CLINICAL PRACTICE

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Subclinical Hypothyroidism

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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A 71-year-old woman reports fatigue and mild depression. She has hypertension and had a myocardial infarction 4 years ago. She has a family history of autoimmune thyroid disease. The physical examination is unremarkable. No thyroid enlargement is present. Laboratory results include normal levels of hemoglobin, creatinine, and calcium and a normal erythrocyte sedimentation rate. The thyrotropin level is 6.9 mIU per liter (reference range, 0.4 to 4.3), whereas the free thyroxine (T_4) level is normal (19 pmol per liter; reference range, 11 to 25). How should she be further evaluated and her symptoms managed?

An audio version of this article is available at NEJM.org

THE CLINICAL PROBLEM

Subclinical hypothyroidism is biochemically defined as an elevated serum thyrotropin level in combination with a serum free T_4 level that is within the population reference range. The incidence of subclinical hypothyroidism varies among populations and ranges from 3 to 15%, with a higher incidence associated with increasing age, female sex, and a suboptimal iodine status.[1,2] The relationship between serum thyrotropin and free T_4 is such that a small decrease in free T_4 can result in a relatively large increase in serum thyrotropin, which can subsequently lead to a thyrotropin level that is above the reference range while the free T_4 level is still within the reference range. In cases of progression to overt hypothyroidism, the thyrotropin level typically continues to increase and the free T_4 level falls below the reference range. In this respect, subclinical hypothyroidism can be seen as a mild form of thyroid failure, one that is caused by autoimmune thyroid disease in the majority of cases. A thyrotropin cutoff level of 10 mIU per liter is commonly used to distinguish between mild and more severe subclinical hypothyroidism.[3,4] Approximately 75% of patients with subclinical hypothyroidism have a thyrotropin level of less than 10 mIU per liter.[1]

Serum thyrotropin and free T_4 show substantial variability among healthy persons, whereas the range of variability within an individual healthy person tends to be relatively narrow.[5] This finding suggests a unique set point of the hypothalamic–pituitary–thyroid axis for each person and probably explains why a thyrotropin level of 10 mIU per liter can be accompanied by a normal free T_4 level in one person but by a decreased free T_4 level in another person (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The heritability of the hypothalamic–pituitary–thyroid axis set point has been estimated to be 65%.[6] Older persons, women, and persons with antibodies to thyroid peroxidase have a stronger log-linear relationship between thyrotropin and free T_4 levels

KEY CLINICAL POINTS

SUBCLINICAL HYPOTHYROIDISM

- Subclinical hypothyroidism is defined as an elevated thyrotropin level with a normal free thyroxine (T_4) level. To confirm the diagnosis, a transient increase in thyrotropin should be ruled out by a repeat measurement of thyrotropin and free T_4 after 2 to 3 months.
- In up to 46% of patients with subclinical hypothyroidism who have a thyrotropin level of less than 7 mIU per liter, the thyrotropin level normalizes within 2 years.
- Subclinical hypothyroidism, particularly when the thyrotropin level is more than 10 mIU per liter, is associated with an increased risk of hypothyroid symptoms and cardiovascular events.
- There are few data from randomized, controlled trials of levothyroxine therapy for subclinical hypothyroidism to inform the effects of treatment on cardiovascular outcomes.
- Treatment is generally recommended for persons 70 years of age or younger who have thyrotropin levels of at least 10 mIU per liter, although long-term benefits have not been shown.
- Among patients who have thyrotropin levels of less than 10 mIU per liter or who are older than 70 years of age, treatment decisions are based on individual patient factors (e.g., symptoms of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or cardiac risk factors).

than do younger persons, men, and persons with lower levels of antibodies to thyroid peroxidase.[7]

The risk of progression of subclinical hypothyroidism to overt hypothyroidism is approximately 2 to 6% per year; the risk is higher among women than among men and among persons with higher thyrotropin levels, those with higher levels of antibodies to thyroid peroxidase, and those with low-normal free T_4 levels.[2,8,9] Among persons who have a single elevated thyrotropin measurement of less than 7 mIU per liter, the thyrotropin level normalizes in up to 46% within 2 years.[8-10]

