Subclinical Thyroid Disease

Scientific Review and Guidelines for Diagnosis and Management

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Context Patients with serum thyroid-stimulating hormone (TSH) levels outside the reference range and levels of free thyroxine (FT_4) and triiodothyronine (T_3) within the reference range are common in clinical practice. The necessity for further evaluation, possible treatment, and the urgency of treatment have not been clearly established.

Objectives To define subclinical thyroid disease, review its epidemiology, recommend an appropriate evaluation, explore the risks and benefits of treatment and consequences of nontreatment, and determine whether population-based screening is warranted.

Data Sources MEDLINE, EMBASE, Biosis, the Agency for Healthcare Research and Quality, National Guideline Clearing House, the Cochrane Database of Systematic Reviews and Controlled Trials Register, and several National Health Services (UK) databases were searched for articles on subclinical thyroid disease published between 1995 and 2002. Articles published before 1995 were recommended by expert consultants.

Study Selection and Data Extraction A total of 195 English-language or translated papers were reviewed. Editorials, individual case studies, studies enrolling fewer than 10 patients, and nonsystematic reviews were excluded. Information related to authorship, year of publication, number of subjects, study design, and results were extracted and formed the basis for an evidence report, consisting of tables and summaries of each subject area.

Data Synthesis The strength of the evidence that untreated subclinical thyroid disease is associated with clinical symptoms and adverse clinical outcomes was assessed and recommendations for clinical practice developed. Data relating the progression of subclinical to overt hypothyroidism were rated as good, but data relating treatment to prevention of progression were inadequate to determine a treatment benefit. Data relating a serum TSH level higher than 10 mIU/L to elevations in serum cholesterol were rated as fair but data relating to benefits of treatment were rated as insufficient. All other associations of symptoms and benefit of treatment were rated as insufficient or absent. Data relating a serum TSH concentration lower than 0.1 mIU/L to the presence of atrial fibrillation and progression to overt hyperthyroidism were rated as good, but no data supported treatment to prevent these outcomes. Data relating restoration of the TSH level to within the reference range with improvements in bone mineral density were rated as fair. Data addressing all other associations of subclinical hyperthyroid disease and adverse clinical outcomes or treatment benefits were rated as insufficient or absent. Subclinical hypothyroid disease in pregnancy is a special case and aggressive case finding and treatment in pregnant women can be justified.

Conclusions Data supporting associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few. The consequences of subclinical thyroid disease (serum TSH 0.1-0.45 mIU/L or 4.5-10.0 mIU/L) are minimal and we recommend against routine treatment of patients with TSH levels in these ranges. There is insufficient evidence to support population-based screening. Aggressive case finding is appropriate in pregnant women, women older than 60 years, and others at high risk for thyroid dysfunction.

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SUBCLINICAL OR "MILD" THYROID disease is a common disorder, particularly in middle-aged and elderly individuals.[1] Greater sensitivity of assays and more frequent assessment of serum thyroid-stimulating hormone (TSH) levels have resulted in more patients requiring interpretation of abnormal thyroid function test results. However, controversy surrounds the definition, clinical importance, and necessity for prompt diagnosis and treatment of subclinical thyroid disease. Previous review articles[2-6] and position statements[7,8] differ in their conclusions and recommendations, often a consequence of difficulties in interpreting inadequate and conflicting data. In the midst of this uncertainty, clinicians still desire expert guidance for the diagnosis and management of subclinical thyroid disease.

See also p 239.

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In an effort to address these controversial issues, representatives of the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society formed a planning committee for a consensus development conference to review the literature and attempt to formulate some recommendations to guide clinical practice. The committee adopted an approach patterned on the National Institutes of Health (NIH) consensus development process. The planning committee drafted a series of clinically relevant questions related to the diagnosis and management of subclinical hypothyroidism and hyperthyroidism. These questions were

- What is the definition of subclinical thyroid disease?
- What is the epidemiology of subclinical thyroid disease?
- What are the consequences of untreated subclinical thyroid disease? How should it be evaluated?
- What are the risks and benefits of treatment for subclinical thyroid disease?
- Is screening for subclinical thyroid disease warranted?

The questions were presented to a panel of 13 experts selected by the planning committee who were either senior endocrinologists not known to publish or be advocates in this area or experts in other relevant fields. Members of the planning committee were not members of the panel. Eight of the panelists were experts in thyroid disease and the remaining 5 had expertise in cardiology, epidemiology, biostatistics, evidence-based medicine, health services research, general internal medicine, and clinical nutrition.

The conference was held September 21-23, 2002. The meeting was open to the public and attended by members of the 3 sponsoring societies. Continuing medical education credit was provided through the Endocrine Society. All potential conflicts of interest were obtained from panelists and speakers and printed in the conference materials. Endocrinologists who were members of any of the 3 organizing societies served without compensation whereas nonendocrinologist panelists received an appropriate honorarium.

