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Subclinical hypothyroidism: When to treat

ABSTRACT

Subclinical hypothyroidism is defined by an elevated serum thyroid-stimulating hormone (TSH) level along with a normal free thyroxine (T_4) level. Whether it should be treated remains controversial. Currently, the best practical approach is to base treatment decisions on the degree of TSH elevation, thyroid autoimmunity, and associated comorbidities.

KEY POINTS

From 4% to 20% of adults have subclinical hypothyroidism, with a higher prevalence in women, older people, and those with thyroid autoimmunity.

Subclinical hypothyroidism can progress to overt hypothyroidism, especially if antithyroid antibodies are present, and has been associated with adverse metabolic, cardiovascular, reproductive, maternal-fetal, neuromuscular, and cognitive abnormalities and lower quality of life.

Some studies have suggested that levothyroxine therapy is beneficial, but others have not, possibly owing to variability in study designs, sample sizes, and patient populations.

Further trials are needed to clearly demonstrate the clinical impact of subclinical hypothyroidism and the effect of levothyroxine therapy.

Dr. Nasr has disclosed teaching and speaking for Eisai, Genzyme/Sanofi, and Shire and membership on an advisory committee or review panel for Exelixis, Nevro, and Pfenex.

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Whether subclinical hypothyroidism is clinically important and should be treated remains controversial. Studies have differed in their findings, and although most have found this condition to be associated with a variety of adverse outcomes, large randomized controlled trials are needed to clearly demonstrate its clinical impact in various age groups and the benefit of levothyroxine therapy.

Currently, the best practical approach is to base treatment decisions on the magnitude of elevation of thyroid-stimulating hormone (TSH) and whether the patient has thyroid autoantibodies and associated comorbid conditions.

HIGH TSH, NORMAL FREE T_4 LEVELS

Subclinical hypothyroidism is defined by elevated TSH along with a normal free thyroxine (T_4).[1]

The hypothalamic-pituitary-thyroid axis is a balanced homeostatic system, and TSH and thyroid hormone levels have an inverse log-linear relation: if free T_4 and triiodothyronine (T_3) levels go down even a little, TSH levels go up a lot.[2]

TSH secretion is pulsatile and has a circadian rhythm: serum TSH levels are 50% higher at night and early in the morning than during the rest of the day. Thus, repeated measurements in the same patient can vary by as much as half of the reference range.[3]

WHAT IS THE UPPER LIMIT OF NORMAL FOR TSH?

The upper limit of normal for TSH, defined as the 97.5th percentile, is approximately 4 or 5

TABLE 1

Causes of elevated thyroid-stimulating hormone

Subclinical hypothyroidism
Autoimmune (Hashimoto) thyroiditis
Suboptimal treatment of overt hypothyroidism
Partial thyroidectomy
Radioactive iodine ablation
External beam radiation of head and neck
Infiltrative diseases of the thyroid (amyloidosis, sarcoidosis, hemochromatosis, Riedel thyroiditis, scleroderma)
Drugs, eg, iodine contrast, amiodarone, lithium, tyrosine kinase inhibitors (sunitinib, sorafenib), interferon alpha, or immune response modulators (ipilimumab, alemtuzumab, pembrolizumab)
Iodine deficiency
Excess iodine
Thyroid dysgenesis
Physiologic increases
Diurnal variation
Recovery phase of euthyroid sick syndrome
Recovery phase of subacute, painless, or postpartum thyroiditis
Other causes
Assay variability
Substances that interfere with TSH assays (heterophile antibodies, rheumatoid factor, biotin, macro-TSH or abnormal TSH isoforms)
Central hypothyroidism or hyperthyroidism
Thyroid hormone resistance
Impaired renal function
Adrenal insufficiency
Obesity
Older age

Based on information in references 1, 2, and 16.

mIU/L depending on the laboratory and the population, but some experts believe it should be lower.[3]

In favor of a lower upper limit: the distribution of serum TSH levels in the healthy general population does not seem to be a typical bell-shaped Gaussian curve, but rather has a tail at the high end. Some argue that some of the individuals with values in the upper end of the normal range may actually have undiagnosed hypothyroidism and that the upper 97.5th percentile cutoff would be 2.5 mIU/L if these people were excluded.[4] Also, TSH levels higher than 2.5 mIU/L have been associated with a higher prevalence of antithyroid antibodies and a higher risk of clinical hypothyroidism.[5]

On the other hand, lowering the upper limit of normal to 2.5 mIU/L would result in 4 times as many people receiving a diagnosis of subclinical hypothyroidism, or 22 to 28 million people in the United States.[4,6] Thus, lowering the cutoff may lead to unnecessary therapy and could even harm from overtreatment.

