CLINICAL PRACTICE

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Subclinical Hyperthyroidism

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

A 65-year-old woman is seen for routine evaluation. She has a history of paroxysmal atrial fibrillation and osteoporosis, which has been treated with a bisphosphonate. She has no history of thyroid disease and reports no symptoms of hyperthyroidism. Her pulse is 80 beats per minute. The left thyroid lobe is enlarged, but the results of physical examination are otherwise normal, as are the results of electrocardiography. The serum thyrotropin level is 0.2 mU per liter (reference range, 0.5 to 4.5) and the free thyroxine (T_4) level 1.2 ng per deciliter (reference range, 0.8 to 1.8). How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

In overt hyperthyroidism, serum levels of free T_4 and triiodothyronine (T_3) or levels of T_3 alone are elevated, and serum thyrotropin levels are suppressed. In subclinical hyperthyroidism, levels of free T_4 and T_3 are normal, thyrotropin levels are suppressed, and thyroid hormone levels are usually in the middle to upper range of normal.[1,2] The prevalence of overt hyperthyroidism ranges from 0.7 to 1.8% in iodine-sufficient populations and 2 to 15% in persons with mild iodine deficiency. Between 65% and 75% of persons with subclinical hyperthyroidism have serum thyrotropin levels of 0.1 to 0.4 mU per liter (referred to here as mild subclinical hyperthyroidism), and the remainder have thyrotropin levels of less than 0.1 mU per liter (severe subclinical hyperthyroidism).[3-5]

CAUSES

The causes of subclinical hyperthyroidism are the same as the causes of overt hyperthyroidism (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The common endogenous causes include toxic multinodular goiter or toxic adenoma[3-5] and Graves' disease, with the latter accounting for 40% of cases in populations with sufficient iodine intake.[2,5] Exogenous subclinical hyperthyroidism resulting from excessive intake of levothyroxine, liothyronine, or desiccated thyroid may reflect inadvertent overtreatment, purposeful overuse (often surreptitious) by the patient, or intentional use to suppress the production of thyrotropin.[6] Exogenous subclinical hyperthyroidism is far more common than endogenous subclinical hyperthyroidism. In endogenous cases, serum T_3 levels are typically normal or at the high end of the reference range, whereas T_3 levels are usually in the middle or lower part of the reference range in patients receiving levothyroxine.[5,7] It is not known whether differences in patterns of thyroid hormone levels between endogenous and exogenous subclinical hyperthyroidism result in disparate effects on the cardiovascular and skeletal systems.

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KEY CLINICAL POINTS

SUBCLINICAL HYPERTHYROIDISM

- Subclinical hyperthyroidism, in which serum thyroid hormone levels are within the reference range but serum thyrotropin levels are subnormal (≤0.4 mU per liter), may be caused by overproduction of endogenous thyroid hormone or excessive ingestion of exogenous thyroid hormone.
- Progression to overt hyperthyroidism may occur, especially when serum thyrotropin levels are less than 0.1 mU per liter.
- Even without progression to overt hyperthyroidism, subclinical hyperthyroidism can be associated with adverse outcomes, including cardiovascular disease (e.g., atrial fibrillation, heart failure, and coronary heart disease), bone loss, fractures, and dementia, particularly in persons older than 65 years of age with severe disease.
- Although data are lacking from randomized clinical trials to guide treatment decisions, professional organizations recommend treatment of subclinical hyperthyroidism in persons older than 65 years of age and postmenopausal women, especially when serum thyrotropin levels are less than 0.1 mU per liter.

POTENTIAL CLINICAL CONSEQUENCES

The potential clinical consequences of subclinical hyperthyroidism include progression to overt hyperthyroidism, cardiovascular conditions, bone loss, fractures, and dementia. Each is discussed below (see also Table 1).

