Subclinical Thyroid Disease—

It **IS** Significant

James E. Griffin, M.D.

Department of Internal Medicine

Medicine Grand Rounds

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James E. Griffin, M.D.
Professor and Associate Dean
Endocrine Division
Interests: Male reproductive physiology, male hypogonadism, disorders of sexual differentiation, androgen resistance syndromes, general clinical endocrinology, thyroid disorders.

Case 1. This 48 year old woman presents to her physician complaining of mild fatigue and gradual weight gain over several years. She has gained about 8 pounds a year for the last three years. Her menstrual periods are regular. She takes no medications except vitamin supplements. She has tried to lose weight for brief periods with various diets but always regains it. Her past medical history and family history are unremarkable. On review of systems she reports mild constipation. On physical exam she is 5'4" tall and weighs 164 pounds. Her vital signs are normal. Other than being overweight, her exam is normal. Specifically she does not have any thyroid enlargement, and her deep tendon reflex relaxation is normal. Routine lab including CBC, urinalysis, and chemistry with lipid panel were normal or acceptable (LDL 136 mg/dl). Serum TSH returned at 8.4 μU/ml (ref 0.4-4.5) with FT_4 estimate of 0.85 ng/dl (ref 0.7-1.79). The patient was given dietary recommendation to follow a weight reduction low fat diet and asked to return in two months. On return the TSH level was 8.9 μU/ml. Antimicrosomal antithyroid antibodies were < 1:100 (ref < 1:100).

Case 2. This 72 year old woman is being followed for health maintenance. She has well-controlled hypertension and mild obesity. Her medications include Quinapril and Prem-Pro. She states that she has noticed some fatigue. Her weight has been stable. On exam she is 5'5" tall and weighs 170 pounds. Her heart rate is 86 and blood pressure 136/74. Other than being overweight, her exam is not remarkable. Specifically, her thyroid gland is not palpably enlarged and her DTRs are normal. As part of evaluation for fatigue a serum TSH is obtained and returns < 0.1 μU/ml. According to the lab algorithm a FT_4 estimate is then measured and found to be 1.29 ng/dl. Subsequently the lab reports a total T_3 of 133 ng/dl (ref 60-180) with a T_3UR of 0.9 (ref 0.8-1.2) and calculated FT_3 index of 120 (ref 60-180). A 24h radioactive iodine uptake is 18% (ref 10-35), and the appearance of the thyroid is reported as somewhat "patchy uptake". She returns for discussion of these results several weeks later. Her vital signs and exam are unchanged. On repeat thyroid lab, her TSH remains undetectable and thyroid hormone levels are similar to the previous values.

These two cases are presented as examples of subclinical thyroid disease. Subclinical hypothyroidism is defined as an increased serum TSH with a normal free T_4 estimate. Most investigators feel that patients with subclinical hypothyroidism and a TSH concentration greater than 10μU/ml are likely to have symptoms, perhaps unrecognized, related to hypothyroidism and thus likely to benefit from treatment. The significance of subclinical hypothyroidism when the TSH is above the normal range but less than 10 μU/ml is unclear. The choice of this subject for Grand Rounds was prompted by Position Papers in the July 15, 1998 Annals of Internal Medicine on screening for thyroid disease (1,2). Specifically in regard to subclinical hypothyroidism the American College of Physicians says:

> "The available evidence is not sufficient to recommend for or against treatment of subclinical hypothyroidism." (1)

Subclinical hyperthyroidism is defined as a low TSH with a normal free T_4 and free T_3 estimate. In regard to subclinical hyperthyroidism the American College of Physicians says:

> "The treatment of patients found by screening to have subclinical hyperthyroidism has not been studied."(1)

These position papers are not consistent with the opinions of most thyroid experts. Thus I will review the literature on these subjects. I will not address the issue of cost effectiveness of thyroid screening in different populations. That could be a subject for grand rounds in itself. Dr. Ladenson and his colleagues have presented an argument for the screening of women for mild thyroid failure beginning at age 35 (3,4). Drs. Helfand and Redfern argue against the desirability of such screening (2). The authors differ in their interpretations of the likelihood of the risks and benefits. Instead I will focus on the significance of subclinical thyroid disease when it is encountered. I will first address subclinical hypothyroidism followed by subclinical hyperthyroidism. There are a number of recent reviews on subclinical thyroid disease (5-10).

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SUBCLINICAL HYPOTHYROIDISM

Prevalence, Etiology, and Natural History

As the term implies, subclinical hypothyroidism occurs in individuals without obvious clinical symptoms of hypothyroidism. Thus the serum TSH is used for screening of various populations. The usefulness of the serum TSH as a reliable indicator of the thyroid status of the individual is greatest in stable outpatients who are not acutely ill. In ill patients, especially those admitted to a hospital, an elevated or decreased serum TSH is more likely to be due to nonthyroidal illness or medication effects than it is to be due to thyroid dysfunction (11).

The prevalence of an increased serum TSH concentration in four survey populations is shown in Table I.

Table I Prevalence of Increased Serum TSH Concentrations

Source, Year	Population	Number	Sex	Age	Prevalence,%
Tunbridge et al,1977(12)	Randomly selected	1494	F	>18	7.5
		1285	M	>18	2.8
Bagchi et al, 1990(13)	Health fair participants	694	F	>55	8.5
		274	M	>55	4.4
Sawin et al, 1985(14)	Unselected subjects	1260	F	>60	13.6
		879	M	>60	5.7
Parle et al, 1991(15)	Individuals in a single practice	683	F	>60	11.6
		510	M	>60	2.9

(adapted from ref 7)

The prevalence of an elevated serum TSH was increased in women compared to men and increased in older individuals. The effect of age is not linear. In the study of an English community (12) in which data were reported by decade, the frequency of an increased TSH in women doubled on reaching the 45-55 age range group and remained around 10%. In the two surveys in which the elevated TSH concentrations were divided into categories of >10 μU/ml and >5.0-10 μU/ml (14,15), the percent of subjects with the mild elevation was about 60%. The overall frequency of overt hypothyroidism i.e. a decreased free T_4, in these groups was less than 2%.

