



Effect of L-thyroxin therapy on thyroid volume and carotid artery Intima-media thickness in the patients with subclinical hypothyroidism

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Abstract

Background: Subclinical hypothyroidism (SCH) is mild-to-moderate thyroid insufficiency that is characterized by thyrotropin (TSH) level higher than the upper limit despite normal serum free thyroxin (fT4) level. Likewise, SCH as well might be a risk factor for cardiovascular diseases. Some placebo-controlled studies showed beneficial effect of L-thyroxin replacement on the risk for early atherosclerosis and CVD in the patients with SCH.

Methods: Fifty-six patients presented to our clinic with subclinical hypothyroidism were included in the study. Forty-six healthy euthyroid subjects were included as the control group. Patients with fT4 > 0.61 ng/dl and TSH > 4.2 uIU/ml were considered as SCH. Serum LDL and HDL cholesterol, triglyceride level, thyroid antibodies (anti-TPOAb and anti-TgAb), and fasting plasma glucose levels of the patients and the control group were measured. Carotid artery intima-media thickness (CIMT) was measured via B-mode ultrasonography and thyroid volume was calculated. L-thyroxin replacement was commenced at a dose of 25-50 mcg/day. CIMT and thyroid volumes of the patients were reevaluated six months after they became euthyroid.

Results: A statistically significant difference ($p < 0.05$) was found between the CIMT values before and after the L-thyroxin therapy in the SCH group. Pretreatment CIMT values were significantly higher than the post-treatment CIMT values ($p = 0.0001$). There was significant difference also between the pre-treatment and post-treatment thyroid volumes in the SCH group ($p < 0.05$).

Conclusion: The present study showed the reduction in CIMT with L-thyroxin therapy in the patients with subclinical hypothyroidism. Therefore, thyroid hormone replacement might help to slow down or prevent atherosclerosis in the subclinical hypothyroidism as well.

Keywords: Subclinical hypothyroidism, intima-media thickness, cardiovascular disease, atherosclerosis

Introduction

Subclinical hypothyroidism (SCH) is mild-to-moderate thyroid insufficiency that is characterized by thyrotropin (TSH) level higher than the upper limit despite normal serum free thyroxin (fT4) level [1]. The prevalence of SCH is 4-10% according to the epidemiological data obtained from large population-based trials [2-9]. In females, this rate notably increases after the age of 45 years [10]. In males, it is similar to females after the 6th decade. Anti-thyroid antibodies are found positive in 80% of the patients with subclinical hypothyroidism and TSH level is less than 10 mIU/L [2].

The etiology of subclinical hypothyroidism is similar to that of manifest hypothyroidism, and autoimmune thyroid diseases are the most common causes [1,11]. On the other hand, it may develop as the consequence of treatments, such as radioactive iodine therapy and external radiotherapy top the head-neck region, that lead to thyroid tissue injury. Serum TSH level temporarily or permanently increases after subacute, postpartum and painless thyroiditis episodes. Actually, 17.6-30% of the cases with manifest hypothyroidism are diagnosed with subclinical hypothyroidism due to inadequate thyroid hormone replacement therapy [3,12]. Drugs such as

tamoxifen, chemotherapy, compounds that include iodine, cytokines (particularly Interferon- α and β), amiodarone, lithium carbonate, aminoglutethimide, ethionamide, sulfonamides and sulfonyleureas cause thyroid dysfunction [13-21]. Moreover, infiltrative diseases (Riedel's thyroiditis, amyloidosis, hemochromatosis, and cystinosis) and infectious diseases (Pneumocystis carinii infection and Kaposi's sarcoma in the patients with AIDS) of thyroid gland and TSH-receptor gene mutations as well may cause subclinical hypothyroidism [13,22,23].

Subclinical hypothyroidism, as well as manifest hypothyroidism, may be a risk factor for cardiovascular diseases, but it is debatable. Various studies reported that there is no relation between subclinical hypothyroidism and cardiovascular risk [24,25]. Contrarily, a meta-analysis concluded that subclinical hypothyroidism is associated with coronary artery disease and atherosclerosis [26]. Some placebo-controlled studies demonstrated that levothyroxine replacement has favorable effect on early atherosclerosis and cardiovascular risk in the patients with subclinical hypothyroidism [27,28]. Measurement of the carotid artery intima-media thickness (C-IMT) via B-mode ultrasonography (Figure 1) provides easy evaluation of atherosclerosis.

