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Subclinical Hypothyroidism
A Review

Bernadette Biondi, MD; Anne R. Cappola, MD, ScM; David S. Cooper, MD

IMPORTANCE Subclinical hypothyroidism, defined as an elevated serum thyrotropin (often referred to as thyroid-stimulating hormone, or TSH) level with normal levels of free thyroxine (FT_4) affects up to 10% of the adult population.

OBSERVATIONS Subclinical hypothyroidism is most often caused by autoimmune (Hashimoto) thyroiditis. However, serum thyrotropin levels rise as people without thyroid disease age; serum thyrotropin concentrations may surpass the upper limit of the traditional reference range of 4 to 5 mU/L among elderly patients. This phenomenon has likely led to an overestimation of the true prevalence of subclinical hypothyroidism in persons older than 70 years. In patients who have circulating thyroid peroxidase antibodies, there is a greater risk of progression from subclinical to overt hypothyroidism. Subclinical hypothyroidism may be associated with an increased risk of heart failure, coronary artery disease events, and mortality from coronary heart disease. In addition, middle-aged patients with subclinical hypothyroidism may have cognitive impairment, nonspecific symptoms such as fatigue, and altered mood. In the absence of large randomized trials showing benefit from levothyroxine therapy, the rationale for treatment is based on the potential for decreasing the risk of adverse cardiovascular events and the possibility of preventing progression to overt hypothyroidism. However, levothyroxine therapy may be associated with iatrogenic thyrotoxicosis, especially in elderly patients, and there is no evidence that it is beneficial in persons aged 65 years or older.

CONCLUSIONS AND RELEVANCE Subclinical hypothyroidism is common and most individuals can be observed without treatment. Treatment might be indicated for patients with subclinical hypothyroidism and serum thyrotropin levels of 10 mU/L or higher or for young and middle-aged individuals with subclinical hypothyroidism and symptoms consistent with mild hypothyroidism.

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Author Affiliations: Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy (Biondi); Perelman School of Medicine, Division of Endocrinology, Diabetes, and Metabolism, the University of Pennsylvania, Philadelphia (Cappola); Associate Editor, *JAMA* (Cappola); Division of Endocrinology, Diabetes, and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Cooper).

Corresponding Author: David S. Cooper, MD, Division of Endocrinology, Diabetes, and Metabolism, The Johns Hopkins University School of Medicine, 1830 E Monument St, Ste 333, Baltimore, MD 21287 (dscooper@jhmi.edu).

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Overt hypothyroidism is present when serum thyroid hormone levels are lower than the reference range, indicating thyroid insufficiency. In overt hypothyroidism due to thyroid dysfunction (primary hypothyroidism), thyrotropin (often referred to as thyroid-stimulating hormone, or TSH) levels are appropriately elevated. Subclinical hypothyroidism exists when serum thyroid hormone levels are within the reference range, but serum thyrotropin levels are elevated outside the reference range.[1] The diagnosis of subclinical hypothyroidism is a biochemical diagnosis solely based on thyroid function testing. In iodine-sufficient populations, subclinical hypothyroidism affects up to 10% of the population, with the highest prevalence among women and elderly individuals.[2,3] However, subclinical hypothyroidism frequently reverts to euthyroidism,[4] and thyrotropin levels rise as people without thyroid disease age,[5-7] making it likely that the prevalence of subclinical hypothyroidism has been overestimated.