The causes of subclinical hypothyroidism are the same as those of overt hypothyroidism. Chronic autoimmune thyroiditis is the most common cause. In the survey of an English community, 67% of the women and 40% of the men with subclinical hypothyroidism had high titers of antimicrosomal (or antithyroid peroxidase) antibodies (12). The other major cause is prior ablative therapy for hyperthyroidism caused by Graves' disease. The eventual cumulative incidence of hypothyroidism following radioiodine therapy for Graves' disease is as high as 70% at 10 years (16). The cumulative incidence of hypothyroidism following subtotal thyroidectomy is somewhat less than following radioiodine (16). Patients may also develop hypothyroidism following head and neck surgery or radiotherapy or certain medications (see 17 for review). Finally, a very common cause of subclinical hypothyroidism is inadequate thyroxine replacement therapy for known overt hypothyroidism. In one study of 2575 unselected older adults, 10% of women and 2.3% of men were taking thyroid hormone. 37% of those definitely hypothyroid had a TSH level > 10 μU/ml despite thyroid therapy (18).

The natural history of subclinical hypothyroidism has been reported in several small studies (Table II). Only about 5% of patients had a normal serum TSH on follow-up. A significant fraction progressed to overt hypothyroidism.

Table II Natural history of subclinical hypothyroidism

Source	Follow-up period, months	Progression to overt hypothyroidism (%)
Rosenthal et al (19)	48	8/24 (33)
Parle et al (15)	12	13/73 (18)
Kabadi (10)	96[a]	16/30 (53)

[a] average follow-up period

The above table should not be interpreted as applying to all subjects with a serum TSH of 5 to 10 μU/ml. In the study with the greatest number of patients (15), the distribution of subjects with mild (5-10 μU/ml) or moderate (>10 μU/ml) TSH elevation is given. Of those with mild TSH elevations 12.7% progressed to overt hypothyroidism compared with 21.4% of those with moderate TSH elevations. Moreover, the presence of positive antimicrosomal antibodies also influenced the likelihood of progression to overt hypothyroidism. 24% of those with positive antibodies progressed to overt hypothyroidism in one year, whereas only 9% of those with negative antibodies did show such progression (Table III).

Table III Progression to overt hypothyroidism 12 months after initial testing with elevated TSH

Initial TSH	Thyroid antibodies	
	Positive	Negative
5-10μU/ml	5/27	2/28
> 10 μU/ml	5/14	1/4

(from ref 15)

In the study of 258 elderly subjects in the U.S., 80% of those with high titers of antimicrosomal antibodies (>1:1600) subsequently became hypothyroid regardless of the initial TSH level (19). In the 20 year follow-up of the English community included in Table I (21), the odds ratios (with 95% of confidence intervals) of developing hypothyroidism with (a) raised serum TSH alone were 8 (3-20) for women and 44 (19-104) for men; (b) positive antithyroid antibodies alone were 8 (5-15) for women and 25 (10-63) for men; (c) both raised serum TSH and positive antithyroid antibodies were 38 (22-65) for women and 173 (81-370) for men. Women in this later group developed hypothyroidism at the rate of 4.3% per year (21).

The underlying disease may also be a factor in the risk for progression to overt hypothyroidism. In one of the studies (20), patients who had autoimmune thyroid disease or radioiodine therapy or high dose external radiation therapy were in the progression group whereas patients who hemithyroidectomy for reasons other than hyperthyroidism or childhood external radiotherapy were in the group who showed persistent subclinical hypothyroidism.

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Effect on Lipids

Hypercholesterolemia is often seen in overt hypothyroidism. Thyroid hormone regulates the number of LDL receptors on the liver, and thus hypothyroidism reduces clearance of LDL from the circulation by decreasing the number of LDL receptors. When patients with hypercholesterolemia are screened for hypothyroidism, the prevalence is about twice that found in the general population (22). However, only those patients with TSH levels greater than 10 μU/ml have normalization of their serum cholesterol following thyroxine therapy to return their TSH to normal (22). Most cross-sectional studies do not find significant differences in total cholesterol concentrations in comparing patients with subclinical hypothyroidism and normal subjects, and total cholesterol levels do not consistently fall on treating patients with subclinical hypothyroidism. A pooled analysis of the published literature noted an overall decrease in mean total cholesterol concentration of 16 mg/dl following treatment (23). In examining the individual studies most had mean pretreatment TSH concentration greater than 10 μU/ml.

When serum LDL levels were measured in subjects with various degrees of hypothyroidism, the mean LDL was not significantly increased until the overt hypothyroid stage (24). When the prevalence of an LDL cholesterol level 2 S.D. above the mean in normal controls was assessed, the group with subclinical hypothyroidism of a moderate degree (TSH > 10) had a prevalence of an elevated LDL of 42.9% compared with 11.4% in controls (Fig. 1) (24).

