Screening for Subclinical Thyroid Dysfunction in Non-Pregnant Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Hyperthyroidism and hypothyroidism are common conditions that have lifelong effects on health.[1,2] About 5% of U.S. adults report having thyroid disease or taking thyroid medication.[1,2] Consequences of untreated hyperthyroidism include atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric disorders. Hypothyroidism causes symptoms that reduce functional status and quality of life.[3]

Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for developing hyperthyroidism and hypothyroidism complications. The goal of screening is to identify and treat patients with subclinical thyroid dysfunction before they develop these complications.[4–6]

The term *subclinical hyperthyroidism* describes conditions characterized by a low thyroid-stimulating hormone (TSH) and normal levels of circulating thyroid hormones (thyroxine and triiodothyronine). Subclinical hyperthyroidism has the same causes as overt hyperthyroidism. These include excessive doses of levothyroxine, Graves' disease, multinodular goiter, and solitary thyroid nodule. Most studies of the course of subclinical hyperthyroidism concern patients whose history, physical examination, ultrasound, or thyroid scan suggests one of these causes. There are relatively few studies of patients who are found by screening to have an undetectable TSH, normal free thyroxine (FT4) and normal free triiodothyronine (FT3) levels, and a negative thyroid evaluation, the largest group identified in a screening program. The prevalence of subclinical hyperthyroidism is about 1% (95% confidence interval [CI], 0.4%–1.7%) in men older than 60 and 1.5% (CI, 0.8%–2.5%) in women older than 60.[7]

The terms *subclinical hypothyroidism* and *mild thyroid failure* refer to patients who have an elevated TSH and a normal FT4 level (Table 1).[6] Subclinical hypothyroidism is common, especially in older women.[1,2,7–16] In an analysis of the Third National Health and Nutrition Examination Survey (NHANES-III), a population-based survey of 17,353 people aged 12 or older representing the U.S. population, the prevalence of subclinical

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Table 1. Classification of Thyroid Dysfunction

	Biochemical Criteria	
	TSH Level	Thyroid Hormone Level
Overt hyperthyroidism	Low or undetectable	Elevated FT4 or FT3
Subclinical hyperthyroidism	Low or undetectable	Normal FT4 and FT3
Overt hypothyroidism	> 5 mU/L	Low FT4
Subclinical hypothyroidism	> 5 mU/L*	Normal FT4

FT4, serum free thyroxine; FT3, serum free triiodothyronine; TSH, thyroid-stimulating hormone.
*Others use different cutoffs.

hypothyroidism was 5.8% among white, non-Hispanic females, 1.2% among black, non-Hispanic females, and 5.3% among Mexican-American females.[1] The prevalence of subclinical hypothyroidism was 3.4% among white men, 1.8% among black men, and 2.4% among Mexican American men. In the Whickham survey, a large, good-quality, population-based study with 20-year follow-up, prevalence was 4% to 5% among women aged 18 to 44, 8% to 10% among women aged 45 to 74, and 17.4% among women older than age 75.[17] The prevalence was 1% to 3% among men aged 18 to 65 and 6.2% among men over age 65.

In this paper, I address whether the primary care physician should screen for thyroid function in patients seen in general medical practice who have no specific indication for thyroid testing and who come to the physician for other reasons. I focus on whether screening should be aimed at detection of subclinical thyroid dysfunction and whether individuals who have mildly abnormal TSH values can benefit.

Methods

In consultation with members of the U.S. Preventive Services Task Force (USPSTF) and an Institute of Medicine expert panel, I defined the population, interventions, and outcomes of interest and developed key questions to guide the literature review.[18] The population of interest was asymptomatic, non-pregnant adults who do not have a goiter, nodule, proptosis, tremor, profound physical tiredness, or a past history of thyroid disease.[19] I also included elderly patients who complained of 1 or 2 nonspecific or mild symptoms, such as cold intolerance, fatigue, weight gain, or constipation, because they are no more likely to have abnormal thyroid function tests than those who have no complaints.[20]

Previous systematic reviews have established that subclinical thyroid function is common and can be diagnosed easily using a TSH test.[7,8,21] In this article, I focus on the following questions:

1. What are the complications of subclinical thyroid dysfunction?
2. What are the benefits of earlier treatment of subclinical hypothyroidism and hyperthyroidism?
3. What are the adverse effects of treatment?

To find articles published before 1998, I searched the reference lists of previous reviews[6,8,9,21–29] and our own files of over 1,600 full-text articles from 1910 to 1998.[1] I then searched MEDLINE® and EMBASE from 1996 to February 2002, PreMEDLINE in March 2002, and the Cochrane Library (2002, Issue 2) to identify recent articles relevant to each question.

For question 1, I searched for studies of the causal relationship between subclinical thyroid dysfunction and any potential complication. I included studies if they were conducted in the general adult population, a demographic segment of the adult population, or among patients seen in the

general clinic setting. I excluded studies of screening for congenital or familial thyroid disorders and studies of screening in pregnant women, inpatients, institutionalized patients, and series of patients seen in specialized referral clinics for depression or obesity.

To examine the benefits and harms of treatment (questions 2 and 3), I included any controlled trial of oral levothyroxine or triiodothyronine that used TSH levels as a criterion for entry, in any population, including patients with known thyroid disease. I also included recent observational (pre/post treatment and time series) studies that had not been included in previous meta-analyses.[7,9,21,30]

I reviewed abstracts and articles to identify studies that met the eligibility criteria and abstracted information about the setting, patients, interventions, and outcomes of each included trial using a standard template. I used predefined criteria from the USPSTF to assess the internal validity of included studies[18] and rated the applicability of each study to screening.