METHODS

The Lewin Group, an independent consulting organization, was contracted to review the literature and summarize the evidence relating to the clinical questions. Relevant articles were identified by searching MEDLINE, EMBASE, Biosis, the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, and several National Health Services (UK) databases, including the Database of Abstracts of Reviews of Effectiveness, the Economic Evaluation Database, and the database of the International Network of Agencies for Health Technology Assessment. Key search terms were *subclinical* (text word) or *subclinic** and *hypothyroidism* or *thyroid deficien** or *thyroid insufficien**; *subclinical* (text word) or *subclinic** and *hyperthyroidism* or *thyrotoxicosis* or *overactive thyroid*. The following areas were evaluated (key words in parentheses): epidemiology (*etiology* or *ethnology* or *epidemiology* or *mortality*), screening (*screening* or *thyroid function tests*), treatment (*therapy* or *treatment* or *radiotherapy* or *surgery* or *complication* or *hormon**), consequences of no treatment (*complications* or *mortality*), and economics (*cost* or *costs* or *cost analysis* or *cost-benefit* or *cost effective**).

All English-language research articles or translations published on the topic from 1995 to July 2002 were reviewed, as well as 21 relevant articles and 4 abstracts published before 1995 that were identified by the planning committee. Excluded were editorials, individual case studies, studies enrolling fewer than 10 patients, and many nonsystematic reviews. The final count was 195 articles, including the earlier relevant publications identified by the planning committee. The report consisted of tables and summaries of each subject area indicating the authors, year of publication, numbers of subjects, nature of study (eg, cohort, blinded, randomized), and principal findings. The complete report is available at http://www.endo-society.org/education/evidence-report.cfm.

On the first 1½ days of the consensus conference, 12 experts identified by the planning committee presented reviews of selected areas including epidemiology, laboratory testing, symptoms, effects on bone, lipids, and cardiovascular systems, screening, and effects of treatment to the panel and audience. These expert presenters left the conference at the end of the information gathering session. Over the remaining 1½ days, the panel discussed the information presented and the data abstracted from the literature review to address the questions posed by the planning committee.

The panel assessed the data for quality, scope, and relevance. Using criteria adopted from the US Preventive Services Task Force (USPSTF),[9] the panel rated the strength of the available evidence as either good, fair, or insufficient as it related to the association of thyroid status or benefits of treatment to specified outcomes (**BOX 1**). Given the paucity of randomized controlled trials (RCTs), the panel relied on the available published evidence as well as that presented during the expert presentations, particularly for data related to clinical outcomes. When evidence was not available, was contradictory, or was judged to be insufficient, the panelists relied on their experience, judgment, and interpretation of the available literature in formulating recommendations for clinical practice. Differences of opinion were settled by a majority vote after extensive discussion. The recommendations for clinical practice were developed on the basis of the evidence evaluations during the conference deliberations.

Each clinical practice recommendation was rated by individual members of the panel for strength of supporting evidence (good, fair, insufficient, or based on expert opinion) (**BOX 2**). Panel members were asked to indicate their level of agreement (none, minimal,

Box 1. Strength of the Overall Evidence

Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.

Insufficient

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.[9]

Box 2. Strength of Panelists' Recommendations Based on Available Evidence

Rating

A: Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes.

B: Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes.

C: Recommends. The recommendation is based on expert opinion.

D: Recommends against. The recommendation is based on expert opinion.

E: Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

F: Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

I: Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.[9]

moderate, or strong) with each recommendation. Panel members submitted their assessments of the strength of evidence and their support for the recommendations during their review of the draft manuscript. A summary of the panelist's assessment of the strength of evidence and his/her degree of support for each recommendation is available at http://www.endo-society.org/education/evidence-report.cfm. All but 2 of the recommendations were supported unanimously.

RESULTS

Subclinical Thyroid Disease: Questions and Recommendations

Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction. Thus, it is critically important that the normal reference range for TSH be standardized and that laboratories engage in appropriate quality control procedures to ensure that the results they report are accurate and reproducible.[10,11] The TSH method used should have a functional sensitivity of at least 0.02 mIU/L and the functional sensitivity should be independently established by each laboratory.

What Is the Definition of Subclinical Hypothyroidism? *Subclinical hypothyroidism* is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free T_4 (FT_4) concentration is within its reference range.[12] Other causes of an elevated serum TSH must be excluded, for example: recent adjustments in levothyroxine dosage with failure to reach a steady state,[13] particularly in poorly compliant patients; transient increase in serum TSH in hospitalized patients during recovery from severe illness[14,15] or during recovery from destructive thyroiditis, including postviral subacute thyroiditis and postpartum thyroiditis; untreated primary adrenal insufficiency[16,17]; patients receiving recombinant human TSH injections[18]; and the presence of heterophilic antibodies against mouse proteins, which cause falsely high TSH concentrations in some assays.[19-21] Although central hypothyroidism (usually hypothalamic) may cause a mildly elevated serum TSH concentration (due to a circulating bioinactive TSH molecule),[22] the serum FT_4 concentration is generally clearly low in these patients.

Serum TSH concentrations in a healthy population have a skewed distribution with a "tail" toward higher TSH concentrations. Because of the relatively high prevalence of subclinical hypothyroidism in the general population, it is likely that some of the skew in the upper limits of normal is a result of inclusion of patients with subclinical disease.

