<0.05

Data are the mean ± SD or %.

* $P < 0.05$ *vs.* euthyroid control. † $P < 0.05$ *vs.* subclinical hypothyroidism.

The common carotid arteries were scanned using a high-resolution ultrasonographic system (Prosound α10; Aloka, Japan) with a 10.0 MHz linear transducer. Scanning was performed on the far wall of the mid- and distal-common carotid artery by a lateral longitudinal projection. The IMT was defined as the distance between the media-adventitia and lumen-intima interfaces, and was measured 20 mm proximal to the origin of the carotid bulb using IMT measurement software (Intimascope; Media Cross Co., Japan). The C-IMT was the mean value of 99 computer-based points in the region. The same investigator, who was blinded to the thyroid status of patients, performed all of the ultrasonographic procedures used to estimate the C-IMT. The intra-observational reproducibility of C-IMT was 2.0%.

Statistical analysis

All of the data are expressed as the mean ± SD or proportion (%). Statistical analyses were performed using the SPSS 11.0 software package (SPSS Inc., Chicago, IL, USA). The comparison among status of thyroid function was performed using a one-way ANOVA followed by a Scheffe's *post hoc* test. The comparisons before and after levothyroxine replacement were analyzed by a paired Student's *t* test. Multiple linear regression analysis was used to assess the independent factors affecting the baseline C-IMT and the decrease in C-IMT. *P* values < 0.05 were considered statistically significant.

Results

Comparison of baseline characteristics according to status of thyroid function

Age, gender, BMI, waist circumference, blood pressure, glucose, and HDL-cholesterol were similar across all thyroid status categories (Table 1). Serum total cholesterol, LDL- cholesterol, and triglyceride levels were the highest in patients with overt hypothyroidism. The participants with subclinical hypothyroidism had higher total cholesterol and LDL-cholesterol levels than those who were euthyroid, along with a non-statistically significant higher triglyceride level (Table 1). The C-IMT was significantly higher in the patients with subclinical and overt hypothyroidism compared with euthyroid controls (0.66±0.10 and 0.70±0.11 *vs.* 0.57±0.08 mm, respectively; $P < 0.05$). The C-IMT was significantly associated with age, systolic blood pressure, glucose, total cholesterol, LDL-cholesterol, and triglycerides. However, in a multivariate regression model that explained 64% of the variation in the C-IMT, age (standardized β=0.480, $P < 0.001$), systolic blood pressure (standardized β=0.276, $P < 0.05$), and LDL-

Table 2. Clinical features of patients with subclinical hypothyroidism after 1 year of achieving euthyroidism with levothyroxine replacement (n=28)

	Before	After	*P*
Body mass index (kg/m^2)	23.0±2.4	22.9±2.3	NS
Waist circumference (cm)	80.2±7.9	79.5±8.0	NS
Glucose (mmol/L)	5.03±0.43	5.06±0.44	NS
Total cholesterol (mmol/L)	4.92±1.05	4.30±0.83	0.018
LDL-cholesterol (mmol/L)	2.91±0.37	2.41±0.22	0.024
HDL-cholesterol (mmol/L)	1.39±0.34	1.38±0.36	NS
Triglyceride (mmol/L)	1.46±0.55	1.12±0.51	0.145
T3 (nmol/L)	1.66±0.41	2.12±0.32	NS
FT4 (pmol/L)	12.5±2.8	14.4±3.2	NS
TSH (mIU/L)	11.48±4.70	1.26±3.30	0.015
Intima-media thickness (mm)	0.67±0.11	0.60±0.10	0.021

Data are the mean ± SD.

Table 3. Multiple regression analysis on factors affecting the change in intima-media thickness of the common carotid artery

	Standardized β	*P*
ΔLDL-cholesterol	0.121	0.041
ΔHDL-cholesterol	-0.065	NS
ΔTriglyceride	0.104	0.089
ΔTSH	0.011	NS
ΔFT4	-0.041	NS

cholesterol (standardized β=0.252, $P < 0.05$) had a significant contribution to the C-IMT, whereas TSH and FT4 did not. Echogenic plaque was not observed in any of the subjects.

Effect of thyroid hormone replacement in patients with subclinical hypothyroidism

Twenty-eight patients with subclinical hypothyroidism completed the follow-up study 12 months after becoming euthyroid. After the replacement of thyroid hormone, the serum levels of TSH were within the reference range in all patients, and T3 and FT4 levels remained within the reference range throughout the treatment period. BMI, waist circumference, and blood pressure were unchanged after treatment. The levels of total cholesterol and LDL-cholesterol were significantly decreased after replacement of thyroid hormone. The levels of HDL-cholesterol and triglycerides were decreased by treatment, although not significantly (Table 2).