This article is based on a larger evidence report that was funded by the Agency for Healthcare Research and Quality (AHRQ) and the Institute of Medicine (available at http://www.preventiveservices.ahrq.gov). Staff of both funding agencies, members of the USPSTF, and members of an Institute of Medicine expert panel reviewed the draft of the larger report and made editing suggestions.

Results

Subclinical Hyperthyroidism

Advocates of screening for subclinical hyperthyroidism argue that early treatment might prevent the later development of atrial fibrillation, osteoporotic fractures, and complicated overt hyperthyroidism. Other potential benefits are earlier treatment of neuropsychiatric symptoms and prevention of the long-term consequences of exposure of the heart muscle to excessive stimulation from thyroid hormones.

Evidence regarding potential complications

Atrial fibrillation. A good-quality cohort study in the Framingham population found that, in patients older than 60 who did not take levothyroxine and had a serum TSH level of 0.1 mU/L or less, the risk of atrial fibrillation was 32% (CI, 14%–71%) over 10 years.[31] The risk for patients who had a normal TSH level was 8%. A more recent cross-sectional study of atrial fibrillation in overt and subclinical hyperthyroidism had serious flaws and was rated as being of poor quality.[32] The clinical consequences of atrial fibrillation in patients who have a low TSH have not been studied. In general, chronic atrial fibrillation is associated with stroke and other complications and with a higher risk for death.[33]

Mortality. A population-based, 10-year cohort study of 1,191 people aged 60 or older found a higher mortality rate among patients who had a low TSH initially.[34] The excess mortality was due primarily to cardiovascular diseases. In this study, the recruitment strategy and the statistical adjustment for potential confounders were inadequate; patients who had a low TSH may have had a higher prevalence of other illnesses, but adjustment was done only for age and sex, not for comorbidity. Comorbidity adjustment would be critical because acutely ill and chronically ill elderly patients often have falsely low TSH levels, presumably because of their illness.[35] Thus, while it is possible that patients who had a low initial TSH had higher mortality because of their thyroid disease, it is also possible that patients who were ill to begin with had a low TSH as a result of their illness.

Osteoporosis and fracture. Most data about the risk for osteoporosis and fracture come from women who take thyroid hormones rather than from untreated women found by screening to have a low TSH. Two meta-analyses of older studies[36,37] suggest that women who have a low TSH because they take thyroid hormones are at higher risk for developing osteoporosis. However, a good-quality study from the Study of Osteoporotic Fractures (SOF) cohort found similar bone loss among women with undetectable, low, and normal TSH levels, but markers of bone turnover were higher in women with a low TSH.[38] In a more recent nested sample of cases and controls

from SOF, the risk for hip fracture among women who had an undetectable TSH was elevated, but of borderline statistical significance (adjusted hazard ratio, 3.6; CI, 1.0–12.9).[39] The risk for vertebral fracture among women who had an undetectable TSH was significantly elevated when compared with 235 controls (odds ratio [OR], 4.5; CI, 1.3–15.6). Among women who had a borderline low serum TSH (0.1–0.5 mU/L), the risk for vertebral fracture (OR, 2.8; CI, 1.0–8.5), but not hip fracture, was elevated.

This analysis has limited relevance to screening because the investigators were not able to obtain serum FT4 or FT3 tests, which could have distinguished between overt and subclinical hyperthyroidism. Also, among the 148 women with hip fractures, 22 had an undetectable serum TSH (< 0.1 mU/L), and of these, approximately 19 (86%) were taking thyroid hormones when their initial TSH measurement was obtained. Bauer and colleagues stated that "thyroid hormone use was not associated with increased risk for ... fracture," but there were not enough women with undetectable TSH levels not taking thyroid hormone to make a valid comparison.[39] Finally, at baseline, the hip fracture cases were significantly older, weighed less, had lower bone density, were less healthy by self-report, and were twice as likely to have a history of hyperthyroidism than controls. The analysis could not exclude the possibility that some of the women with low TSH levels had several interacting risk factors and that other factors concomitant with age or socioeconomic status could have been confounders.

Other studies of the risk for osteoporosis among patients not taking levothyroxine concern small numbers of patients with nodular thyroid disease or Graves' disease[40–43] rather than patients who have no obvious clinical signs of thyroid disease.

Complicated thyrotoxicosis and progression to overt hyperthyroidism. Overt thyrotoxicosis can be complicated by severe cardiovascular or neuropsychiatric manifestations requiring hospitalization and urgent treatment. There are no data linking subclinical hyperthyroidism to the later development of complicated thyrotoxicosis. Such a link is unlikely to be made because 1) complicated thyrotoxicosis is rare, 2) one-half of cases occur in patients with known hyperthyroidism, and 3) complications are associated with social factors, including insurance status, that may also affect access to screening and follow-up services.[44]

Progression from subclinical to overt hyperthyroidism is well documented in patients with known thyroid disease (goiter or nodule), but not in patients found by screening to have a low TSH and no thyroid signs. Based on the sparse data from screening studies, a previous meta-analysis estimated that each year, 1.5% of women and 0% of men who have a low TSH and normal FT4 and FT3 levels develop an elevated FT4 or FT3.[7,45,46]

Symptoms and cardiac effects. In the setting of nodular thyroid disease, Graves' disease, or long-term use of suppressive doses of levothyroxine, subclinical hyperthyroidism has been associated with cognitive abnormalities, abnormalities in cardiac contractility, and exercise intolerance.[47–52] However, the frequency of symptoms or myocardial contractility abnormalities in patients who have subclinical hyperthyroidism found by screening has not been studied; no study has linked abnormalities in cardiac contractility or output to the development of clinically important heart disease.