The third National Health and Nutrition Examination Survey (NHANES III)[23] examined serum TSH values in a "disease-free" subset (n=13 344) of an ethnically diverse reference popula-

tion, aged 12 years and older (excluding pregnant women, individuals taking estrogens, androgens, or lithium, and those with detectable antithyroid antibodies to thyroid peroxidase [TPO] or laboratory evidence of hypothyroidism or hyperthyroidism). In this selected population, the reference range of TSH concentration (2.5th-97.5th percentile) was 0.45 to 4.12 mIU/L, and the geometric mean TSH concentration was 1.4 mIU/L. The reference range varied as a function of age, sex, and ethnic group, but because the differences are relatively small, it is not considered necessary to adjust the reference range for these factors in clinical practice.

Some investigators suggest that the upper limit of normal for serum TSH concentration should be 2.5 mIU/L[11] in a population rigorously screened to exclude thyroid disease or drugs that influence thyroid function. In support of this position is a higher rate of progression to overt hypothyroidism and a higher prevalence of antithyroid antibodies in individuals with serum TSH higher than 2.5 mIU/L compared with those with serum TSH between 0.5 and 2.5 mIU/L.[24] Although a serum TSH concentration higher than 2.5 but less than 4.5 mIU/L may identify some individuals with the earliest stage of hypothyroidism and those suspect for Hashimoto thyroiditis, there is no evidence for associated adverse consequences. Furthermore, serum TSH concentrations between 2.5 and 4.5 mIU/L may be due to minor technical problems in the TSH assay, circulating abnormal TSH isoforms, or heterophilic antibodies; normal individuals with serum TSH concentrations in this range would be misidentified as having hypothyroidism. Given these concerns as well as the pulsatile nature and continuous distribution of serum TSH concentrations, the panel defined the reference range of normal serum TSH concentration as 0.45 to 4.5 mIU/L.

What Is the Definition of Subclinical Hyperthyroidism? *Subclinical hyperthyroidism* is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and T_3 concentrations are within their reference ranges.[12] Other causes of a low serum TSH must be excluded. Subclinical hyperthyroidism may result from endogenous overproduction of thyroid hormone or intended, or inadvertent, overadministration of thyroid hormone. Among other causes of a low serum TSH concentration with normal concentrations of FT_4 are delayed recovery of the pituitary TSH-producing cells during or after therapy for hyperthyroidism,[25] normal pregnancy,[26] various nonthyroidal illnesses (euthyroid sick syndrome),[27,28] or the administration of dopamine,[29] glucocorticoids,[30,31] and possibly dobutamine.[32] Although subnormal serum TSH concentrations are common in a variety of severe nonthyroidal illnesses, undetectable serum TSH concentrations (<0.01 mIU/L) are rare unless patients are receiving concomitant glucocorticoids (usually in high doses) or dopamine. Although patients with pituitary or hypothalamic failure (including anorexia nervosa) frequently have subnormal serum TSH concentrations, the FT_4 is also usually subnormal.[12] When serum FT_4 is in the normal range, it is almost invariably in the lower part of the range in those with nonthyroidal illness in contrast to the high normal FT_4 concentration of typical subclinical hyperthyroidism.

What Is the Epidemiology of Subclinical Thyroid Disease? The prevalence of subclinical hypothyroidism in the US adult population is about 4% to 8.5% in those without known thyroid disease.[1,23] The prevalence increases with age, and in women older than 60 years, subclinical hypothyroidism is present in up to 20%.[1,33,34] The data are less consistent in men; in those older than 65 years, the prevalence increases and approaches that of women in some, but not all, studies.[23] In patients found to have an elevated TSH level, approximately 75% have values lower than 10 mIU/L.[1] The prevalence of subclinical hypothyroidism in blacks is one third that in whites,[23] and a similar low prevalence is seen in some populations with iodine deficiency.[35,36] Factors such as previous hyperthyroidism, type 1 diabetes mellitus, a family history of thyroid disease, or previous head and neck cancer treated with external beam radiation all raise the likelihood of subclinical hypothyroidism. About 20% of patients taking thyroid medications (not otherwise specified) have subclinical hypothyroidism.[1]

Of patients with subclinical hypothyroidism, approximately 2% to 5% per year will progress to overt hypothyroidism. Overt hypothyroidism is generally defined as a low serum FT_4 concentration with elevated serum TSH concentration,[34,37] but in some cases individuals with hypothyroid symptoms and high TSH (>10 mIU/L) with low normal FT_4 have been among those defined as having overt hypothyroidism.[24] The rate of progression is proportional to the baseline serum TSH concentration and is higher in individuals with antithyroid antibodies.[24] In individuals not taking thyroid hormone, serum TSH returns to normal after 1 year of follow-up in approximately 5% but remains elevated in the remainder.[34]

Subclinical hyperthyroidism is much less common than subclinical hypothyroidism. When the lower limit of TSH is less than 0.4 mIU/L, 3.2% of the population is defined as having subclinical hyperthyroidism.[23] If patients with known thyroid disease are excluded, the prevalence decreases to 2%. Subclinical hyperthyroid disease is more common in women than men, in blacks than whites, in the elderly,[34] and in patients with low iodine intake.[38] The presence of goiter, personal history of previous thyroid disease, family history of thyroid disease, atrial fibrillation, or ingestion of iodine-containing drugs such as amiodarone all make subclinical hyperthyroidism more likely. If the diagnosis is limited to only those with a serum TSH level lower than 0.1 mIU/L, the prevalence of subclinical hyperthyroidism decreases to 0.7%.[23] However, subclinical hyperthyroidism is common in individuals treated with levothyroxine, being present in 14% to 21% of such patients.[39,40]

Overt hyperthyroidism is defined as a serum TSH level lower than 0.1 mIU/L with serum FT_4, T_3, or FT_3 concentrations above the normal reference range.

