The Effectiveness of Thyroid Hormone Replacement Therapy on Carotid Artery Intima Media Thickness in Adult Patients With Subclinical Hypothyroidism

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Recommended Citation
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Abstract
Background: Subclinical hypothyroidism (SCH) is defined as an elevation in thyroid stimulating hormone (TSH), in the absence of reductions in free thyroxine (FT4). An estimated 4.6 to 8.6 million Americans meet the criteria for SCH, but are without a significant symptom burden. Carotid artery intima media thickness (CIMT) assessment with ultrasound technology is a non-invasive modality to assess atherosclerosis and cardiovascular health. Research has demonstrated increases in CIMT in subjects with overt hypothyroidism at baseline; however, following levothyroxine therapy, CIMT was reduced. The objective of this literature review is to determine if levothyroxine treatment results in CIMT reduction in adult subjects with subclinical hypothyroidism.

Methods: An extensive literature search was performed using MEDLINE, CINAHL, Google Scholar and ISI Web of Science. Studies were selected for analysis based on the following inclusion/ exclusion criteria: published in the English language, human subjects, since 1998 and assessing subclinical hypothyroid and carotid artery intima media thickness. Four studies met the criteria and were included in the analysis.

Results: The four studies analyzed indicated that treatment with levothyroxine resulted in a significant decrease in CIMT in subjects with SCH. Correlations were found between CIMT and lipid profile variables. Additionally, age, LDL-C, systolic blood pressure, and anti-thyroglobulin antibodies were important predictors of CIMT variation.

Conclusion: Treatment of subclinical hypothyroidism with levothyroxine decreases carotid artery intima media thickness, which is an important measure of atherosclerosis and cardiovascular risk. Although debate still exists whether SCH should be screened for, and treated in clinical practice, considerations should be made based on the cardiovascular risk and history of the patient on an individual basis. Additional randomized controlled trials with a greater number of subjects are needed to further investigate the effects of SCH treatment on CIMT and other cardiovascular markers. Moreover, research is needed to further illuminate the long-term effects of SCH treatment and cardiovascular risks and events.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Second Advisor
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Keywords
Subclinical hypothyroidism, carotid artery, thyroid replacement therapy

Subject Categories
Medicine and Health Sciences

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The Effectiveness of Thyroid Hormone Replacement Therapy on Carotid Artery Intima Media Thickness in Adult Patients With Subclinical Hypothyroidism

Marissa E. Moritz

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 14th, 2010

Faculty Advisor: Annjanette Sommers, MS, PA-C Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
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**Conclusion:** Treatment of subclinical hypothyroidism with levothyroxine decreases carotid artery intima media thickness, which is an important measure of atherosclerosis and cardiovascular risk. Although debate still exists whether SCH should be screened for, and treated in clinical practice, considerations should be made based on the cardiovascular risk and history of the patient on an individual basis. Additional randomized controlled trials with a greater number of subjects are needed to further investigate the effects of SCH treatment on CIMT and other cardiovascular markers. Moreover, research is needed to further illuminate the long-term effects of SCH treatment and cardiovascular risks and events.

**Keywords:** Subclinical hypothyroidism, carotid artery, thyroid replacement therapy
Acknowledgements

To Dad, Mom, Taylor and Hayley: Thank you all for your endless support, even from hundreds of miles away. I miss you all every day and am so thankful for such an amazing family. Dad- thank you for the many articles, books, clinical pearls & wisdom, early morning pigs’ feet suturing, the drive from Montana, and for passing on the passion for medicine. Mom- thank you for the frequent pep talks, understanding my occasional moodiness, teaching me the business side of medicine, and for your never-ending confidence in me. Tay- thank you for the laughter you bring and share with me, for keeping in touch and checking in on me, for visiting us and for your refusal to “nerd out” with me and Dad. ShaWn- thank you for checking in on me via phone calls, txts and facebook, for the encouragement you gave me, and for visiting us. I love you all so much and could not have done this without you. Thank you all.

To Aaron, my best friend and love of my life: My endless thanks for all of your support, love, and patience. I know this has been a long 27 months and I could not have gotten through it without you. Thank you for always remaining calm and being the voice of reason; you are my calm blue ocean. Thank you for visiting me and for getting me safely to rotations, despite Spokane’s best efforts to keep us there. Thank you for being you, simply amazing. I love you, Aaron Mikey.