Individuals have a range of values for serum thyrotropin and free thyroxine (FT_4) that are maintained within a narrower range than the broader population reference range.[8] Because of the exquisitely sensitive relationship between pituitary thyrotropin secretion and serum FT_4 levels, an individual's serum thyrotropin level may be higher than the upper limit of the population-based reference range if that individual's serum FT_4 level falls below that individual's FT_4 reference range, even though his/her FT_4 level is still within the population-based FT_4 reference range. This intraindividual thyroid axis set point is largely genetically determined.[9] The hypothalamic-pituitary-thyroid axis is highly sensitive to minimal decrements in serum levels of thyroxine (T_4), so that decreases in FT_4 levels, even within the broad population reference range, result in increased secretion of pituitary thyrotropin. However, in subclinical hypothyroidism, due to thyroid inflammation or other intrinsic thyroid disease, thyroidal hormonal output does not appropriately increase in response to the elevated serum thyrotropin, leading to chronically elevated thyrotropin levels. Subclinical hypothyroidism may be categorized as grade 1 when thyrotropin levels are between the upper limit of the reference range and 9.9 mU/L and as grade 2 if serum thyrotropin levels are 10 mU/L or higher.[10] Approximately 90% of patients with subclinical hypothyroidism have serum thyrotropin levels lower than 10 mU/L.[11,12] This article provides a current review of the controversies related to the clinical significance, diagnosis, and therapeutic considerations related to subclinical hypothyroidism. This review does not cover subclinical hypothyroidism in women who are

pregnant or are attempting to become pregnant. Pregnancy and subclinical hypothyroidism is covered elsewhere.[13]

Methods

We searched the PubMed database through March 13, 2019, for English-language studies related to the management of subclinical hypothyroidism. The search was updated on May 30, 2019. Guidelines of major professional societies, meta-analyses, and randomized trials were prioritized for review. Selected articles were mutually agreed upon by the authors.

Differential Diagnosis of Elevated Serum Thyrotropin Levels

Mild thyroid failure due to autoimmune thyroiditis is the most common cause of mildly elevated serum thyrotropin levels. Although elevated serum thyrotropin levels are characteristic of primary thyroid failure, other clinical conditions (eg, external radiotherapy to the neck), drugs (eg, lithium), or laboratory anomalies (eg, heterophilic antibodies in the serum) may result in elevated serum thyrotropin levels (**Box**). The most important of these is the increase in serum thyrotropin levels, which is likely a normal consequence of aging. Epidemiological studies have shown a rise in serum thyrotropin levels (usually <8 mU/L) in healthy elderly people without clinical or biochemical evidence of intrinsic thyroid disease.[5] The cause of the increase in serum thyrotropin is uncertain, but it is clear that older individuals who have mildly elevated serum thyrotropin in the absence of thyroid disease are not at risk of increased morbidity and mortality.[7,14] Some studies suggest that elevated serum thyrotropin levels in this context are associated with better health outcomes and improved functional status.[15,16] Other conditions that may lead to mild elevations in serum thyrotropin that can mimic subclinical hypothyroidism include untreated adrenal insufficiency,[1] mutations in the thyrotropin receptor protein on thyroid follicular cells causing "thyrotropin resistance,"[17] and extreme obesity (ie, body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], >40 to 45).[18] The latter is probably due to the effects of leptin, a hormone secreted by adipose tissue, on hypothalamic thyrotropin-releasing hormone secretion, leading to increased levels of serum thyrotropin.[19,20] Obesity-related increases in serum thyrotropin are reversible with weight loss but can be perceived as hypothyroidism-related overweight.[20] In critically ill hospitalized patients, serum thyrotropin levels can be suppressed due to the effects of cytokines and other factors on the hypothalamic-pituitary-thyroid axis, as part of the disorder known as the "euthyroid sick syndrome." During recovery, serum thyrotropin levels can rebound, but levels rarely are more than 10 mU/L.[21] In this setting, the diagnosis of hypothyroidism should be deferred until the patient has fully recovered.[22] In patients undergoing thyroid lobectomy for benign or malignant thyroid nodules, there is often a transient rise in serum thyrotropin postoperatively that can last for several months. Permanent hypothyroidism, which is typically subclinical, can occur in up to 60% of patients after thyroid lobectomy and may occur more than 1 year after surgery. Patients with preoperative serum thyrotropin levels higher than approximately 2 mU/L, especially if thyroid peroxidase (TPO) antibodies are present, are more likely to develop postoperative hypothyroidism.[23,24]

Box. Differential Diagnosis of Elevated Serum Thyrotropin and Normal Serum Free Thyroxine[a]