SYMPTOMS

Although many patients with subclinical hypothyroidism are asymptomatic, such patients tend to report symptoms of overt hypothyroidism more often than age-matched controls; these symptoms are usually milder than those in patients with overt hypothyroidism and tend to increase in both number and severity with higher thyrotropin levels. Some studies have shown higher rates of depressive symptoms and reduced quality of life, cognitive function, and memory among persons with subclinical hypothyroidism than among persons with normal thyroid function.[1,11-14] Increased rates of fatigue, muscle weakness, weight gain, cold intolerance, and constipation have also been reported variably in association with subclinical hypothyroidism.[1,15] Elderly persons seem to have fewer symptoms than younger persons.[16-18] One study involving patients older than 70 years of age even suggested that those who had subclinical hypothyroidism had a faster walking speed and better maintenance of physical function than did the euthyroid controls,[17] but this finding was not confirmed in a more recent study.[19] Differences in study results may be related to differences in the way that patients were identified for inclusion in the studies (e.g., by biochemical screening of a population vs. selection of patients with preexisting symptoms) as well as by differences in the age of the patients, the severity of the subclinical hypothyroidism, and the instruments that were used to assess symptoms.

LONG-TERM CLINICAL CONSEQUENCES

Concern exists regarding the long-term adverse effects of subclinical hypothyroidism, particularly with respect to the risk of cardiovascular disease. In a meta-analysis of individual participant data from 11 prospective cohorts totaling more than 55,000 participants, the risk of fatal and nonfatal events of coronary heart disease increased with higher baseline thyrotropin levels,[4] with hazard ratios for events of coronary heart disease of 1.00 (95% confidence interval [CI], 0.86 to 1.18) among patients with a thyrotropin level between 4.5 and 6.9 mIU per liter, 1.17 (95% CI, 0.96 to 1.43) among patients with a thyrotropin level between 7.0 and 9.9 mIU per liter, and 1.89 (95% CI, 1.28 to 2.80) among patients with a thyrotropin level between 10.0 and 19.9 mIU per liter ($P<0.001$ for trend).[4] Subclinical hypothyroidism, particularly among persons with thyrotropin levels of more than 7 mIU per liter, has also been associated with increased risks of congestive heart failure[20] and fatal stroke[21]

Table 1. Causes of Elevated Thyrotropin Levels, Unrelated to Chronic Mild Thyroid Failure.*

Causes of a transient increase in the thyrotropin level combined with a normal free T_4 level
Recovery from nonthyroidal illness
Recovery phase of various types of thyroiditis
Medication, such as amiodarone and lithium
Lack of adherence to treatment with levothyroxine or problems with resorption of levothyroxine in persons with hypothyroidism who are already receiving levothyroxine
Causes of a persistent increase in the thyrotropin level combined with a normal free T_4 level
Physiologic adaptation to aging (a widening of the reference range in elderly persons who have lived in regions with historical iodine sufficiency has been described)
Assay interference (e.g., caused by heterophilic antibodies)
Obesity
Adrenal insufficiency (very rare)
Thyrotropin-releasing hormone resistance or thyrotropin resistance (extremely rare)

* T_4 denotes thyroxine.

in similar meta-analyses based on individual participant data. Subclinical hypothyroidism is associated with increased total cholesterol levels and low-density lipoprotein cholesterol levels and with subclinical measures of cardiovascular disease.[15] However, it is unclear whether the associations with cardiovascular disease are mediated through lipid metabolism or through other mechanisms. Other meta-analyses did not show significant associations between subclinical hypothyroidism and cognitive decline[22] or between subclinical hypothyroidism and the risk of fractures.[23]

Higher serum thyrotropin levels are associated with increased body-mass index and increased waist circumference.[24] However, substantial weight loss typically results in a decrease in the thyrotropin level, which suggests that subclinical hypothyroidism is an unlikely cause of obesity.