To my friends: Thank you all for your support and understanding. I have been nearly completely engrossed in this, but have not forgotten any of you or how much you mean to me. I promise to be better at answering my phone, returning phone calls, and to be a presence in your lives. My PA school besties- thank you for the countless hours of study time filled not only with hard work, but laughs, bubble teas, gummies and support. You ladies helped me stay [somewhat] sane and make it through. To all my friends, thank you and I love you.
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<tr>
<td>SCH</td>
<td>Subclinical hypothyroidism</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
<td>FT4</td>
<td>Free tyroxine</td>
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<tr>
<td>L-T4</td>
<td>Levothyroxine</td>
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<tr>
<td>CIMT</td>
<td>Carotid artery intima media thickness</td>
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<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<tr>
<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>TPO antibodies</td>
<td>Anti-thyroid peroxidase antibodies</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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The Effectiveness of Thyroid Hormone Replacement Therapy on Carotid Artery Intima Media Thickness in Adult Patients With Subclinical Hypothyroidism

BACKGROUND

Overview

The thyroid gland is critical to the proper functioning and regulation of various physiological pathways and processes. It relies on, and is directly influenced by, thyroid stimulating hormone (TSH) to function. TSH is emitted by the thyrotrope cells of the anterior pituitary gland.\(^1\), \(^2\) The synthesis and release of TSH is regulated by thyroid releasing hormone (TRH) secreted by the hypothalamus. In response to stimulation from TSH, the thyroid produces and releases thyroid hormones, primarily l-thyroxine (T4).\(^2\) Once in the serum, the thyroid hormones act, via a negative feedback system, on the anterior pituitary gland and hypothalamus to regulate further release of TSH and TRH, respectively.\(^2\) The clinical diagnosis of hypothyroidism or hyperthyroidism is made relative to the serum concentration of the thyroid hormone levels, namely free T4 (FT4). However, in the last several decades, the identification of subclinical hypothyroidism, defined as an elevation in TSH without a decrease in FT4, has led to the questioning of the previously accepted thyroid dysfunction algorithm. Moreover, the relationship between clinical hypothyroidism and cardiovascular risk is well documented,\(^2\)-\(^4\) but recent research efforts have been aimed at elucidating the effects of subclinical hypothyroidism on cardiovascular health.\(^5\)-\(^10\)

Epidemiology of Subclinical Hypothyroidism

Subclinical hypothyroidism (SCH) is defined as an elevation in TSH in the absence of low free T4,\(^1\), \(^5\), \(^6\), \(^11\)-\(^13\). Based on the generally symptom-free nature of SCH,
the percentage of the population who meet the clinical diagnostic criteria is difficult to determine. A large United States population based study, the National Health and Nutrition Examination Survey (NHANES III),\textsuperscript{12} found that 4.3% of the study population met the diagnostic criteria for SCH, with a range from 1.6% to 4.8%, depending on the ethnicity of the subjects. Another study of Colorado residents who participated in a health fair, found that 9% of subjects met diagnostic criteria for SCH based on laboratory results alone.\textsuperscript{14} Other reviews\textsuperscript{1, 13} have estimated that 2-8% of the general population, with up to 16% in women over 60 years old, meet the criteria for SCH.\textsuperscript{1}

**Etiology of Subclinical Hypothyroidism**

The etiology of SCH is the same as that for overt hypothyroidism.\textsuperscript{1, 2} The majority of SCH cases are a result of autoimmune, or Hashimoto’s, thyroiditis, where laboratory results demonstrate elevated levels of anti-thyroid peroxidase (TPO) antibodies.\textsuperscript{2, 15} Other causes include treatment for hyperthyroidism, specifically surgical intervention and radioactive iodine administration, or pharmacological agents used in the treatment of other medical conditions, such as lithium, iodine, phenylbutazone and sulfonamides.\textsuperscript{1, 2}

Debate still exists in the medical community over the likelihood of patients with SCH developing overt hypothyroidism with time. One review reports that 20% to 50% of people will develop overt hypothyroidism within four to eight years following initial laboratory evidence of SCH.\textsuperscript{1} Fatourechi\textsuperscript{13} described more specific criteria and stated that a TSH level greater than 10mIU/L is more predictive of progression to overt hypothyroidism than a TSH level less than 6mIU/L.

**Carotid Artery Intima Media Thickness as a Marker for Cardiovascular Health**
Carotid artery intima media thickness (CIMT), measured by ultrasound, has been identified as a surrogate variable to assess the likelihood of cardiovascular event occurrence and cardiovascular health in general. A study done by Baldassarre et al found a correlation between CIMT and the number of cardiovascular risk factors. Furthermore, the researchers were able to identify the subjects with previous cardiovascular events, including peripheral artery disease (PAD) and congestive heart failure (CHF), using the data from the CIMT ultrasound. Bots et al demonstrated that increased CIMT and carotid plaques are markers of increased risk of stroke, coronary heart disease and death over a 10-12 year period in subjects 55 years and older. Assessment of CIMT via ultrasonography has become regarded as a relatively inexpensive, yet informative, modality to evaluate cardiovascular health and the likelihood of cardiovascular events.

**Carotid Artery Intima Media Thickness and Hypothyroidism**

Research has been conducted to examine the relationship between carotid artery intima media thickness (CIMT) in patients with overt hypothyroidism. Nagasaki et al demonstrated that, in patients with overt, untreated hypothyroidism, CIMT was significantly higher at baseline when compared to age and gender matched euthyroid controls. After one year of treatment with levothyroxine, the hypothyroid patients had a significant reduction in CIMT, such that they were comparable to matched controls.