Table 1. Quality of Evidence on the Strength of Association and Risks/Benefits of Treatment of Subclinical Hypothyroidism

	Strength of Association		Benefits of Treatment	
Clinical Condition	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L
Progression to overt hypothyroidism	Good	Good	*	*
Adverse cardiac end points	Insufficient	Insufficient	No evidence	No evidence
Elevations in serum total and LDL cholesterol	Insufficient	Fair	Insufficient	Insufficient
Cardiac dysfunction	†	Insufficient	Insufficient	Insufficient
Systemic hypothyroid symptoms	None	Insufficient	Insufficient	Insufficient
Neuropsychiatric symptoms	None	Insufficient	Insufficient	Insufficient

Abbreviations: LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.
*Thyroid hormone therapy normalizes serum TSH at any TSH concentration. Overt hypothyroidism occurs earlier in untreated patients with serum TSH >10 mIU/L than in those with serum TSH between 4.5 and 10 mIU/L.
†Data did not distinguish between serum TSH concentrations between 4.5 and 10 mIU/L and >10 mIU/L.

Few persons with a serum TSH between 0.1 and 0.45 mIU/L progress to overt hyperthyroidism,[24,34] whereas 1% to 2% per year of those with serum TSH lower than 0.1 mIU/L develop overt hyperthyroidism.[34] Serum TSH normalizes in many of these individuals over time.[41-43] Patients with large nodular thyroids and subnormal serum TSH concentrations may be at particular risk for developing overt hyperthyroidism when exposed to high concentrations of iodine.[44]

Subclinical Hypothyroidism: Questions and Recommendations

What Are the Consequences of Untreated Subclinical Hypothyroidism?

Possible consequences of subclinical hypothyroidism include cardiac dysfunction[45-48] or adverse cardiac end points (including atherosclerotic disease and cardiovascular mortality),[49,50] elevation in total and low-density lipoprotein (LDL) cholesterol,[51,52] systemic hypothyroid symptoms[1,53-60] or neuropsychiatric symptoms,[1,56,57] and progression to overt, symptomatic hypothyroidism[24,61] (TABLE 1).

Assessment of Evidence. The literature on subclinical hypothyroidism often arbitrarily separates patients into 2 groups determined by the degree of serum TSH elevation. To allow ease of comparison with the published literature, the panel assessed the evidence for individuals with serum TSH concentrations between 4.5 and 10 mIU/L and those with a serum TSH higher than 10 mIU/L, when such data were available. The panel examined the quality of the evidence for the strength of an association with certain adverse consequences of subclinical hypothyroid disease and the quality of the evidence addressing the risks and benefits of treatment (Table 1).

CARDIAC DYSFUNCTION AND ADVERSE EVENTS. Numerous small studies reveal subtle decreases in myocardial contractility detected by echocardiography in patients with subclinical hypothyroidism.[48] However, limitations in study design, including lack of blinding, inclusion of patients with previous overt hyperthyroidism, and possible selection bias in control group patients, temper the conclusion that clinically important reductions in cardiac contractility can be expected in subclinical hypothyroidism. In addition, these studies included individuals with high serum TSH without further stratification. It remains to be determined whether a continuum of cardiac dysfunction can be expected across the spectrum of subclinical hypothyroidism.

Whether untreated subclinical hypothyroidism affects important cardiovascular outcomes such as angina pectoris, myocardial infarction (MI), and cardiovascular death remains an unanswered question. One large, cross-sectional epidemiologic study[49] concluded that subclinical hypothyroidism was a risk factor for aortic atherosclerosis and MI with a risk comparable to that associated with diabetes mellitus, hypercholesterolemia, and smoking. However, a longitudinal component of this study did not confirm an increased risk of MI in patients with subclinical hypothyroidism, and a 10-year cohort study[50] found no such association. No randomized studies have assessed the impact of levothyroxine replacement on important clinical cardiac end points. Many small interventional trials demonstrate improvement in cardiac function, but these changes are of uncertain clinical importance. Although results of several studies suggest that thyroid hormone therapy will reduce total and LDL cholesterol levels in individuals with subclinical hypothyroidism,[51] this finding has not been confirmed in RCTs.[56,62]

SYSTEMIC SYMPTOMS. Baseline data from an RCT[55] illustrated an increased prevalence of hypothyroid symptoms among individuals with subclinical hypothyroidism. One health fair–based cross-sectional study of 25 862 participants[1] reported more hypothyroid symptoms in individuals with subclinical hypothyroidism than in euthyroid individuals but fewer symptoms than in overtly hypothyroid individuals. This study was not population-based and did not distinguish between untreated subclinical hypothyroidism and undertreated overt hypothyroidism. Other cross-sectional[58,59] and case-control studies[53] did not confirm these observations, but they were conducted among selected or referred populations often involving elderly hospitalized patients.