Another argument against lowering the upper limit of normal for TSH is that, with age, serum TSH levels shift higher.[7] The third National Health and Nutrition Education Survey (NHANES III) found that the 97.5th percentile for serum TSH was 3.56 mIU/L for age group 20 to 29 but 7.49 mIU/L for octogenarians.[7,8]

It has been suggested that the upper limit of normal for TSH be adjusted for age, race, sex, and iodine intake.[3] Currently available TSH reference ranges are not adjusted for these variables, and there is not enough evidence to suggest age-appropriate ranges,[9] although higher TSH cutoffs for treatment are advised in elderly patients.[10] Interestingly, higher TSH in older people has been linked to lower mortality rates in some studies.[11]

Authors of the NHANES III[8] and Hanford Thyroid Disease study[12] have proposed a cutoff of 4.1 mIU/L for the upper limit of normal for serum TSH in patients with negative antithyroid antibodies and normal findings on thyroid ultrasonography.

SUBCLINICAL HYPOTHYROIDISM IS COMMON

In different studies, the prevalence of subclinical hypothyroidism has been as low as 4% and as high as 20%.[1,8,13] The prevalence is higher in women and increases with age.[8] It is higher in iodine-sufficient areas, and it increases in iodine-deficient areas with iodine supplementation.[14] Genetics also plays a role, as subclini-

cal hypothyroidism is more common in white people than in African Americans.[8]

A difficulty in estimating the prevalence is the disagreement about the cutoff for TSH, which may differ from that in the general population in certain subgroups such as adolescents, the elderly, and pregnant women.[10,15]

A VARIETY OF CAUSES

The most common cause of subclinical hypothyroidism, accounting for 60% to 80% of cases, is Hashimoto (autoimmune) thyroiditis,[2] in which thyroid peroxidase antibodies are usually present.[2,16]

Other causes include suboptimal treatment of hypothyroidism due to other reasons such as thyroidectomy, radioactive iodine treatment, external radiation, infiltrative diseases (eg, amyloidosis, sarcoidosis, hemochromatosis), and drugs (eg, iodinated contrast, amiodarone, lithium, tyrosine kinase inhibitors) (**Table 1**).[1,2,16]

Also important to rule out are false-positive elevations due to substances that interfere with TSH assays (eg, heterophile antibodies, rheumatoid factor, biotin, macro-TSH); reversible causes such as the recovery phase of euthyroid sick syndrome; subacute, painless, or postpartum thyroiditis; central hypo- or hyperthyroidism; and thyroid hormone resistance.

SUBCLINICAL HYPOTHYROIDISM CAN RESOLVE OR PROGRESS

"Subclinical" suggests that the disease is in its early stage, with changes in TSH already apparent but decreases in thyroid hormone levels yet to come.[17] And indeed, subclinical hypothyroidism can progress to overt hypothyroidism,[18] although it has been reported to resolve spontaneously in half of cases within 2 years,[19] typically in patients with TSH values of 4 to 6 mIU/L.[20] The rate of progression to overt hypothyroidism is estimated to be 33% to 55% over 10 to 20 years of follow-up.[18]

The risk of progression to clinical disease is higher in patients with thyroid peroxidase antibody, reported as 4.3% per year compared with 2.6% per year in those without this antibody.[20,21] In one study, the risk of developing overt hypothyroidism in those with subclinical hypothyroidism increased from 1% to 4% with doubling of the TSH.[21] Other risk factors for progression to hypothyroidism include female sex, older age, goiter, neck irradiation or radioactive iodine exposure, and high iodine intake.[18,22]