**Subclinical Hypothyroidism and Cardiovascular Health**

An estimated 4.6 to 8.6 million Americans meet the clinical diagnosis guidelines for SCH without a significant symptom burden that would prompt a visit to their practitioner. Despite lack of symptoms, treatment of SCH may be indicated based on
the physiological effects that elevated TSH may have. The relationship between TSH elevations and cardiovascular health has been well documented; nonetheless, debate still exists when considering subjects with SCH. \cite{2,6,14,22} Hak et al \cite{5} reported that SCH is independently associated with increased aortic atherosclerosis and myocardial infarction rate in a population based study of older women. A study by Walsh et al \cite{23} demonstrated that SCH is an independent predictor of coronary heart disease and patients with SCH had significantly more fatal and non-fatal coronary heart disease events than their euthyroid controls. \cite{23}

In contrast, a study by Rodondi et al \cite{22} found that elderly patients with SCH did not have increased coronary heart disease events, strokes, PAD, cardiovascular mortality, or total mortality when compared to euthyroid controls. The researchers \cite{22} did find higher total cholesterol levels and increased incidence and recurrence of CHF in SCH subjects.

In general, studies point towards increased cardiovascular risks with SCH, but the risks of untreated SCH and the decision to treat continues to be a topic of debate in the medical community.

**Purpose of Study**

Research has illustrated that both overt and subclinical hypothyroidism have negative effects on cardiovascular markers and health. \cite{2,5,14} The use of ultrasound to determine carotid artery intima media thickness has come to be accepted as a cost effective way to investigate cardiovascular health and risk of cerebrovascular and cardiovascular events. It has been shown \cite{20} that treatment with thyroid replacement hormone significantly reduces CIMT in patients with overt hypothyroidism. However, clinical guidelines for the treatment of SCH have largely ignored the issue of CIMT. The
purpose of this paper is to perform a systematic review of the literature to determine if treating patients with subclinical hypothyroidism will lead to decreased carotid artery intima media thickness, and thereby improve cardiovascular health and reduce in the risk of events.

Clinical Question

Treatment of SCH is an ongoing debate in the medical community, therefore it is important to examine the effects that elevated TSH can have on the cardiovascular system and the outcomes that result from SCH treatment using thyroid hormone replacement therapy.

METHODS

Search Strategy

A systematic review of the literature was completed by performing an exhaustive search of MEDLINE, Google Scholar, ISI Web of Science, and CINAHL using the MeSH terms hypothyrodism, carotid artery, and therapeutics. Additional searches using more specific, non-MeSH terms, specifically subclinical hypothyroidism and levothyroxine, were also completed. Original research articles examining the effects of thyroid replacement medications on carotid artery intima media thickness in patients with diagnosed subclinical hypothyroidism were included in this review. Randomized controlled trials, cohort studies and case control studies were included. Meta-analyses and case reports were excluded. Four studies met the inclusion criteria and were obtained and analyzed for valid and significant results. Investigation of the bibliographic information in the four articles was completed to ensure an exhaustive search.

Inclusion/ Exclusion Criteria
Studies examined were limited to those done in adult subjects, published in the English language, within the last 12 years. Studies were excluded if thyroid replacement therapy was compared to a different class of pharmaceutical agent, or if patients were diagnosed with overt hypothyroidism.

After considering these criteria, four articles were appraised using an original, seven point scoring system designed to evaluate the validity and quality of the studies. The criteria included two questions from the Jadad scoring guidelines and five additional questions. These additional questions were designed to assess homogeneity of subjects in specific measures between and within studies, quality definitions and measurements of the variables of interest, and the awareness and/or assessment of confounding variables. There was no minimum score needed, therefore, all four studies were reviewed and included. See Table 1 for the appraisal criteria score.

RESULTS

A thorough exploration of the literature, followed by appraisal of the validity and quality of the studies yielded the articles that were examined for this systematic review. See Table 2 for a summary of the articles included. One study included is a double blind, placebo-controlled trial and the remaining three studies are cohort studies, specifically therapy/prevention designs. Sample size ranged from 57-112 subjects. The duration of time between obtaining TSH normalization in the treatment groups and reassessing study variables ranged from four months to 18 months. All four studies demonstrated significant reductions in carotid artery intima media thickness (CIMT) in subjects treated with levothyroxine (L-T4). The studies were individually evaluated using the aforementioned appraisal criteria score.
A randomized controlled trial by Monzani et al. was conducted at the University of Pisa in Italy and published in the *Journal of Clinical Endocrinology and Metabolism*. The design was a double-blind, placebo-controlled study to examine the effects of levothyroxine (L-T4) treatment on carotid artery intima media thickness (CIMT) and lipid profiles in subjects with subclinical hypothyroidism (SCH). Subjects with SCH were recruited from the outpatient clinic of the Internal Medicine department and were selected based on a TSH >3.6mIU/L for at least six months before the study. A total of 45 SCH subjects (37 female) were enrolled in the study; 36 were positive for anti-thyroid peroxidase (TPO) antibodies, and nine had received radioiodine therapy for multinodular toxic goiter or toxic adenoma. Thirty-two euthyroid control subjects (27 female) were selected from staff and relatives of SCH subjects. The control participants were matched based on sex, age and BMI. All euthyroid subjects had normal thyroid function tests and were negative for TPO antibodies, which indicates lack of thyroid dysfunction. All subjects were in good health, had normal routine chemistry laboratory studies, and were not taking medications. Subjects were excluded if they were postmenopausal or pregnant, 55 years or older, obese, smokers, had hypertension, diabetes mellitus, renal or hepatic failure, or other systemic diseases. This study was the only randomized controlled trial that met the inclusion criteria for this review and it received a 7 out of 7 on the appraisal criteria score.