Subclinical Hypothyroidism Due to Mild Thyroid Failure
- Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)
- Inadequate levothyroxine replacement therapy for overt hypothyroidism
- Following thyroid lobectomy
- Following antithyroid drug or radioiodine therapy for hyperthyroidism
- Following external beam radiotherapy to the head and neck
- Infiltrative disorders such as amyloidosis and Riedel thyroiditis
- Following an episode of subacute (granulomatous) thyroiditis
- Drug induced, especially in patients with underlying lymphocytic thyroiditis
  - Lithium carbonate
  - Iodine-containing compounds, including amiodarone
  - Interferon alfa
- Tyrosine kinase inhibitors, immune check point inhibitors

Physiological Transient Rises in Thyrotropin Levels
- Recovery after severe nonthyroidal illness
- During recovery from various forms of thyroiditis
- Following withdrawal of chronic levothyroxine therapy in a euthyroid individual
- Seasonal (wintertime) increases in serum thyrotropin

Elevated Serum Thyrotropin Levels That Are Not True Subclinical Hypothyroidism
- Common causes
  - Increases in elderly persons without thyroid disease
  - Increases in patients with marked obesity, typically with body mass index of more than 40
- Uncommon causes
  - Anomalous laboratory results due to heterophilic antibodies or macroTSH
  - Untreated adrenal insufficiency

Abbreviation: TSH indicates thyroid-stimulating hormone (thyrotropin).

[a] Modified from Cooper and Biondi.[1]

Depending on the assay system, serum thyrotropin levels can be elevated due to a measurement artifact in patients with circulating antibodies to mouse immunoglobulin called HAMA (human antimouse antibodies).[25] Artifactual elevations in serum thyrotropin can also be seen in patients who have circulating macroTSH (similar to macroprolactin), in which thyrotropin is complexed to antithyrotropic IgG to form a high molecular-weight complex with low biological activity.[26] The prevalence of macroTSH is not well delineated, but it might be present in as many as 1% to 2% of patients diagnosed with subclinical hypothyroidism.[26]

Risk of Progression to Overt Disease

In 60% of patients with grade 1 subclinical hypothyroidism, thyrotropin declines to the normal range over 5 years.[27,28] The annual rate

of progression to overt disease is about 2% to 4% in such patients, depending on TPO antibody status.[28-31] In elderly participants (≥65 years) enrolled in the Cardiovascular Health Study,[4] the rate of thyrotropin normalization over 2 years was 46% in participants with grade 1 subclinical hypothyroidism with thyrotropin levels of 4.5 to 6.9 mU/L compared with 7% for grade 2 subclinical hypothyroidism. Normalization occurred in 48% of participants with subclinical hypothyroidism who did not have TPO) antibodies. Conversely, grade 2 subclinical hypothyroidism is associated with increased rates of progression to overt hypothyroidism, especially in women and in patients with positive TPO antibodies.[32,33] In 1 prospective study,[29] 40% of patients with baseline thyrotropin levels of 10 to 14.9 mU/L and 85% with thyrotropin levels of 15 to 19.9 mU/L developed overt hypothyroidism during a mean follow-up period of 31.7 months.

Clinical Manifestations

Grade 1 subclinical hypothyroidism is rarely associated with hypothyroid and neuropsychiatric symptoms or alterations in mood or cognition.[1,28] New onset of symptoms of hypothyroidism, especially when numerous and severe, usually suggests the diagnosis of grade 2 subclinical hypothyroidism or overt disease.[34] Although quality of life is not altered in patients with subclinical hypothyroidism compared with euthyroid controls,[35] a mild impairment of declarative, working memory, and mood has been reported in middle-aged patients with grade 2 subclinical hypothyroidism.[36] No significant difference in depressive symptoms has been found between euthyroid and subclinical hypothyroidism patients.[37,38]

In elderly individuals, hypothyroid symptoms usually fail to identify thyroid hormone deficiency, even in overt hypothyroidism.[39] At baseline, participants enrolled in the Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism (TRUST) trial[40] involving 737 adults 65 years or older (mean age, 74.4 years; mean thyrotropin, 6.40 mU/L) had hypothyroid symptom scores similar to or lower than the general population.