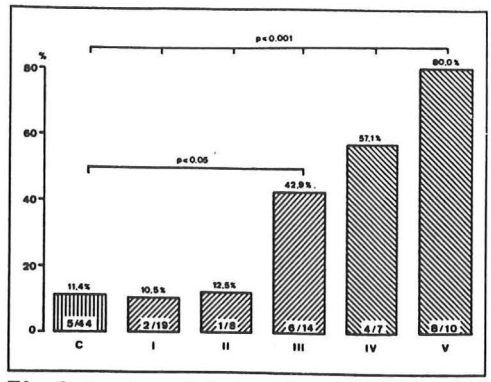

Fig. 1 ***Prevalence of elevated LDL-C levels in hypothyroidism.*** **The prevalence of elevated LDL-C levels (greater than 4.5 mmol/L, which are 2 SD above the mean in normal controls) is shown for the patients with hypothyroidism (grades I to V) and for the euthyroid controls (C) in the same manner as in Figures 1 and 2, with increasing severity from left to right.**

In a recent meta-analysis of 14 studies of subclinical hypothyroidism, the mean serum LDL cholesterol concentration decreased by 11 mg/dl and serum HDL cholesterol concentration increased by 2 mg/dl during thyroxine replacement (25). This lowering of HDL cholesterol levels observed in some studies of subclinical hypothyroidism is in contrast to the typical patients with overt hypothyroidism in which there is no change. This difference has prompted one group to postulate an interplay of the effects of androgens and thyroid hormone on hepatic lipase as the explanation for a decrease in HDL levels in subclinical hypothyroidism (26). The maintenance of free T_4 levels keeps SHBG levels low and enhances effects of androgens on stimulating hepatic lipase in addition to the direct effects of thyroxine. In untreated overt hypothyroidism the very low free T_4 levels may oppose the androgenic stimulatory effect on hepatic lipase.

There are inconsistent reports regarding lipoprotein (a) [Lp(a)] in subclinical hypothyroidism. In one study all subjects had a fall in Lp(a) following treatment with thyroxine with a mean decrease of 23% (27). In another report mean Lp(a) levels did not change (28).

Smokers with subclinical hypothyroidism have been found to have greater elevations in LDL cholesterol compared to nonsmokers (29), adding to their higher risk of cardiac events. A coronary angiographic study found greater progression of lesions in hypothyroid patients with mild undertreatment (i.e. subclinical hypothyroidism) compared with those whose TSH levels were maintained in the normal range (30).

In summary, the major lipid changes are seen in overt hypothyroidism with elevations of total and LDL cholesterol levels (and often triglyceride levels). There is little question of the presence of similar (but lesser) increases in LDL levels in subclinical hypothyroidism when the TSH concentration is greater than 10 μU/ml. Since the adverse effects of elevations of LDL cholesterol appear to be a continuum with no threshold (see Dr. Dietschy's recent Grand Rounds), even the mild and/or inconsistent lipid changes

observed in subclinical hypothyroidism with TSH concentrations of 5-10 μU/ml are likely to have some adverse effect.

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Cardiac Function

In two studies from Boston the effect of thyroxine replacement in patients with subclinical hypothyroidism on the systolic time interval was assessed as a measure of myocardial contractility. In the first study, two different measures of the systolic time interval, the ratio of pre-ejection period to the left ventricle ejection time (PEP/LVET) and the pulse wave arrival time (QK_d), were shown to decrease following thyroxine replacement (Fig. 2) (31).

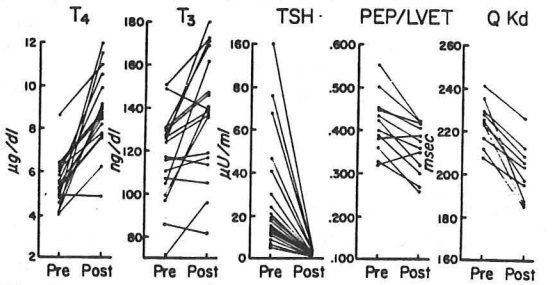

Fig. 2 The response of STI and serum T_4, T_3, TSH, and cholesterol levels to L-T_4 therapy. Pretreatment serum T_4 and T_3 levels were normal, and STI time intervals were either normal or slightly above the normal range. PEP/LVET and QK_d intervals as well as thyroid hormone levels were consistently changed by doses of L-T_4 which normalized serum TSH levels.

The normalization of the serum TSH was associated with changes in one marker of systolic time interval in even those patients with minimal elevation of TSH. In no instance was the post-treatment systolic time interval below normal to suggest over-treatment. A subsequent placebo-controlled, double-blind trial reported by the same group used patients with even less severe elevations of TSH, mean level about 11 μU/ml in both groups (32). In this study only those patients with an initially prolonged systolic time interval had a reduction in PEP/LVET.

Two studies from the same group in Edinburgh evaluated left ventricular ejection fraction (LVEF) as assessed by radionuclide ventriculography (33, 34). Both reports are consistent in demonstrating an improvement in LVEF following thyroxine replacement only with exercise. In the second study sodium nitroprusside was given for afterload reduction. Sodium nitroprusside caused similar increases in resting cardiac output but in subclinical hypothyroidism this resulted from a large increase in heart rate (26±4 beats/minute) and reduction in stroke volume (11±4%), whereas in the euthyroid state, the heart rate increment was less (10±4 beats/minute) and stroke volume was unchanged. The authors concluded that a true reduction in myocardial contractility and compensating tachycardia are present in subclinical hypothyroidism.

Finally, in a Swedish study, women with minimal TSH elevation (mean 7.7 μU/ml) were studied in a double-blind crossover 12-month trial of thyroxine treatment (35). These 17 women had not been previously treated for hyperthyroidism as in the Boston studies and were recruited from a population study. Two different measures of systolic time interval decreased significantly following normalization of the TSH. Thus subclinical hypothyroidism appears to adversely affect myocardial contractility.

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Constitutional and Neuropsychiatric Symptoms

Patients with subclinical hypothyroidism usually do not have the symptoms of overt hypothyroidism. However, they may have nonspecific symptoms such as fatigue or constipation that may or may not be related to thyroid hormone deficiency. Two previously mentioned studies of thyroxine replacement have assessed a symptom score of hypothyroidism (the Billewicz symptom score) in groups of patients before and after thyroxine replacement (32,35). In the first study, at baseline the number of symptoms per patient (2.2) was twice that in euthyroid controls (1.1). Improvement in a given symptom

occurred in 8 of 17 thyroxine-treated patients compared with 3 of 16 placebo-treated patients, and worsening of a given symptom occurred in 6 of the placebo-treated patients compared with 4 of the thyroxine-treated patients (32). In the second study, a small double-blind study of women recruited from a population study with a mean TSH of 7.7 μU/ml, 8 of 16 women had improvement in symptom score and correctly identified the active treatment period (35).