TREATMENT. A double-blind RCT reported significant improvement in symptomatic patients with subclinical hypothyroidism treated with levothyroxine compared with placebo.[55] However, study patients were primarily treated hyperthyroid patients, including those with serum TSH concentrations in the 40 to 50 mIU/L range. A second clinical trial reporting symptomatic improvement used a crossover design but did not ensure that the treated patients were euthyroid rather than subclinically hyperthyroid.[60] One study that showed improvement in neuromuscu-

lar symptoms and dysfunction when patients were treated with levothyroxine was not an RCT.[54] The 2 RCTs restricted to individuals with TSH levels lower than 10 mIU/L found no improvement in symptoms with levothyroxine therapy.[56,57]

How Should Subclinical Hypothyroidism Be Evaluated?

If the serum TSH concentration is high and serum FT_4 concentration has not been measured, the TSH measurement should be repeated along with an FT_4 measurement at a minimum of 2 weeks, but no longer than 3 months, after the initial assessment. The panel recommends thyroid hormone therapy in individuals with elevated serum TSH concentrations whose FT_4 concentration is below the reference range (0.8-2.0 ng/dL [10.3-25.7 pmol/L]).

If a high serum TSH concentration is confirmed on repeat testing and serum FT_4 is within the reference range, the patient should be evaluated for signs and symptoms of hypothyroidism, previous treatment for hyperthyroidism (radioiodine, partial thyroidectomy), thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should be reviewed. Women who are pregnant or hope to become pregnant in the near future deserve special consideration.

The evidence was insufficient to recommend either for or against routine measurement of anti-TPO antibodies in patients with subclinical hypothyroidism. The presence of anti-TPO antibodies identifies an autoimmune etiology for thyroid dysfunction and predicts a higher risk of developing overt hypothyroidism (4.3% per year vs 2.6% per year in antibody-negative individuals).[24] Still, antibody presence or absence does not change the diagnosis of subclinical hypothyroidism (which is based on serum TSH measurements) or the expected efficacy of treatment.

What Are the Risks and Benefits of Treating Subclinical Hypothyroidism? Among patients with untreated subclinical hypothyroidism, there is no single level of serum TSH at which clinical action is always either indicated or contraindicated. As the serum TSH concentration increases above 10 mIU/L, however, the basis for initiating treatment is more compelling. Clinical context is particularly important. This opinion reflects clinical experience and judgment as well as the literature that suggests improvement in symptoms[55] and possible lowering of LDL cholesterol.[56] There are no studies that demonstrate decreased morbidity or mortality with treatment. The potential risks of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine.[39,40]

Subclinical Hypothyroidism With Serum TSH of 4.5 to 10 mIU/L. Although some studies suggest an association between subclinical hypothyroidism and systemic hypothyroid symptoms[1,55] or cardiac dysfunction,[48] others do not.[53,58,59] No population-based studies examined symptoms in patients with serum TSH concentrations between 4.5 and 10 mIU/L. The likelihood of progression to overt hypothyroidism appears to be higher than for those with TSH levels lower than 4.5 mIU/L[14] (Table 1). Although early levothyroxine therapy does not alter the natural history of the disease, it may prevent symptoms and signs of overt disease in those who do progress. The available data do not confirm clear-cut benefits for early therapy compared with treatment when symptoms or overt hypothyroidism develop[56,57] (Table 1). Therefore, the panel does not recommend routine levothyroxine treatment for patients with TSH levels between 4.5 and 10 mIU/L, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor for improvement or worsening in TSH level.

The panel realizes that some individuals with TSH levels between 4.5 and 10 mIU/L have symptoms compatible with hypothyroidism. Clinicians and patients may decide on a several-month trial of levothyroxine, while monitoring for improvement in hypothyroid-type symptoms. Continuation of therapy should be predicated on clear symptomatic benefit. Still, the panel considers the likelihood of improvement small, and it must be balanced against the inconvenience, expense, and potential risks of therapy. Physicians and patients must understand that there is insufficient evidence to expect therapeutic benefit in patients in this group and that distinguishing a true therapeutic effect from a placebo effect in an individual patient is difficult. Still, the possibility that some patients may benefit cannot be ruled out. Physicians and patients should understand the natural history of subclinical hypothyroidism and the small but definite risk of progression to overt hypothyroidism. The special case of pregnancy or the planned pregnancy in women with subclinical hypothyroidism is discussed below.

Subclinical Hypothyroidism With Serum TSH Higher Than 10 mIU/L. Levothyroxine therapy is reasonable for patients with subclinical hypothyroidism and serum TSH higher than 10 mIU/L. The rate of progression is 5% in comparison with patients with lower levels of TSH, and treatment may potentially prevent the manifestations and consequences of hypothyroidism in those patients who do progress. Still, the evidence that therapy will reduce total and LDL cholesterol levels and improve symptoms in these patients is inconclusive (TABLE 2).

Subclinical Hypothyroidism During Pregnancy. The panel gave a rating of "fair" to the evidence of an association between subclinical hypothyroidism and adverse outcomes of pregnancy for either the fetus or the mother. However, the panel made the following recommendation: a TSH level might be obtained in pregnant women and women who wish to become pregnant if they have a family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, or a personal history of autoimmune disorders. For women who already take levothyroxine but whose TSH level is in the subclinical hypothyroidism range, compliance and appropriateness of dose should be assessed.