Clinical Significance

Cardiovascular Risk

Cardiovascular abnormalities (left ventricular systolic and diastolic dysfunction and impaired vascular relaxation) have been described in patients with grade 1 and grade 2 subclinical hypothyroidism.[41] A meta-analysis[42] involving 675 patients younger than 60 years reported that patients with subclinical hypothyroidism, even those with mild disease, had significantly worse parameters of left ventricular diastolic function assessed by tissue Doppler echocardiography when compared with a healthy control group matched for age and sex. The slowed rate of left ventricular relaxation may impair ventricular filling during exercise, leading to left ventricular systolic dysfunction and impairing the physical activity of patients with subclinical hypothyroidism.[28] Vascular abnormalities, such as increased systemic vascular resistance and altered endothelial-mediated vasorelaxation and vascular compliance have also been reported in patients with grade 1 and grade 2 subclinical hypothyroidism.[43]

Hypothyroidism is one of the most frequent secondary causes of dyslipidemia (elevated low-density lipoprotein [LDL] cholesterol and triglyceride levels), and screening for hypothyroidism is recommended for individuals with hypercholesterolemia.[44] Metabolic alterations can develop in grade 2 subclinical hypothyroidism, especially in patients with insulin resistance.[45] A meta-analysis[46] of 16 observational studies confirmed alterations in lipid pattern (increased concentrations of serum total cholesterol, LDL cholesterol, and triglyceride levels) in patients with grade 2 subclinical hypothyroidism; weaker evidence was found for the association with HDL cholesterol levels. Adverse consequences of insulin resistance and changes in lipid metabolism may contribute to a higher prevalence of nonalcoholic fatty liver disease (NAFLD) across the spectrum of hypothyroidism, although the incidence of NAFLD was not increased in a meta-analysis[47] involving patients with subclinical hypothyroidism. Grade 2 subclinical hypothyroidism was associated with increased carotid intima-media thickness (CIMT) in a meta-analysis[48] involving 3602 patients. A higher CIMT was found among adult patients with grade 2 subclinical hypothyroidism compared with mild disease and euthyroid controls in a meta-analysis of 12 trials.[49]

These alterations in myocardial function, metabolic profile, and vascular function suggest that patients with untreated subclinical hypothyroidism may be at increased risk of adverse cardiovascular outcomes. However, individual-patient meta-analysis performed by the Thyroid Studies Collaboration,[11,50-52] a consortium of cohort studies with data from more than 75 000 participants, did not demonstrate an association of subclinical hypothyroidism with increased risk of atrial fibrillation,[52] heart failure,[50] stroke,[51] coronary heart disease events,[11] mortality from coronary heart disease,[11] or overall mortality[11] compared with euthyroid individuals (**Table**). In contrast, when data were analyzed, stratified by degree of thyrotropin elevation, thyrotropin levels of 10 mU/L or higher were associated with increased risk of heart failure, coronary heart disease events, and mortality from coronary heart disease compared with normal thyrotropin values.[11,50] In addition, thyrotropin values of 7.0 to 9.9 mU/L were associated with increased risk of fatal stroke and mortality from coronary heart disease.[11,51] The presence of TPO antibodies was not associated with higher risk of coronary heart disease events beyond the degree of thyrotropin elevation.[53] The findings from these studies suggest that the severity of subclinical hypothyroidism is associated with greater cardiovascular risk. One limitation common to all the cohorts included in these meta-analyses is that thyroid function testing was only performed at one time point, resulting in analysis of participants with transient and persistent subclinical hypothyroidism together. A separate analysis[54] conducted in one of the cohorts with repeated measures of thyroid function showed that persistent subclinical hypothyroidism was not associated with coronary heart disease, heart failure, or cardiovascular death, similar to analyses using a single thyroid function measurement.

Cognitive Decline and Dementia

A meta-analysis[55] including prospective and cross-sectional studies supports an association of subclinical hypothyroidism with cognitive impairment in patients younger than 75 years, but no association in persons who are older than 75 years. This is consistent with 2 other studies. In one, a mild serum thyrotropin increase was not associated with cognitive dysfunction, anxiety, or depression in participants 65 years or older.[56] In the other, a meta-analysis[57] including 11 prospective cohorts involving patients with a mean age of 65 years or older, there was no association between subclinical hypothyroidism and dementia or a decline in cognition.