In more recent reports not involving studies before and after thyroid replacement, statistically significant abnormalities in Billewicz symptom score were noted in patients with even minimal TSH elevations (24). A modification of the Billewicz symptom score has been proposed (36), and by this new clinical score euthyroid controls had a score of 1.6 ± 1.4 compared with 6.1 ± 3.0 ($p < 0.001$) and 3.4 ± 2.0 ($p < 0.001$) in patients with overt and subclinical hypothyroidism, respectively. However, using the criteria in this paper, only 62% of all overt hypothyroid and 24% of subclinical hypothyroid patients would be classified as clinically hypothyroid. Thus such scoring is not meant to be used for the purpose of establishing the diagnosis of hypothyroidism but rather to assess the severity of tissue hypothyroidism.

In regard to individual nonspecific symptoms, dry skin, cold intolerance, and easy fatigability appear to be reported significantly more frequently by subclinical hypothyroid patients compared to euthyroid controls (32). Muscle cramps, constipation, and poor energy were reported with similar frequency in the two groups. Although it may not relate to reported constipation, small intestinal motility has been found to be very sensitive to changes in thyroxine concentration (37). In a group of elderly treated hypothyroid subjects, withdrawal of their thyroxine for one week resulted in an increase in the median small intestine transit time from 75 to 135 minutes ($p < 0.01$). During this week off medication the free T_4 fell only 22.6% and was still in the normal range for almost all subjects.

Some authors have claimed an association of depression with subclinical hypothyroidism. In one study of patients with major depression, 19 of 139 subjects were found to have subclinical hypothyroidism (38). However, this apparent enrichment for subclinical hypothyroidism must be viewed in the context of the history of prior lithium therapy in some patients. Chronic lithium therapy may induce transient TSH elevations or frank hypothyroidism likely due to lithium causing autoimmune thyroid disease (for review see 17). Another group assessed the lifetime history of major depression by structured interviews using a standardized instrument in 16 subjects with subclinical hypothyroidism and 15 subjects with normal thyroid function (39). The lifetime frequency of depression was 56% in the hypothyroid group compared to 20% in the euthyroid group.

There is consistency in the reports of mild cognitive dysfunction in subclinical hypothyroidism. Two studies assessed the Wechsler Memory Scale in groups of patients with subclinical hypothyroidism (40,41). Significant decreases in logic memory, digit span, and visual memory as well as overall memory quotient were found in the subclinical hypothyroid patients compared to the controls in the first study; and all but

digit span showed significant improvement after treatment with thyroxine (40). In this study in which the controls were only matched for age and sex, the hypothyroid subjects were also found to have some differences from the controls on scales to assess mood. In the second study, attempts were made to optimize selection of controls by only studying consecutive patients who presented with goiter (41). The patients were divided into subclinical hypothyroid or euthyroid based on laboratory tests. Psychopathological assessment on scales for depression (HRSD), anxiety (HRSA), and a comprehensive psychiatric rating (BRRS) did not show significant differences between the patients with subclinical hypothyroidism and euthyroid goiter, but Wechsler Memory Scale (WMS) showed differences in the same memory categories as the first study (Table IV).

Table IV Scores for measures of psychiatric and memory parameters in goiter patients with subclinical hypothyroidism (SCH) or euthyroid (EUT) goiter

	SCH goiter		EUT goiter
	baseline	treated	
HRSD	9.2 ± 1.1	8.5 ± 1.2	7.1 ± 1.4
HRSA	13.0 ± 1.3	11.8 ± 1.5	13.8 ± 1.6
BPRS	26.6 ± 1.1	25.8 ± 1.2	28.5 ± 1.7
WMS			
-logical	4.1 ± 0.8^a	5.2 ± 0.7^b	6.7 ± 0.8
-digit span	9.7 ± 0.5	10.8 ± 0.5^c	10.9 ± 0.4
-visual	6.5 ± 0.8	7.6 ± 0.8^c	8.2 ± 1.0
-total memory	92.0 ± 3.6	99.2 ± 4.0^d	96.0 ± 3.9

(from ref. 41), HRSD, Hamilton Rating Scale for Depression; HRSA, Hamilton Rating Scale for Anxiety; BPRS, Brief Psychiatric Rating Scale; WMS, Wechsler Memory Scale. SCH vs. EUT goiter patients: $^a p < 0.05$; SCH patients pre vs. post-treatment: $^b p < 0.05$, $^c p < 0.03$, $^d p < 0.003$.

In summary in regard to constitutional and neuropsychiatric symptoms, although the studies are few and small in number of subjects, it appears that there is an improvement in symptoms in as many as half of patients with subclinical hypothyroidism following treatment with thyroid hormone. Although the importance of subclinical hypothyroidism in contributing to depression is controversial, subclinical hypothyroidism does appear to have mild adverse effects on cognitive function.

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Metabolic Expense

Many patients who are overweight consult a physician seeking a hormonal explanation for their weight problem. Hypothyroidism is one common endocrine disorder that may be associated with weight gain. However, the 2% incidence of overt hypothyroidism cannot be the explanation for the 60% of the population who are overweight. Can mild subclinical hypothyroidism (TSH 5-10 μU/ml) contribute to weight gain? Investigators from Montreal performed an interesting study of resting energy expenditure (REE) in a small group of hypothyroid subjects on stable thyroxine replacement with normal TSH levels (42). The thyroxine dosage was changed twice in each patient at 6-8 week intervals to result in increases and decreases of TSH spanning the range of 0.1 μU/ml and about 10 μU/ml with the free T_4 maintained in the normal range. [Note that this is the range of subclinical hypothyroidism to subclinical hyperthyroidism that the ACP suggests is not significant.] REE decreased approximately 15% when TSH increased between 0.1 and 10 μU/ml. For example a 60 year old woman (BMI 34) with Hashimoto's thyroiditis had a REE of 1549 Kcal/d at a TSH concentration of 0.14 μU/ml and a REE of 1329 Kcal/d at a TSH concentration of 7.1 μU/ml, a 14.2% decrease in energy expenditure. This 220 Kcal decrease in energy expenditure would require a similar decrease in caloric intake to prevent weight gain. The REE was normalized to fat free mass (FFM) and the data for all 9 subjects pooled. There was a significant negative correlation between REE and TSH in each individual subject as well as the pooled data ($r^2 = 0.64$, $p < 0.001$). In addition initial REE and its change between the highest and the lowest thyroxine dose were significantly correlated with respectively, initial serum TSH and the change in serum TSH from highest to lowest (Fig 3A and 3B).

