APPROACH TO THE PATIENT

Approach to the Patient with Subclinical Hyperthyroidism

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Endogenous subclinical hyperthyroidism, defined by normal circulating levels of free T4 and T3 and low levels of TSH, is a common clinical entity and is typically caused by the same conditions that account for the majority of cases of overt hyperthyroidism: Graves’ disease, toxic multinodular goiter, and solitary autonomously functioning thyroid nodules. Subclinical hyperthyroidism has been associated with an increased risk of atrial fibrillation and mortality, decreased bone mineral density in postmenopausal women, and mild hyperthyroid symptoms. Treatment of subclinical hyperthyroidism remains controversial, given the lack of prospective randomized controlled trials showing clinical benefit with restoration of the euthyroid state. Nevertheless, it seems reasonable to treat older individuals whose serum TSH levels are less than 0.1 mU/liter and certain high-risk patients, even when the serum TSH is between 0.1 and the lower limit of the normal range. (J Clin Endocrinol Metab 92: 3–9, 2007)

The Case

A 75-yr-old woman is found to have abnormal thyroid function tests when screened by her primary care physician, and she is referred for further evaluation. She has a history of dyslipidemia and type 2 diabetes. She has no personal or family history of thyroid disease and no history of neck irradiation. Her physical examination is generally normal except for a bilaterally enlarged nodular thyroid gland with an estimated size of 40 g. Results of thyroid function tests are as follows: free T₄, 1.3 ng/dl (0.8–1.8); T₃, 135 ng/dl (80–180); TSH, 0.13 mU/liter (0.5–4.5). Thyroid sonography reveals a bilaterally enlarged gland with multiple isoechoic and hyperechoic nodules ranging in size from 1 to 3 cm. The nodules all have a spongiform appearance and a sonolucent halo. A thyroid radionuclide scan using I123 shows a bilaterally enlarged gland with multiple areas of increased and decreased tracer uptake consistent with a multinodular goiter. The 24-h thyroidal radioiodine uptake is 22%. A bone densitometry study done 2 yr earlier showed osteopenia in the lumbar spine and hip.

Background

This elderly woman has subclinical hyperthyroidism, the mildest form of hyperthyroidism, as defined by the presence of a low or undetectable serum TSH level in the face of normal serum free T₄ and T₃ (or free T₃) levels. It was not identified as a clinical entity until the development of second-and third-generation TSH assays in the late 1980s, when it became possible to distinguish low from normal serum TSH values. The etiology of subclinical hyperthyroidism can be divided into two categories: exogenous subclinical hyperthyroidism due to the ingestion of intentional or unintentional suppressive doses of thyroid hormone, and endogenous subclinical hyperthyroidism caused by the usual conditions leading to thyrotoxicosis, i.e. Graves’ disease, toxic multinodular goiter, autonomously functioning solitary nodules, and various forms of thyroiditis.

The prevalence of endogenous subclinical hyperthyroidism varies with the TSH cutoff used to define it. For example, in the NHANES III study, the prevalence was 0.7% using a cutoff of 0.1 mU/liter and 3.2% using a TSH cutoff of a 0.4 mU/liter (1). The prevalence of subclinical hyperthyroidism also varies inversely with a population’s iodine intake, being more common when dietary iodine is relatively deficient (2), reflecting the higher prevalence of toxic nodules and toxic multinodular goiter in these populations (3).

Differential Diagnosis of a Low Serum TSH

In addition to bona fide subclinical hyperthyroidism, other possibilities need to be considered in patients with isolated serum TSH suppression in other clinical settings: central hypothyroidism, physiological lowering of serum TSH at the end of the first trimester of pregnancy, and low serum TSH levels in the critically ill. In addition, low serum TSH levels may be seen in apparently healthy elderly people with no underlying thyroid disease (4, 5). In these elderly people, the low serum TSH may due to an altered hypothalamic-pituitary-thyroid axis set point that may occur with aging (4).

