Chapter 7
Subclinical Hyperthyroidism: Case Report and Review of the Literature

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Objectives

- Appropriately diagnose and evaluate the underlying potential causes of subclinical hyperthyroidism.
- Understand the risks of adverse outcomes related to cardiovascular risks, bone health, and possibly cognitive decline associated with subclinical hyperthyroidism.
- Determine the necessity and type of treatment that may be recommended in some individuals with subclinical hyperthyroidism.

Case Presentation

A 66-year-old female presents after an incidental finding of abnormal serum thyroid function tests obtained following a routine visit with her primary care doctor. Her medical history consists of hypertension, atrial fibrillation, systemic lupus erythematous, pre-diabetes, and osteoporosis. She has had prior cesarean section for identical twins in her early 20s. Her family history is notable for Hashimoto's thyroiditis in her mother. She currently lives with her husband and drinks socially during the weekends and denies any smoking history or illicit drug use. Her medications include metoprolol, rivaroxaban, plaquenil, mycophenolate mofetil, and an over-the-counter calcium and vitamin D combination pill. She has been post-menopausal since age 51. Upon further review of systems, she notes unintentional weight loss of

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5 pounds over the past 2 months, anxiety, insomnia, heat intolerance, hand tremors, and palpitations, all of which she initially attributed to aging. She denies any symptoms of loose stools, vision changes, proptosis, or eye swelling.

On physical exam, her vitals showed a temperature of 37 °C, heart rate of 80 beats per minute, blood pressure of 120/80 mmHg, respiratory rate of 18 breaths per minute, 100% oxygen saturation on room air, and body mass index of BMI 25.0 kg/m^2. Her exam was notable for mildly pressured speech, fine bilateral hand tremors of her outstretched hands, and a diffusely enlarged, nontender thyroid gland. Her biochemical workup revealed a thyroid-stimulating hormone (TSH) of 0.09 mIU/L (reference range, 0.3–4.7 mIU/L), free thyroxine (FT4) of 1.6 ng/dL (reference range, 0.8–1.7 ng/dL), and free tri-iodothyronine (FT3) of 400 (reference range, 222–383 pg/dL). These blood tests remained persistent on repeat assessment 3 months later. Previous thyroid function tests over the last 5 years were all within their mid-normal ranges. Serum thyroid peroxidase (TPO), thyroid-stimulating immunoglobulin (TSI), and TSH receptor antibody (TRAb) were all negative.

A thyroid radioactive iodine uptake and scan showed three dominant hot nodules in the superior, middle, and inferior poles of the right thyroid lobe with overall increased radioiodine uptake at 6 (28%, normal 6–18%) and 24 hours (54%, normal 15–30%). A thyroid ultrasound showed three discrete solid, isoechoic nodules in the right superior, middle, and inferior poles of the thyroid gland, all measuring slightly less than 1.0 cm each and with well-defined borders, no calcifications, no increased Doppler flow, and no extrathyroidal extension. A bone dual-energy X-ray absorptiometry (DXA) performed the previous year showed a T score of −2.6 in lumbar spine, −2.5 in left femoral neck, and −2.7 in left total hip, consistent with osteoporosis.

The patient was diagnosed with subclinical hyperthyroidism arising from a multinodular goiter and started on propranolol 10 mg three times a day as needed for hyperthyroid symptoms. Due to her underlying risk factors including older age (greater than 65 years), cardiac history with atrial fibrillation, osteoporosis, symptoms of hyperthyroidism, and serum TSH <0.1 mIU/L, a recommendation was made to treat the patient. Given her autonomous thyroid nodules, definitive therapy was desired. She successfully received radioactive iodine therapy with 21.6 mCi of ^{131}I. Over the next several months, her symptoms resolved, and her weight normalized to that of her baseline. Repeat serum thyroid function tests 3 months later showed normal TSH, FT4, and FT3 concentrations. A repeat bone DXA scan 2 years later showed an approximate 5% gain of bone mineral density at each site to the osteopenic range.

Discussion

Subclinical hyperthyroidism was first described in the 1970s upon the advent of the TSH immunoassay. Over the past couple of decades, increased understanding on this topic has allowed refined recommendations on how diagnosed patients should

best be monitored and treated. The condition is a biochemical diagnosis that is defined by a decreased serum TSH and normal serum T4 and T3 concentrations. In contrast, overt hyperthyroidism is defined by a decreased TSH in the setting of elevated serum T3 and/or T4 levels. Furthermore, a proposed grading system distinguishes mild from severe subclinical hyperthyroidism, according to the degree of TSH reduction (mild, TSH 0.1–0.4 mIU/L; severe, TSH <0.1 mIU/L) [1].