Efficacy of Treatment for Subclinical Hyperthyroidism

No controlled trials of treatment for subclinical hyperthyroidism have been done. Small observational studies in patients with nodular thyroid disease not detected by screening have shown improvements in bone metabolism and hemodynamic measures after treatment.[53–56]

Subclinical Hypothyroidism

Evidence regarding potential complications

Progression to overt hypothyroidism. There is good evidence from well-conducted longitudinal studies that subclinical hypothyroidism is a strong risk factor

for the later development of overt hypothyroidism. In addition to the TSH level, older age, antithyroid antibodies, and female sex are also strong risk factors. In the Whickham survey, for a 50-year-old woman who has a serum TSH level of 6 mU/L and positive antithyroid antibodies, the risk for developing overt hypothyroidism over 20 years was 57%; for a 50-year-old woman with a serum TSH level of 9 mU/L, the risk was 71%.[57] A 50-year-old woman who had a normal TSH and negative antibody test had a risk of only 4% over 20 years. The risk for progression was not evenly distributed throughout the follow-up period. Nearly all women who developed hypothyroidism within 5 years had an initial serum TSH greater than 10 mU/L.

Symptoms, mood, and quality of life. In its 1998 review and guideline, the American College of Physicians concluded that, in the general population, it was not clear that the prevalence and severity of symptoms and the quality of life differs for individuals who have mildly elevated TSH levels compared with those who do not.[7,20,58] Since then, 2 cross-sectional studies in volunteers have addressed this question, with mixed results. An interview survey of 825 Medicare enrollees in New Mexico found no differences in the age-adjusted frequency of self-reported symptoms between participants with serum TSH elevations from 4.7 to 10 mU/L and those with normal TSH concentrations.[14] A larger survey from Colorado (n = 25,862) is less pertinent because it included patients who took levothyroxine in the analysis of symptoms. It also found no difference between euthyroid patients and those with subclinical hypothyroidism in current symptoms, but found a higher percentage of "changed symptoms" in the subclinical hypothyroid group (13.4% vs 15.4%).[2]

Patients who have subclinical hypothyroidism, a TSH >10 mU/L, and a history of antithyroid treatment for Graves' disease or nodular thyroid disease have a higher prevalence of symptoms than healthy controls.[22,59] This observation is probably valid, but an important limitation of the evidence should be noted: the appropriate comparison group is not healthy volunteers, but patients who have a normal TSH and a history of antithyroid treatment. This is because euthyroid patients who have a history of treatment for hyperthyroidism also have a higher prevalence of anxiety, depression, and psychosocial dysfunction than healthy controls.[60]

Hyperlipidemia. Overt hypothyroidism has long been known to be associated with elevated levels of cholesterol,[61] but patients in the earliest studies had severe hypothyroidism. In more recent studies, there is a clinically important increase in total cholesterol and low-density lipoprotein (LDL) cholesterol among men[62] and women[63,64] with overt hypothyroidism in those who have serum TSH levels higher than 20 mU/L.

In women with subclinical hypothyroidism, the relation between TSH and total cholesterol or LDL cholesterol is inconsistent. In the Whickham survey, there was no relationship between subclinical hypothyroidism and hyperlipidemia.[17] In the Rotterdam study[16] (discussed in detail below), lipid levels were significantly lower among women with subclinical hypothyroidism than among euthyroid women. The New Mexico Elder Health Survey, a fair-quality study of randomly selected Medicare recipients, found no differences in levels of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, or triglycerides between patients who had a serum TSH less than 4.6 (n = 684) and those who had a serum TSH between 4.7 and 10 mU/L (n = 105). There were non-significant increases in LDL cholesterol and HDL cholesterol among women who had a serum TSH greater than 10 mU/L (LDL cholesterol 3.7 mmol/L [143 mg/dL] vs 3.3 mmol/L [128 mg/dL] in euthyroid women, $P = 0.08$; HDL cholesterol 1.07 mmol/L [41.6 mg/dL] vs 1.23 mmol/L [47.5 mg/dL], $P = 0.053$).[14]

Conversely, a recent cross-sectional study of 279 women older than age 65 found a strong relationship between hyperlipidemia and serum TSH levels.[65] Of the 279 women, 19 (6.8%) had a serum TSH greater than 5.5 mU/L. After adjustment for age, weight, and estrogen use, women who had a serum TSH greater than 5.5 mU/L had 13% higher LDL cholesterol (95% CI, 1%–25%) and 13% lower HDL cholesterol (CI, –25% to 0%) than those with

a normal serum TSH (0.1–5.5 mU/L). However, 2 of the 19 women who had an elevated TSH used levothyroxine, suggesting they had inadequately treated overt hypothyroidism. Because FT4 and FT3 levels were not measured, it is possible that others in this group had overt hypothyroidism as well.

Men with a mildly elevated TSH generally do not have an increased risk for hyperlipidemia, but data on men are sparse. Men with hypercholesterolemia do not have a higher prevalence of subclinical hypothyroidism than men with normal lipid levels.[66]

Atherosclerosis. The relationship between subclinical hypothyroidism and the later development of atherosclerosis is unclear.[14,16,67] The Whickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of follow-up.[67]

A widely publicized population-based study of 1,149 women aged 55 or older from Rotterdam came to a different conclusion.[16] The main analysis in the paper was cross-sectional. In that analysis, after adjustment for age, body mass index, cholesterol level, blood pressure, and smoking status, a serum TSH greater than 4.0 mU/L was associated with a history of myocardial infarction (OR, 2.3; CI, 1.3–4.2) and with atherosclerosis of the abdominal aorta, which was diagnosed by blinded review of a lateral radiograph of the lumbar spine (OR, 1.9; CI, 1.2–3.1). An analysis of incident myocardial infarction over 3 to 6 years of follow-up found a statistically non-significant increased risk in women with a serum TSH greater than 4.0 mU/L (adjusted relative risk, 2.5; CI, 0.7–9.1).