Clinical Considerations

In approaching this patient to determine the significance of her thyroid function test abnormalities and whether they warrant treatment, I would be thinking about three main

Abbreviations: AF, Atrial fibrillation; LVH, left ventricular hypertrophy; RR, relative risk.
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issues. These include potential adverse effects on the cardiovascular system and the skeleton, and the presence or absence of symptoms or mood disturbance consistent with thyrotoxicosis. Because subclinical hyperthyroidism is, in reality, a “mild” form of overt hyperthyroidism, it is reasonable to assume that potential adverse outcomes would be related to the degree of TSH suppression. Although this may not always be the case, as discussed below, an expert consensus panel has suggested that patients with serum TSH levels less than 0.1 mU/liter are at higher risk than those patients with TSH levels between 0.1 and 0.5 mU/liter (6). The potential negative effects of subclinical hyperthyroidism on the cardiovascular system and the skeleton have been the most thoroughly studied. The presence of hyperthyroid symptoms and effects on mood and quality-of-life have also been examined, although in less detail. In the following discussion, I will review studies of endogenous subclinical hyperthyroidism that have investigated these issues, and I will present what I consider to be key data on the possible benefits of treatment. Two excellent reviews on the subject of subclinical hyperthyroidism have been published recently (7, 8).

**Cardiovascular effects of subclinical hyperthyroidism**

The well-known inotropic, chronotropic, and lusitropic effects of thyroid hormone on the heart and vascular tree (9) to increase cardiac output and decrease systemic vascular resistance are also seen to a lesser degree in patients with subclinical hyperthyroidism. All studies of endogenous subclinical hyperthyroidism have observed an increase in mean 24-h heart rate compared with controls (10–12). In addition, one study also noted a statistically significant increase in the frequency of atrial and ventricular premature beats (10).

Left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular morbidity and mortality (13). Doppler echocardiography has shown an increase in left ventricular mass in patients with subclinical hyperthyroidism (11, 12, 14). One of these reports also suggested that patients with subclinical hyperthyroidism and hypertension had left ventricular wall thickness that was greater than seen in patients with hypertension alone (14). However, in a recent large population-based study involving 1510 individuals, subclinical hyperthyroidism was not associated with LVH, whereas a positive association with LVH was seen in overt hyperthyroidism (15).

Possible deleterious effects of subclinical hyperthyroidism on systolic and diastolic function have also been examined. Three studies found minimal or no effect on systolic function (10, 12, 16), and one showed slightly enhanced systolic function (11). Biondi et al. (11) also reported a statistically significant impairment in diastolic function with decreased transmural blood flow due to slowed left ventricular relaxation, but significant changes were not observed in two other studies (10, 12). Although deleterious effects of exogenous subclinical hyperthyroidism on exercise tolerance have been found (17, 18), there are no data to address this question in patients with endogenous subclinical hyperthyroidism.

Because of its obvious clinical importance, an increase in the frequency of atrial fibrillation (AF) in patients with subclinical hyperthyroidism has attracted a great deal of attention. Tenerz et al. (19) were among the first to report a higher frequency of AF in endogenous subclinical hyperthyroidism. This was followed by the report by Sawin et al. (20) of individuals more than age 60 yr who were prospectively followed over a 10-yr period. These authors observed a relative risk (RR) of 3.1 for AF among individuals with TSH levels less than 0.1 mU/liter and a RR of 1.6 (95% confidence interval, 1.0–2.5; P < 0.04) for those individuals with TSH levels between 0.1 and 0.4 mU/liter. In a retrospective report on persons in their mid-60s by Auer et al. (21), AF was seen in 2% of 22,300 euthyroid individuals, 14% of 725 patients with overt hyperthyroidism, and 13% of 613 patients with endogenous subclinical hyperthyroidism (defined as serum TSH < 0.4 mU/liter) (RR for AF: 5.8 and 5.2 for overt and subclinical hyperthyroidism, respectively). Finally, in a recent report by Cappola et al. (22), 496 subjects with a mean age of 73 yr with subclinical hyperthyroidism (serum TSH < 0.1–0.44 mU/liter) and 2639 euthyroid subjects were followed prospectively for a mean of 13 yr. After adjustment for age, sex, and other risk factors for AF, the RR of subclinical hyperthyroidism for AF was 1.98 (95% confidence interval, 1.29–3.03). Furthermore, the risk for AF was similar when only those subjects with serum TSH levels 0.1–0.44 mU/liter were included in the analysis.