Table 2. Quality of Evidence on the Strength of Association and Benefits of Treatment of Subclinical Hyperthyroidism

	Strength of Association		Benefits of Treatment	
Clinical Condition	Serum TSH 0.1-0.45 mIU/L	Serum TSH <0.1 mIU/L	Serum TSH 0.1-0.45 mIU/L	Serum TSH <0.1 mIU/L
Progression to overt hyperthyroidism	Insufficient	Good	None	None
Adverse cardiac end points apart from atrial fibrillation	Fair	*	None	None
Atrial fibrillation	Insufficient	Good	None	None
Cardiac dysfunction	Insufficient	Fair	*	Insufficient
Systemic hyperthyroid and neuropsychiatric symptoms	Insufficient	Insufficient	None	Insufficient
Reduced bone mineral density	None	Fair†	None	Fair
Fractures	None	Insufficient	None	None

Abbreviation: TSH, thyroid-stimulating hormone.
*Data did not distinguish between serum TSH concentrations of 0.1 to 0.45 mIU/L and TSH lower than 0.1 mIU/L.
†Noted particularly in postmenopausal women and women with previous history of overt hyperthyroidism.

Pregnant women or women of childbearing potential planning to become pregnant who are found to have elevated serum TSH should be treated with levothyroxine to restore the serum TSH concentration to the reference range. This recommendation is based on the possible association between high TSH and either increased fetal wastage or subsequent neuropsychological complications occurring in the offspring due to thyroid insufficiency.[63] Although there are no published intervention trials assessing the benefits of thyroid hormone replacement in this special population, the potential benefit-risk ratio of levothyroxine therapy justifies its use. It is important to note that the requirement for levothyroxine in treated hypothyroid women frequently increases during pregnancy. Therefore, serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy and the levothyroxine dose modified as needed. The risks of appropriately managed levothyroxine therapy in pregnancy are minimal. Continuation of levothyroxine treatment post partum is beyond the scope of this discussion.

Subclinical Hypothyroidism in Treated Overt Hypothyroid Individuals. When subclinical hypothyroidism is noted in levothyroxine-treated patients with overt hypothyroidism, the dosage of levothyroxine should be adjusted to bring the serum TSH into the reference range. Whether the target TSH level should be in the lower half of the reference range is controversial because there are no data demonstrating improved clinical outcomes with this strategy. Nevertheless, when the serum TSH is in the upper half of the reference range and levothyroxine-treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase the levothyroxine dosage to bring the serum TSH into the lower portion of the reference range. The rapidity of the dosage adjustment depends on the patient's age and medical comorbidities. Minimal TSH elevations may not require dosage adjustment in patients who feel well, particularly those with arrhythmias or other cardiac disorders.

Subclinical Hyperthyroidism: Questions and Recommendations

What Are the Consequences of Untreated Subclinical Hyperthyroidism?

Assessment of Evidence. The panel evaluated the strength of the evidence for the association of untreated subclinical hyperthyroidism and the following clinical outcomes: progression to overt hyperthyroidism,[1,64-67] adverse cardiac end points,[50] atrial fibrillation,[43,68,69] cardiac dysfunction,[48,70-76] systemic and neuropsychiatric symptoms,[42,71,72,77,78] reduced bone mineral density,[79-87] and fractures[88,89] (Table 2). The panel also assessed the strength of the association between the TSH level and the risks and benefits of treatment (Table 2). Similar to the approach taken in many reported studies, the panel classified patients with subclinical hyperthyroidism into 2 categories: those with mildly low but detectable serum TSH (0.1-0.45 mIU/L) and those with a clearly low serum TSH (<0.1 mIU/L). In all clinical settings, causes of subnormal serum TSH concentration other than subclinical hyperthyroidism must be excluded.

Cardiac Dysfunction, Arrhythmias, and Adverse Events. Exogenous and endogenous subclinical hyperthyroidism have been reported to increase heart rate, left ventricular (LV) mass, and cardiac contractility, to cause diastolic dysfunction (delayed relaxation), and atrial arrhythmias, but not to increase the prevalence of ventricular arrhythmias.[48] The panel interpreted reported echocardiographic changes in cardiac function in persons with subclinical hyperthyroidism vs comparison groups to be small and of uncertain clinical importance. Only 3 small and unblinded studies have assessed cardiac function in patients with endogenous subclinical hyperthyroidism.[71,73,74] Few studies included stratified analyses for patients whose TSH was in the 0.1 to 0.45 mIU/L range. One study reported increased all-cause (up to 2.2-fold) and cardiovascular mortality (up to 3-fold) in individuals older than 60 years with endogenous subclinical hyperthyroidism and serum TSH concentration lower than 0.5 mIU/L.[50]

One study reported a 3-fold increased risk of atrial fibrillation over 10 years in men and women at least 60 years of age with serum TSH of 0.1 mIU/L or lower with endogenous and exogenous subclinical hyperthyroidism. Although some believe the risk of atrial fibrillation is also increased in patients with a serum TSH level of 0.1 to 0.4 mIU/L, evidence for this is limited, whereas evidence for an increased risk of atrial fibrillation when the TSH value is lower than 0.1 mIU/L is solid.[43] A second study found a 5-fold increased risk of atrial fibrillation in individuals with endogenous subclinical hyperthyroidism (age not specified) and TSH lower than 0.4 mIU/L compared with euthyroid individuals aged at least 45 years.[69] A third

study of individuals with endogenous subclinical hyperthyroidism (mean age, 65 years) and serum TSH lower than 0.1 mIU/L reported a 2.8-fold increased risk of atrial fibrillation over 2 years compared with aged-matched euthyroid controls.[68] No studies demonstrated an increased incidence of arterial embolism in patients with subclinical hyperthyroidism. However, atrial fibrillation due to overt hyperthyroidism is a known risk factor for arterial embolism.[90,91]