Table. Summary of Results From Meta-analyses Using Individual Patient Data Reporting Risks of Incident Clinical Outcomes in Participants With Subclinical Hypothyroidism

Clinical Outcome	Source	Participants	Median Age Range per Study, y	Women, %	Euthyroid (Thyrotropin [TSH] Range, 0.45-4.49, mU/L)		Subclinical Hypothyroidism (Thyrotropin [TSH] Range, mU/L)							
							All (4.5-19.9)		Grade 1 (4.5-6.9)		Grade 1 (7.0-9.9)		Grade 2 (10.0-19.9)	
					No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)
Cardiovascular														
Coronary heart disease events[a]	Rodondi et al,[11] 2010	25 977; 7 cohorts	46-85	52	4040/23 957	1 [Reference]	430/2020	1.18 (0.99-1.40)	264/1344	1.01 (0.86-1.18)	96/441	1.22 (0.99-1.49)	70/235	1.86 (1.22-2.82)
Heart failure[a]	Gencer et al,[50] 2012	24 742; 6 cohorts	58-75	54	1762/22 674	1 [Reference]	250/2068	1.22 (0.93-1.59)	156/1422	1.01 (0.81-1.25)	54/422	1.78 (0.94-3.38)	40/224	1.59 (1.15-2.19)
Stroke events[b]	Chaker et al,[45] 2015	37 842; 12 cohorts	46-85	51	2301/35 250	1 [Reference]	246/2592	0.97 (0.77-1.22)	161/1799	1.01 (0.85-1.19)	53/507	1.68 (0.91-3.09)	32/286	1.26 (0.89-1.79)
Fatal stroke[b]	Chaker et al,[45] 2015	47 244; 17 cohorts	46-85	51	910/43 648	1 [Reference]	104/3596	1.11 (0.82-1.50)	72/2544	1.09 (0.71-1.67)	22/699	1.65 (1.16-2.33)	10/353	1.79 (0.88-3.63)
Atrial fibrillation[c,d]	Baumgartner et al,[46] 2017	3765; 11 cohorts	46-85	52	187/777	1 [Reference]	Not provided	Not provided	149/1365	0.91 (0.74-1.14)	43/377	0.95 (0.68-1.33)	22/189	0.93 (0.60-1.44)
Musculoskeletal[e]														
Hip fracture	Blum et al,[12] 2015	62 396; 12 cohorts	51-85	61	2600/58 637	1 [Reference]	229/3759	0.98 (0.85-1.14)	168/2696	1.02 (0.87-1.20)	38/676	1.01 (0.63-1.62)	23/365	1.22 (0.80-1.87)
Any fracture	Blum et al,[12] 2015	27 673; 8 cohorts	51-85	61	2203/25 901	1 [Reference]	204/1772	1.05 (0.90-1.24)	148/1229	1.13 (0.91-1.39)	37/344	1.09 (0.77-1.53)	18/183	0.93 (0.52-1.67)
Nonspine fracture	Blum et al,[12] 2015	23 195; 8 cohorts	51-85	61	1745/21 722	1 [Reference]	166/1473	1.12 (0.91-1.38)	121/1003	1.25 (0.95-1.65)	27/288	1.03 (0.64-1.66)	17/167	1.05 (0.63-1.76)
Spine fracture	Blum et al,[12] 2015	21 759; 6 cohorts	51-85	61	255/20328	1 [Reference]	24/1431	1.00 (0.59-1.71)	15/974	0.95 (0.50-1.82)	7/288	1.67 (0.80-3.47)	2/160	2.17 (0.73-6.44)
Mortality[a]														
Coronary heart disease	Rodondi et al,[11] 2010	54 301; 10 cohorts	46-85	60	1958/50 953	1 [Reference]	210/3348	1.15 (0.99-1.34)	132/2363	1.06 (0.88-1.28)	50/652	1.53 (1.13-2.07)	28/333	1.54 (1.07-2.23)
Total	Rodondi et al,[11] 2010	55 287; 11 cohorts	46-85	60	8749/51837	1 [Reference]	915/3450	1.13 (0.98-1.29)	640/2431	1.07 (0.96-1.20)	170/672	1.11 (0.92-1.33)	105/347	1.24 (0.82-1.87)

Abbreviation: HR, hazard ratio; TSH, thyroid-stimulating hormone.