Several other epidemiological studies have examined cardiovascular risk in patients with subclinical hyperthyroidism with varying conclusions. In the first, 1191 subjects 60 yr of age or older with baseline TSH levels measured in 1988–1989 were followed for 10 yr (23). All-cause and cardiovascular mortality were greater in subjects with serum TSH levels less than 0.5 mU/liter at 2, 3, 4, and 5 yr of follow-up. In the second study, by Gussekloo et al. (24) a cohort of individuals over age 85 yr was followed for 4 yr. Those with low serum TSH values had the highest rates of mortality, compared with both euthyroid and hypothyroid individuals. In contrast, Walsh et al. (25) followed a younger cohort (mean age 50 yr) of 2108 subjects and found no increased frequency of coronary artery disease or cardiovascular mortality. The frequency of AF was not specifically examined in any of these studies. Finally, in their prospective study, Cappola et al. (22) also found no increase in overall cardiovascular mortality in subclinically hyperthyroid patients.

**Effects of treatment on cardiovascular indices**

There are very few studies that have examined the impact of treatment on cardiovascular abnormalities in patients with subclinical hyperthyroidism. One early report noted that cardioversion of AF was unsuccessful in four such patients, but after normalization of thyroid function with radioiodine or antithyroid drugs, one patient converted to normal sinus rhythm spontaneously and the other three responded favorably to cardioversion (26). In another study, six women with subclinical hyperthyroidism were studied before and after normalization of serum TSH with methimazole (27). After treatment, there was an 11% reduction in mean heart rate (P < 0.02), a 19% reduction in cardiac output (P < 0.05), and a 30% increase in systemic vascular resistance (P < 0.02). Finally, in a nonrandomized study in which all patients (median age 59 yr, n = 10) were treated with methimazole, there
were statistically significant decreases in mean heart rate (82 vs. 74 beats/min, \( P = 0.008 \)), the number of atrial (87 vs. 11, \( P = 0.002 \)) and ventricular (8 vs. 0, \( P = 0.003 \)) premature beats/24 h, and left ventricular mass index (90 vs. 71 g/m²) to values different from age-matched controls (12).

In my patient with type 2 diabetes, dyslipidemia, and likely coronary artery disease, I closely questioned her about possible cardiac rhythm disturbances and other symptoms (palpitations, angina, dyspnea, etc.), and she had had none, and she had had a normal stress test 3 yr earlier. Although there are no data that pertain exclusively to subclinically hyperthyroid patients who have concomitant cardiovascular disease, it seems reasonable to assume that the risk for adverse cardiovascular outcomes would be magnified in persons who already have cardiac disease.

**Skeletal effects of subclinical hyperthyroidism**

Overt hyperthyroidism increases bone turnover and is a well-known risk factor for osteoporosis and fracture (28). This observation has naturally led to studies of the effects of subclinical hyperthyroidism on skeletal integrity. Bone mineral density is lower at all sites in postmenopausal women, especially in sites that are predominantly cortical bone (29, 30). In contrast, the bone density in premenopausal women with subclinical hyperthyroidism appears to be normal (31), although bone turnover markers, including bone alkaline phosphatase, urinary pyridinoline, and urinary deoxypyridinoline were elevated in a group of premenopausal women with subclinical hyperthyroidism whose TSH levels were 0.4 mU/liter or less, compared with antithyroid drug-treated women whose TSH levels were maintained within the normal range (32).

Only a few studies have examined the risk of fractures in patients with subclinical hyperthyroidism, and none of them have exclusively studied a cohort of women with endogenous subclinical hyperthyroidism. In one report that examined a cohort of women 65 yr of age or older, the risk of vertebral fracture was elevated 4-fold and hip fracture was elevated 3-fold in patients with serum TSH values 0.1 mU/liter or less compared with women with normal serum TSH levels (33). Women with TSH values between 0.1 and 0.5 mU/liter had no increased risk of fracture. However, this study did not distinguish between women with exogenous and endogenous subclinical hyperthyroidism. Furthermore, because serum free \( T_4 \) and \( T_3 \) values were not reported, it is possible that some of the women in the cohort may actually have had overt hyperthyroidism rather than subclinical hyperthyroidism.

**Effects of therapy on bone metabolism**

Perhaps the strongest evidence for an effect of endogenous subclinical hyperthyroidism on bone mineral density comes from intervention trials, although none have been randomized or placebo-controlled. In one small study, postmenopausal women with subclinical hyperthyroidism were followed prospectively for 2 yr, with one group (n = 8) receiving methimazole to normalize thyroid function and the other group (n = 8) remaining untreated (34). At the end of the follow-up period, distal forearm bone mineral density was stable and significantly higher in the treatment group compared with the untreated group. In the second study, postmenopausal women with multinodular goiter and subclinical hyperthyroidism were given radioactive iodine if they had compressive symptoms (n = 16), or remained untreated if asymptomatic (n = 12) (35). At the end of the 2-yr follow-up period, bone mineral density remained stable in the spine in the treatment group and continued to fall in the untreated group. Similarly, bone mineral density in the hip increased significantly after 2 yr in the treatment group but fell in the untreated group. In a small randomized study of premenopausal women, bone mineral density at baseline was slightly but not significantly different from age-matched controls and did not improve after 6 months of euthyroidism (36).