The risks of female infertility, spontaneous abortion, and other complications associated with pregnancy, such as gestational hypertension and preeclampsia, are increased in women with subclinical hypothyroidism and thyroid autoimmunity. During pregnancy, pronounced changes occur in thyroid homeostasis, including an increased demand for thyroid hormone, which is mediated by high levels of the pregnancy hormone human chorionic gonadotropin. These pregnancy-specific changes and the increased demand for thyroid hormone may worsen preexisting mild thyroid dysfunction. Cutoff values for the levels of thyrotropin and free T_4 for the diagnosis and treatment of subclinical hypothyroidism in pregnant women differ from those in nonpregnant women. The recommendations in this article therefore do not apply to women who are currently pregnant or to young women who may potentially become pregnant; the management of subclinical hypothyroidism in women who are pregnant or who are infertile is reviewed elsewhere.[25]

STRATEGIES AND EVIDENCE

EVALUATION

Subclinical hypothyroidism is purely a biochemical diagnosis that is defined as an elevated serum thyrotropin level and a normal free T_4 level. Because multiple factors, such as subacute thyroiditis, recovery from nonthyroidal illness, and medication (e.g., amiodarone and lithium), can cause transient abnormalities in the serum thyrotropin level, a transient increase in the thyrotropin level should be ruled out before a diagnosis of subclinical hypothyroidism is made (Table 1).[26,27] At least one repeat measurement of thyrotropin and free T_4 is indicated, together with a test for antibodies to thyroid peroxidase, after a 2-to-3-month interval.[26] The presence of antibodies to thyroid peroxidase supports an autoimmune cause of subclinical hypothyroidism and is associated with a risk of progression to overt hypothyroidism that is approximately twice the risk associated with a negative test for antibodies to thyroid peroxidase (cumulative incidence at 9 years,

59% vs. 23%).[2,9] Serum levels of antibodies to thyroid peroxidase generally decrease over time; repeated tests for antibodies to thyroid peroxidase do not contribute to the management of subclinical hypothyroidism and are not recommended.[28] Although a hypoechoic or inhomogeneous pattern on ultrasound examination of the thyroid may provide additional evidence of thyroid autoimmunity, ultrasonography is not recommended routinely for the evaluation of subclinical hypothyroidism.

RATIONALE FOR CONSIDERATION OF TREATMENT

Symptoms

In a large, randomized, controlled trial, the results of which are reported in this issue of the *Journal*,[29] Stott et al. investigated the effects of treatment with levothyroxine on subclinical hypothyroidism in participants older than 65 years of age; the trial showed no benefit of treatment with levothyroxine on thyroid-related quality of life. However, participants had very mild elevations in thyrotropin levels (mean level, 6.4 mIU per liter) and lacked clear symptoms at the start of treatment, with symptom scores similar to those of presumed euthyroid controls whose scores were used to validate the thyroid-specific quality-of-life questionnaire used in this trial.[30] A smaller, randomized, placebo-controlled trial involving 66 women (mean age, 57 years) with more pronounced subclinical hypothyroidism (a mean thyrotropin level of 11.7 mIU per liter and symptom scores that indicated borderline hypothyroidism) likewise did not show a greater reduction in symptoms overall with levothyroxine treatment than with placebo.[31] However, significant improvement with levothyroxine treatment was reported specifically in the subgroup of patients who had a pretreatment thyrotropin level of more than 12 mIU per liter, although it was not clear whether this subgroup analysis was prespecified.[31] A randomized, controlled trial with a crossover design, in which 100 participants (mean age, 54 years) received levothyroxine or placebo for subclinical hypothyroidism (mean thyrotropin level, 6.6 mIU per liter), suggested a benefit of treatment with levothyroxine for some symptoms, but a reduction in tiredness was the only symptom for which a significant difference between the two groups was seen after correction for multiple testing.[12] Some[32,33] but not all[11,34,35] trials that have investigated memory function have shown improvement in memory function after treatment with levothyroxine for subclinical hypothyroidism. Differences in study results may be explained by differences in thyrotropin levels at baseline and by differences in the extent of symptoms at baseline (with generally less benefit of treatment seen among persons with lower thyrotropin levels and milder symptoms), as well as by differences in the sample size, the age of the participants, and the neurocognitive tests that were used.

In general, these data suggest that levothyroxine treatment is unlikely to reduce symptoms in persons with modest elevations in thyrotropin levels and with minimal symptoms at baseline, but such treatment may have benefit in symptomatic patients, particularly in those who have a serum thyrotropin level above 10 to 12 mIU per liter.