The clinical presentation of subclinical hyperthyroidism is variable and can range from the absence of symptoms to mild or even pronounced symptoms of hyperthyroidism such as arrhythmias, heat intolerance, insomnia, increased appetite, diarrhea, weight loss, hair loss, diaphoresis, abnormal menses, and hand tremors. The diagnosis of subclinical hyperthyroidism should be confirmed by repeating thyroid function tests in 3–6 months, as the entity can be transient due to thyroiditis, lab error, or other causes [2]. Due to the ubiquity of thyroid function tests which are now available in most major laboratories, and an increase in ordering of these tests by clinicians, it is important to understand the pathophysiology of the disease and current societal guidelines to help identify those who would require treatment and those who can be closely monitored.

From the TEARS Scottish population study, the annual incidence of subclinical ranges from 17.5% to 56.1% per 100,000 persons with increasing annual prevalence from 0.05% seen in 1994 to 0.63% in 2008 [1]. In this cohort, very few patients (0.5–0.7%) developed overt hyperthyroidism at 2, 5, and 7 years of follow-up, and an increasing number of cases reverted back to the euthyroid state over longitudinal monitoring (17.2% at 2 years of follow-up, compared to 35.6% at 7-year follow-up), especially in those with baseline TSH levels between 0.1 and 0.4 mIU/L and those of younger age [1]. Contributing factors to the diagnosis of subclinical hyperthyroidism include older age, female sex, and higher socioeconomic status [1]. Thyroid autoimmunity with either thyroid peroxidase (TPO) or TSH receptor antibodies (TRAb) does not appear to be a risk factor of conversion from subclinical hyperthyroidism to the euthyroid state [1].

Several studies have shown that particularly severe subclinical hyperthyroidism (i.e., TSH <0.1 mIU/L) is negatively associated with adverse effects on cardiovascular health, particularly arrhythmias such as atrial fibrillation, strokes, and bone health, including increased risk of fractures [2–4]. With correction of the subclinical hyperthyroidism, these negative adverse events and risks are reversible, thus stressing the importance of clinicians to identify those who would benefit from treatment [2–4]. In addition, some studies have also assessed the potential associations between subclinical hyperthyroidism, dementia, and cognitive decline, but the results are equivocal [5, 6].

When evaluating the underlying cause of subclinical hyperthyroidism, it is recommended to group causes based on endogenous versus exogenous etiologies, as well as transient versus persistent sources. Diagnostic workup may include the ascertainment of serum thyroid antibodies including thyroid-stimulating immunoglobulin (TSI), TSH receptor antibody (TRAb), thyroid peroxidase (TPO) titers, thyrotropin-binding inhibitory immunoglobulin (TBII), serum thyroglobulin, thyroid ultrasound with Doppler flow, and radioactive iodine uptake scan [2].

Endogenous causes include toxic thyroid nodule(s), toxic multinodular goiter (TMNG), and Graves' disease. Toxic nodule(s) and TMNG are the most common causes of persistent subclinical hyperthyroidism especially in older individuals, whereas Graves' disease is the second most common cause that is seen more commonly in younger individuals [2]. Exogenous causes include intentional use of a supraphysiologic thyroid hormone dose to manage postoperative hypothyroidism such as in patients with differentiated thyroid cancers, as well as iatrogenic overestimation of thyroid hormone replacement for hypothyroidism and the surreptitious use of thyroid hormone for weight loss. Transient forms of subclinical hyperthyroidism can be seen during the course of treatment of hyperthyroidism with radioiodine therapy or antithyroid medications and in various forms of thyroiditis such as subacute thyroiditis, postpartum thyroiditis, and thyroiditis due to lithium, amiodarone, or immune checkpoint inhibitor use. Furthermore, it is important to also rule out other clinical scenarios which can cause a low serum TSH value. These include pregnancy, acute or chronic iodine load from iodine-rich medications or radiologic contrast media, psychiatric disorders, non-thyroidal illness, hypothalamic or pituitary dysfunction, and spurious laboratory assays due to interfering antibodies, paraproteins, or medications such as biotin [2].

Once a diagnosis of subclinical hyperthyroidism has been confirmed and is found to be persistent, the goal is to identify the individual's risk factors to determine if treatment would be beneficial. If warranted, the goal of treatment is to normalize serum thyroid function, in order to achieve a euthyroid state and reduce cardiac, bone, and other complications. The American Thyroid Association (ATA) recommends treatment in patients age <65 years with subclinical hyperthyroidism if the serum TSH is <0.1 mIU/L, especially if the individual has hyperthyroid symptoms (Table 7.1) [2]. The guidelines also advocate treatment in those age ε 65 years if the serum TSH is <0.1 mIU/L; if there are cardiac risk factors or known heart disease