[a] Adjusted for sex, age, systolic blood pressure, current and former smoking, total cholesterol, and diabetes.

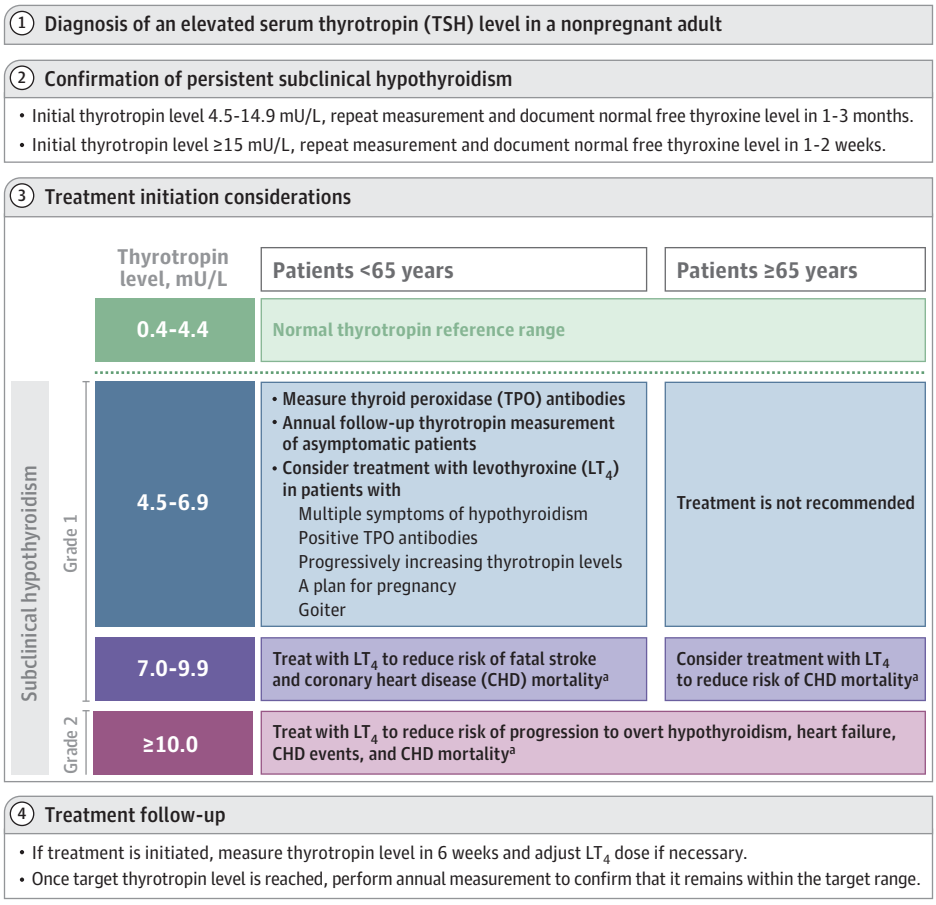
[b] Adjusted for sex, age, systolic blood pressure, current and former smoking, and diabetes.

[c] Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes, total cholesterol, and prevalent cardiovascular disease.

[d] Referent group is thyrotropin 3.5 to 4.49 mU/L.

[e] Adjusted for sex, age, current and former smoking, and body mass index.

Figure. General Therapeutic Approach to the Management of Subclinical Hypothyroidism in Nonpregnant Adults



[a] Recommendation is based on an association of subclinical hypothyroidism with increased rates to the outcomes listed and is not based on clinical trial evidence that treatment can reduce these outcomes.

TSH indicates thyroid-stimulating hormone.