Long-Term Clinical Consequences

Although observational studies show a significant association between subclinical hypothyroidism and cardiovascular outcomes, data are lacking from randomized, controlled trials to inform the effects of treatment of subclinical hypothyroidism on these long-term clinical outcomes (Table 2). A 2007 Cochrane systematic review of 12 studies concluded that treatment with levothyroxine had beneficial effects on surrogate markers for cardiovascular risk (i.e., lower serum cholesterol levels, decreased carotid-wall intima–media thickness, and increased cardiac function).[36] However, an improvement in these surrogate markers of cardiac and vascular function after levothyroxine therapy[12,37,38] does not imply similar beneficial effects on the risk of cardiovascular events and death; moreover, evidence suggests that the link between subclinical hypothyroidism and cardiovascular diseases may be independent of traditional cardiovascular risk factors.[4,20,21] It is therefore unclear whether ameliorating cardiovascular risk factors with the use of levothyroxine treatment will decrease the risk of cardiovascular events.

Observational studies involving patients with subclinical hypothyroidism have shown a significantly lower risk of heart failure events,[39] death from any cause,[40] and events associated with ischemic heart disease[41] among patients who received levothyroxine than among patients who did not receive levothyroxine. A prespecified

Table 2. Associations Between Subclinical Hypothyroidism and Clinical Outcome, and Consequences of Treatment.*

Outcome of Subclinical Hypothyroidism	Strength of the Association		Benefits of Treatment
	Thyrotropin 4.5–9.9 mIU/liter	Thyrotropin ≥10 mIU/liter	
Progression to overt hypothyroidism	Strong	Stronger	Early treatment before development of overt hypothyroidism with more severe symptoms
Symptoms of hypothyroidism (e.g., tiredness, decreased cognition)	Strong	Stronger	Inconsistent, with large trial involving persons with mildly elevated thyrotropin levels (<10 mIU/liter) and very few symptoms showing no effects, and small trials involving persons with thyrotropin levels >10 mIU/liter showing benefits
Surrogate markers of cardiovascular risk (e.g., elevation in total cholesterol and LDL cholesterol levels, increased carotid-wall intima–media thickness, and decreased cardiac function)	Strong	Stronger	Moderate for reduction in total cholesterol and LDL cholesterol levels but unclear whether this is accompanied by a decreased risk of cardiovascular events
Risk of coronary heart disease	Weak	Stronger	Insufficient data to inform benefits
Risk of congestive heart failure	Weak	Stronger	Insufficient data to inform benefits
Risk of stroke	Weak	Weak	Insufficient data to inform benefits
Cognitive decline	Weak	Weak	Insufficient data to inform benefits

* This table is adapted and updated from Surks et al.[3] LDL denotes low-density lipoprotein.

subgroup analysis in the study that assessed events associated with ischemic heart disease showed a lower risk of such events among patients who were 70 years of age or younger and received levothyroxine than among patients in the same age group who did not receive levothyroxine; in contrast, among patients older than 70 years of age, the risk of such events did not differ according to whether the patients received treatment with levothyroxine.[41] However, observational studies are subject to selection bias and confounding and must be interpreted with caution.

Factors to Consider in the Initiation of Treatment

Treatment is generally recommended for persons 70 years of age or younger who have thyrotropin levels of 10 mIU per liter or higher, although long-term benefits have not been shown and the risks of such treatment are unknown (Fig. 1). For persons older than 70 years of age or for persons who have a thyrotropin level of less than 10 mIU per liter, treatment decisions should be guided by individual patient factors, including the extent of thyrotropin elevation and whether the patient has symptoms of hypothyroidism, antibodies to thyroid peroxidase, goiter, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors.[26,27,41] Patients who test positive for antibodies to thyroid peroxidase are twice as likely to have progression to overt hypothyroidism as patients without antibodies.[2,9,26,27] If treatment is started because of symptoms of hypothyroidism, the treatment should be discontinued if no alleviation of the symptoms is observed after 3 to 6 months or if adverse effects occur. If no treatment is started, the thyrotropin level should be monitored every 6 to 12 months, and treatment should be initiated if the level increases to 10 mIU per liter or more in persons younger than 70 years of age or if other indications for treatment become apparent.