At the initiation of the study, fasting laboratory values were obtained on all subjects, and CIMT was evaluated using ultrasonography. A total of eight segments from the left and right common carotid arteries were averaged to obtain the mean CIMT and the maximum thickness of any of the eight segments was measured for use in analysis.
Subsequent to baseline measurements, SCH participants were randomized to receive levothyroxine (L-T4) replacement therapy (n=23) or placebo (n=22). The 23 subjects receiving L-T4 therapy were started with 25 µg and had repeat thyroid function testing done every three months. Levothyroxine dosage adjustments were made in 25 µg increments if TSH remained above 3.6 mIU/L. Laboratory tests were repeated quarterly until TSH normalization was reached. The 22 placebo subjects also had repeat laboratory testing every three months and some subjects received additional placebo pills to maintain blindness. All subjects underwent repeat CIMT measurement and fasting laboratory work after six months of TSH normalization in L-T4 replacement subjects and six months following the last dosage assignment in the placebo subjects.

At baseline, the SCH participants (n=45) had significantly elevated mean CIMT compared to euthyroid controls. In the analysis, the SCH subjects were stratified into two groups, under 35 years old and over 35 years old, in order to account for age effects on CIMT. When analyzed in separate groups, the mean CIMT of the older group remained significantly greater than the euthyroid controls; however, the mean CIMT in the younger group no longer varied significantly from the euthyroid controls. The SCH group had significantly elevated total cholesterol and LDL-C compared to euthyroid controls.

After six months of TSH normalization, the L-T4 subjects sustained significant reductions in mean CIMT, with a mean reduction of 0.09 mm or 10% (95% CI 0.06-0.11). While mean CIMT was reduced in the L-T4 treated subjects, the group (n=45) did not reach the levels of the euthyroid controls during the study period. However, when stratified by age, the younger group obtained mean CIMT equivalent to euthyroid
controls. Levothyroxine treated subjects also illustrated significant reductions in total cholesterol and LDL-C.

When comparing the SCH L-T4 treated subjects with the SCH placebo subjects, there were no significant differences in laboratory results or CIMT measurements at baseline. Following six months of stable TSH normalization, the mean-CIMT of the L-T4 treated participants was significantly lower than the placebo treated group (p=0.03). Significance remained when subjects were analyzed in separate age groups as well.

Additional analyses revealed that 46% of the variation in mean CIMT was accounted for by age, and that absolute reductions in mean CIMT were directly related to decreases in absolute total cholesterol and in TSH values.

Monzani et al concluded that treatment with levothyroxine reduces carotid artery intima media thickness and improves lipid profiles in subjects with subclinical hypothyroidism. Additionally, the researchers reported strong evidence to suggest that age is an influential determinant of CIMT.

Kim et al published results of a cohort study in *Endocrine Journal*. The study was designed to determine if subclinical hypothyroidism is associated with increased carotid artery intima media thickness (CIMT) and if levothyroxine treatment reduces CIMT and improves lipid profiles. In this study, the researchers included three subject groups: newly diagnosed subclinical hypothyroid (TSH >5.5 mIU/L with a normal FT4 between 11.4 and 22.6 pmol/L), overt hypothyroid (TSH >5.5 mIU/L with a free T4 (FT4) <11.4 pmol/L), and euthyroid control subjects (normal TSH between 0.35 and 5.50 mIU/L and a normal FT4 between 11.4 and 22.6 pmol/L). Both thyroid dysfunction groups were recruited consecutively from an outpatient clinic in Korea and were
determined to have thyroid dysfunction following a minimum of two abnormal thyroid function laboratory tests conducted at least two months apart. Additionally, thyroid dysfunction subjects were required to have positive anti-thyroid peroxidase (TPO) antibodies and evidence of Hashimoto’s thyroiditis on thyroid ultrasound. At the start of the study, there were 36 SCH subjects (31 female), 40 overt hypothyroid subjects (36 female) and 32 euthyroid control subjects (27 female). The healthy, euthyroid control subjects were matched based on age, gender and BMI. Subjects were excluded from the study if they had previous thyroid disease and underwent treatment, diabetes mellitus, hypertension, elevated creatinine, were smokers, or were taking medications that affect the lipid profile. Additionally, female subjects were excluded if they were currently or previously pregnant within the last year, or were postmenopausal. The study received a 5 out of 7 on the appraisal criteria score due to the inability to assess if SCH subjects met the three-month duration requirements for SCH diagnosis and the fact that the subjects were not randomized.