Progression to Overt Hyperthyroidism

The best predictor of progression from subclinical hyperthyroidism to overt hyperthyroidism is the baseline serum thyrotropin level[20,21] rather than the cause of the disease.[22] Serum thyrotropin levels in patients with mild subclinical hyperthyroidism frequently normalize during follow-up, whereas patients with thyrotropin levels lower than 0.1 mU per liter usually have persistent disease or progression to overt hyperthyroidism.[20,21,23] Patients with nodular thyroid disease and subclinical hyperthyroidism are at increased risk for progression to overt hyperthyroidism after exposure to a large iodine load.[24] Pretreatment with methimazole may reduce this risk, but its efficacy is uncertain.[25]

Cardiovascular Conditions

Sinus tachycardia, premature atrial and ventricular beats, and diastolic dysfunction are associated with severe subclinical hyperthyroidism.[26,27] Population-based studies,[9-11] prospective observational studies,[12] and meta-analyses[13,14,28] have shown a significantly higher risk of atrial fibrillation,[9,10,12,13] heart failure,[11,14] death from coronary heart disease,[13] death from any cause,[11,13,28] and major adverse cardiovascular events[11] among patients who have severe subclinical hyperthyroidism than among those who do not (Tables S2 and S3 in the Supplementary Appendix). Some studies indicate greater cardiovascular risks, especially the risk of atrial fibrillation, with greater thyrotropin suppression[13,14]; absolute risks, but not relative risks, increase with age.[11,13,14] Increases in cardiovascular disease and arrhythmia[29] and cardiovascular mortality[30] are also associated with doses of thyroxine that suppress thyrotropin to levels below 0.1 mU per liter.

Bone Loss and Fractures

The risk of osteoporotic fractures is significantly increased among patients with severe endogenous subclinical hyperthyroidism[15-17]; some studies also show an increased risk of fracture among those with mild cases of the disease (Table S2 in the Supplementary Appendix). Exogenous subclinical hyperthyroidism in patients whose serum thyrotropin levels are lower than 0.03 mU per liter has also been associated with an increased risk of fractures and fracture-related deaths.[29] Subclinical hyperthyroidism among men older than 65 years of age has been associated with an increased risk of frailty.[31]

Dementia

Associations have been reported between subclinical hyperthyroidism and cognitive impairment or dementia.[18,32] A prospective cohort study involving persons in their 70s showed a higher risk of dementia among participants with severe subclinical hyperthyroidism (but not among those with mild subclinical hyperthyroidism) than among those with normal thyroid function.[19]

Table 1. Clinical Outcomes in Mild and Severe Endogenous Subclinical Hyperthyroidism and Possible Benefits of Treatment.*

Outcome	Strength of Association†		Benefits of Treatment
	Mild Subclinical Hyperthyroidism‡	Severe Subclinical Hyperthyroidism‡	
Symptoms	Insufficient data	Possible in young patients; usually absent in patients older than 65 yr	Nonrandomized studies involving young adults with severe subclinical hyperthyroidism suggest benefit
Risk of progression	Progression may occur but less frequently than in patients with severe disease; risk increases after large iodine load	Definite according to prospective studies	Early treatment can prevent development of known adverse effects of overt hyperthyroidism
Cardiovascular manifestations or ectopic rhythm§	Insufficient data	Possible	Nonrandomized studies involving patients with severe subclinical hyperthyroidism suggest benefit
Atrial fibrillation	Definite, especially in middle-aged and elderly patients with risk factors for atrial fibrillation	Definite	Insufficient data
Heart failure	Possible, especially with advanced age and in patients with risk factors for heart failure	Definite	Insufficient data
Death from coronary heart disease	Possible, especially in adults with cardiovascular risk factors	Definite	Insufficient data
Stroke[8]	Available data suggest no statistically significant increase in risk, but data are limited and conflicting	Insufficient data	Insufficient data
Cognitive dysfunction or dementia	Data from prospective studies are limited and conflicting	Definite according to meta-analyses	Insufficient data
Osteoporosis	Possible in patients with risk factors for osteoporosis; unlikely in young adults without risk factors for osteoporosis	Definite	Nonrandomized studies involving postmenopausal women with severe subclinical hyperthyroidism suggest improvement in bone density; data insufficient to inform benefits in elderly men
Fractures	Possible, especially in patients with risk factors for osteoporosis; unlikely in young adults without risk factors for osteoporosis	Definite in postmenopausal women, elderly men, and patients with risk factors for osteoporosis	Insufficient data

* Data on stroke are derived from are derived from Chaker et al.[8]. All other data are derived from Cooper and Biondi,[1] Vadiveloo et al.,[9] Selmer et al.,[10,11] Cappola et al.,[12] Collet et al.,[13] Gencer et al.,[14] Yan et al.,[15] Blum et al.,[16] Yang et al.,[17] Rieben et al.,[18] and Aubert et al.[19]

† Associations are considered to be definite when supported consistently by results of meta-analyses, possible when there are some but inconsistent supporting data (including heterogeneous results of meta-analyses), and insufficient when data are limited.