METHOD OF TREATMENT

The goal of treatment for subclinical hypothyroidism should be to restore the thyrotropin level to within the reference range.[26,27] Oral levothyroxine therapy taken once daily is the treatment of choice. No evidence exists to support the use of liothyronine, either alone or in combination with levothyroxine, in patients with subclinical hypothyroidism.[26,27] Because of differences in the biologic availability of various levothyroxine products, switches between different levothyroxine products should be avoided in patients whose condition is stable.[26,42] In cases in which such a switch is made, the thyrotropin level should be rechecked after 6 to 8 weeks. The dose of levothyroxine that is needed to normalize the thyrotropin level is usually lower for patients with subclinical hypothyroidism than for those

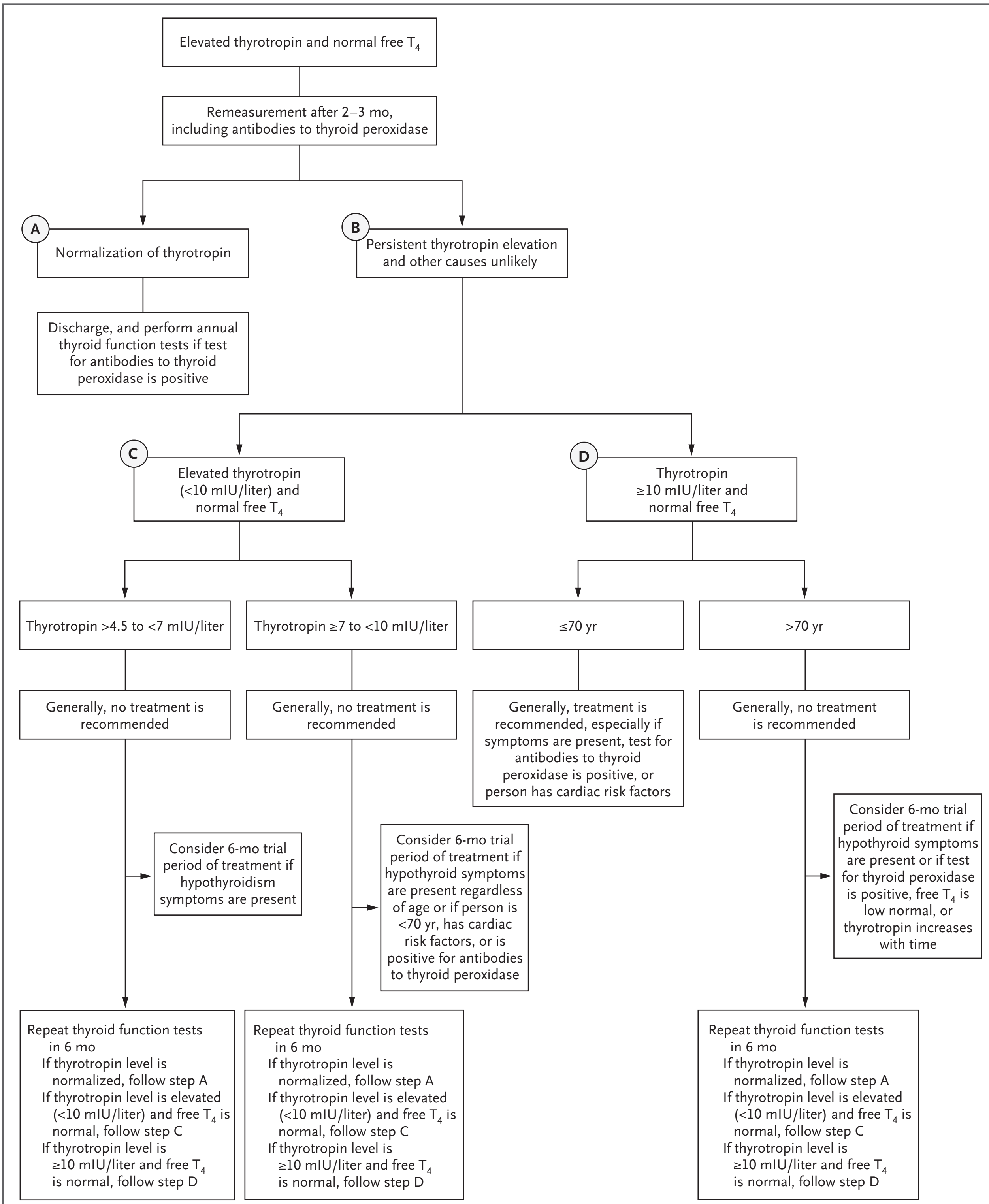

Figure 1. Treatment Algorithm for Subclinical Hypothyroidism.