The strengths of the Rotterdam study are the relatively large sample size, adjustment for some potential confounders, and validated, blinded assessment of outcomes. Because the study was primarily cross-sectional, however, the findings do not prove that an elevated TSH precedes the development of atherosclerosis. The prospective part of the study adds little because, at baseline, the women who had an elevated TSH had a higher prevalence of atherosclerotic disease; they would be expected to have a higher incidence of myocardial infarction over 3 to 6 years, in any case. The prospective analysis would have been more consequential if patients who had atherosclerosis at baseline had been excluded.

In the Rotterdam study, women with subclinical hypothyroidism had lower lipid levels than euthyroid women; this might be an artifact of higher use of diet or other lipid-lowering therapy in women with known cardiovascular risk factors, but it also might suggest that atherosclerosis developed by another mechanism. One hypothesis is that elevations in both homocysteine and cholesterol may contribute to the elevated risk for atherosclerosis in overt hypothyroidism. In cross-sectional studies, including an analysis of the Second National Health and Nutrition Examination Survey (NHANES-II) sample, patients with overt hypothyroidism had higher homocysteine levels than euthyroid patients.[68,69] The association of elevated homocysteine and overt hypothyroidism appears to persist after controlling for serum folate levels, which are decreased in overt hypothyroidism.[68–72] However, in the only study concerning patients who had subclinical hypothyroidism, there was no association.[73]

Efficacy of Treatment

I identified 14 randomized trials of levothyroxine therapy, 8 of which met the inclusion criteria.[58,59,74–79] Six concerned patients with elevated TSH levels, 1 concerned hyperlipidemic patients with high-normal TSH levels,[75] and the last trial concerned patients with a normal TSH who had symptoms of hypothyroidism.[77]

Randomized trials of levothyroxine treatment in subclinical hypothyroidism and in symptomatic patients who have a normal TSH are described in Table 2 (quality ratings) and Table 3 (description and results). The first 2 trials in the tables concerned patients followed in thyroid specialty clinics. In both trials, patients had a mean serum TSH above 10 mU/L. The first trial (Cooper et al) concerned patients who had been treated for Graves' disease in whom TSH was increasing relatively quickly.[59] Symptoms were rated on the Cooper Questionnaire, a 24-point scale that records how 6 symptoms of hypothyroidism change over time. After 1 year, patients taking levothyroxine improved

by 2.1 points, while patients taking placebo deteriorated by 1.2 points ($P = 0.037$). The difference (3.3 points) is roughly equivalent to complete relief of 1 symptom and partial relief of a second symptom per patient. Eight (47%) of 17 treated patients reported reduced or milder symptoms, 4 felt worse, and 5 reported no change in symptoms. In the placebo group, 3 (19%) of 16 patients felt better, 6 felt worse, and 7 reported no change. The difference between the proportion of patients who felt better in each group was 0.28 (CI, –0.09 to 0.65), indicating that the number needed to treat to benefit 1 patient was 3.5.[59] Treatment had no effect on lipid levels. The internal validity of this trial was rated as good quality; it was the highest-quality trial of the group.

The second trial (Meier et al) concerned patients with thyroiditis or a history of Graves' disease.[76] Treatment with levothyroxine had no effect on symptoms. In reporting results, the authors emphasized that there was a significant reduction in LDL cholesterol in the levothyroxine-treated group, from 4.0 to 3.7 mmol/L ($P = 0.004$), and no significant reduction in the placebo group. The difference appears to be related to an imbalance in the groups at baseline: pre-treatment LDL cholesterol was 4.0 mmol/L (154 mg/dL) in the treatment group versus 3.7 mmol/L (143 mg/dL) in the placebo group. In fact, post-treatment LDL cholesterol was the same in both groups (3.7 ± 0.2 mmol/L [143 ± 7 mg/dL, $P = 0.11$]). When the results were analyzed as a randomized trial, the difference between the treatment and control groups' lipid levels was not significant. The discrepancy suggests that randomization may have been flawed.

The rated relevance of these 2 studies to screening is low. The Cooper et al study supports treatment in patients with a history of treated Graves' disease, especially if the serum TSH is above 10 mU/L. However, it has little relevance to screening because the natural history of treated Graves' disease differs from the natural history of spontaneous hypothyroidism in the general population.[59]

The third trial recruited patients known to have Hashimoto's thyroiditis, positive antithyroid antibodies, and mildly elevated TSH levels.[78] When analyzed as a randomized trial, there were no significant differences between levothyroxine-treated and placebo groups on any lipid variable. When analyzed as a pre-/post-treatment study, there was a statistically significant reduction in LDL cholesterol levels (3.6 mmol/L [139 mg/dL] to 3.1 mmol/L [120 mg/dL]) in the levothyroxine-treated group, but not in the control group. The study appeared to be unblinded, which is a major flaw because differential attention to lipid levels in the treatment and control groups could lead to different behavioral approaches to reducing lipid levels. If the results are valid, they would be relevant to screening; the mean TSH was only slightly elevated, and patients who have antithyroid antibodies and a modestly elevated TSH are found commonly in screening programs.