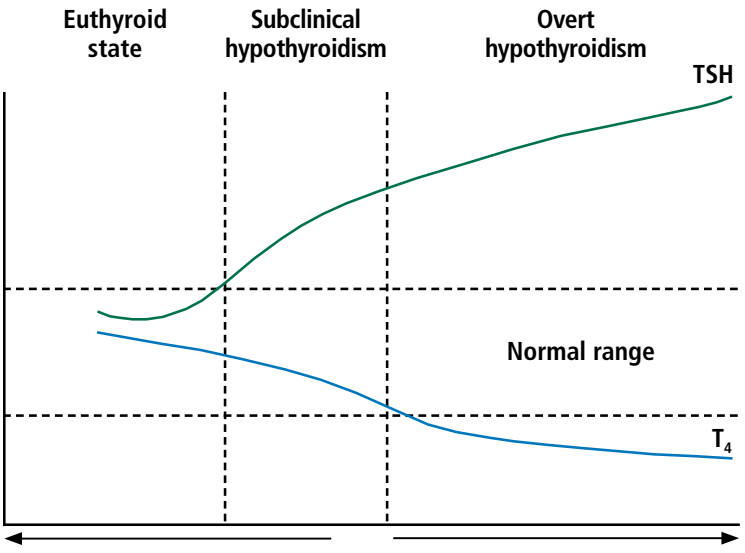

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Figure 1. Natural course of subclinical hypothyroidism (TSH = thyroid-stimulating hormone, T_4 = free thyroxine).

The upper limit of normal for serum TSH is controversial

Figure 1 shows the natural history of subclinical hypothyroidism.[1]

GUIDELINES FOR SCREENING DIFFER

Guidelines differ on screening for thyroid disease in the general population, owing to lack of large-scale randomized controlled trials showing treatment benefit in otherwise-healthy people with mildly elevated TSH values.

Various professional societies have adopted different criteria for aggressive case-finding in patients at risk of thyroid disease. Risk factors include family history of thyroid disease, neck irradiation, partial thyroidectomy, dyslipidemia, atrial fibrillation, unexplained weight loss, hyperprolactinemia, autoimmune disorders, and use of medications affecting thyroid function.[23]

The US Preventive Services Task Force

TABLE 2

Adverse effects of subclinical hypothyroidism and the role for levothyroxine

Adverse effect	Evidence of adverse effect	Role for treatment with levothyroxine
Metabolic syndrome, obesity, diabetes	Associations observed, but cause and effect are unclear[23,24]	No evidence to support
Dyslipidemia	Relationships observed between thyroid-stimulating hormone (TSH) elevation and altered lipid profiles[13,43]	Associated with improved lipid profiles[2,34,44–46]
Cardiovascular endothelial dysfunction	Increased risk of myocardial infarction, atherosclerosis, aortic calcification,[48] cardiovascular disease and mortality[37]; increased arterial stiffness and systemic vascular resistance[45,53]	Lessens cardiovascular risk and mortality in patients < 65 years
Stroke	Conflicting data: no association in patients ≥ 65 years, but some association in those < 65	Lessens cardiovascular risk and mortality in patients < 65 years
Psychiatric and cognitive dysfunction	Associated with worsened preexisting depression and bipolar disease; may affect cognition[65]	May improve mood, anxiety, cognition in older patients[35]
Neuromuscular dysfunction, exercise intolerance	Associated with skeletal muscle dysfunction, exercise intolerance[71]	Limited data on treatment; role is unclear[75]
Bone health	Associated with increased risk of hip fracture attributed to suppression of bone turnover by elevated TSH[18,76,77]	Too few clinical studies to define a role
Thyroid cancer	Some data suggest elevated TSH is associated with higher risk[79–82]	More studies needed to understand association
Infertility, recurrent miscarriage	Inconclusive evidence links subclinical hypothyroidism with infertility[86]; infertility rate is higher in women who also have positive thyroid peroxidase antibody than in women without autoimmunity[87]	Some studies have shown lower rates of miscarriage with levothyroxine when TSH > 4.0 mIU/L[86,91–92]; insufficient data to support its use in patients with subclinical hypothyroidism and infertility; however, consider in euthyroid patients with positive peroxidase antibody and recurrent miscarriage[90]
Pregnancy complications	Associated with several pregnancy-related complications including preeclampsia, hypertension, placental abruption, and postpartum hemorrhage in some studies,[26,96] but not in others; if present, screen for autoimmunity	No recommendations; insufficient evidence to evaluate role of treatment
Preterm delivery, pregnancy loss	Associated with high risk of miscarriage, preterm delivery, pregnancy loss at even mildly elevated TSH levels (2.5–5 mIU/L)[99;104–107]; risk is as high as 60% with TSH levels > 6 mIU/L and higher with positive thyroid peroxidase antibody[108–110]	Improves maternal and fetal outcomes, including risk of low birth weight and low Apgar score, in women with subclinical hypothyroidism and TSH 2.5–10 mIU/L[93,106]; evidence less clear with TSH 2.5–4 mIU/L[86]; not recommended for the subgroup of pregnant patients with negative thyroid peroxidase antibody and TSH within pregnancy-specific range or < 4 mIU/L