One year after achieving a euthyroid state, there was a significant decrease in the C-IMT, averaging 0.07±0.06 mm. Twenty-six of 28 patients with subclinical hypothyroidism had a decrease in the C-IMT; 1 patient had no change and 1 patient had a slight increase. Using the change in the C-IMT as the dependent variable in multiple regression analysis, the absolute decrement of the C-IMT was independently associated with the absolute reduction in LDL- cholesterol levels, but there was no association with the reduction in TSH levels (Table 3).

Discussion

Whether subclinical hypothyroidism results in increased risks of cardiovascular disease and whether thyroid hormone substitution reverses or prevents these risks remain controversial. The findings of the current study showed that subclinical hypothyroidism resulted in an increased C-IMT and thyroid hormone replacement reversed this atherosclerotic change in the

carotid artery. Thus, regression of the C-IMT can be achieved by improving the atherogenic lipid profile, especially the LDL-cholesterol level.

Many studies have examined the relationship between subclinical hypothyroidism and cardiovascular disease. However, the studies have yielded contradictory results, with some studies showing subclinical hypothyroidism to increase cardiovascular risk [6, 12, 13] and others studies showing no such effect [4, 5, 14]. This may be due to serious design limitations in the studies, such as short follow-up periods, the inclusion of individuals taking thyroid hormone or medications that affect the lipid profile, or heterogeneous causes of hypothyroidism. Recently, well-controlled studies have documented a relationship between subclinical hypothyroidism and a reversible atherosclerotic vascular lesion. Monzani *et al*. [8] and Nagasaki *et al*. [15] reported that patients with subclinical hypothyroidism have a higher C-IMT and increased brachial-ankle pulse wave velocity, a useful indicator of arterial stiffness, respectively, and that thyroid hormone replacement regress C-IMT and decrease brachial-ankle pulse wave velocity. The current study confirms this association. Subclinical hypothyroidism resulted in an early atherosclerotic change in the vascular wall, and thyroid hormone replacement reversed this change. A decrement in LDL-cholesterol after thyroid hormone replacement was independently associated with regression of the increased C-IMT. One reason why the current study showed a clear association between subclinical hypothyroidism, lipid metabolism, and C-IMT compared to previous studies was the homogeneity of the subjects. We included only young subjects with Hashimoto's thyroiditis who had no risk factors for hyperlipidemia or atherosclerosis except hypothyroidism, and who were taking no medications affecting these conditions (thyroid hormone, statins, or anti-hypertensive agents). Furthermore, a significant difference in the C-IMT at baseline was observed between euthyroid controls and patients with subclinical hypothyroidism despite subclinical state, and after achieving euthyroidism for 1 year; the C-IMT in patients with subclinical hypothyroidism decreased to that of euthyroid controls. In conditions in which no consensus exists on the thyroid hormone replacement for subclinical hypothyroidism, these findings suggest the need of active replacement of thyroid hormone in patients with subclinical hypothyroidism.

Indeed, other mechanisms may be involved in the pathogenesis of atherosclerotic vascular alterations resulting from subclinical hypothyroidism. Recently, it has been reported that Hashimoto's thyroiditis results in low-grade chronic inflammation, which causes endothelial dysfunction, a promoter of atherosclerosis [16, 17]. However, thyroid hormone replacement and the consequent normalization of thyroid function and the lipid profile is not associated with complete reversal of endothelial dysfunction [18, 19]. Also, chronic activation of the immune system due to Hashimoto's thyroiditis is considered an alternative mechanism for inducing atherosclerosis [20], but the mechanism is not well-elucidated. Some have reported that autoantibody titers and the erythrocyte sedimentation rate remained uncorrected by thyroid hormone substitution [18], but others have shown the opposite results [21]. Furthermore, there are no studies which have investigated the association between the degree of autoimmunity and cardiovascular disease. Although we did not measure markers of inflammation or oxidative stress, and did not perform follow-up measurement of autoantibody titers, the current study suggested that the altered lipid metabolism was a major mechanism leading to early atherosclerotic vascular changes in subclinical hypothyroidism.

There were some limitations in the present study. The number of subjects participating in this study was small and the design was not placebo-controlled. Although the C-IMT is an important forecaster for atherosclerotic cardiovascular disease, we did not observe more direct cardiovascular events and mortality. Therefore, a long-term study will be needed to investigate the effect and mechanism of subclinical hypothyroidism on atherosclerosis or cardiovascular disease, and the benefit of thyroid hormone replacement in subclinical hypothyroidism.

In conclusion, our study suggests that patients with subclinical hypothyroidism are characterized by an increment in the C-IMT resulting from an adverse lipid profile, which can be reversed by thyroid hormone replacement. Therefore, thyroid hormone replacement may be helpful to prevent or at least slow down atherosclerosis in subclinical hypothyroidism.

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