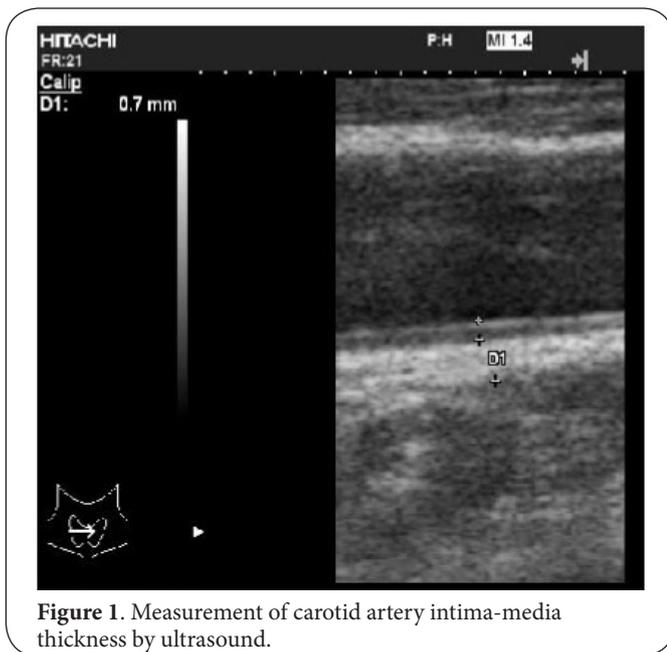


Figure 1. Measurement of carotid artery intima-media thickness by ultrasound.

The present study aimed to show the reduction in C-IMT and thyroid volume with L-thyroxine therapy in the patients with subclinical hypothyroidism.

Materials and methods

Fifty-six patients presented to our outpatient clinic with subclinical hypothyroidism were included in the study from our outpatient clinic. Forty-six healthy euthyroid subjects were

included as the control group. Patients with normal serum free thyroxine and TSH > 4.2 uIU/ml were considered as SCH. The protocol was approved by the local Ethics Committee and all the participants provided written informed consent.

We examined their physical examination, biochemical tests, and history of medications (Interferon- α and β , amiodarone, lithium carbonate, aminoglutethimide, ethionamide, statins, corticosteroids) or cardiovascular diseases (coronary artery disease, peripheral artery disease or stroke). The routine laboratory chemistry was normal in all participants.

L-thyroxine replacement was commenced at a dose of 25-50 mcg/day. The dosage taken was individualized for each patient and was given once a day before breakfast in the morning. CIMT and thyroid volumes of the patients were reevaluated six months after they became euthyroid.

Those participants who had previous thyroid disease, anti-thyroid medications, thyroid hormone treatment, thyroidectomy, radioiodine therapy, and medications known to affect the lipid profile (e.g., statin), history of alcohol use, obesity, diabetes mellitus, arterial hypertension, liver, or renal diseases, were suffering from any cardiovascular disease were excluded from the study.

Biochemical evaluation

Serum free thyroxine (fT4), thyroid stimulating hormone (TSH), thyroid peroxidase anti-body (anti-TPO) and thyroglobulin anti-body (anti-Tg) were measured with chemiluminescence assay (Advia Centaur, Siemens Healthcare Diagnostics, USA) and specific electrochemiluminescence immunoassays (Elecsys 2010 Cobas, Roche Diagnostics, Mannheim, Germany). The levels of total-cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined with enzymatic colorimetric assays by spectrophotometry (BioSystems S.A., Barcelona, Spain). The low density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald formula. Serum glucose, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using commercial enzymatic kits.

Thyroid volume (TV) and CIMT

Thyroid volume was assessed using a high-resolution ultrasound machine with a 13 megahertz high-frequency linear transducer (Hitachi EUB 7000 HV). Thyroid volumes were calculated by multiplication of three diameters and the constant value 0.52 [29,30].

Carotid artery intima-media thickness (CIMT) was measured via high-resolution B-Mode ultrasonography using a 13-MHz linear probe (Hitachi EUB 7000 HV). Three arterial wall segments of the common carotid artery were measured bilaterally after imaging from a fixed lateral transducer angle and designated as mean CIMT. IMT was defined as the distance from the leading edge of the lumen intima-interface to the leading edge of the media-adventitia.

To avoid subjective error, both CIMT and thyroid volume

measurements were taken by the same person.

Statistical analyses

Data of the study were evaluated by SPSS 15.0 package program. Distribution of frequency and percentage of the data was demonstrated. After data normality test, difference between the groups was analyzed by Independent Samples t-test for the variables with normal distribution and by Mann Whitney U Test for the variables distributed not normally. Dependency between variables was analyzed using Chi-square test and the difference between initially and subsequently measured variables was analyzed using Wilcoxon Signed Rank test.

Level of significance for between group analyses was considered to be 0.05 and it was expressed that there is significant difference between the groups in case $p < 0.05$, but there is no significant difference between the groups in case $p > 0.05$.

Results

Serum TSH and HDL- cholesterol levels were significantly higher in SCH compared with healthy control subject (Table 1).