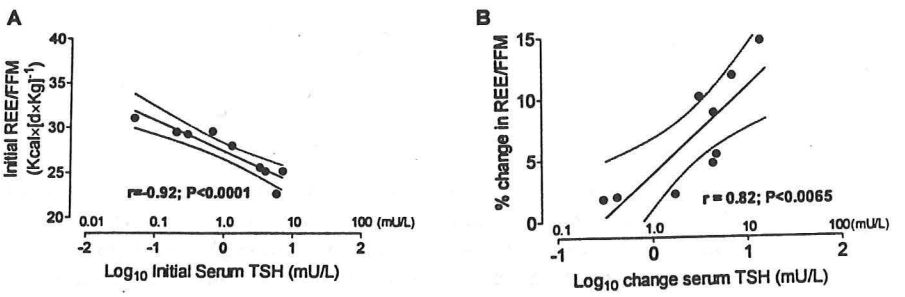

Fig. 3A, 3B Correlations between initial serum TSH and resting energy expenditure normalized by fat-free mass (REE/FFM; *panel A*) and between the excursion in TSH and the percent change in REE/FFM between the highest and the lowest dose of T_4 for each patient (*panel B*). TSH values were log-transformed (see *Materials and Methods*) for regression analysis. Regression equations: A: REE/FFM = 27.41–3.45×log TSH; and B: %ΔREE/FFM = 3.88+logΔTSH. *Curves* depict the regression lines ± $S_{y.x}$. R and *P* values are shown. See Tables 1 and 3 for individual numerical values.

In terms of our Case 1, if we postulated that increasing from a TSH of about 1.0 μU/ml (the mean for an apparently normal population) to about 9.0 μU/ml results in a 5 to 6% decrease in REE, failure to change caloric intake accordingly could more than account for 8 pounds weight gain per year. Of course, there are many other factors affecting weight

gain, and replacing thyroxine in someone with subclinical hypothyroidism usually does not result in weight loss unless other measures are employed as well.

Abnormal skeletal muscle function in overt hypothyroidism has been attributed to impaired mitochondrial metabolism (43). Studies in subclinical hypothyroidism also support abnormalities in muscle energy metabolism (44). A study of 12 patients with mean TSH concentration of 5.9 μU/ml and mild muscle symptoms were compared with 10 sex and age-matched controls in regard to hand-grip dynanometer exercise by sampling forearm blood for glucose, lactate, and pyruvate. During exercise blood lactate levels were significantly higher in the subclinical hypothyroid patients than in controls (Fig.4) (44). No significant difference was evident in pyruvate values between the two groups at any workload.

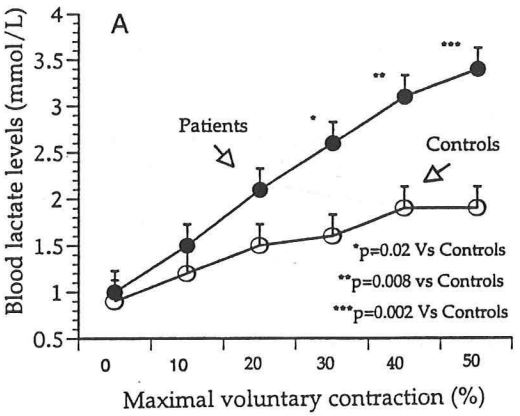

Fig. 4 Blood lactate (A) and pyruvate (B) levels and lactate/pyruvate ratio (C) at rest and at each interbout interval during aerobic dynamic exercise in sHT patients (Patients) and control subjects (Controls). Data are the mean ± SE.

The mean lactate increment was directly related ($r^2 = 0.44$, $p < 0.02$) to the duration of subclinical hypothyroidism (range 1 to 36 months). [The patients had been followed prospectively following surgery, radioiodine, or diagnosis of Hashimoto's]. In contrast, no correlation was found between mean lactate increments and serum TSH or free T_4 levels. Excessive lactate production during submaximal exercise is a marker of in vivo functional mitochondrial impairment (45). The authors interpret these results as consistent with the possibility that during step-up exercise, muscle glycolysis exceeds pyruvate oxidation resulting in rate of lactate production and release in excess of simultaneous lactate uptake. The higher lactate/pyruvate ratio of the subclinical hypothyroidism patients and the normal pyruvate absolute concentrations suggest that more severe intracellular acidosis may be responsible for pushing the excess pyruvate through the lactate dehydrogenase reaction. The authors suggest that exposure (i.e. time × concentration) of skeletal muscle to thyroid hormones may be an important parameter in the coupling of glycolysis and oxidation. Minute decrements in hormone synthesis

may over time lead to both biochemical signs and clinical symptoms qualitatively similar to those of overt hypothyroidism.