Kidney Function

Thyroid hormone deficiency can worsen renal hemodynamics by decreasing cardiac output, leading to a progressive decline in glomerular filtration rate. In a meta-analysis[58] of 16 studies, there was no association between subclinical hypothyroidism and decline in kidney function. However, in patients with renal failure requiring hemodialysis, subclinical hypothyroidism was associated with higher mortality than with the euthyroid state.[59]

Musculoskeletal Outcomes

Among elderly patients, there was no association of subclinical hypothyroidism with bone mineral density or fracture risk compared with euthyroid controls in 2 meta-analyses.[12,60] There was also no consistent association between subclinical hypothyroidism and frailty either at baseline or during follow-up in community-dwelling elderly people.[61]

Women Undergoing Assisted Reproductive Technologies

A meta-analysis[62] of 4 randomized clinical trials (RCTs) involving 787 infertile couples undergoing vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) therapies did not find an association of levothyroxine therapy with improved conception or live birth rates in women with subclinical hypothyroidism. The American Thyroid Association recommends that women with subclinical hypothyroidism who are undergoing IVF or ICSI be treated with LT_4 to achieve a serum thyrotropin concentration of 2.5 mU/L.[13]

Treatment Rationale

Possible indications for treating subclinical hypothyroidism include improvement in symptoms, prevention of overt hypothyroidism, and prevention of adverse events (**Figure**). These potential benefits of thyroid hormone supplementation should be weighed against the risks of reducing thyrotropin values below the reference range and causing iatrogenic subclinical or overt hyperthyroidism. Randomized trials of treatment of subclinical hypothyroidism have not focused specifically on patients with symptoms of hypothyroidism. The largest trial to date, the TRUST trial,[40] did not demonstrate symptomatic benefit to treatment of older individuals with subclinical hypothyroidism. The TRUST trial randomized 737 men and women 65 years and older with persistent subclinical hypothyroidism to levothyroxine or placebo. There was no effect of levothyroxine on the coprimary outcomes of hypothyroid symptoms and fatigue scores after 12 months of therapy nor on the secondary outcomes of quality of life, handgrip strength, cognitive function, blood pressure, weight, BMI, waist circumference, CIMT, or carotid

plaque thickness.[40] The majority of participants had grade 1 subclinical hypothyroidism (mean baseline thyrotropin, 6.4 mU/L), and the levothyroxine dose was low (median dosage, 50 µg/d), reducing the thyrotropin level by approximately 2 mU/L. No excess of adverse events or hyperthyroid symptoms was observed in the levothyroxine group.[40] A meta-analysis[63] of 21 trials including the TRUST trial found no difference in general quality of life or thyroid-related symptoms between participants with subclinical hypothyroidism treated with levothyroxine compared with placebo. No difference was found for multiple secondary outcomes, including depression, cognitive function testing, fatigue or tiredness, muscle strength, systolic blood pressure, or BMI.[63] One meta-analysis[49] of 12 randomized trials that did not include the TRUST trial found that treatment with levothyroxine was associated with decreased CIMT and improved lipid profile.

In contrast, in a substudy of the TRUST trial,[64] participants who were taking levothyroxine had no difference in CIMT after 18 months of therapy compared with the placebo group. The US Preventive Services Task Force[65] found a potential treatment benefit of levothyroxine on lipids but reported that the effects were inconsistent, not statistically significant in most studies, and of uncertain clinical significance. None of the randomized trials to date has had sufficient power to examine the effects of treatment of subclinical hypothyroidism on end points such as incidence of cardiovascular events, dementia, or fracture. These studies provide strong evidence against treating an unselected group of elderly patients with subclinical hypothyroidism. However, whether these findings can be extrapolated to patients with more marked symptoms of hypothyroidism, those with grade 2 subclinical hypothyroidism, or individuals younger than 65 years is not known.

One retrospective study[66] of individuals with mild subclinical hypothyroidism reported an association of levothyroxine treatment, compared with nontreatment, with lower all-cause mortality and reduced ischemic heart disease events in patients who were younger (40-70 years), but not in patients older than 70 years. In another similarly designed study,[67] levothyroxine treatment was associated with a reduction in all-cause mortality in patients younger than 65 years but not myocardial infarction or cardiovascular death in this age group and not with these outcomes in older patients.