Based on these clinical studies, I would be concerned about further bone loss in my patient who already had osteopenia on a dual-energy x-ray absorptiometry study done 2 yr earlier, and it would be reasonable to repeat this study now that subclinical hyperthyroidism has been detected.

**Symptoms and quality of life in subclinical hyperthyroidism**

There are few studies that have examined the possibility that endogenous subclinical hyperthyroidism could cause mild hyperthyroid symptoms or affect quality of life. One of the earliest studies compared 20 patients with overt hyperthyroidism, 20 with “pre-clinical hyperthyroidism” (with normal serum \( T_3 \) and \( T_4 \) but suppressed TSH responses to TRH), and 20 euthyroid controls (37). Subjects with subclinical hyperthyroidism had increased anxiety, irritability, and decreased attentiveness and concentration. Furthermore, they also had the same prevalence of hyperthyroid symptoms as patients with overt hyperthyroidism using the Crooks’ index of hyperthyroidism. In a group of elderly individuals with subclinical hyperthyroidism (serum TSH < 0.1 mU/liter) reported by Stott et al. (38), an increase in hyperthyroid symptoms were not seen, but these individuals had a higher score on the Wayne index, a clinical index of hyperthyroidism. In another study (39), patients with subclinical hyperthyroidism (serum TSH \( \leq 0.2 \) mU/liter) had a frequency of hyperthyroid symptoms that was intermediate between normal controls and patients with overt hyperthyroidism. The ability to concentrate and short-term memory were normal in all groups. The same researchers paradoxically found that individuals with subclinical hyperthyroidism had an increased frequency of palpitations but had normal mood, sleep quality, and psychometric testing (40). More recently, two other studies also described an increase in typical hyperthyroid symptoms (palpitations, tremor, heat sensitivity, sweating, nervousness) in young and middle-aged patients with endogenous subclinical hyperthyroidism (11, 12). Using the Short Form-36 (SF-36) health questionnaire, Biondi et al. (11) also observed a statistically significant reduction in both the mental and physical component scores in patients with subclinical hyperthyroidism (mean serum TSH, 0.15 mU/liter). The reductions in quality of life were proportional to the degree of hyper-
thyroid symptoms experienced by the group using a validated symptom rating scale. On the other hand, in a community-based sample of 127 persons aged 65 yr and older with subclinical hyperthyroidism, there were no significant differences in mood, anxiety, or cognition between subclinically hyperthyroid persons and those who were euthyroid (41).

**Effects of the therapy on symptoms and quality of life**

Only one study has examined the effect of treatment on hyperthyroid symptoms in patients with endogenous subclinical hyperthyroidism, and none have examined quality of life or mood. Using a nonrandomized study design, Sgarbi et al. (12) investigated 10 patients with subclinical hyperthyroidism (mean serum TSH, 0.05 mU/liter) before and 6 months after restoration of a euthyroid state with methimazole. The Wayne index, a validated hyperthyroid symptom instrument, declined from a mean of 12 points to a mean of 2 points, which was a highly significant change, and close to the score seen in a healthy control group.

To assess the potential impact of subclinical hyperthyroidism on my patient, I inquired about typical hyperthyroid symptoms, but there were none. I also inquired about changes in mood (especially anxiety) and possible alterations in cognitive function. However, most current data do not support an association between these problems and subclinical hyperthyroidism, at least in older patients.

**Other metabolic effects of subclinical hyperthyroidism**

A recent study of 13 patients with subclinical hyperthyroidism (mean age, 58 yr; mean TSH, 0.14 mU/liter) showed an increased basal oxygen consumption compared with age-matched controls that decreased to normal (210 vs. 142 ml O₂/min·m²) after treatment with methimazole (42). In another study, patients with subclinical hyperthyroidism (n = 24; mean age, 53 yr; serum TSH, 0.005–0.02 mU/liter) were found to have decreased muscle strength compared with controls, as well as decreased midtibial cross-sectional area compared with controls, both of which normalized 6–9 months after treatment with radioiodine or surgery (43).