Before initiating levothyroxine (L-T4) treatment, all subjects underwent a detailed medical history, physical exam, fasting laboratory studies of glucose and lipid profile, and carotid artery assessment. Carotid arteries were scanned using ultrasonography and the mean CIMT was calculated using the values of 99 computer-based points within a region of the common carotid artery.

After baseline measurements, all hypothyroid subjects were started on L-T4, which was adjusted periodically to maintain TSH and FT4 levels within the reference ranges. All tests were repeated in the SCH group after one year of TSH normalization, which was, on average, 18 months after initiation of L-T4. Of the 36 SCH at the start of
the study, 28 completed the follow-up; three were lost to follow up, four transferred to other institutions and one refused follow-up CIMT measurement.

The researchers reported that age, gender, BMI, waist circumference and HDL-C were similar across all three groups at baseline. In contrast, participants with SCH had significantly higher CIMT, total cholesterol and LDL-C than euthyroid controls at baseline. The CIMT in subjects with overt hypothyroidism did not differ significantly from that of SCH subjects. Analyses illustrated that CIMT was associated with age, systolic blood pressure, glucose, total cholesterol, LDL-C and triglycerides. After 12 months of TSH normalization, the SCH subjects had significant decreases in CIMT, averaging 0.07 mm ± 0.06 mm (p=0.021). SCH participants also had significant reductions in total cholesterol and LDL-C.

Kim et al concluded that subclinical hypothyroidism resulted in increased CIMT associated with disturbances in the lipid profile; however, levothyroxine treatment decreased CIMT and improved lipid profiles and thereby, slowed and possibly prevented atherosclerosis.

In a cohort design study by Kebapcilar et al published in Medical Science Monitor, CIMT and other measures of cardiovascular health were compared in euthyroid control subjects and subjects with subclinical hypothyroidism (SCH), both before and after levothyroxine (L-T4) treatment. The study was conducted between January and November 2007 at University Hospital of Dokuz Eylul University in Izmir, Turkey. It compared 38 SCH subjects (31 female) mean age 49.79 ± 10.04 years and 19 euthyroid control subjects (12 female) mean age 49.95 ± 8.12 years. Of the 38 SCH subjects, 24 had autoimmune thyroiditis, 10 had subtotal resection of multinodular goiter, and 4 had
SCH of unknown etiology. The authors defined SCH as a TSH > 5.0 mIU/L with a normal free T4 level between 0.8 and 1.9 ng/dL on two separate laboratory studies at least two months apart. Subjects were excluded from the study if they were diabetic, had cardiac, renal, hepatic or other systemic diseases, were morbidly obese, had familial hyperlipidemias, had a history of malignancy, or were taking antihyperlipidemic medications, antihypertensive agents, aspirin, antihistamines, corticosteroids, hormone replacement medications, multivitamins, or were consuming excessive amounts of alcohol. The control subjects underwent history, physical exam and laboratory chemical analysis to ensure lack of disease prior to enrollment. The study earned a 4 out of 7 on the appraisal criteria score due to the fact that subjects were not gender matched, failure to randomize subjects, and an inadequate duration of SCH diagnosis.

All study subjects had fasting laboratory studies done at baseline and the SCH subjects had repeat studies three months after TSH normalization was reached, which was an average of six months after initiation of L-T4. Carotid artery intima media thickness (CIMT) of the right and left common carotid arteries was measured in three non-neighboring locations using ultrasonography. The mean value was calculated for an average CIMT in all subjects at baseline. The SCH subjects had repeat CIMT measurements taken an average of six months after treatment with L-T4. The SCH and control subjects were matched based on age, smoking habit, waist circumference and BMI.

All SCH subjects were placed on L-T4 following baseline evaluation. Levothyroxine treatment was taken orally and was initiated at 25-50 µg in all SCH
subjects; the dose was increased every four weeks, as needed, following reevaluation of TSH levels.⁹

At baseline, the mean CIMT of the SCH subjects was significantly higher than the controls. Following treatment and TSH normalization in the SCH subjects, there were significant reductions in mean CIMT, total cholesterol, and HDL-C. The average reduction in CIMT was 0.01 mm (p = 0.008), but despite reductions in CIMT, the SCH subjects did not reach thicknesses equivalent to those of euthyroid controls.⁹ Additional statistical analyses revealed that age and anti-thyroid antibodies were significant predictors of elevated CIMT in SCH subjects. Furthermore, it was demonstrated that reductions in CIMT were independent of lipid profile changes.

Kebapcilar et al⁹ concluded that L-T4 treatment reduced mean CIMT, and thereby decreased atherosclerotic risk in subjects with subclinical hypothyroidism.