As mentioned previously, progression rates to overt hypothyroidism are low in patients with grade 1 subclinical hypothyroidism (2%-4% per year, depending on TPO positivity), and observational studies do not show an increase in adverse events in this subgroup. These findings in conjunction with the clinical trial results support continued observation instead of treating asymptomatic patients with grade 1 subclinical hypothyroidism. Despite potential benefits of treatment on lipid levels and echocardiographic parameters, no randomized trials have had sufficient statistical power to examine cardiovascular events and observational data have focused on participants without preexisting cardiovascular disease. In the absence of sufficient clinical trial information in patients with grade 2 subclinical hypothyroidism (thyrotropin ≥10 mU/L), the high risk of progression to overt hypothyroidism and observational data demonstrating increased cardiovascular risk without treatment provide the rationale to treat this subgroup of patients (Figure). Initiation of treatment can be considered for patients with a thyrotropin level of 7.0 to 9.9 mU/L based on observational data indicating increased cardiovascular risk, and a therapeutic trial of levothyroxine can be considered for patients with grade 1 subclinical hypothyroidism who have substantial symptoms.

Method of Treatment

Because subclinical hypothyroidism is frequently transient,[27] it is recommended that a second abnormal thyrotropin level be confirmed 1 to 3 months after the initial test and prior to initiating treatment. If the initial thyrotropin value is more than 15 mU/L, testing should be repeated in 1 to 2 weeks. The FT_4 measurement should also be performed at the same time as follow-up testing for thyrotropin levels. Normalization of serum thyrotropin is the goal of therapy in patients who are treated for subclinical hypothyroidism. Levothyroxine is the treatment of choice.[68-71] Because the degree of thyroid dysfunction is mild, small (eg, 25-75 µg) doses of levothyroxine are adequate to restore normal serum thyrotropin levels in the majority of nonpregnant patients. Serum thyrotropin levels should be assessed 6 weeks after initiating the medication, and at 6-week intervals after subsequent changes in the medication dose. Once the thyrotropin target has been achieved, annual thyroid function tests are recommended to document that serum thyrotropin is still within the target range. Importantly, an unacceptably high proportion of patients treated with levothyroxine (15%-38%) have been found to have thyrotropin levels lower than the reference range, indicating over replacement and emphasizing the need for continued monitoring of serum thyrotropin levels.[72,73] Risks of overtreatment (iatrogenic thyrotoxicosis) are particularly problematic in older patients and postmenopausal women and include atrial fibrillation, osteoporosis, and fractures.[74] Because the benefits of therapy are perhaps the lowest in persons 65 years or older and because this group is most susceptible to the dangers of overtreatment, treatment should be individualized and implemented cautiously in this age group (Figure).

Guidelines vary with respect to the target thyrotropin, with some recommending target thyrotropin levels within the reference range[68,69] and others recommending thyrotropin levels within the lower part of the reference range in nonelderly patients.[70,71,75] There is no evidence that adjusting the dose of levothyroxine to alter serum thyrotropin levels within the reference range results in improvement in persistent symptoms or metabolic function.[76-78] Some guidelines recommend relaxation of thyrotropin targets for elderly patients to 1 to 5 mU/L[70] or 4 to 6 mU/L.[69,71] If treatment is withheld, annual monitoring of serum thyrotropin levels seems reasonable. Unfortunately, even though there are clinical practice guidelines that make specific recommendations about subclinical hypothyroidism management, there are large knowledge gaps due to the absence of large randomized trials that include symptomatic patients with a spectrum of ages and serum thyrotropin levels.

Conclusions

Subclinical hypothyroidism is common and most individuals can be observed without treatment. Treatment might be indicated for patients with subclinical hypothyroidism and serum thyrotropin levels of 10 mU/L or higher or for young and middle-aged individuals with subclinical hypothyroidism and symptoms consistent with mild hypothyroidism.

ARTICLE INFORMATION

Author Contributions: Dr Cooper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Cooper, Cappola.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Cooper.
Supervision: All authors.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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