This algorithm does not apply to pregnant women or to young women who may potentially seek pregnancy and is based on current U.S. and European guidelines.[26,27] However, the U.S. guidelines do not make an explicit distinction according to age, and neither guideline specifies differential management according to the degree of thyrotropin elevation below 10 mIU per liter.

with overt hypothyroidism. Depending on the degree of elevation of the thyrotropin level, an initial dose of 25 to 75 μg of levothyroxine per day can be considered[27]; lower starting doses (e.g., 25 μg per day) are recommended in patients with stable angina pectoris or in patients who have a clearly increased risk of cardiovascular disease. After the start of therapy or an increase in the dose, the serum thyrotropin level should be checked after 4 to 8 weeks. The clinical response and the subsequent thyrotropin levels then guide further dose adjustments.

In practice, many patients with hypothyroidism who receive levothyroxine continue to have thyrotropin levels that are outside the reference range.[43,44] A recent study from the United Kingdom showed that 5 years after the initiation of levothyroxine therapy, more than 10% of patients still had thyrotropin levels above 10 mIU per liter, and almost 6% had suppressed thyrotropin levels of less than 0.1 mIU per liter.[43] A suppressed thyrotropin level is associated with increased risks of atrial fibrillation, osteoporosis, and fractures, especially in persons older than 60 years of age.[14,23]

AREAS OF UNCERTAINTY

Adequately powered randomized, controlled trials that assess long-term outcomes such as cardiovascular events are needed. Such trials can provide information about the benefits and risks of levothyroxine therapy for subclinical hypothyroidism.

The applied reference ranges of thyroid function tests, particularly the upper limit of the reference range for thyrotropin, are a subject of debate.[45,46] Some,[47,48] but not all,[7,49] studies suggest that the values for serum thyrotropin level representing the 97.5th percentile of the population tend to increase with increasing age, particularly in persons older than 70 years of age.[7,47-49] This increase in thyrotropin seems to be independent of the presence of circulating thyroid antibodies. Differences among the studies might be explained in part by differences in (historical) intake of iodine.[49,50] On the basis of these findings, it has been suggested that a mild elevation in the thyrotropin level of up to 7.0 mIU per liter in persons older than 70 years of age who have lived in a region in which the population has historically had sufficient iodine intake might be considered to be a physiologic adaptation to aging.[47]

Several observations support the hypothesis of a higher upper limit of the normal range for thyrotropin levels in the elderly. As described above, elderly persons with subclinical hypothyroidism appear to report fewer symptoms than are reported by younger persons.[16-18] In addition, in an analysis of data from persons with subclinical hypothyroidism in a general-practitioner database, persons 70 years of age or younger who received treatment with levothyroxine had a lower risk of ischemic heart disease events than those who did not receive treatment, whereas among patients older than 70 years of age, no beneficial effect of levothyroxine treatment was observed.[41] An observational study involving 599 persons who were older than 85 years of age suggested a survival benefit associated with subclinical hypothyroidism,[16] but this finding was not replicated in a large meta-analysis involving more than 2500 participants older than 80 years of age.[4]

On the basis of this evidence, most experts and societies generally advise higher treatment cutoffs for thyrotropin in the elderly.[26,27,48] However, to date, reference ranges for thyroid function in adults are not age-adjusted,[42,48] and information is lacking regarding appropriate cutoffs for different age categories.

GUIDELINES

Associations from the United States and Europe recommend treatment[26] or consideration of treatment[27] of subclinical hypothyroidism for patients with thyrotropin levels of 10 mIU per liter or higher, recommendations that are similar to those shown in Figure 1. Table 3 summarizes key recommendations according to thyrotropin level; the guidelines of the European Thyroid Association (ETA) tailor these recommendations according to patient age. The recommendations in the current article are generally consistent with those in these guidelines and follow the recommendation of the ETA for the consideration of age in treatment decisions. Although the goal of treatment should be to restore the thyrotropin level to within the limits of the reference range,[26,27] the ETA guideline provides a further specification, which aims for a thyrotropin level in the lower half of the reference range (0.4 to 2.5 mIU

Table 3. Differences Between American and European Guidelines Regarding Key Recommendations for Treatment of Subclinical Hypothyroidism.*