Andrees et al¹⁰ conducted a cohort study designed to examine the effects of 18 months of levothyroxine treatment on women with subclinical hypothyroidism. The study was published in Clinical Endocrinology. Subjects with SCH were identified during routine thyroid function tests and were referred by a general practice to a tertiary referral hospital, where they underwent further screening to determine eligibility for the study. To be included, SCH subjects had to be females between the ages of 30 and 60, with consistently elevated TSH and normal free T4 levels for at least six months, and be non-smokers, free of the following: hypertension, diabetes mellitus, impaired fasting glucose or a history of ischemic heart disease or transient ischemic attacks. Control subjects were recruited from the general population, were not taking any medications, and were free of any diseases.¹⁰ At the start of the study, 56 SCH and 56 age and BMI matched control
subjects were enrolled; however, four subjects in the SCH cohort were not included in the analysis due to celiac disease (n=1), pernicious anemia (n=1) and need for antihypertensive therapy (n=2) that occurred during the study. Of the 56 SCH subjects, 42 had positive anti-thyroid peroxidase antibodies, indicating autoimmune thyroiditis, the remaining 14 had SCH of an unidentified origin. Additionally, eight of the control subjects had positive anti-thyroid peroxidase antibodies, but did not display other signs of autoimmune thyroiditis, namely, elevated TSH. This study received a 4 out of 7 on the appraisal criteria score because there was no discussion or statistical analysis of potential confounding variables that could have affected or accounted for changes in CIMT, subjects were not randomized into study groups, and the authors failure to provide normal reference ranges for TSH and free T4 levels according to the laboratory used.

All study subjects (56 SCH, 56 control) underwent laboratory testing to assess cardiovascular risk factors at baseline and the 52 remaining SCH subjects who completed 18 months of levothyroxine (L-T4) had repeat testing following treatment. Carotid artery intima media thickness (CIMT) was measured at baseline in 20 SCH subjects, who did not differ significantly from the other 36 SCH subjects. Using ultrasound technology, a mean value was calculated with three measurements from the right and left common carotid arteries. CIMT measurements were repeated in the same 20 subjects following 18 months of L-T4 treatment. CIMT was not measured in control subjects at either time point in this study.

Following baseline assessments, all SCH subjects were started on 50 µg of L-T4. TSH was reassessed every three months and L-T4 dosage adjustments made accordingly in order to reach TSH normalization.
Adrees et al\textsuperscript{10} reported that mean CIMT was significantly reduced following 18 months of L-T4 treatment in the 20 SCH subjects evaluated. Mean CIMT across the subjects decreased by 0.11 mm or 12\% (p=0.046).\textsuperscript{10} At baseline, SCH subjects had significantly higher markers of cardiovascular risk including total cholesterol, LDL-C, and systolic and diastolic blood pressure when compared to euthyroid control subjects. Following treatment, the SCH subjects had decreases in all of the aforementioned variables and were no longer significantly different from their matched controls.

The authors\textsuperscript{10} concluded that 18 months of levothyroxine treatment in subjects with SCH resulted in decreases of CIMT that were associated with reductions in additional cardiovascular risk markers.

**DISCUSSION**

The aim of this systematic review was to analyze the current literature to determine whether thyroid hormone replacement therapy reduced CIMT in adults with subclinical hypothyroidism. All four studies analyzed in this review concluded that treatment of SCH with levothyroxine resulted in significant decreases in CIMT.\textsuperscript{7-10} Furthermore, improvements in lipid profiles were seen in all four studies as a result of L-T4 treatment. The combination of decreased CIMT and improved lipid profiles led the researchers to draw the conclusion that levothyroxine treatment lowers cardiovascular risk, specifically atherosclerosis, in subjects with SCH.\textsuperscript{7-10}

Each of the studies measured additional variables that were not included in the analysis for this review, and therefore not addressed in the results section.

Carotid artery intima media thickness measurement is a noninvasive, efficient and relatively low-cost modality to evaluate cardiovascular health and risk.\textsuperscript{16, 18} Yet,
traditionally, laboratory lipid studies have been used to assess these measures. The four studies\textsuperscript{7-10} analyzed included both CIMT measurements and lipid profiles in their protocols and three of the studies determined the statistical relationship between the variables.\textsuperscript{7-9} Monzani et al\textsuperscript{7} and Kim et al\textsuperscript{8} reported that the reduction in CIMT was directly related to the decrease in total cholesterol and LDL-C, respectively. Kebapcilar et al\textsuperscript{9} demonstrated significant decreases in LDL-C, but did not discuss these decreases in the context of CIMT reductions. Three of the research teams\textsuperscript{7-9} identified age as a significant predictor of CIMT variability, specifically increasing age as it relates to greater CIMT. In fact, Kim et al\textsuperscript{8} and Monzani et al\textsuperscript{7} reported that age accounted for 64\% and 46\% of the variation in CIMT, respectively. Other factors that explained variability in CIMT included TSH\textsuperscript{7}, LDL-C\textsuperscript{7,8}, systolic blood pressure\textsuperscript{8}, and anti-thyroglobulin antibodies\textsuperscript{9}.

Of the four studies examined in this review, three studies explicitly state either their funding\textsuperscript{9} or that the authors do not have conflicts of interest\textsuperscript{8} or disclosure of note\textsuperscript{10}. However, Monzani et al\textsuperscript{7} do not mention their source of funding or report conflicts of interest. When considering the results of a pharmacological study, it is important to consider the funding of the research and notable conflicts of interest of the authors.