in 2014 found insufficient evidence on the benefits and harms of screening.[24]

The American Thyroid Association (ATA) recommends screening adults starting at age 35, with repeat testing every 5 years in patients who have no signs or symptoms of hypothyroidism, and more frequently in those who do.[25]

The American Association of Clinical Endocrinologists recommends screening in women and older patients. Their guidelines and those of the ATA also suggest screening people at high risk of thyroid disease due to risk factors such as history of autoimmune diseases, neck irradiation, or medications affecting thyroid function.[26]

The American Academy of Family Physicians recommends screening after age 60.[18]

The American College of Physicians recommends screening patients over age 50 who have symptoms.[18]

Our approach. Although evidence is lacking to recommend routine screening in adults, aggressive case-finding and treatment in patients at risk of thyroid disease can, we believe, offset the risks associated with subclinical hypothyroidism.[24]

CLINICAL PRESENTATION

About 70% of patients with subclinical hypothyroidism have no symptoms.[13]

Tiredness was more common in subclinical hypothyroid patients with TSH levels lower than 10 mIU/L compared with euthyroid controls in 1 study, but other studies have been unable to replicate this finding.[27,28]

Other frequently reported symptoms include dry skin, cognitive slowing, poor memory, muscle weakness, cold intolerance, constipation, puffy eyes, and hoarseness.[13]

The evidence in favor of levothyroxine therapy to improve symptoms in subclinical hypothyroidism has varied, with some studies showing an improvement in symptom scores compared with placebo, while others have not shown any benefit.[29–31]

In one study, the average TSH value for patients whose symptoms did not improve with therapy was 4.6 mIU/L.[31] An explanation for the lack of effect in this group may be that the TSH values for these patients were in the high-normal range. Also, because most subclinical hypothyroid patients have no symptoms, it is difficult to ascertain symptomatic improvement. Though it is possible to conclude that levothyroxine therapy has a limited role in this group, it is important to also consider the suggestive evidence that untreated subclinical hypothyroidism may lead to increased morbidity and mortality.

TABLE 3

Factors favoring levothyroxine therapy in subclinical hypothyroidism

Thyroid-stimulating hormone (TSH) level > 2 times the upper limit of normal or > 8 mIU/L
Progressive rise in TSH
Goiter
Positive antithyroid antibodies
Pregnancy or planning pregnancy
Infertility or ovulatory dysfunction
Childhood or adolescence
Dyslipidemia
Established cardiovascular disease or risk factors for cardiovascular disease
Depression or bipolar disease
Therapeutic trial for clinical symptoms of hypothyroidism
Patient preference

The most common cause of subclinical hypothyroidism is Hashimoto (autoimmune) thyroiditis

ADVERSE EFFECTS OF SUBCLINICAL HYPOTHYROIDISM, EFFECTS OF THERAPY

Subclinical hypothyroidism has been associated with adverse metabolic, cardiovascular, neuromuscular, and cognitive effects and has been shown to have a detrimental impact on quality of life. However, studies of levothyroxine therapy in subclinical hypothyroidism have yielded mixed results.[16] Subclinical hypothyroidism affects many biologic systems, and levothyroxine may have a role (**Table 2**).[32–117]