My patient did not have dyspnea on exertion, symptoms suggesting a decrease in exercise tolerance, or muscle weakness. No formal studies were performed to assess for these possibilities.

**The risk of progression to overt hyperthyroidism**

Patients with subclinical hyperthyroidism are at risk for progressing to overt hyperthyroidism, but the natural history is poorly defined. In patients with detectable serum TSH values, subclinical hyperthyroidism may frequently resolve spontaneously. For example, Parle et al. (44) observed, in a cohort of patients with subclinical hyperthyroidism followed for 12 months, that serum TSH values reverted to normal in 38 of 50 patients with serum TSH values between 0.05 and 0.5 mU/liter but remained undetectable in 14 of 16 patients with baseline TSH less than 0.05 mU/liter. With regard to progression to overt hyperthyroidism, Sawin et al. (45) reported a 4.1% rate of progression to overt hyperthyroidism over 4 yr among a group of elderly individuals with serum TSH levels less than 0.1 mU/liter. Stott et al. (38) reported over a mean of 7 months (range, 4–12 months) of follow-up that seven of 15 patients reverted to TSH levels greater than 0.2 mU/liter, whereas four of 15 developed overt hyperthyroidism. A somewhat lower rate of progression was observed by Parle et al. (23), who observed a rate of approximately 4% (three of 70 people) over a 10-yr follow-up period. The etiology of subclinical hyperthyroidism may play a role in determining whether subclinical hyperthyroidism resolves or progresses. For example, Woeb (46) observed that serum TSH values normalized in five of seven patients with Graves’ disease and subclinical hyperthyroidism (baseline TSH < 0.03–0.06 mU/liter) followed for 3–19 months, whereas it remained subnormal (baseline TSH 0.1–0.29 mU/liter) in patients with multinodular goiters followed for 11–36 months.

**Treatment Considerations**

A review of guidelines promulgated by various professional groups shows a uniform uncertainty about the appropriate management of subclinical hyperthyroidism (Table 1). In 2005, an expert panel composed of members of the American Thyroid Association, The Endocrine Society, and The American Association of Clinical Endocrinologists produced, for the first time, evidence-based recommendations for treatment of subclinical hyperthyroidism (6). The panel concluded, based on “fair evidence,” that treatment should be offered to “elderly” individuals and those with other risk factors (especially cardiac disease and osteoporosis), whose

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**TABLE 1. Review of guidelines promulgated by various professional groups**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline</th>
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</thead>
<tbody>
<tr>
<td>American Thyroid Association (ATA) (48)</td>
<td>No opinion</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists (AACE) (49)</td>
<td>Periodic assessment to determine individual therapeutic options</td>
</tr>
<tr>
<td>Royal College of Physicians (50)</td>
<td>No agreement on benefits of detecting/treating SH</td>
</tr>
<tr>
<td>American College of Physicians (51)</td>
<td>No agreement on benefits of detecting/treating SH</td>
</tr>
<tr>
<td>ATA, AACE, Endocrine Society Consensus Conference (6)</td>
<td>Treat older individuals or patients with risks (cardiac, postmenopausal if TSH &lt; 0.1 (Category B) (Category E for TSH &gt; 0.1))</td>
</tr>
</tbody>
</table>

SH, Subclinical hyperthyroidism.

*a Category B: Recommend. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes.

*b Category E: Recommend against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
serum TSH levels are less than 0.1 mU/liter. The panel also concluded that the evidence was insufficient to recommend therapy for patients with serum TSH greater than 0.1–0.45 mU/liter. Interestingly, these recommendations are only partly consistent with the results of a survey of members of the American Thyroid Association (47) conducted in 2002. Given hypothetical cases of subclinical hyperthyroidism, respondents were more likely to recommend therapy in patients with undetectable (<0.01 mU/liter) vs. more mildly suppressed serum TSH values (0.2 mU/liter) and were more likely to recommend treating older vs. younger patients. However, only 66% of respondents would have recommended therapy in an older osteopenic female patient with a serum TSH less than 0.01 mU/liter. Furthermore, 13% would have recommended treatment in a 28-yr-old patient with a serum TSH value of 0.1–0.5 mU/liter.