**Limitations of Studies**

While there are clinically relevant outcomes in each of the studies analyzed in this review, it is important to consider the limitations of the research.

One important limitation of all of the included studies\textsuperscript{7-10} was the small sample sizes. The number of subjects with subclinical hypothyroidism in each of the studies ranged from 36\textsuperscript{8} to 56\textsuperscript{10}. However, in the study\textsuperscript{10} with 56 SCH subjects, only 20
underwent CIMT measurements. Although none of the studies had large drop out rates, a greater number of subjects would increase statistical power and possibly the clinical relevance of the results.

Each of the studies\(^7\)\(^-\)\(^10\) included a euthyroid control group that was used for pre-treatment comparison and had laboratory and CIMT measurements done at baseline. However, none of the studies performed repeat testing in the euthyroid control groups following four to 18 months of levothyroxine treatment in the SCH participants. Kebapcilar et al\(^9\), Andrees et al\(^10\), and Monzani et al\(^7\) compared both SCH pre- and SCH post-treatment data to euthyroid controls, but used baseline measurement for euthyroid control subjects. The trepidation about using baseline data to compare with post-treatment data is the likelihood of change in baseline data over the course of the study intervention. In one study,\(^10\) 18 months elapsed between baseline and post-treatment measurements which could be time enough for CIMT and lipid variable to change.

Three of the reviewed studies\(^8\)\(^-\)\(^10\) used cohort, within-subject designs, as opposed to randomized controlled trials. While the participants in these studies were used as their own controls following treatment, all of them received levothyroxine making the placebo effect a possible confounder. Furthermore, Kim et al\(^8\) performed only pre- and post-treatment analyses in the SCH group and did not include post-treatment comparisons to overt hypothyroid or euthyroid control subjects.

Kim et al\(^8\) required two abnormal TSH levels at least two months apart, making the exact timeline difficult to interpret. Likewise, in the study by Kebapcilar et al,\(^9\) subjects were considered to have SCH if they had laboratory evidence of elevated TSH for two months. It is documented\(^2\) and generally accepted in clinical practice, that
patients should have an elevated TSH for at least three months before considering a thyroid dysfunction diagnosis and subsequent treatment. Therefore, time until diagnosis was inadequate⁹ or impossible to determine⁸ in the two aforementioned studies.

Andrees et al¹⁰ included eight subjects with evidence of autoimmune thyroid disease, specifically positive anti-thyroid peroxidase (TPO) antibodies, in their control group. TPO antibodies are evidence of thyroid dysfunction and thereby, those eight subjects had the potential to distort the picture of euthyroid controls, particularly when considering the small sample size. Additionally, the normal reference ranges for the thyroid function laboratory tests were not included in their paper. Without these values, it is difficult to determine if subjects, in fact, met laboratory criteria for SCH and euthyroidism. Lastly, Andrees et al¹⁰ did not include any statistical analysis or discussion of the influence that other study variables, such as age or lipid profile values, had on CIMT. As seen in the other studies,⁷⁻⁹ these variables were statistically related to and accounted for portions of the CIMT changes.

Andrees et al¹⁰ and Kebapcilar et al⁹ did not indicate if the women in the study were pre- or post-menopausal. Menopause is associated with many physiological changes and thyroid function is possibly one of them. In fact, one study¹ found that up to 16% women 60 years and older meet criteria for subclinical hypothyroidism. Additionally, research² has demonstrated that menopause can affect both thyroid function and coronary disease, both of which were critical variables in this review. Therefore, it is important to indicate menopause status when considering thyroid function and cardiovascular health.

Similarly, Kebapcilar et al⁹ did not gender match the subjects for analysis. While the remaining three gender-matched studies⁷,⁸,¹⁰ did not report results separated by
gender, it has been documented that both thyroid disorders and coronary disease\textsuperscript{2} differ in incidence based on sex. Therefore, to decrease the influence of subject gender on results, subjects should be matched between the euthyroid and the control groups.

Lastly, all four studies\textsuperscript{7-10} used the mean of between three and 99 measurements of carotid artery intima media thickness (CIMT) to be used in analysis. While statistically this may have been the most reasonable method to obtain a single number to represent CIMT, the value could have been distorted in either direction. Importantly, the value of CIMT used in analysis could have been low or normal in a given patient despite an area with large amounts of plaque that could potentially harmful in the near future. This is an important ethically issue to consider when deciding on treatment or intervention in an individual patient.

**Future Research**

Additional studies to investigate the correlation between subclinical hypothyroidism and cardiovascular health are indicated. As evidenced by the studies examined in this review, larger sample sizes are needed in order to increase both statistical power and clinical significance. Moreover, additional randomized controlled trials would strengthen the evidence of the relationship between thyroid replacement treatment and reductions in cardiovascular risk factors in subjects with SCH.

