

Chapter 6

Subclinical Hyperthyroidism Due to a Multinodular Thyroid

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Objectives

Subclinical hyperthyroidism is defined as a state of mild thyroid overactivity, in which serum free thyroxine (T_4) and free triiodothyronine (T_3) levels are within the normal range but serum thyroid-stimulating hormone (TSH) levels are subnormal. Whether the serum TSH level needs to be extremely low (e.g., undetectable), very low (e.g., <0.1 mU/L), or simply just below the lower limit of normal of the typical TSH assay (e.g., <0.4 mU/L) remains somewhat controversial. We report the case of a 50-year-old woman with mild hyperthyroidism due to a multinodular thyroid. We review the issues surrounding establishing the diagnosis, and discuss risks and benefits of treatment in this individual.

Case Presentation

Ms. D.W. is a 48-year-old premenopausal woman who was found by her primary care physician to have abnormal thyroid function tests during routine screening as part of her annual physical examination. At that time, she was noted to have a serum TSH of 0.17 mU/L. She was referred to the endocrine clinic for further evaluation. She had no prior history of thyroid disease and no family history of thyroid disease. She had no symptoms suggestive of hyperthyroidism, and has felt completely well. She had no compressive symptoms in the neck including dysphagia, hoarseness, or neck pain. Her past history was significant for mild hypertension treated with hydrochlorothiazide. The review of systems was normal, and the patient's menses were regular. The physical examination was entirely normal except for mild obesity, with a body mass index (BMI) of 30. Her pulse was 84 beats per minute. The thyroid gland was difficult to palpate, but no nodules were identified. Repeat thyroid function tests were as follows: free T_4 1.4 ng/dL, T_3 135 ng/dL, and

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TSH 0.11 mU/L. Antithyroid antibodies were negative. A thyroid scan using iodine 123 showed a mildly heterogeneous gland with several foci of increased uptake bilaterally. Thyroid ultrasound showed multiple isoechoic and hyperechoic nodules bilaterally, with overall normal thyroid size. The largest nodules measured 1.5 cm in the left lobe and 2.0 cm in the right lobe, and both corresponded to areas of increased uptake on the radionuclide scan.

Background

Subclinical hyperthyroidism is a common finding in the general population. In several large epidemiologic studies, the frequency has been approximately 1%, without a clear relationship to age [1]. This is in contrast to what is seen in subclinical hypothyroidism, which has a much higher prevalence of 8% to 10%, and an even higher prevalence in older individuals, approaching 15% to 20% [1,2]. The most common cause of subclinical hyperthyroidism undoubtedly is iatrogenic or inappropriate thyroid hormone use (exogenous subclinical hyperthyroidism). On the other hand, *endogenous* subclinical hyperthyroidism is typically caused by mild Graves' disease, solitary toxic nodules, or multinodular goiter. Some patients who are in remission after antithyroid drug therapy or following radioactive iodine therapy for overt hyperthyroidism commonly have subclinical hyperthyroidism.

It should also be noted that a low serum TSH is not the *sine qua non* of thyroidal autonomy, and may be present in patients with central hypothyroidism and severe nonthyroidal illnesses (especially if dopamine or high doses of glucocorticoids are used). In addition, low serum TSH values are seen physiologically at the end of the first trimester pregnancy due to high circulating human chorionic gonadotropin (HCG) levels, and may also be observed in the elderly with normal thyroid function due to a possible altered "set point" of the hypothalamic-pituitary-thyroid axis [3, 4].

In patients with true endogenous subclinical hyperthyroidism, progression to overt hyperthyroidism may occur, with rates of progression varying from 1% to 5% per year [5, 6]. Not surprisingly, subclinical hyperthyroidism in patients with Graves' disease who are in remission presages eventual relapse [7]. Finally, subclinical hyperthyroidism can be transient, so that treatment should only be considered when thyroid function abnormalities are clearly stable after repeated measurements over 6 to 12 months. For example, in one study, 38 of 50 untreated patients with baseline serum TSH values between 0.05 and 0.5 mU/L had normal serum TSH values 1 year later, whereas the majority of patients with TSH levels <0.05 mU/L persisted in having subnormal values [8].

The principal issues surrounding the clinical management of subclinical hyperthyroidism are [1] possible symptoms of mild hyperthyroidism; [2] bone loss, especially in postmenopausal women; and [3] possible cardiovascular disease, especially atrial fibrillation. Whether patients with endogenous subclinical hyperthyroidism have symptoms of hyperthyroidism is controversial. Studies have suggested that mild symptoms may be present in some patients [9, 10], which may

be reversible with antithyroid drug treatment [10]. Unfortunately, this latter study was not placebo-controlled, so that the possibility remains that the improvement in subjective symptoms was a placebo effect.

Women with subclinical hyperthyroidism may have diminished bone mineral density compared to age-matched controls, with improvement following therapy to correct the hyperthyroidism [11, 12]. Evidence of an increase in fractures in patients with subclinical hyperthyroidism has also been presented, but in this study it is uncertain that the patients truly had subclinical hyperthyroidism rather than overt hyperthyroidism, since only TSH measurements were available [13]. Whether premenopausal women with subclinical hyperthyroidism are at risk for bone loss is uncertain. One study showed increased levels of circulating bone turnover markers in premenopausal women with subclinical hyperthyroidism [14], but bone mineral density appears to be normal [15] or slightly lower than in controls [16].