The next 3 studies may have had more relevance to screening or primary care: they generally concerned patients, mostly women, with subclinical hypothyroidism who were not previously treated for Graves' disease or nodular thyroid disease. However, 2 of the 3 studies had poor internal validity. In the fair-quality trial by Jaeschke and colleagues, 37 patients with subclinical hypothyroidism were recruited from the outpatient clinics of a community hospital and randomized to levothyroxine treatment or placebo.[74] Patients given placebo did as well or better than those given levothyroxine. After 6 months, in the levothyroxine group, 8 patients improved, 3 worsened, and 5 remained the same, according to the Cooper Questionnaire. In the placebo group, 11 patients improved, 1 worsened, and 4 remained the same. After 11 months, patients treated with levothyroxine had a small but statistically significant improvement in short-term memory, but treatment did not improve general health status as measured by a standardized questionnaire, the Sickness Impact Profile (SIP). The other negative trial was too small to achieve balance in the compared groups and had a high rate of loss to follow-up.[79]

A small crossover trial[58] concerned women identified by screening in the general population. The 20 patients were women older than age 50 who had an initial serum TSH between 4 and 15 mU/L. After 6 months of treatment, the mean symptom score improved by 1.81 units, equivalent to complete

Table 2. Quality of Randomized Trials of Thyroxine Replacement Therapy*

Study, Year	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Cooper et al, 1984[59]	Yes, by individual	Not stated	LT4 patients were older (58.2 vs 50.2) and had fewer symptoms (2.1 vs 2.4) but otherwise similar	Yes	Yes	Probably (1 of 2 investigators is said to be blinded)
Meier et al, 2001[76]	Sequential assignment using a predefined list; randomized by matched pairs	No	LT4 patients had higher TSH (14.4 ± 1.7 vs 11.3 ± 1.0) and LDLc (4.1 vs 3.7) but were otherwise similar for the whole groups (n = 66); comparisons were not presented for the analyzed group (n = 63)	Yes	Not stated	Yes
Caraccio et al, 2002[78]	Yes, by individual	Not stated	Generally yes, but mean TSH (6 vs 4.9) and LDLc (3.6 vs 3.3) were higher in LT4 group	Yes	No	No

FT4, serum free thyroxine; LDLc, low-density lipoprotein cholesterol; LT4, levothryroxine; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone.

*Values reported with plus/minus signs are means ± SD.

† Symptomatic group only.

Table 2. Quality of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Patient Unaware of Treatment?	Intention-to-Treat Analysis?†	Maintenance of Comparable Groups?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score (Good/ Fair/ Poor)
Yes, not verified	No	The number of patients randomized appears to be 41; 33 patients were analyzed. It is not clear to which group the other 8 belonged.	Partially	Unclear; probably not	Yes, except it did not address dropouts	Good
Yes, not verified	No	Yes	No	No	No, analyzed as RCT, but reported primarily as a before/after study	Poor
Probably were aware, since dosing and length of follow-up differed. It is not clear whether patients were informed of their lipid levels.	Yes, assuming that completion of study was not a criterion for inclusion	Probably	No	No	Yes (when analyzed as an RCT)	Poor

continue

Table 2. Quality of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Study, Year	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Jaeschke et al, 1996[74]	Yes, by individual	Not stated	LT4 patients had higher TSH (12.1 vs 9.4) and slightly more symptoms (14 vs 13) but similar in age	Yes	Yes	1 investigator was not blinded but was not involved in assessment or care
Kong et al, 2002[79]	Yes, in blocks of 6	Yes	LT4 patients were older (53 vs 45 yrs), had lower FT4 (0.9 vs 1), and higher TSH (8 vs 7.3)	Yes	Yes	1 was not blinded but was not involved in care
Nystrom et al, 1988[58]	Not stated	Not stated	No baseline data were given for the groups initially assigned LT4 and placebo	Yes	Yes	Yes
Michalopoulou et al, 1998[75]	Yes, method not stated	Not stated	Inadequately described. LDL was higher in 50 mg group (6.8 vs 6.2)	Yes	Not stated	Not stated
Pollock et al, 2001[77]	Yes, by coin toss in blocks of 4	No	No baseline data were given for the groups initially assigned LT4 and placebo	Yes	Not stated	Yes

Table 2. Quality of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Patient Unaware of Treatment?	Intention-to-Treat Analysis?†	Maintenance of Comparable Groups?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score (Good/ Fair/ Poor)
Yes, not verified	No	Probably, 3 dropouts in each group	Partially	Overall 6 out of 40 dropped out	Yes, except it did not address dropouts	Fair
Yes, not verified	No	Unknown	Yes	Yes, especially for lipid comparison	Yes, except it did not address dropouts	Poor
Probably aware, verified	No	Yes	No	No	No, no baseline comparisons or results provided about the first assignment	Poor
Not stated	Probably	Yes	No	No	No, analyzed as before/after	Poor
Yes, verified	No	Probably, but all 3 dropouts were from the LT4 group	No	No	Yes	Fair

Table 3. Description and Results of Randomized Trials of Thyroxine Replacement Therapy*