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Treatment Considerations

Given the above concerns about possible progression of subclinical hypothyroidism to overt hypothyroidism and adverse effects of subclinical hypothyroidism itself, which patients should be treated? The opinion of the American Thyroid Association is that most such patients should be treated (46). The authors of the reviews cited above concur (5-8,10). Serum TSH is elevated in over 12% of patients with hyperlipidemia, and thus TSH should be measured in all patients with hyperlipidemia. Conversely, all patients with increased TSH should have an LDL measurement. The presence of a serum TSH level of greater than 10 μU/ml or positivity for antithyroid antibodies, abnormal serum lipids, smoking, or nonspecific but suggestive symptoms when the TSH level is less than 10 μU/ml would probably be acceptable reasons for initiating treatment to most endocrinologists. In light of the subtle effects of subclinical hypothyroidism on memory and metabolism I feel that the potential benefits (and minimal risks) favor treating almost all patients with minimal persistent TSH elevations.

Finally, returning to Case 1, she does not have prior treatment of hyperthyroidism or positive antimicrosomal antibodies to suggest rapid progression to overt hypothyroidism. However, she is overweight and has nonspecific symptoms and a mild increase in LDL. I would initiate thyroxine replacement.

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SUBCLINICAL HYPERTHYROIDISM

Prevalence, Course, and Causes

Subclinical hyperthyroidism is defined as a low serum TSH concentration and normal serum T_4 and T_3 concentrations. The standard TSH assay used in most clinical labs is a second generation assay usually with a functional assay sensitivity of 0.1 μU/ml. Patients with overt hyperthyroidism almost always have an undetectable serum TSH by these assays. Patients with nonthyroidal illness as the cause of a low TSH may have measurable levels by more sensitive third generation assays, whereas patients with overt

hyperthyroidism generally have undetectable TSH concentrations even by the more sensitive assays. However, it is not possible to distinguish between the causes of a low serum TSH on the basis of the serum TSH value. A low TSH concentration in an acutely ill hospitalized patient is more likely due to nonthyroidal illness or medications than to thyroid disease (see above) (11). Some outpatients may have a low serum TSH concentration due to nonthyroidal illness as well (47), and thus, as for patients with elevated TSH levels, an abnormal value should be confirmed by repeat measurement. Some healthy elderly individuals have slightly low serum TSH concentrations apparently due to a decreased need for TSH as a result of the decrease in T_4 clearance with normal aging (reviewed in 17). Some patients with secondary hypothyroidism have low serum TSH concentrations although the TSH is more commonly normal.

The prevalence of subclinical hyperthyroidism has been assessed in several community and clinic surveys and summarized in a recent review (Table V)(9).

Table V Prevalence of a low serum TSH concentration in community or clinic populations (1988-1995).

Study	No. of patients	Age (years)	Low serum TSH (%)	T4 Therapy (%)*
Mölnlycke, Sweden	1929	≥ 18	68(4)	‡
Salford, UK	2573	NA	102(4)	63(62)
Detroit, US	968	≥ 56	33(3)	16(48)
Birmingham, UK	1210	≥ 60	74(6)	4(5)
Gothenburg, Sweden	886	≥ 85	13(2)	6(46)
Ludwigshafen, Germany	6884	≥ 18	200(3)	NA
Framingham, US	2007	≥ 60	248(12)	55(22)
Whickham, UK	1704	≥ 38	59(4)	26(44)
San Francisco, US	2969	≥ 21	409(16)	NA

(adapted from ref. 9, see ref for sources)
NA = not available, * percentage of low serum TSH group,
‡ patients taking thyroid hormone were excluded from the survey

The prevalence of subclinical hyperthyroidism in most surveys was around 4%. It is not clear how many of these patients actually had thyroid disease. About three-fourths of the subjects with low TSH had detectable values. About 20 to 60% of subjects with low TSH were taking thyroxine (Table IV). In one study designed to assess patients receiving thyroxine and the adequacy of their treatment, 23% of patients had a TSH concentration < 0.3 μU/ml (48).

The course of subclinical hyperthyroidism is variable (Table VI) (9). Most patients do not progress to overt hyperthyroidism, and about 40% have normal TSH months to years later.

Table VI Follow-up results in patients with low serum TSH concentrations

Study	Duration of follow-up	No. of patients	Normal TSH (%)	Low TSH (%)	Overt Hyper-thyroidism (%)
Mölnlycke, Sweden	2-3 wks	56	27(48)	29(52)	NA
Salford, UK	1 yr	54	19(35)	35(65)	NA
Vasteras, Sweden	2 yrs	29	4(14)	17(59)	8(28)
Birmingham, UK	1 yr	66	38(61)	26(39)	1(2)
Glasgow, UK	4-12 mos.	15	7(47)	4(27)	4(27)
Framingham, US	10 yrs	36	19(53)	25(69)*	5(2)‡
King, WI, US$^{\Delta}$	0.5-5.5 yrs	40	18(45)	11(28)	3(8)

(adapted from ref. 9, see ref for sources).
N.A. = not available, * percentages exceed 100 because some patients had multiple measurements during follow-up; ‡ percentage of original 248 patients with low TSH; Δ nursing home residents

The causes of subclinical hyperthyroidism in addition to thyroid hormone therapy are autonomously functioning thyroid adenomas, nontoxic nodular goiters, and Graves' disease either before or after treatment. Transient subclinical hyperthyroidism may be seen with subacute, painless, or postpartum thyroiditis or with interferon or amiodarone – induced thyroiditis.

Patients with autonomously functioning thyroid adenomas and nontoxic nodular goiters have some degree of thyroid autonomy leading to variable degrees of TSH suppression. As thyroid volume increases in nodular goiter, TSH decreases (49). In 375 patients with autonomous thyroid adenomas who were initially clinically euthyroid, about 4% per year became hyperthyroid (50). In a study of 74 patients with multinodular goiter, 12 (16%) became hyperthyroid in 2.5 to 17.4 years (51). In two other studies in which the subclinical hyperthyroidism was well characterized in 55 patients with goiter, 12 patients (22%) progressed to symptomatic hyperthyroidism in 2 years (52,53).

