
به نام خدا

# Subclinical Hyperthyroidism

## Case Presentation

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?***

# DEFINITION

- **Overt hyperthyroidism**
- **Subclinical hyperthyroidism**

# CAUSES

## *Endogenous*

- Toxic multinodular goiter
- Toxic adenoma
- Graves'disease

## *Exogenous*

excessive intake of:

- levothyroxine
- liothyronine
- desiccated thyroid

## 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

- Progression to overt hyperthyroidism
- Cardiovascular conditions
- Bone loss, fractures
- Dementia

**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.

# DIAGNOSIS

The diagnosis of subclinical hyperthyroidism is based on laboratory results, but several other common clinical situations are associated with similar laboratory findings

**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

# EVALUATION

Older patients with subclinical hyperthyroidism are usually asymptomatic, but younger persons may have mild adrenergic symptoms.

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.

# EVALUATION

Levels of freeT4 and T3 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, most often in those with mild disease.

# TREATMENT

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.

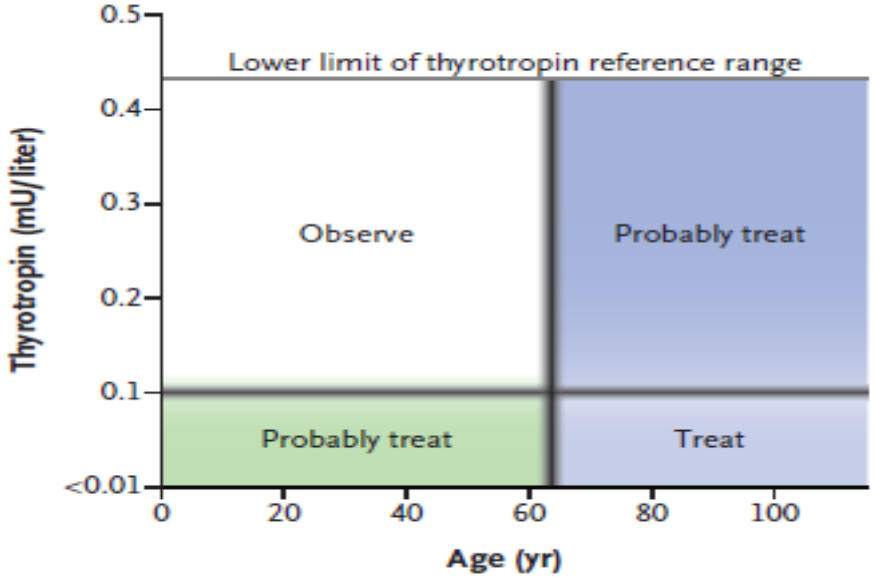


**Figure 1. General Therapeutic Approach to Endogenous Subclinical Hyperthyroidism.**

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.

# TREATMENT

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.

# TREATMENT

**There are three effective therapeutic options:**

1. Antithyroid Agents
2. Radioiodine therapy
3. Surgery

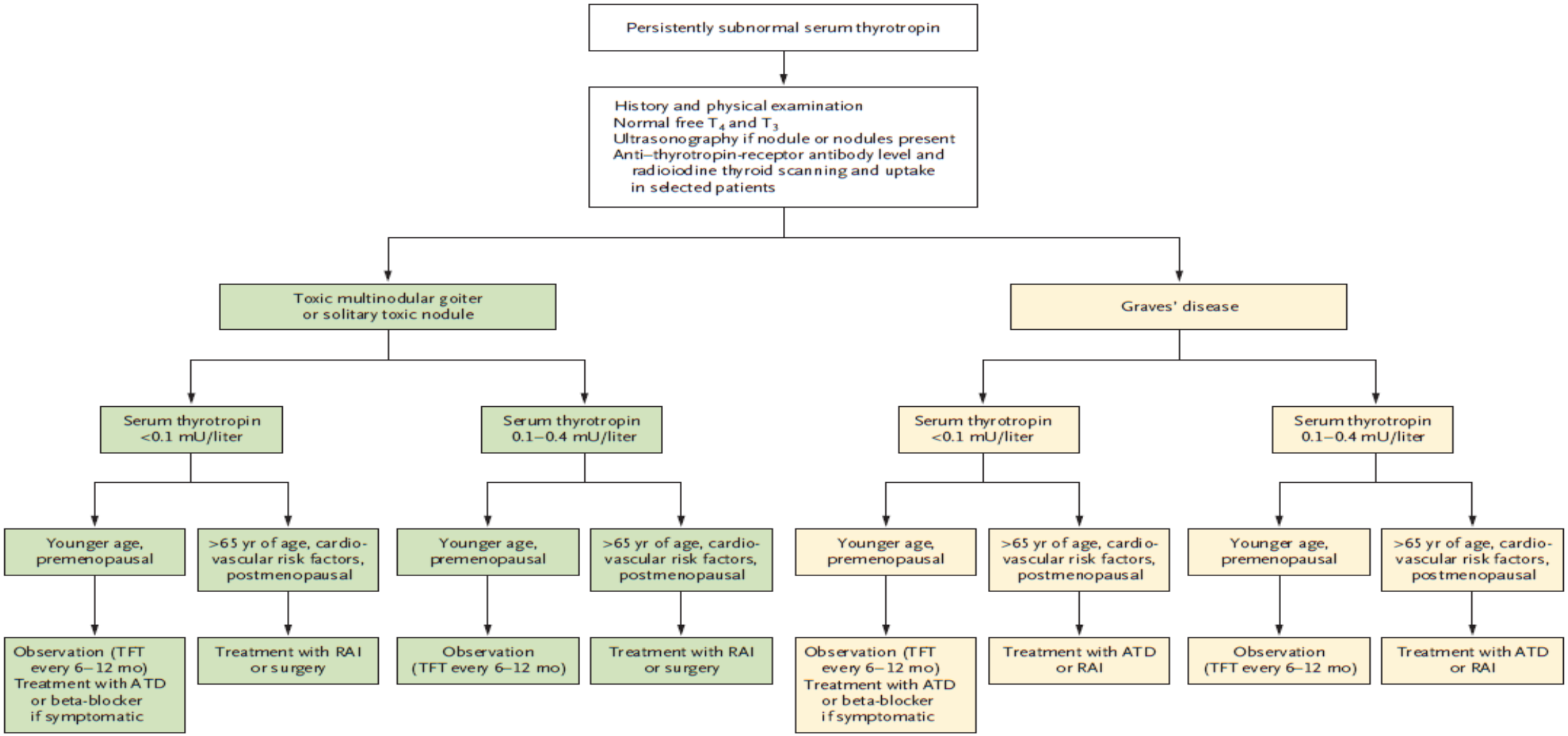


**Figure 2. Management of Endogenous Subclinical Hyperthyroidism.**

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.

# CONCLUSIONS AND RECOMMENDATIONS

Since mild suppression of the serum thyrotropin level often resolves over time, her thyrotropin level should be measured again **within 2 to3 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.

# CONCLUSIONS AND RECOMMENDATIONS

Given the patient's age, history of atrial fibrillation, and osteoporosis, we would favor treatment, even though her thyrotropin level is only mildly suppressed.

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.