INDIVIDUALIZED MANAGEMENT AND SHARED DECISION-MAKING

The management of subclinical hypothyroidism should be individualized on the basis of

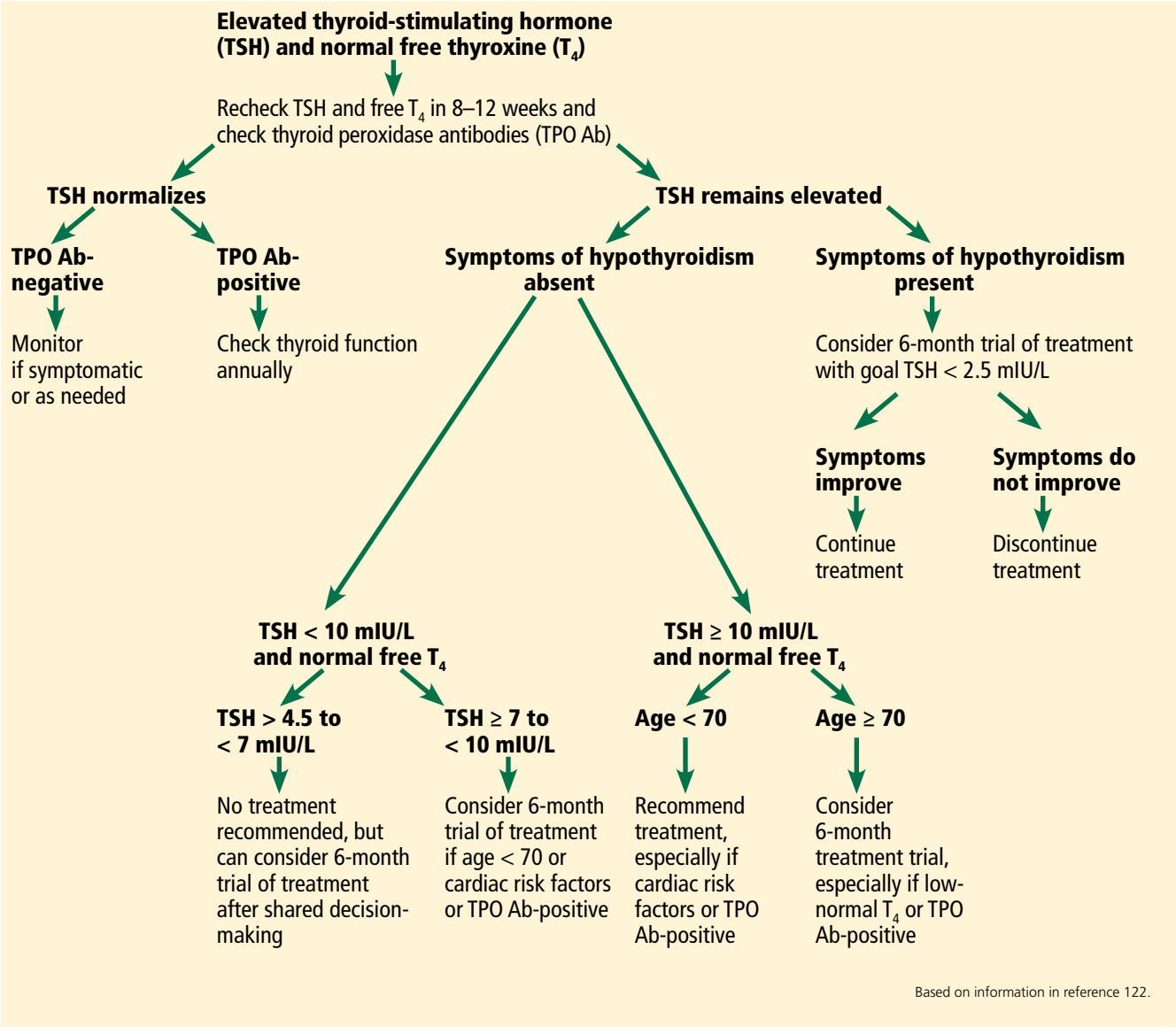

Figure 2. Treatment algorithm for subclinical hypothyroidism in nonpregnant patients.

extent of thyroid dysfunction, comorbid conditions, risk factors, and patient preference.[118] Shared decision-making is key, weighing the risks and benefits of levothyroxine treatment and the patient's goals.