Degree of Subclinical Hypothyroidism	ATA and AACE†	ETA‡
Mildly increased thyrotropin levels (≤10.0 mIU per liter in the American guidelines; <10.0 mIU per liter in the European guideline)	Treatment should be considered on the basis of individual factors (i.e., symptoms suggestive of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases). (Grade B, because of a lack of randomized, controlled trials)	Younger patients (<65 to 70 yr): A trial period of treatment with levothyroxine should be considered when symptoms suggestive of hypothyroidism are present. (Grade 2, intervention short of a randomized, controlled trial or large, observational studies) Older patients (especially >80 to 85 yr): Careful follow-up with a wait-and-see strategy, generally avoiding hormonal treatment, is recommended. (Grade 3, expert opinion)
Markedly increased thyrotropin levels (>10.0 mIU per liter in the American guidelines; ≥10.0 mIU per liter in the European guideline)	Levothyroxine should be considered because of an increased risk of heart failure and death from cardiovascular causes. (Grade B, because of a lack of randomized, controlled trials)	Younger patients (<65 to 70 yr): Treatment with levothyroxine is recommended, even in the absence of symptoms. (Grade 2, large observational studies) Older patients (>70 yr): Treatment with levothyroxine should be considered if clear symptoms of hypothyroidism are present or if the risk of vascular events is high. (Not a graded recommendation, but part of the treatment algorithm)

* The American guidelines were cosponsored by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE),[27] and the European guideline was developed by the European Thyroid Association (ETA).[26]

† The recommendations are evidence-based (grades A, B, and C, with A being the highest level of evidence) or are based on expert opinion because of a lack of conclusive clinical evidence (grade D). The "best evidence" rating level, which corresponds to the best conclusive evidence found, accompanies the recommendation grade.[27]

‡ The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used for the recommendations. The quality of the literature regarding each aspect of the statement was graded as high (evidence from a randomized, controlled trial; level [grade] 1); moderate (intervention short of a randomized, controlled trial or large, observational studies; level [grade] 2), or low (case series, case reports, expert opinion; level [grade] 3), according to modified GRADE criteria.[26]

per liter) for younger patients (≤70 or 75 years of age) and a higher target range (approximately 1 to 5 mIU per liter) for older patients.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has fatigue, mild depression, and a slightly elevated thyrotropin level with a normal free T_4 level, a presentation that is consistent with subclinical hypothyroidism. A transient increase in the thyrotropin level should be ruled out by remeasurement of the thyrotropin and free T_4 levels after 2 to 3 months (see Fig. 1). Antibodies to thyroid peroxidase should also be measured, since a positive test for antibodies to thyroid peroxidase doubles the risk of progression to overt hypothyroidism. Given the mild elevation in the patient's thyrotropin level, the probability of normalization of the thyrotropin level during the follow-up period is high. The fact that her free T_4 level is not in the low-normal range further suggests that the risk of progression to overt hypothyroidism is small. I would consider treatment if either of two scenarios develops. First, if her thyrotropin level increases during the follow-up period, and especially if both the test for antibodies to thyroid peroxidase is positive and the free T_4 level decreases, overt hypothyroidism will probably develop. At that stage, I would probably recommend that the patient start treatment, depending on her preference. Second, even if her thyrotropin level remains stable, the presence of symptoms could be an additional reason to consider treatment. Although the trial by Stott et al. in this issue of the *Journal* did not show improved quality of life after treatment with levothyroxine in patients with a mildly elevated thyrotropin level, the patients in this trial did not have decreased quality of life at baseline[29,30]; it remains possible that treatment with levothyroxine could ameliorate this patient's fatigue and depression. In this case, a dose of 50 μg of levothyroxine would probably be sufficient. If symptoms are not reduced after 6 months of treatment, the treatment should be stopped.

I would not consider the history of cardiovas-

cular disease to be an indication for treatment, given the lack of association between a thyrotropin level of 4.5 to 6.9 mIU per liter and the risk of cardiac events or death that was shown in a large meta-analysis,[4] as well as the lack of data from randomized, controlled trials to show that treatment with levothyroxine reduces cardiovascular risk.[41] Any potential benefits of therapy must be weighed against any potential risks of even a small degree of overtreatment.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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