‡ Mild subclinical hyperthyroidism is defined as a thyrotropin level of 0.1 to 0.4 mU per liter, and severe subclinical hyperthyroidism as a thyrotropin level of less than 0.1 mU per liter.

§ Cardiovascular manifestations include sinus tachycardia while at rest, premature atrial and ventricular beats, reduced variability in heart rate, increased left ventricular mass, diastolic dysfunction, and reduced exercise tolerance.

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Table 2. Overt Primary Hyperthyroidism, Subclinical Hyperthyroidism, and Other Causes of Low Serum Thyrotropin Levels.

Overt primary hyperthyroidism
Suppressed thyrotropin levels and elevated levels of free thyroxine (T_4) and triiodothyronine (T_3) or elevated levels of T_3 only
Subclinical hyperthyroidism
In mild cases, low but detectable serum thyrotropin levels (0.1 to 0.4 mU per liter) with normal levels of free T_4 and T_3
In severe cases, undetectable serum thyrotropin level (<0.1 mU per liter) with normal levels of free T_4 and T_3
Other causes of low serum thyrotropin levels
The following causes of low serum thyrotropin levels should be ruled out before a diagnosis of subclinical hyperthyroidism is made:
Severe nonthyroidal illness
Administration of drugs that suppress serum thyrotropin levels (e.g., dopamine, high doses of glucocorticoids, dobutamine, somatostatin analogues, amphetamines, bromocriptine, and bexarotene)
Pituitary or hypothalamic disease that causes thyroid hormone or thyrotropin deficiency
Psychiatric illness
Late first-trimester of pregnancy
Hyperemesis gravidarum
Older age (i.e., age-induced changes in the hypothalamic–pituitary thyroid axis in areas of the world with iodine deficiency)
African descent (thyrotropin levels are below the reference range in 3 to 4% of patients

STRATEGIES AND EVIDENCE

EVALUATION

Older patients with subclinical hyperthyroidism are usually asymptomatic,[33] but younger persons may have mild adrenergic symptoms.[26] Physical examination may reveal an enlarged or nodular thyroid or Graves' ophthalmopathy, but tachycardia, tremor, and other adrenergic signs of thyroid overactivity may be absent. The diagnosis of subclinical hyperthyroidism is based on laboratory results, but several other common clinical situations are associated with similar laboratory findings (see Table 2). Levels of free T_4 and T_3 should be promptly assessed in patients with a serum thyrotropin level of less than 0.1 mU per liter to rule out overt hyperthyroidism. In the absence of overt disease, it is reasonable to defer further evaluation for 2 to 3 months, at which time repeat testing should be performed; subnormal serum thyrotropin levels are transient in up to 50% of patients,[34] most often in those with mild disease.[20,21,23] If a subnormal serum thyrotropin level persists, further testing is indicated to determine the cause.[3,4] Table 3 reviews tests that are useful in the diagnosis of subclinical hyperthyroidism and the assessment of potential complications of the condition.

TREATMENT

Data from randomized trials are lacking regarding the effects of treatment on symptoms and adverse outcomes in patients with previously untreated subclinical hyperthyroidism. Uncontrolled studies have shown improvements in various cardiac measures (e.g., effects on premature beats and exercise capacity after antithyroid drug therapy,[27] radioiodine therapy,[35-37] or beta-blockade[38]). Beta-blockers may be considered in symptomatic patients with thyroid cancer who are taking thyrotropin-suppressive doses of levothyroxine.[38] Several nonrandomized studies have shown more stability in bone mineral density with treatment than with no treatment among postmenopausal women who have subclinical hyperthyroidism,[39,40] but not among premenopausal women.[41]

The goal of treatment, when initiated, is normalization of serum thyrotropin levels. The adverse effects of persistent subclinical hyperthyroidism in older persons has led professional organizations to recommend treatment of severe and possibly mild subclinical hyperthyroidism in persons older than 65 years of age, despite the absence of hard evidence of benefit[3,4] (Fig. 1). Doses of levothyroxine should be lowered in patients with hypothyroidism and in those with low-risk thyroid cancer with no measurable disease. Among patients with thyroid cancer with measurable disease, the benefits of suppression must be weighed against the risks of iatrogenic thyrotoxicosis.[6]

Endogenous subclinical hyperthyroidism may be treated with methimazole (propylthiouracil is no longer a first-line therapy owing to its association with the rare complication of hepatotoxicity), radioiodine therapy, or surgery (Fig. 2). Methimazole is appropriate for adults with Graves' disease who are 65 years of age or younger, since Graves' disease may remit after 12 to 18 months of therapy, and remission is more likely in patients with mild disease than in patients with more severe disease[42,43] (Fig. 2). Some experts

Table 3. Means of Establishing the Cause and Assessing the Risks Associated with Subclinical Hyperthyroidism.