Treatment. Several studies have assessed the effects of treatment on cardiac function. Successful treatment of endogenous subclinical hyperthyroidism decreased the heart rate and cardiac output and increased the systemic vascular resistance in an unblinded study of 6 patients.[74] There is limited evidence that treatment of subclinical hyperthyroidism facilitates spontaneous reversion or cardioversion of atrial fibrillation to normal sinus rhythm.[92] Among patients with exogenous subclinical hyperthyroidism, decreasing the levothyroxine dose normalized the heart rate and resulted in a nonsignificant reduction in LV ejection fraction,[75] whereas β-blockers decreased atrial premature beats and LV mass index and improved diastolic filling.[76]

Systemic and Neuropsychiatric Symptoms. Several relatively small case-control, cross-sectional, and cohort studies found more hyperthyroid-type signs and symptoms in individuals with subclinical hyperthyroidism (compared with euthyroid individuals) but fewer than in individuals with overt hyperthyroidism.[42,71,72,77] However, some of these studies involved patients selected from hospital clinics or elderly inpatients. The only large, population-based study (N=6884) of an unselected, healthy cohort found no association between those with TSH lower than 0.21 mIU/L (who were not taking levothyroxine) and physical or psychological symptoms of hyperthyroidism; nor were differences in concentration, depression, or anxiety detected by means of validated instruments.[78]

Skeletal System. Two meta-analyses reported declines in bone mineral density (BMD) during prolonged subclinical hyperthyroidism.[83,84] These analyses concluded that exogenous subclinical hyperthyroidism resulted in a significant loss of BMD among postmenopausal women but not among premenopausal women. Considering the data from individual studies, one prospective study found no association between low serum TSH and accelerated loss in BMD.[85] One study reported no increased fracture risk in levothyroxine-treated patients with serum TSH lower than 0.05 mIU/L or in those with serum TSH between 0.05 and 4.0 mIU/L.[93] However, another prospective study reported an increased risk of hip and spine fracture in levothyroxine-treated women older than 65 years whose serum TSH was 0.1 mIU/L or lower, but this study did not distinguish between overt and subclinical hyperthyroidism.[88] The risk of fractures was not increased in women with serum TSH between 0.1 and 0.5 mIU/L when adjustment was made for prior hyperthyroidism. Overt thyrotoxicosis increased the risk of fracture in most[88,89] but not all[94] studies. Prolonged subclinical hyperthyroidism prior to overt hyperthyroidism may contribute to the increased risk of fracture in patients with thyrotoxicosis.[89]

Treatment. Treatment of hyperthyroidism to restore the TSH level to within the reference range preserves BMD, but normalization of bone turnover may be delayed for up to 1 year.[86,87] Two studies of endogenous subclinical hyperthyroidism (TSH <0.2 mIU/L[81] and TSH <0.1 mIU/L[82]) in postmenopausal women demonstrated significant continued bone loss in untreated patients compared with bone stabilization in treated patients. Only one[82] of these studies was randomized and neither included a placebo group.

How Should Subclinical Hyperthyroidism Be Evaluated? *Individuals With Serum TSH 0.1 to 0.45 mIU/L Not Treated With Levothyroxine.* If serum TSH is reported to be between 0.1 and 0.45 mIU/L, the measurement should be repeated for confirmation. The panel recommends measuring FT_4 and either total T_3 or FT_3 levels to exclude central hypothyroidism or nonthyroidal illness. Clinical circumstances dictate when the retesting should occur. For patients with atrial fibrillation, cardiac disease, or other serious medical conditions, repeat testing within 2 weeks is prudent. When these factors are absent, repeat testing is recommended within 3 months.

If the repeat serum TSH concentration remains higher than 0.1 but lower than 0.45 mIU/L, with normal FT_4 and T_3 concentrations, and the patient has no signs or symptoms of cardiac disease, atrial fibrillation, or other arrhythmias, retesting should occur at 3- to 12-month intervals, until either serum TSH normalizes or the clinician and patient are confident that the condition is stable. Patients with known nodular thyroid disease may develop overt hyperthyroidism when exposed to excess iodine (eg, radiographic contrast agents) and require special consideration.[44]

Individuals With a Serum TSH Lower Than 0.1 mIU/L. If serum TSH concentration is lower than 0.1 mIU/L, the panel recommends repeating the measurement, along with an FT_4 and a total T_3 or FT_3, within 4 weeks of the initial measurement. If the patient has signs or symptoms of cardiac disease, atrial fibrillation or other arrhythmia, or medical issues requiring urgent diagnosis and treatment, these tests should be performed within a shorter interval, particularly if there are signs or symptoms of hyperthyroidism.