Study, Year	Patients	Setting	Age, Gender	Eligibility Criteria	Other Population Characteristics	Exclusion Criteria	Funding Sources and Role of Funder	Interventions (Dose, Duration)	Control	Baseline TSH Level	Number Screened/ Eligible/ Enrolled
Known history of thyroid disease											
Cooper et al, 1984[59]	Previously treated Graves' disease, stage C subclinical hypothyroidism	Thyroid specialty clinic, Boston, MA	32 women and 1 man; mean age, 55 yrs	TSH > 3.5 mU/L on 2 occasions	History of Graves' disease	None stated	U.S. Public Health Service (armour supplied LT4)	LT4, 50 micrograms then titrated up	Placebo	11 (mean) 3.6-55.3 (range) mean TSH in control group increased to ~15 by the end of the study	656/91/41
Meier et al, 2001[76]	Autoimmune thyroiditis (n = 33), previously treated Graves' disease (n = 22), previously treated goiter (n = 7)	Thyroid specialty clinic, Switzerland	63 women; mean age, 58.5 ± 1.3 yrs	Women 18-75 yrs; TSH > 6.0 mU/L on 2 occasions; exaggerated TSH response to TRH; good general health	History of autoimmune thyroiditis (n = 33), Graves' disease (n = 22), goiter (n = 7). Only 4 had Idiopathic subclinical hypothyroidism	Coronary heart disease lipid-lowering drugs, history of poor compliance (estrogen therapy allowed)	Swiss Research Foundation, Henning Berlin, Sandoz, Roche	LT4 titrated over 6 months (mean final dose, 85.5 ± 4.3), with similar visits and changes in control group. Total follow-up, 50 wks	Placebo	12.8 (mean) 5-50 (range)	NR/NR/66
Caraccio et al, 2002[78]	Hashimoto's thyroiditis (n = 48) or Graves' disease (n = 1)	Medical school internal medicine clinic, Italy	42 premeno-pausal women, 7 men	TSH > 3.6 mU/L for > 6 mos, + atP and anti-Tg, good general health	Subjects had higher TC, LDL, and ApoB levels than healthy controls	Diabetes, renal or liver disease, TC > 7.8 mmol/L	Grant from university	LT4, 25 then titrated up	Placebo	5.43 (mean) 3.65-15 (range)	NR/NR/49
No known history or not stated											
Jaeschke et al, 1996[74]	Diagnosis of subclinical hypothyroidism	Unclear setting, Ontario, Canada	28 women and 9 men over age 55; mean age, 68 yrs	TSH > 6 mU/L on 2 occasions	None stated	Medications that interfere with thyroid function test results; serious medical conditions	Ontario Ministry of Health, Boots Pharma-ceuticals	LT4 25 then titrated up (mean final dose, 68 ± 21)	Placebo	9.4 (mean) 6-32 (range)	NR/NR/37

Anti-TG, anti-thyroglobulin; ApoB, Apolipoprotein B; atP, antithyroid-peroxidase; ECG, electrocardiogram; GHQ, General Health Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Questionnaire; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; NNT, number needed to treat for benefit; SF-36, Medical Outcomes Study Short Form; SIP, Sickness Impact Profile; TC, total cholesterol; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

*Values presented with a plus/minus sign are means ± SD .

† Symptomatic group only.

Table 3. Description and Results of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Patients Withdrawn/ Analyzed	Outcomes Assessed/ When Assessed	How Were Symptoms Assessed (eg, Scales Used)?	LT4 vs Placebo Group Results	Before/After Results	Adverse Effects Assessed?	Adverse Effects	Quality Rating (Good/ Fair/Poor)	Relevance to Screening	Comments and Questions
8/33	Symptoms, lipid profile at 1 yr	Symptom change scores (Cooper Questionnaire)	Improved symptoms (–1.2 vs 2.1) in LT4 group. 47% improved in LT4 group vs 19% in placebo group (NNT = 3.6). No difference in lipid profiles	Placebo group's TSH and symptoms rose during the year, suggesting the patients had rapidly advancing subclinical hypothyroidism	Only through symptom scores	4 patients in LT4 group felt worse, vs 6 in placebo group	Good	Low	Well-conducted trial, but subjects had known thyroid disease and the study is not relevant to screening. What proportion of all patients who had elevated TSH and normal FT4 were eligible for the study?
3/63	Symptoms, lipid profile at 1 yr	Thyroid symptom questionnaire	Post-treatment LDLc was the same in both groups (3.7 ± 0.2, $P = 0.11$), and symptoms scores were not significantly different ($P > 0.2$)	LDLc reduced from 4.0 to 3.7 in the LT4 group ($P = 0.004$) and there were borderline improvements in symptom scores ($P = 0.02$). Placebo group TSH was stable	No	Not assessed	Poor	Low	The discrepancy between before/after results and LT4 vs placebo results suggests that randomization was probably flawed. Were patients informed of their LDLc levels?
0/49	Lipid profile at 6 mos for placebo group vs about 11 mos for LT4 group	Not assessed	No significant differences between LT4 and placebo groups in any lipid variable	LT4 group: TC reduced from 5.5 to 5.0; LDLc from 3.6 to 3.1	No	Not assessed	Poor	Fair	Analyzed as an open, uncontrolled study. Was completion of the study a criterion for inclusion in the analysis? How many patients were screened, eligible, enrolled, and randomized? Were patients and providers aware of treatment? How was randomization done? Were baseline differences statistically significant? What proportion of subjects in each group had a TC > 6.2?
6/31	Quality of life, symptoms, lipid profile at 6 mos	Chronic Thyroid Questionnaire, Cooper Questionnaire, SIP, cognitive tests	No improvement in symptoms or lipids; improved memory in LT4 group (mean difference of 0.58 on z-score scale, described as "small and of questionable clinical importance")	Placebo group's TSH rose from 9.42 to 10.32 over 6 mos	Only through dropouts	1 case of atrial fibrillation and 1 case of angina in LT4 group	Fair	Fair	Description of recruitment was inadequate. Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?