Objective	Patient Population	Rationale or Interpretation
Establishment of cause		
Evaluation of anti–thyrotropin-receptor antibodies (thyroid-stimulating antibody or thyroid-stimulating immunoglobulin)	Patients with normal results on thyroid examination or those in whom Graves' disease is suspected (e.g., diffuse thyroid enlargement, Graves' ophthalmopathy)	Positive result for anti–thyrotropin-receptor antibodies is virtually diagnostic of Graves' disease; however, test is less sensitive in patients with milder disease (e.g., subclinical hyperthyroidism) than in those with overt disease.
Color-flow Doppler ultrasonography of thyroid to document and characterize thyroid nodules and goiter	Patients in whom thyroid nodule or goiter is suspected on physical examination	Documentation of ≥1 nodule on ultrasonography, especially if >2 cm in diameter, suggests one or more autonomous thyroid nodules are causing subclinical hyperthyroidism.
Thyroid scintigraphy and 24-hr radioactive iodine uptake to identify autonomous thyroid tissue	Patients with one or more thyroid nodules or goiter detected on ultrasonography	Documentation of functional thyroid nodules establishes the likely cause of subclinical hyperthyroidism (radioiodine is the preferred therapy). Low uptake suggests thyroiditis or iodine exposure.
Assessment of 24-hr urinary iodine excretion	Patients with suspected or known excessive exposure to iodine, usually from iodinated contrast agents	Patients with nodular thyroid disease are susceptible to iodine-induced thyrotoxicosis (the Jod–Basedow phenomenon), especially in areas of the world with iodine insufficiency.
Assessment of risks		
Evaluation for cardiovascular risk factors, underlying cardiovascular disease, or both	All patients, especially those >65 yr	Patients >65 yr may be at increased risk for cardiac consequences of chronic subclinical hyperthyroidism, especially if they have underlying cardiovascular disease.
Electrocardiography	Patients with symptoms of cardiovascular disease (e.g., palpitations)	Assessment of heart rate and detection of arrhythmias.
Holter monitoring	Patients with symptoms of cardiovascular disease and patients with underlying heart disease or new-onset atrial fibrillation, heart failure, or coronary heart disease	Assessment of heart rate and detection of arrhythmias.
Echocardiography	Patients with symptoms of cardiovascular disease and patients with underlying heart disease, heart failure, atrial fibrillation, or coronary heart disease	Assessment of cardiac structure and ventricular function.
Assessment for risk factors for stroke	Patients with atrial fibrillation	Hypertension, diabetes mellitus, history of congestive heart failure, older age (≥65 yr), history of stroke or transient ischemic attack are associated with increased risk of stroke.
Dual-energy radiographic absorptiometry (bone-density test)	Postmenopausal women, men >65 yr, and patients with other risk factors for low bone mineral density	If bone mineral density is low, intake of calcium and vitamin D should be increased. Antiresorptive therapy should be considered in patients with osteoporosis after assessment of the risks and benefits of therapy.

recommend definitive treatment in patients with Graves' disease who are older than 65 years of age, since remissions are not necessarily lifelong, and relapses may be asymptomatic and thus go unrecognized[3,4] (Fig. 2). Radioiodine is preferred in patients with subclinical hyperthyroidism that is caused by toxic multinodular goiter or toxic adenoma[3,4] (Fig. 2). Surgery is reserved for patients with large goiters and compressive symptoms or coexisting hyperparathy-

roidism or those in whom thyroid cancer is suspected[3,4] (Fig. 2).