Endogenous Subclinical Hyperthyroidism (TSH Lower Than 0.45 mIU/L). The panel recommends further evaluation to establish the etiology of the low serum TSH. A radioactive iodine uptake measurement and scan can distinguish between destructive thyroiditis and hyperthyroidism due to Graves disease or nodular goiter.

What Are the Risks and Benefits of Treatment of Subclinical Hyperthyroidism? The risks of treatment of subclinical hyperthyroidism with antithyroid drugs are potential allergic reactions including agranulocytosis. Radioactive iodine therapy commonly

causes hypothyroidism and may cause exacerbation of hyperthyroidism or Graves eye disease.[95]

Exogenous Subclinical Hyperthyroidism With TSH 0.1 to 0.45 mIU/L. When the serum TSH concentration is between 0.1 and 0.45 mIU/L in a levothyroxine-treated individual, the indication for thyroid hormone therapy should be reviewed. Many patients with thyroid cancer and some patients with thyroid nodules require TSH suppression, and the target TSH level should be reviewed by the treating endocrinologist or other physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range. This dosage adjustment may be particularly important when the serum TSH is in the lower part of the range (Table 2).

Exogenous Subclinical Hyperthyroidism With TSH Lower Than 0.1 mIU/L. When the serum TSH concentration is lower than 0.1 mIU/L in a levothyroxine-treated individual, the indication for thyroid hormone therapy should be reviewed. For patients with thyroid cancer and thyroid nodules, the target serum TSH value should be reviewed by the patient's endocrinologist or treating physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range.

Endogenous Subclinical Hyperthyroidism (Serum TSH 0.1-0.45 mIU/L). The panel recommends against routine treatment for all patients whose TSH is mildly decreased (0.1-0.45 mIU/L). The panel found insufficient evidence to establish a clear association between this mild degree of hyperthyroidism and adverse clinical outcomes, including atrial fibrillation. However, because of a possible association with increased cardiovascular mortality,[50] clinicians might consider treatment of elderly individuals, despite the absence of supportive data from intervention trials.

Endogenous Subclinical Hyperthyroidism (Serum TSH Lower Than 0.1 mIU/L). Subclinical hyperthyroidism due to destructive thyroiditis (including postviral subacute thyroiditis and postpartum thyroiditis) resolves spontaneously. Treatment, apart from symptomatic therapy (eg, β-blockers), is usually not required.

The panel recommends that treatment be considered for subclinical hyperthyroidism (TSH <0.1 mIU/L) due to Graves or nodular thyroid disease. The panel recognizes the paucity of intervention trials, apart from those demonstrating stabilization of bone density. However, the panel was concerned about the risk of atrial fibrillation and/or bone loss, particularly in the elderly. Specifically, treatment should be considered for patients who are older than 60 years and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism. Younger individuals with subclinical hyperthyroidism and serum TSH persistently (months) lower than 0.1 mIU/L may be offered therapy or follow-up depending on individual considerations.

Is Screening for Subclinical Thyroid Disease Warranted? The rationale for population screening hinges on the high prevalence of subclinical thyroid dysfunction in the adult population and on the potential health benefits and risks of detecting and treating these diseases. We used the US Preventive Services Task Force criteria[96] for recommending a screening test, which requires evidence of effectiveness of early detection. One of the most important criteria for recommending a screening test is that screening asymptomatic persons and treating them for the condition should result in improved measurable and important health outcomes when compared with persons who are not screened and who present with signs or symptoms of the disease. An alternative to population screening is aggressive case finding, defined as the application of a test to a person presenting to a clinician for a reason usually unrelated to the test being applied to determine the person's likelihood of having a particular disease or condition.

Thyroid dysfunction is more prevalent in certain population groups, including women older than 60 years, persons with previous radiation treatment of the thyroid gland (radioactive iodine or therapeutic external beam radiation), those who have had previous thyroid surgery or thyroid dysfunction, and those who have type 1 diabetes mellitus, a personal history of autoimmune disease, a family history of thyroid disease, or atrial fibrillation. The panel recommends aggressive case finding in these high-risk groups. The panel also endorses thyroid function testing (serum TSH measurement) for patients seeking medical care who have signs or symptoms suggestive of thyroid dysfunction[8] or those being evaluated for palpable thyroid abnormalities.

The panel recommends against population-based screening for thyroid disease. Case ascertainment in certain high-risk groups is encouraged. The panel finds the evidence insufficient to recommend for or against routine determination of TSH levels (screening) in pregnant women or women planning to become pregnant. It is reasonable to consider serum TSH measurement for women with a family history of thyroid disease, prior thyroid dysfunction, symptoms or physical findings suggestive of hypothyroidism or hyperthyroidism, an abnormal thyroid gland on examination, type 1 diabetes mellitus, or a personal history of an autoimmune disorder.

CONCLUSION

Our review of the literature revealed a striking paucity of evidence bearing on the major clinical questions examined. Our recommendations are based on the existing evidence and the panels' clinical experience, but they are limited by the paucity of definitive data. Well-conceived and executed intervention trials are needed to bring definitive data to light on these questions. Until such data are available, clinical judgment and patients' preferences remain paramount. Although the panel recom-

mended against population screening for subclinical thyroid disease, clinicians are encouraged to make individual patient assessments when determining the need for testing and treatment.

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