Table 1. Baseline characteristics of the study population.

	Euthyroid control (n=46)	Subclinical hypothyroidism (n=56)	p
Age (year)	36.07±10.580	41.32±14.485	0.037
Gender (%)			
Female	54.35	91.07	--
Male	45.65	8.93	--
TSH (uIU/ml)	1.65±0.913	6.77±2.902	0.000
HDL-C (mg/dl)	47.93±12.153	53.76±12.071	0.017
LDL-C (mg/dl)	111.72±28.141	117.84±30.272	0.297
C-intima media thickness (mm)	0.5±0.086	0.53±0.112	0.115
Thyroid volume (ml)	13.07±6.320	11.48±4.646	0.167

Data are the mean±SD

Of the patients in the SCH group, 51(91.1%) were female and 5(8.9%) were male, whereas the control group comprised 25 (54.3%) females and 21(45.7%) males. A statistically significant difference ($p < 0.05$) was found between the CIMT values before and after the L-thyroxin therapy in the SCH group. Pretreatment CIMT values were significantly higher than the post-treatment CIMT values. There was significant difference also between the pre-treatment and post-treatment thyroid volumes in the SCH group ($p < 0.05$); pretreatment thyroid volumes were significantly higher than the post-treatment thyroid volumes (Table 2). No significant difference was determined between the SCH and the control group in terms of pretreatment CIMT values ($p > 0.05$). When the SCH group was divided into two

Table 2. Before or after Levothyroxine therapy.

	Before LT4	After LT4	p
TSH (uIU/ml)	6.773±2.902	2.734±1.166	0.0001
C-intima media thickness (mm)	0.533±0.112	0.507±0.126	0.0001
Thyroid volume (ml)	11.484±4.646	9.294±3.906	0.0001

Data are the mean±SD

as TSH level less than 7 uIU/ml (n=39) and TSH level higher than 7 uIU/ml (n=17), no significant difference was found between the groups in terms of CIMT values and thyroid volumes ($p > 0.05$).

Discussion

Many studies have examined the relationship between subclinical hypothyroidism and cardiovascular disease. However, contradictory results have been obtained in the studies and whilst some studies determined an increase in cardiovascular risk with subclinical hypothyroidism [31-33], some studies failed to demonstrate such a relation [24,25,34]. For example, Rotterdam study demonstrated that myocardial infarction and aortic calcification are associated with SCH [31]. Contrarily, Wickham study observed no increase in cardiac mortality over the course of 20-year follow-up [35]. In addition, numerous meta-analyses and observational studies determined relation between coronary artery disease and SCH [36-38]. However, some recent observational studies demonstrated no relation between cardiovascular events, mortality and unrecognized SCH [24]. Analysis of 7 cohort studies demonstrated increase in all-cause mortality in SCH, particularly in the presence of comorbidities, as compared to the euthyroid individuals [39]. Another meta-analysis comprising 15 studies revealed an increase in the incidence and prevalence of cardiovascular mortality in young population [26].

Studies demonstrated that, thyroid hormones inhibit collagen-stimulated platelet aggregation and inhibition is not observed in the absence of thyroid hormone deficiency [40]. Hypothyroidism is accompanied by endothelial dysfunction and impaired nitric oxide production, which are also encountered in the early stage of atherosclerosis [41-44].

Carotid artery intima-media thickness is an important marker for atherosclerosis stage. The intima-media thickness of the common carotid artery (C-IMT) is an established measure of early atherosclerotic changes and is used as a surrogate end points of vascular outcomes in clinical trials [42,43]. This parameter is included in European guidelines on prevention of cardio-vascular disorders. Threshold value for IMT is considered to be 0.9 mm. An increase in IMT over threshold value indicates progression of atherosclerosis. Similar to the classical risk factors such as diabetes, hyperlipidemia and obesity, this is an independent risk factor for CHD. Positive correlation has been reported between coronary artery IMT and degree of atherosclerotic changes [44]. Measurement of the carotid artery

intima-media thickness (CIMT) via B-mode ultrasonography provides easy evaluation of atherosclerosis. In the present study, CIMT measurement was not different in the SCH group as compared to the control group. However, CIMT decreased after levothyroxine replacement in the SCH group and this was statistically significant. The results from the present study show that subclinical hypothyroidism is associated with elevated cardiovascular risk as assessed by CIMT.