The current number of Americans with untreated SCH\textsuperscript{21} begs the questions of cost to treat them and more importantly, the long-term risk reduction in cardiovascular events that would follow. A longitudinal study aimed at investigating these outcomes would be useful when considering the cost-benefit ratio of treatment in clinical practice.
The intentions of this review are not to advise clinicians to use carotid artery ultrasonography as a means to diagnose or assess the severity of thyroid dysfunction in patients. Rather, it is to demonstrate, using CIMT as a surrogate variable, that subclinical hypothyroidism has detrimental effects on cardiovascular health that can be slowed or reversed with levothyroxine treatment. While treatment may not be indicated in all patients with laboratory diagnosed subclinical hypothyroidism, clinicians should consider the patients on an individual basis and include important historical information in the decision to treat.

**CONCLUSION**

The decision to screen for and treat subclinical hypothyroidism remains a question of debate in the medical community. There is evidence that thyroid hormone replacement therapy decreases carotid artery intima media thickness in subjects with subclinical hypothyroidism, as illustrated by this literature review. However, the cost and long-term outcomes of treatment in the estimated 4.6-8.6 million Americans that meet laboratory criteria for SCH should be considered. While there is a need for further research to assist in the decision to treat, it is ultimately a clinician’s duty to consider each patient as an individual and to take into account pertinent family and personal history, as well as other existing cardiovascular risk factors.
REFERENCES


15. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228-238.


### Table 1. Appraisal Scoring Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes (1)</th>
<th>No (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized*?</td>
<td></td>
<td></td>
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<tr>
<td>Was there a description of withdrawals and dropouts*?</td>
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<tr>
<td>Did the subjects have an elevated TSH or diagnosis of subclinical hypothyroidism for at least 3 months prior intervention?</td>
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<tr>
<td>Did subjects meet the laboratory criteria for subclinical hypothyroidism (elevated TSH and normal Free T4) respective to the study?</td>
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<tr>
<td>At baseline, were subjects’ age and gender matched between groups?</td>
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<tr>
<td>Were at least 3 measurements of carotid intima media thickness used to obtain a mean value utilized in analyses?</td>
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<tr>
<td>Were the effects of pertinent confounding variables discussed and/or adjusted for with regards to carotid artery intima media thickness?</td>
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*Part of Jadad score
<table>
<thead>
<tr>
<th>Author(s), Study Type, &amp; Year Published</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Comparison between Subjects</th>
<th>Outcome(s)</th>
<th>Appraisal Criteria Score, out of 7</th>
<th>Comments</th>
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</table>
| Monzani et al, Randomized Controlled Trial 2004 | • 45 (37 female) SCH subjects; Mean age 37 ± 11 yrs. Divided into >35 yrs & <35 yrs for some analyses  
  • 32 (27 female) euthyroid controls; Mean age 35 ± 10 yrs. | • L-T4 at 25μg; titrated every 3 months as needed (n=23)  
  • Placebo; similar titration (n=22)  
  • None | CIMT (mm) | Significant ↓ in CIMT in L-T4 treated SCH subjects compared to control (mean = 0.09mm, 95% CI: 0.06-0.11)  
  Significant ↓ in CIMT in L-T4 treated SCH subjects <35 yrs equal to controls | 7/7 | At baseline, CIMT significantly higher in >35 yrs SCH compared to euthyroid controls |
| Kim et al, Cohort 2009 | • 36 (31 female) SCH subjects; Mean age 36.0 ± 6.2 yrs.  
  • 40 (36 female) overt hypothyroid subjects; Mean age 37.8 ± 6.3 yrs.  
  • 32 (27 female) euthyroid controls; Mean age 36.1 ± 5.4 yrs. | • L-T4; adjustments made on individual basis  
  • None | CIMT (mm) | Significant ↓ in CIMT in SCH subjects (mean = 0.07mm, p=0.021) | 5/7 | Failure to randomize; Unable to determine duration of SCH diagnosis before study |
| Kebapcilar et al, Cohort 2010 | • 38 (31 female) subjects with SCH; Mean age 49.79 ± 10.04 yrs  
  • 19 (12 female) age-matched, euthyroid controls; Mean age 49.94 ± 8.12 yrs. | • L-T4 at 25-50μg; titrated every 4 weeks as needed  
  • None | CIMT (mm) | Significant ↓ in CIMT in SCH subjects (mean = 0.01mm, p=0.008) | 4/7 | Failure to randomize; Only 2 months SCH diagnosis; Subjects not gender matched |
| Andrees et al, Cohort 2009 | • 56 females with SCH; Mean age 50 ± 9 yrs.  
  • 56 age-matched, euthyroid female controls; Mean age 47 ± 8 yrs. | • L-T4 at 50μg; titrated every 3 months as needed  
  • None | CIMT (mm) | Significant ↓ in CIMT in SCH subjects (mean = 0.11mm, p=0.046) | 4/7 | Failure to randomize; No normal lab reference ranges provided; No comment of analysis of confounding variables on CIMT |

Key: SCH: Subclinical hypothyroidism; L-T4: levothyroxine; CIMT: Carotid artery intima media thickness; TPO: antithyroid peroxidase antibodies