Patients with Graves' disease who have been treated with radioiodine, surgery, or antithyroid drugs may have a prolonged period of subclinical hyperthyroidism following treatment. In one study of 389 subjects treated with radioiodine 2-35 years previously who had normal serum free T_4 concentrations, 73 (19%) had low serum TSH concentrations (54). At follow-up two years later 50% had persistent low values whereas the remainder had normal values. In another study of 18 Graves' disease patients 1.5 to 15 years after subtotal thyroidectomy, 3 (17%) had low TSH (55). In this same study low serum TSH concentrations were found in 18 of 75 (24%) patients treated with antithyroid drugs 1 to 14 years previously who were clinically euthyroid with normal T_4 and T_3 at the time of evaluation. All of these patients presumably had ongoing Graves' disease but of a mild degree. If subclinical hyperthyroidism can persist for a prolonged period after treatment of Graves' disease, there is no reason not to accept that it is the explanation for so called "euthyroid Graves' disease" in which low TSH is associated with ophthalmopathy and could be the explanation for the low TSH found in some patients who have not had overt hyperthyroidism and do not have other explanations such as medication effect or nodular goiter.

The relative frequency of the causes of subclinical hyperthyroidism has been evaluated in several studies. In general the results were variable and may reflect referral

thyroiditis (56), and others having a predominance of nodular goiters in 68% of 40 patients (52) and 58% of 50 patients (57). These studies used nuclear scans, sonograms, thyroid antibodies, and serum thyroglobulin for evaluation in selected patients. Graves' disease was thought to be difficult to diagnose because of the absence of thyromegaly in some patients (56).

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Cardiovascular Effects

Patients with overt hyperthyroidism often have a number of cardiovascular manifestations including tachycardia, atrial fibrillation, and systolic hypertension. There appears to be an increased risk of atrial fibrillation in older patients with subclinical hyperthyroidism. In the 10 year follow-up of the Framingham Heart Study subjects 60 years and older, 13 of 61 (21%) with a serum TSH $\leq$ 0.1 μU/ml developed atrial fibrillation compared with 23 of 187 (12%) with a slightly low TSH (> 0.10 to 0.4 μU/ml) and 133 of 1576 (8%) with normal TSH (Fig. 5) (58). The relative risk of new atrial fibrillation with an undetectable TSH was 3.1 (1.7-5.5), significantly different ($p < 0.001$) from that in the normal group. The frequency of atrial fibrillation in the group with low but measurable serum TSH was not significantly different from the normal TSH group before adjustment for the presence of other risk factors for atrial fibrillation. After adjustment, this slightly low TSH group had a relative risk of 1.6 (1.0-2.5; $p < 0.05$).

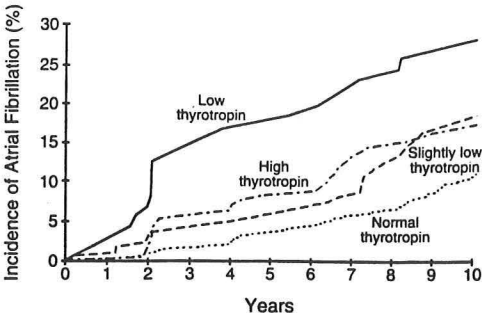

Fig. 5 Cumulative Incidence of Atrial Fibrillation among Subjects 60 Years of Age or Older, According to Serum Thyrotropin Values at Base Line.

Low serum thyrotropin values were defined as ≤0.1 mU per liter; slightly low values, >0.1 to 0.4 mU per liter; normal, >0.4 to 5.0 mU per liter; and high, >5.0 mU per liter.

A similar enrichment for atrial fibrillation was found in a smaller study mentioned previously (52). In another report of patients with atrial fibrillation and acute arterial embolism, 6 of 64 patients had subclinical hyperthyroidism (59).

The effect of subclinical hyperthyroidism on cardiac function has been evaluated with variable conclusions. A recent study of thyroid cancer patients on thyroxine suppression with mean TSH concentrations of 0.03 μU/ml found that patients had increased symptoms of adrenergic tone, but no abnormalities of rate or extrasystolic or echocardiographic abnormalities (60). Although the left ventricular mass index was within the normal range, it was higher (117 ± 35 g/m^2) in the patients than in the control group (92 ± 31 g/m^2, $p < 0.05$). These authors concluded that in the absence of symptoms of hyperthyroidism patients treated with TSH-suppressive doses of thyroxine need not be evaluated further (60). In a series of four papers in the JCEM (61-64) an Italian group has presented evidence for significant abnormalities of cardiac function. In 20 patients with serum TSH < 0.05 μU/ml who were receiving long term thyroxine suppression, the average heart rate was higher than in controls (84 ± 7 vs. 70 ± 6 beats/min; $p < 0.01$); the prevalence of atrial premature beats was higher (100% vs. 60%; $p < 0.006$); and there was an increased left ventricular mass index (97 ± 24 vs. 80 ± 18 g/m^2; $p < 0.02$) (61). The increase in left ventricular mass index was proportional to the duration of subclinical hyperthyroidism. Treatment with a β-blocker (bisoprolol) while continuing thyroxine was shown to significantly decrease symptoms, heart rate, atrial arrhythmias, and left ventricular mass index (106 ± 23 before vs. 91 ± 18 g/m^2 after; $p < 0.003$) after 6 months of combined therapy (62). In the third study indices of diastolic dysfunction were shown to be abnormal, and a subgroup with adrenergic symptoms was treated with β-blockade for four months with improvement in isovolumic relaxation time and ratio of early to late diastolic flow velocity (63). Finally, these same authors reported impaired cardiac reserve and exercise capacity in a similar group of 10 thyroxine-treated patients who had effort dyspnea and adrenergic symptoms. During submaximal physical exercise (bicycle ergometer), LVEF increased in the controls from $58 \pm 2\%$ to $65 \pm 2\%$ ($p < 0.001$), whereas in the patients it fell from $63 \pm 2\%$ to $53 \pm 2\%$ ($p < 0.01$). Maximal

exercise capacity was markedly impaired in the patients as documented by reduction in peak workload and exercise duration despite double product values similar to controls. β-blockade for 4 months prevented the fall in ejection fraction with exercise and improved exercise tolerance (Fig. 6) (64).