In SCH, left ventricle relaxation time shortens, vascular tonus increases, and left ventricle systolic dysfunction and endothelial dysfunction occurs with exercise. There are some studies that demonstrate improvement in cardiac contractility and systolic time interval with levothyroxine therapy [45]. However, there is no evidence supporting the relation between a serum TSH level below 10 mIU/L and heart failure. Many studies have evaluated the patients with a serum TSH concentration higher than 10 mIU/L. Therefore, the results that strongly suggest the presence of relation for TSH concentration higher than 10 mIU/L would be insufficient for TSH concentration less than 10 mIU/L. Benefit of levothyroxine therapy could not be demonstrated in a study in which TSH concentration was 5-10 mIU/L [46]. In the present study, CIMT was higher in the group with TSH concentration higher than 7 IU/mL; but this was not statistically significant. The number of subjects participating in this study was small and the design was not placebo-controlled. Spectrum of TSH levels in SCH should be confirmed by larger randomized studies.

Several factors such as body mass index, fat distribution, lipid profile, and vascular dysfunction may contribute to CV risk in SCH. Population-based studies demonstrated a relation between MI, aortic sclerosis and SCH in elder women independent from serum cholesterol concentration [27]. Nevertheless, Soo-Kyung KIM et al., stated that decrease in CIMT might be due to improvement in atherogenic lipid profile (LDL-cholesterol in particular) with thyroid hormone replacement [33]. In the present study as well, however, decrease in CIMT with levothyroxine therapy independent from LDL cholesterol level in SCH patients was found to be statistically significant.

Enlargement of the thyroid gland is due to several factors, such as hormonal or immunological stimulation, inflammatory, proliferative, infiltrative, or metabolic disorders. It is thought that many factors (GSF, Growth Stimulating Factor) that leads to development of non-toxic goiter are important causes of enhancement in follicular cell replication. These factors arise from either systemic circulation (endocrine) or thyroid follicular or stromal cells (autocrine or paracrine effect). Thyrotropin (TSH) is the main extrathyroid GSF of thyroid [47,48]. Endogen TSH stimulation has been shown to increase thyroid gland size. Moreover, thyroid volume was found to be associated with age, height, weight, body surface area, iodine status, hyperinsulinemia, and luteinizing hormone (LH) [30]. Hegedus et al., reported that the difference between males and females in terms of the mean thyroid gland volume is significant [49] and correlated with body weight and age [49].

Ueda found thyroid gland volume to be correlated with age, height, weight and body surface area with no difference found between males and females [50]. In the present study, no difference was determined between the patients with SCH and the control group in terms of thyroid volume. This might be associated with higher number of female patients in the SCH group versus the control group. However, thyroid volume statistically significantly decreased after levothyroxine therapy in SCH individuals. Although there is no cut-off value for TSH level on this subject, there was no statistically significant difference when the patients with serum TSH level less than 7 uIU/mL and higher than 7 uIU/mL (because the mean TSH was 6.77 ± 2.902 in the SCH group) were compared; but thyroid volume was found to be higher in the group with TSH level higher than 7 uIU/mL.

Limitation of this study is that we did not placebo-controlled. Also, Female patients in SCH group was more than control group. Thus, the changes in IMT and thyroid volume could be related to the gender (Table 3).

Table 3. Changes of CIMT and thyroid volume in patient groups according to different TSH level.

	TSH<7 uIU/ml	TSH≥7 uIU/ml	p
C-intima media thickness (mm)	0.52±0.10	0.56±0.13	0.427
Thyroid volume (ml)	11.15±4.82	12.15±4.26	0.196

Data are the mean±SD

In conclusion, our study showed the reduction in CIMT with L-thyroxin therapy in the patients with subclinical hypothyroidism. Early stage atherosclerosis are encountered also in the hypothyroidism. SCH and hypothyroidism may have adverse effects on endothelial function independently of other well-known atherosclerotic risk factors. Thyroid hormone replacement might help to slow down or prevent atherosclerosis in the subclinical hypothyroidism as well. Therefore, patients with subclinical hypothyroidism should be treated same as hypothyroidism. CIMT is an important marker for atherosclerosis; but long-term and placebo-controlled studies that would evaluate benefit of thyroid hormone replacement on cardiovascular events and mortality in SCH are needed.

List of abbreviations

SCH: Subclinical hypothyroidism
TSH: Thyroid stimulating hormone
CIMT: Carotid artery intima-media thickness
CVD: Cardiovascular disease
HDL-C: High density lipoprotein cholesterol
LDL-C: Low density lipoprotein cholesterol

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	IO	OT	EC	NC	BK	AG	MS	ET	BU	TD	MK	MC	EC	TD
Research concept and design	✓	--	--	--	--	--	--	--	--	--	--	--	✓	✓
Collection and/or assembly of data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data analysis and interpretation	✓	--	--	--	--	--	--	--	--	--	--	--	✓	✓
Writing the article	✓	--	--	--	--	--	--	--	--	--	--	--	--	--
Critical revision of the article	✓	--	--	--	--	--	--	--	--	--	--	--	--	--
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	✓	--	--	--	--	--	--	--	--	--	--	--	✓	--

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