Controversies and Unanswered Questions

Uncertainty about the proper management of subclinical hyperthyroidism will remain as long as there are no randomized prospective trials. However, there is a consensus that therapy is reasonable and appropriate in elderly individuals and in persons with heart disease or evidence of bone loss who have serum TSH levels less than 0.1 mU/liter. On the other hand, the proper management of similarly at-risk patients with serum TSH levels greater than 0.1 but less than 0.4 is an unanswered question. Although some epidemiological evidence suggests that the risks of death and AF are similar to those in patients with serum TSH less than 0.1 mU/liter, few clinical studies have examined the effects of subclinical hyperthyroidism on the heart, skeleton, or symptoms in patients with serum TSH levels that are subnormal but greater than 0.1 mU/liter. A second unresolved issue is the appropriate management of premenopausal women and younger men with subclinical hyperthyroidism. The only data showing adverse consequences in these groups are from the one study showing an increase in bone turnover markers in premenopausal women (32) and the few studies showing an increase in myocardial structure or heart rate (11, 12) or symptoms (11, 12) that have included middle-aged patients. Finally, there are healthy elderly persons whose serum TSH levels are less than 0.1 mU/liter who have serum free T₄ and T₃ levels that are in the lower half of the normal range and have no evidence of thyroid or pituitary disease (4). Whether such persons have an altered set point of the pituitary thyroid axis, subtle thyroid dysfunction, or unrecognized nontypical illness is uncertain. But, it is difficult to believe that they are at the same risk for adverse cardiac or skeletal outcomes as persons with thyroid hormone levels that are in the upper part of the normal range. Yet, with recommendations targeted to the serum TSH level alone, therapy is deemed advisable, but may be unnecessary. Figure 1 is an algorithm that outlines a proposed plan for the evaluation and therapy of subclinical hyperthyroidism.

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**Fig. 1.** An algorithm that outlines a proposed plan for the evaluation and therapy of subclinical hyperthyroidism. *, Based on data showing higher mortality (23, 24), atrial fibrillation (20–22), bone loss (29–31), symptoms or reduced quality of life (11, 12) in some studies. **, Based on higher mortality (23, 24) and atrial fibrillation (22) in some studies. ***, Radioiodine preferred in patients with toxic multinodular goiter or solitary autonomous nodules. ****, Little evidence of clinically significant benefit in younger asymptomatic individuals without heart disease or bone loss.
The patient was elderly, had coexisting cardiovascular risk factors, and had a serum TSH that was near (0.15 mU/liter) the threshold at which the Consensus Panel recommends therapy (<0.1 mU/liter). Therefore, therapy with radioiodine was offered to the patient. Radioiodine was chosen rather than antithyroid drugs because multinodular goiter was the cause of her subclinical hyperthyroidism. Had Graves’ disease been the etiology, a 12- to 18-month course of antithyroid drugs would also have been reasonable. After discussing the potential risks of worsening hyperthyroidism and postablatative hypothyroidism, and the theoretical benefits of a decreased risk of AF and stabilization or improvement in bone mineral density, she received a dose of 30 mCi 131I. The dose was roughly calculated based on an estimated gland size of 40 g, a desired treatment dose of 150 μCi/g of thyroid tissue, and the 24-h radioiodine uptake of 22%. Unlike the case in overt hyperthyroidism, there are currently no recommendations to pretreat elderly patients with subclinical hyperthyroidism with antithyroid drugs to normalize thyroid function before radioiodine administration. Accordingly, she did not receive antithyroid drugs first, and although thyroid function was not monitored sooner than 6 wk after therapy, there were no acute clinical adverse effects (i.e. worsening hyperthyroid symptoms, AF, etc.). Thyroid function was unchanged at 6 wk, but 3 months later her serum TSH had risen to 0.25 mU/liter, and after 6 months it rose to 0.3 mU/liter, with a decline in serum free T4 to 1.0 ng/dl. Thyroid function has remained normal over 18 months of follow-up. A repeat bone density determination done 6 months after radioiodine therapy was unchanged compared with the prior study done 2 yr earlier.

Conclusions

Endogenous subclinical hyperthyroidism is a frequent medical problem and may cause several adverse outcomes, especially in the elderly. Although treatment guidelines have been proposed, it remains uncertain whether treatment prevents subsequent cardiovascular morbidity or mortality. Only randomized prospective trials will be able to provide the answer to this important clinical problem. Future trials should also include younger patients, as well as older patients with serum TSH values between 0.1 and 0.4 mU/liter.

Acknowledgments

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The author has nothing to declare.

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