continue

Table 3. Description and Results of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Study, Year	Patients	Setting	Age, Gender	Eligibility Criteria	Other Population Characteristics	Exclusion Criteria	Funding Sources and Role of Funder	Interventions (Dose, Duration)	Control	Baseline TSH Level	Number Screened/ Eligible/ Enrolled
No known history or not stated, continued											
Kong et al, 2002[79]	Women with a diagnosis of subclinical hypothyroidism	Referrals from GPs for thyroid function tests, London, UK	45 women; mean age, ~49 yrs	Women over 18 yrs; TSH level, 5 < 10 mU/L	Most patients were referred because of symptoms	History of thyroid disease, psychiatric disorder, anticipated pregnancy	Medical Research Council	LT4, 50 then titrated up to 100 if TSH > 6 mU/L	Placebo	~7.7 (mean)	NR/52/45
Nystrom et al, 1988[58]	Women identified by screening	Population-based screening study, Gothenburg, Sweden	20 women; aged 51-73	Women over 18 yrs; TSH level, 4 < 15 mU/L, exaggerated TSH response to TRH	Symptoms did not differ between subjects and healthy controls	History of or signs of thyroid disease, history of cardiovascular disease	Non-industry grants (Nyegaard supplied LT4)	LT4, 50 for 2 wks, then 100 mg for 2 wks, then 150 daily	Placebo	~7.7 (mean) 2.9-16.3 (range)	1,192/22/20
Biochemically euthyroid patients											
Michalopoulou et al, 1998[75]	Patients referred for lipid assessment	Preventive medicine (lipid) hospital-based clinic, Greece	Not stated	TC > 7.5 mmol/L and TSH 0.4-4.0 mU/L	None stated	Conditions and medications that affect lipid profiles	Not stated	LT4, 50	LT4 25 mg	Stratified: 1.0 (mean) or ~2.6 (mean)	NR/NR/110
Pollock et al, 2001[77]	Symptomatic patients with normal serum free thyroxine and TSH levels	Referrals from GPs, hospital clinic, and response to newspaper ad, Glasgow, UK	25 symptomatic and 19 asymptomatic subjects, sex and age not given	Recent thyroid function tests within the reference range plus (a) at least 3 symptoms of hypothyroidism (tiredness, lethargy, weight gain, or 3 others) or (b) no symptoms	Symptomatic patients weighed more and had worse memory and psychological function than healthy controls	Current medical disorders	Association of Clinical Biochemists	LT4, 100	Placebo	1.9 (mean)	NR/NR/25†

Table 3. Description and Results of Randomized Trials of Thyroxine Replacement Therapy* (cont)

Patients Withdrawn/ Analyzed	Outcomes Assessed/ When Assessed	How Were Symptoms Assessed (eg, Scales Used)?	LT4 vs Placebo Group Results	Before/After Results	Adverse Effects Assessed?	Adverse Effects	Quality Rating (Good/ Fair/Poor)	Relevance to Screening	Comments and Questions
10/34 (for quality of life) 18/27 for lipids	Quality of life, symptoms, lipid profile at 6 mos	Thyroid symptom questionnaire, GHQ-30, HADS	No improvement in symptoms or lipids	Placebo group's TSH dropped from 7.3–5.6 over 6 mos	Only through symptom scores	Anxiety scores were higher in the LT4 group	Poor	Fair	High dropout rate, but patients were relevant to primary care: symptomatic with borderline TSH values
3/17	Quality of life, psychometric symptoms, tests, vital signs, ECG, lipid profile at 6 mos	Thyroid symptom questionnaire, reaction time, Bingley's memory test	No difference in lipids	Symptom scores improved by the equivalent of 1 symptom per subject ($P < 0.001$), and 4 patients felt better with LT4 than with placebo	Only through dropouts	In LT4 group, 1 subject dropped out because of nervousness, 1 because of a sense of tachycardia	Poor	Good	The flaws in analyzing data make the study uninterpretable, but the patients are most like those encountered in screening
0/110	Lipid profile	Not assessed	LDL reduced from 6.2 to 6.1 in 25-mg group and from 6.8 to 5.9 in 50-mg group	LDLc reduction was significant in 50-mg group	No	Not assessed	Poor	Fair	Description of recruitment was inadequate. Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?
3/22†	Symptoms, vital signs, biochemical tests after 14 wks	SF-36 plus validated cognitive/ memory testing	Among symptomatic patients (n = 22), there were no important differences between LT4 and placebo groups in any SF-36, memory, or cognitive measures	Placebo significantly improved SF-36 general health and physical health scores	Not assessed, except for SF-36 scores	In asymptomatic patients, LT4 significantly reduced SF-36 vitality scores	Fair	N/A	Too small; authors note that it is only a "pilot study." Placebo effect, adverse effect of LT4 in healthy subjects, and baseline difference in cholesterol levels (6.3 vs 5.2) between symptomatic and asymptomatic subjects deserve more study

relief of 1 symptom per patient. As judged by subjective improvement and cognitive measures, 4 (24%) of the 19 patients who received levothyroxine improved, while 2 (12%) felt worse with treatment.

The last 2 studies listed in Table 3 (Michalopoulou et al and Pollock et al) concern patients who have TSH levels in the normal range. In the study by Michalopoulou and colleagues, 50 micrograms of levothyroxine therapy reduced LDL cholesterol levels from 6.8 to 5.9 mmol/L (262–228 mg/dL) in patients with elevated total cholesterol levels (> 7.5 mmol/L [> 290 mg/dL]) and normal TSH levels.[75] In the study by Pollock and colleagues, levothyroxine was ineffective in patients who had symptoms of hypothyroidism but normal TSH and FT4 levels.[77] The latter study, designed as a crossover study, found that levothyroxine significantly reduced the Short Form-36 (SF-36) vitality score in healthy patients and also documented a clinically important and statistically significant effect of placebo.