Table 7.1 American Thyroid Association recommendations for the management of subclinical hyperthyroidism (*Adapted from* Ref. [2])

		TSH 0.1–0.4 mU/L[a] (mild subclinical hyperthyroidism)	TSH < 0.1 (severe subclinical hyperthyroidism)
Age < 65 years old[b,c]	Asymptomatic	Monitor	Consider treating
	Asymptomatic with risk factors[d]	Consider treating	Consider treating
	Symptomatic	Consider treating	Treat
Age ε65 years old[b]	Asymptomatic	Consider treating	Treat
	Asymptomatic with risk factors[d]	Consider treating	Treat
	Symptomatic	Consider treating	Treat

[a]TSH of 0.4 mU/L is the lower limit of most reference ranges
[b]Ensure persistence of subclinical hyperthyroidism by repeating labs in 3–6 months
[c]In pregnant patients, treatment of subclinical hyperthyroidism is not recommended
[d]Risk factors: cardiac disease, osteoporosis, menopausal women not on estrogens or bisphosphonates

or osteoporosis; in postmenopausal women who are not taking estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms [2]. For those who have a TSH between 0.1 and 0.4 mU/L and have underlying risk factors (i.e., heart disease, osteoporosis, menopausal state not on hormonal or bisphosphonate therapy) or hyperthyroid symptoms, treatment may also be appropriate [2]. Monitoring without treatment is appropriate for those age < 65 years who have a TSH value between 0.1 and 0.4 mU/L and are asymptomatic (Table 7.1) [2].

Options for treatment of subclinical hyperthyroidism will be dependent on the underlying cause and follow the same principles as overt hyperthyroidism. These include thionamides such as methimazole or propylthiouracil, thyroid surgery, and/or radioactive iodine therapy. Beta-blockers such as propranolol, atenolol, or metoprolol may be additionally used to mitigate hyperthyroid symptoms if present.

Learning Points

- Accurate diagnosis of subclinical hyperthyroidism is important, due to the many mimickers of the biochemical pattern that defines this entity.
- Serum thyroid function tests should be repeated in 3–6 months after an initial abnormal set to confirm their persistence and thus a diagnosis of subclinical hyperthyroidism.
- The presentation of subclinical hyperthyroidism can vary from the lack of symptoms to the presence of mild or pronounced symptoms of hyperthyroidism.
- Subclinical hyperthyroidism is associated with increased risks of cardiovascular-related adverse outcomes, bone loss, and, in some studies, cognitive decline**.**
- Appropriate evaluation of an individual's risk factors is needed to correctly differentiate between patients who can be monitored with serial serum thyroid function tests and those who will require further diagnostic workup.
- Considerations for treatment include the etiology of the subclinical hyperthyroidism, anticipated long-term natural history of the condition, potential benefits of correcting the thyroid dysfunction, and the risks and benefits of each treatment option.

Multiple-Choice Questions

1. Which of the following is the correct biochemical definition of subclinical hyperthyroidism?

   (a) Normal free T4, low TSH
   (b) Elevated free T4, low TSH
   (c) Low FT4, low TSH
   (d) Low FT4, high TSH

2. Which of the following is/are the next best step(s) if a patient was found to have initial biochemical evidence of subclinical hyperthyroidism?

   (a) Order radioactive iodine-123 thyroid uptake scan.
   (b) Review patient's prescription medications and over-the-counter supplements, in order to consider whether there may be potential culprit medications that may be causing the serum thyroid function abnormalities.

(c) Repeat serum TSH, FT4, and FT3 concentrations in 3–6 months to confirm the persistence of subclinical hyperthyroidism.
(d) Order thyroid ultrasound.
(e) Order thyroid antibodies [i.e., thyroid peroxidase antibodies (TPO), thyroid-stimulating immunoglobulin (TSI), and TSH receptor antibody (TRAb)].
(f) Both (b) and (c).

3. Which of the following is *not* a cause of low serum TSH concentrations and should *not* be considered as a differential diagnosis when evaluating a patient for subclinical hyperthyroidism?

(a) Use of glucocorticoids
(b) Pituitary dysfunction
(c) Serum heterophile antibodies
(d) Aging
(e) Pregnancy
(f) Non-thyroidal illness
(g) Amiodarone-induced thyroiditis

4. Which of the following should be considered when deciding if a patient with subclinical hyperthyroidism should be treated?

(a) Age
(b) Sex
(c) Bone loss (i.e., osteopenia, osteoporosis)
(d) Cardiovascular risk factors (i.e., atrial fibrillation)
(e) Presence of hyperthyroid symptoms
(f) Postmenopausal patients who are not on estrogens or bisphosphonates
(g) All of the above except (b)
(h) All of the above

Answers

1. (a)
2. (f)
3. (d)
4. (g)

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