Adverse effects of methimazole include agranulocytosis (<0.5% of patients) and drug-induced liver disease (<0.1%).[43,44] However, the small doses (e.g., 5 to 10 mg per day) generally administered to patients with subclinical hyperthyroidism are less likely than higher doses to cause adverse effects.[43,44] Radioiodine causes hypothyroidism routinely in patients with Graves' disease and infrequently in those with nodular thyroid disease. Radioiodine may also result in transient worsening of hyperthyroidism[3,4]; pretreatment with antithyroid drugs may be considered in patients older than 65 years of age.[3] Among patients with Graves' disease, radioiodine may worsen ophthalmopathy, and radioiodine is generally contraindicated in patients with active eye disease.[3,4] Surgery results in hypothyroidism and may cause hypoparathyroidism (<2% of patients) or recurrent laryngeal nerve damage (<1% of patients)[3,4]; rates are lower with experienced surgeons.

AREAS OF UNCERTAINTY

Data are lacking in regard to the effectiveness of treatment in reducing the risks of the adverse outcomes associated with subclinical hyperthyroidism (Table 3). It is not known whether the effects of treatment vary according to the cause of subclinical hyperthyroidism, patient age, or serum thyrotropin level.

GUIDELINES

The U.S. Preventive Services Task Force found insufficient evidence to recommend screening or treatment for subclinical thyroid disease.[44] Both the American Thyroid Association[4] and the European Thyroid Association[3] have published guidelines for the evaluation and management of the condition. In general, the recommendations in this article are consistent with these guidelines (see Figs. 1 and 2).

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette meets the criteria for mild subclinical hyperthyroidism, with a serum thyrotropin level between 0.1 and 0.5 mU per liter and a normal free T_4 level. She has a history of paroxysmal atrial fibrillation and osteoporosis, both of which can be caused or exacerbated by mild hyperthyroidism in older persons. The patient should be asked whether she has taken levothyroxine or had recent exposure to iodinated contrast material.

Since mild suppression of the serum thyrotropin level often resolves over time, her thyrotropin level should be measured again within 2 to 3 months. If the thyrotropin level remains low, we would recommend ultrasonography of the thyroid to determine whether there is a nodule on the left side of the thyroid. If a nodule is found, radionuclide scanning should be performed to determine whether the nodule is functional. If no nodule is found, Graves' disease is the most likely diagnosis.

Given the patient's age, history of atrial fibrillation, and osteoporosis, we would favor treat-

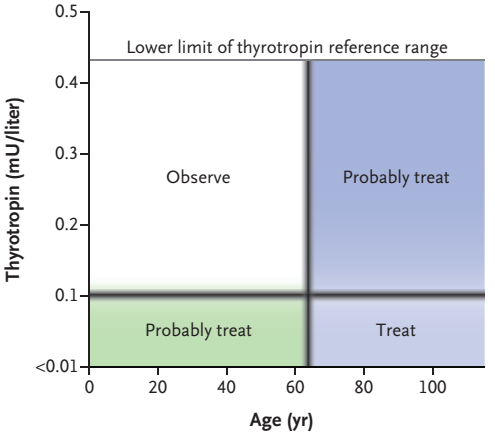

Figure 1. General Therapeutic Approach to Endogenous Subclinical Hyperthyroidism.

Postmenopausal women and patients older than 65 years of age should be treated if serum thyrotropin levels are persistently lower than 0.1 mU per liter. Older patients with serum thyrotropin levels between 0.1 and 0.4 mU per liter should be considered for treatment. Premenopausal women and younger patients should be considered for treatment if serum thyrotropin levels are less than 0.1 mU per liter and they have symptoms of hyperthyroidism or coexisting conditions such as osteopenia, osteoporosis, or cardiovascular disease. There is no indication for treatment in younger patients who do not have coexisting conditions if the serum thyrotropin level is 0.1 mU per liter or higher. The blurring of the boundaries between the quadrants is intended to illustrate that the cutoffs of age and thyrotropin level for therapy are not precisely defined.