Finally, an increased risk of cardiac abnormalities including increased heart rate, increased left ventricular mass, diastolic dysfunction, and a higher frequency of atrial fibrillation in the elderly has been well documented (reviewed in ref. 17). Furthermore, an increase in all-cause mortality and cardiovascular mortality has also been observed in older individuals with subclinical hyperthyroidism [18]. In another more recent prospective study of individuals older than 60 years of age, an increased risk of atrial fibrillation was noted even when the serum TSH was 0.1 to 0.5 mU/L, but there was no increase in cardiovascular mortality [19]. Data such as these have led to the recommendation that elderly individuals with subclinical hyperthyroidism and TSH levels <0.1 mU/L should receive therapy [20], whereas appropriate management in younger individuals or those whose TSH levels are between 0.1 and 0.4 mU/L remains uncertain [20].

How the Diagnosis Was Made

The diagnosis of subclinical hyperthyroidism was made on the basis of the patient's normal free T_4 and T_3 with a subnormal but still detectable serum TSH. There have been rare reports of patients with overt hyperthyroidism with elevated free T_3 levels despite normal total T_3 levels [21], but normal free T_3 measurements are not considered to be necessary to make the diagnosis of subclinical hyperthyroidism. The etiology of our patient's subclinical hyperthyroidism was established with the radionuclide thyroid scan and thyroid sonography, showing findings consistent with a multinodular thyroid and areas of autonomy within the gland. The negative antithyroid antibodies are evidence against autoimmune thyroid disease as the etiology of her hyperthyroidism.

After performing a dual-energy x-ray absorptiometry (DEXA) study, which was normal, and discussing the pros and cons of treatment with the patient, it was elected not to treat her, based on the lack of clear evidence of benefit. The plan was as follows: thyroid function was to be monitored every 6 months and consideration of radioactive iodine therapy would be more seriously entertained when she becomes

postmenopausal, or if thyroid function deteriorates further. After 2 years of follow-up, thyroid function has remained stable and she still has not received therapy.

Lessons Learned

1. Subclinical hyperthyroidism is commonly detected on routine screening of the general population, but it is only one tenth as common as subclinical hypothyroidism.
2. Subclinical hyperthyroidism may have consequences in terms of hyperthyroid symptoms, bone loss, and cardiac abnormalities, especially atrial fibrillation. Bone loss and atrial fibrillation are particularly noteworthy in postmenopausal women and the elderly (over age 60) population, respectively.
3. Other conditions besides subclinical hyperthyroidism can cause serum TSH levels to be diminished, and it is important to exclude them.
4. Treatment, either with antithyroid drugs or radioiodine, is based on underlying risk factors, especially age, underlying heart disease, or the presence or risk of bone loss.

References

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Multiple-Choice Questions

1. A 25-year-old woman notes feelings of anxiety, and is found to have a normal physical examination. She has the following laboratory results: free T₄ 1.3 ng/dL, T₃ 120 ng/dL, and TSH 0.4 mU/L. What of the following is true?
 - A. She is 12 weeks pregnant.
 - B. She has mild Graves' disease.
 - C. She is biochemically euthyroid.
 - D. She requires further evaluation with a thyroid scan.

Answer: C. The patient is biochemically euthyroid and requires no further evaluation.

2. A 75-year-old woman with a long-standing multinodular goiter has developed progressive decreases in serum TSH. She has no symptoms suggesting hyperthyroidism, but has osteoporosis on bone densitometry treated with alendronate. Recent thyroid function tests are as follows: free T₄ 1.6 ng/dL, T₃ 132 ng/dL, and TSH 0.04 mU/L. Which one of the following statements is correct?

- A. Her risk for fracture is elevated vs. similar women without subclinical hyperthyroidism.
- B. She is at increased risk for myocardial infarction.
- C. Treatment will lower her risk of atrial fibrillation in the future.
- D. Treatment with radioactive iodine is preferred over antithyroid drugs.

Answer: D. The patient is a higher risk of atrial fibrillation in the future, but it is unclear that treating her will lower the risk, since there have been no intervention trials with this endpoint. It is unclear that her risk of fracture is elevated compared to euthyroid women who are also on bisphosphonates. There is no evidence for higher risk of myocardial infarction. Treatment with antithyroid drugs would be less desirable than radioactive iodine in a patient with a multinodular goiter.

3. Which of the following patients might have low serum TSH levels?
- A. A 30-year-old woman being treated with 10 mg of prednisone daily for asthma
 - B. A 40-year-old man who is otherwise healthy
 - C. A 25-year-old woman who is 35 weeks pregnant
 - D. An 82-year-old otherwise healthy woman

Answer: D. High (e.g., >40 mg prednisone/day) doses of glucocorticoids are associated with low serum TSH. Low serum TSH values can be normally seen at the end of the first trimester pregnancy, but not later in pregnancy. Elderly people sometimes have low serum TSH values in the setting of otherwise normal thyroid function and no obvious illness or underlying thyroid disease, due to an altered “set point” of the hypothalamic-pituitary-thyroid axis.