Many observational studies have examined the effects of treatment in patients with subclinical hypothyroidism. A recent meta-analysis of both observational and randomized studies found that, in previously untreated patients, total cholesterol was reduced by 0.14 mmol/L (5.6 mg/dL).[80] Another review concluded that levothyroxine treatment might reduce serum cholesterol by 8% in selected patients who have both a serum TSH of 10 mU/L or greater and an elevated total cholesterol of 6.2 mmol/L or greater (240 mg/dL).[7] About 7% of individuals with subclinical hypothyroidism meet these criteria.

The studies on which these analyses are based have important limitations.[21] Many were before/after studies in which reductions in serum lipids could have been due to regression toward the mean. Samples were small, selection of patients was poorly described, clinicians and patients were aware of the treatment and of the need to lower lipid levels, and outcome assessment may have been biased. That is, the problem is not that these studies are observational, but that many of them are poor quality.

The hazards of relying on observational studies of the effect of drug therapy is illustrated by a large (n = 139) open study of levothyroxine to treat symptoms of hypothyroidism in patients who had normal thyroid function tests. This study found that the mean number of signs and symptoms of hypothyroidism decreased from 13 to 3 following 6 months or more of treatment; 76% of patients had improvement or resolution of over 12 findings.[81] Whether or not these effects are real (a subsequent randomized trial had negative results [Table 3] but was too small to exclude a clinically significant effect), they illustrate that only well-controlled trials can determine the effects of thyroxine therapy in patients with subclinical hypothyroidism.

Adverse Effects of Levothyroxine Treatment

Adverse effects of replacement doses of levothyroxine include nervousness, palpitations, atrial fibrillation, and exacerbation of angina pectoris. Adverse effects were not assessed carefully in the randomized trials listed in Table 3, although some reported them incidentally. In 1 of the trials, 2 of 20 (10%) patients taking levothyroxine quit the protocol because of nervousness and a sense of palpitations.[58] In another, 2 of the 18 (11%) patients assigned to levothyroxine withdrew because of complications, 1 because of an increase in angina, and the second because of new-onset atrial fibrillation.[74] In a third, anxiety scores were higher in the levothyroxine group.[79]

A systematic review of observational studies published from 1966 to 1997 found that replacement doses of levothyroxine (restoring TSH to normal levels) have not been associated with osteoporosis or with any other serious long-term adverse effects.[82] A short-term randomized trial of levothyroxine for subclinical hypothyroidism confirms this view.[83]

The harms of overtreatment with levothyroxine, indicated by an undetectable TSH, are uncertain. About one-fourth of patients receiving levothyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause the TSH to be undetectable.[2,31] Data from the Framingham cohort suggest that 1 excess case of atrial fibrillation might occur for every 114 patients treated with doses of levothyroxine sufficient to suppress the

TSH.[31] As mentioned above, some information suggests that, in patients taking levothyroxine, an undetectable TSH is associated with an increased risk for osteoporosis[36,37] and fractures,[39] but other studies have found no difference in bone density[38] or hip fracture rates.[84] Suppressive doses of levothyroxine can temporarily increase heart rate and left ventricular mass,[85] but there is no evidence that this causes long-term complications.

Another potential harm is treatment of healthy patients based on false-positive test results. In screening programs and in the primary care clinic, many patients found to have an abnormal TSH revert to normal over time. In 1 randomized trial, for example, mildly elevated TSH level reverted to normal in 8 of 19 patients given placebo.[74] In older patients, only 59% (range, 14%–87%) of patients with an undetectable TSH on initial screening had an undetectable TSH level when the TSH was repeated.[45,86] In the Framingham cohort, screening identified 41 people with an undetectable serum TSH (≤ 0.1 mU/L) and a normal serum FT4 level (< 129 nmol/L).[87] After 4 years of follow-up, when 33 of these people were retested, 29 had higher serum TSH levels (> 0.1 mU/L).

Discussion

The ability of screening programs to detect subclinical thyroid dysfunction has been demonstrated in good-quality cohort studies. There is also good evidence that, in the general population, an undetectable TSH level is a risk factor for the later development of atrial fibrillation, but there have not been any studies of early treatment to prevent this complication.

An elevated TSH level—even a mildly elevated one—is a risk factor for the later development of overt hypothyroidism. Early treatment would prevent this progression, but the balance of benefits and harms is unclear. The key uncertainties are:

1. Without screening or prophylaxis, how long would overt hypothyroidism be undetected?
2. How much morbidity would undiagnosed overt hypothyroidism cause while undetected?
3. What are the harms of treatment in those who do not progress?

Data showing that progression to overt disease is associated with significant burden of illness would strengthen the case for preemptive treatment.

Other potential harms of subclinical thyroid dysfunction are not well established. Data regarding osteoporosis, fracture, hyperlipidemia, and atherosclerotic disease are inconsistent, and most data come from patients who take levothyroxine or have clinically evident thyroid disease.

Not surprisingly, experts give conflicting advice about the treatment of subclinical hypothyroidism.[6,21,26,28] There is good evidence that levothyroxine reduces symptoms (but not lipid levels) in patients who have a markedly elevated TSH level (> 10 mU/L) following surgery or radioiodine treatment. However, in apparently healthy patients who have mildly elevated TSH levels (4–7 mU/L), the largest group identified by screening, the frequency of hyperlipidemia and symptoms may be no different from that of euthyroid individuals. The main gap in the evidence is the lack of convincing data from controlled trials that early treatment reduces lipid levels, symptoms, or the risk for cardiovascular disease for patients with mild thyroid dysfunction detected by screening.

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