Table S1.

Causes of Overt and Subclinical Hyperthyroidism

Common causes

Endogenous causes

- Produced by antiTSH receptor (TSHR) stimulating antibodies
  - o Graves Disease (Subclinical hyperthyroidism usually transient with remission or progression to overt disease over time)
- Thyroidal autonomy produced by activating mutations in TSHR or G protein and functional autonomous benign neoplasia
  - o Solitary toxic adenoma and toxic multinodular goiter (characterized by persistent thyroid autonomy over time with possible progression to overt disease, especially after iodine exposure)

Exogenous causes

- Inadvertent or intentional excessive therapy with L-T4
- Intentional TSH suppression during treatment with L-T4 in patients with high-risk differentiated thyroid cancer

Less Common Causes

- Inflammatory disorders with transient TSH suppression due to the release of stored hormones:
  - o Subacute thyroiditis (likely due to viral infection)
  - o Silent (painless thyroiditis) and post-partum thyroiditis (autoimmune)
  - o Palpation thyroiditis after parathyroid surgery
  - o Acute thyroiditis (acute bacterial or fungal infection)
  - o Radiation thyroiditis
  - o Drug induced thyroiditis: (type 2 amiodarone-induced destructive thyroiditis , interferon alfa, lithium, tyrosine kinase inhibitors, immune checkpoint inhibitors)
- Hemorrhagic infarction of thyroid adenoma
- Exposure to iodine-containing drugs (e.g., radiographic contrast agents) inducing non-autoimmune hyperthyroidism

Uncommon causes

- Metastatic follicular thyroid carcinoma
- Excessive secretion of human chorionic gonadotropin (trophoblastic tumors such as choriocarcinoma or hydatidiform mole)

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.

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

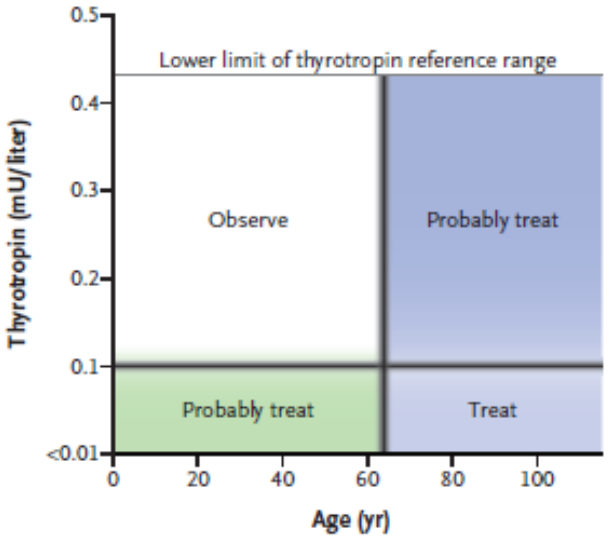

Figure 1. General Therapeutic Approach to Endogenous Subclinical Hyperthyroidism.

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.