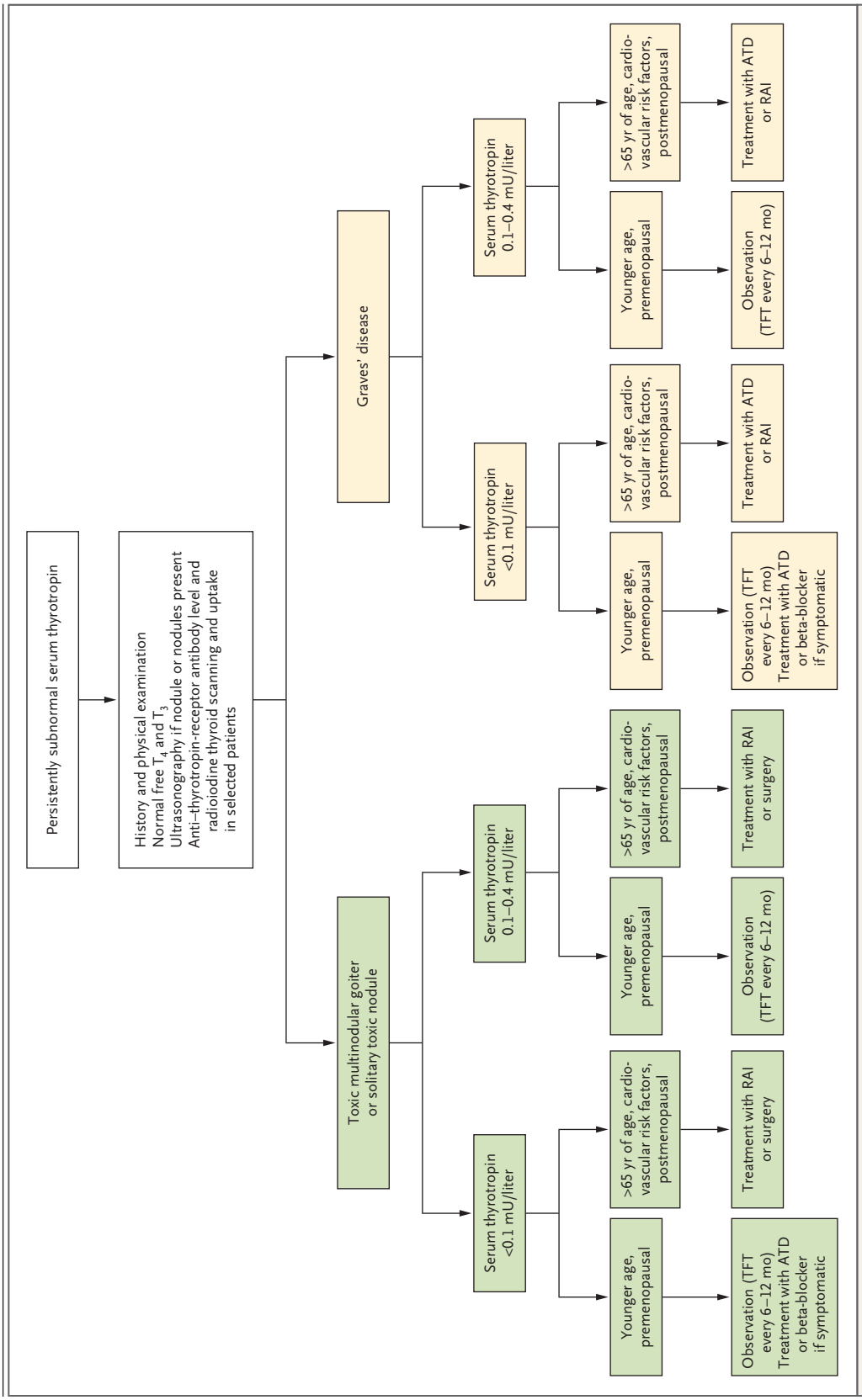

Figure 2. Management of Endogenous Subclinical Hyperthyroidism.

Once subclinical hyperthyroidism is verified with normal levels of free thyroxine (T_4) and triiodothyronine (T_3) and a persistently subnormal level of serum thyrotropin, a diagnosis should be made on the basis of laboratory tests for antithyrotropin-receptor antibodies (to test for Graves' disease), imaging studies (radionuclide scanning or ultrasonography), or both, depending on the clinical circumstances. The decision to treat and the nature of the treatment depend on the underlying diagnosis, the degree of thyrotropin suppression, patient age, and any coexisting conditions. Antithyroid drugs or radioiodine are the preferred treatment in patients with Graves' disease, whereas radioiodine is preferred in patients with toxic nodular disease. Surgery is an option in patients with large goiters that are causing obstructive symptoms when the patient has no major coexisting conditions. ATD denotes antithyroid drug, RAI radioactive iodine, and TFT thyroid function test.

ment, even though her thyrotropin level is only mildly suppressed.[3,4] If her thyroid function worsens and the serum thyrotropin level falls below 0.1 mU per liter, treatment would clearly be advisable. If a functioning left thyroid nodule is found, we would discuss with the patient the benefits and risks of radioiodine therapy. Low-dose methimazole or radioiodine therapy would be recommended if the patient has Graves' disease.

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

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