There is some evidence to support levothyroxine treatment in nonpregnant patients with overt hypothyroidism (TSH > 10 mIU/L) or in patients with TSH 5 to 10 mIU/L with symptoms or hyperlipidemia and in younger patients at risk of cardiovascular disease.[118] **Table 3** describes various patient factors that should be considered during clinical evaluation and decisions about levothyroxine treatment in subclinical hypothyroidism.

The risks of treatment should be kept in mind and explained to the patient. Levothyroxine has a narrow therapeutic range, causing a possibility of overreplacement, and a half-life of 7 days that can cause dosing errors to have longer effect.[118,119]

Adherence can be a challenge. The drug needs to be taken on an empty stomach because foods and supplements interfere with its absorption.[118,120] In addition, the cost of medication, frequent biochemical monitoring, and possible need for titration can add to financial burden.

When choosing the dose, one should consider the degree of hypothyroidism or TSH elevation and the patient's weight, and adjust the dose gently.

If the TSH is high-normal

It is proposed that a TSH range of 3 to 5 mIU/L overlaps with normal thyroid function in a great segment of the population, and at this level it is probably not associated with clinically significant consequences. For these reasons, levothyroxine therapy is not thought to be beneficial for those with TSH in this range.

Pollock et al[121] found that, in patients with symptoms suggesting hypothyroidism and TSH values in the upper end of the normal range, there was no improvement in cognitive function or psychological well-being after 12 weeks of levothyroxine therapy.

However, due to the concern for possible adverse maternal and fetal outcomes and low IQ in children of pregnant patients with subclinical hypothyroidism, levothyroxine therapy is advised in those who are pregnant or planning pregnancy who have TSH levels higher than 2.5 mIU/L, especially if they have thyroid peroxidase antibody. Levothyroxine therapy is not recommended for pregnant patients with negative thyroid peroxidase antibody and TSH within the pregnancy-specific range or less than 4 mIU/L if the reference ranges are unavailable.

Keep in mind that, even at these TSH values, there is risk of progression to overt hypothyroidism, especially in the presence of thyroid peroxidase antibody, so patients in this group should be monitored closely.

If TSH is mildly elevated

The evidence to support levothyroxine therapy in patients with subclinical hypothyroidism with TSH levels less than 10 mIU/L remains inconclusive, and the decision to treat should be based on clinical judgment.[2] The studies that have looked at the benefit of treating subclinical hypothyroidism in terms of cardiac, neuromuscular, cognitive, and neuropsychiatric outcomes have included patients with a wide range of TSH levels, and some of these studies were not stratified on the basis of degree of TSH elevation.

The risk that subclinical hypothyroidism will progress to overt hypothyroidism in patients with TSH higher than 8 mIU/L is high, and in 70% of these patients, the TSH level rises to more than 10 mIU/L within 4 years. Early treatment should be considered if the TSH is higher than 7 or 8 mIU/L.

If TSH is higher than 10 mIU/L

The strongest evidence in favor of treating subclinical hypothyroidism is in patients with TSH levels higher than 10 mIU/L.[2] Thyroid dysfunction with this degree of TSH elevation has been associated with adverse cardiometabolic, neuromuscular, cognitive, and psychiatric effects as described above, and has been shown to improve with levothyroxine therapy.

Figure 2 outlines an algorithmic approach to subclinical hypothyroidism in nonpregnant patients as suggested by Peeters.[122]

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CORRECTION

Subclinical hypothyroidism

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In Azim S, Nasr C, "Subclinical hypothyroidism: When to treat," Cleve Clin J Med 2019; 86(2):101–110, on page 103, in the section "Subclinical hypothyroidism can resolve or progress," the sentence "The rate of progression to overt hypothyroidism is estimated to be 33% to 35% over 10 to 20 years of follow-up" contained an error. The correct rate of progression is 33% to 55%. This error has been corrected online.