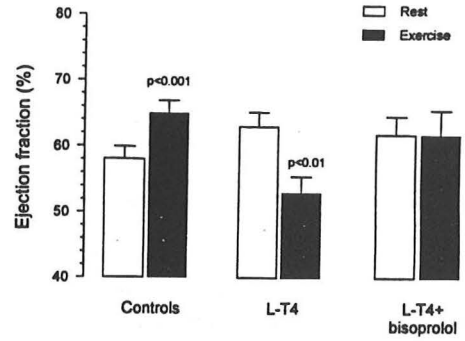

Fig. 6 Left ventricular ejection fraction at rest and during physical exercise in patients receiving long term l-T_4 therapy, before and after β-adrenergic blockade, and in control subjects. *P* values indicate significance *vs.* the respective basal value.

In summary in regard to cardiac function, patients receiving thyroxine therapy to suppress TSH without increasing the free T_4 or T_3 above normal are at risk for specific cardiac alterations characterized by increased myocardial mass, diastolic dysfunction, normal systolic function at rest, impaired systolic performance on effort, and impaired exercise capacity. Cardiac morphology and function can be partially restored by β-adrenergic blockade.

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Skeletal Effects

Overt hyperthyroidism is associated with increased bone resorption, low bone density, and an increased risk for fracture. The changes are greatest in the cortical bone (wrist), least in the trabecular bone (lumber spine), and intermediate in the mixed cortical-trabecular bone (hip). The studies of bone abnormalies in subclinical hyperthyroidism can be divided by the source of the thyroid excess, endogenous or exogenous.

Bone density may be decreased in women with endogenous subclinical hyperthyroidism, and treatment of the cause of the subclinical hyperthyroidism either prevents further loss or leads to partial restoration of bone mass. In a comparison of 23 women with subclinical hyperthyroidism and serum TSH < 0.1 μU/ml due to nodular goiter and 54 women with euthyroid goiter, Z-scores of both the distal and proximal forearm density were significantly lower ($p < 0.05$)(65). The free T_4 correlated inversely with Z-scores of both distal and proximal forearm bone densities in the subjects with subclinical hyperthyroidism (65). In a follow-up study by the same group, 8 of 16 postmenopausal women with multinodular goiter and subclinical hyperthyroidism were randomly assigned to be treated with methimazole for 2 years (66). In the second year the distal forearm bone density increased slightly in the methimazole group whereas it decreased 5% in the control group ($p < 0.05$) (Fig. 7) (66).

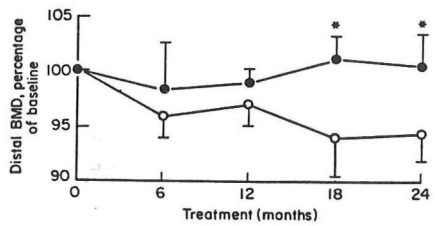

Fig. 7 Mean (± SEM) percentage of base-line bone mineral density in distal forearm in post-menopausal women with subclinical hyperthyroidism during ●, treatment with methimazole or ○, no treatment. Significant differences between the groups are indicated by asterisks ($P < 0.05$).

In another prospective nonrandomized study radioiodine therapy was used to treat the nodular goiter in patients with TSH < 0.2 μU/ml (67). Sixteen postmenopausal woman were treated with radioiodine, and 12 were followed without treatment. The treated patients had an increase of bone density of approximately 2% at both the spine and the hip whereas the control group had a 5% loss at the spine and 2% loss at the hip at 2 years.

The effect of exogenous subclinical hyperthyroidism on bone density has been reported in more than 40 cross-sectional studies with conflicting conclusions. The initial

claims of general adverse affect in women were refined to indicate that only post-menopausal women seemed at risk. Then concern was raised that what was being observed was only a result of studying women with prior overt hyperthyroidism and that it was the prior overt hyperthyroidism that resulted in the low bone density. More recent studies have shown a lesser effect in general. Most studies have had bone density measured at various sites by different methods with variable criteria of decreased TSH in small numbers of patients. In the most recent and comprehensive meta-analysis including 41 cross-sectional studies with about 1250 patients, thyroid hormone suppressive therapy had a detrimental effect on all sites (including spine and hip) in post-menopausal women (68). Suppressive therapy was defined as a serum TSH below normal, i.e. both measurable and unmeasurable values. The statistically significant detrimental effect for suppressive therapy in postmenopausal women represent a bone loss of 7% (CI, 4-10%) for the spine, 5% (CI, 2-8%) for the femoral neck, and 7% (CI, 1-13%) for the distal radius. The overall detrimental effect was less than 0.5 SD. Although no significant increase in the rate of fracture has been reported for thyroid hormone suppressive therapy in postmenopausal women (69), the fracture rate for a 5 year period for women with suppressed TSH was 2.5% versus 0.9% for women with normal TSH (p NS). The calculated increased theoretical fracture risk in the meta-analysis was 1.6 for both hip and lumbar spine.

There is also similar disagreement among longitudinal studies of exogenous subclinical hyperthyroidism. Two small studies (14 and 10 patients, respectively) found a significant decrease in bone density only in the spine over 12 to 36 months (70,71). In another study 41 postmenopausal women taking exogenous thyroid hormone with serum TSH < 0.1 μU/ml had no more bone loss in 4 to 6 years than a group also on thyroxine with serum TSH 0.1-5.5 (72). Baseline total hip bone mineral density was 6% lower among women with serum TSH < 0.1, and both osteocalcin and bone-specific alkaline phosphatase were elevated. In yet another study, 64 postmenopausal women on thyroxine with normal or suppressed serum TSH and 36 control women were studied at baseline and for 2 years (73). After baseline measurements, 18 women with suppressed TSH had their thyroxine dose reduced to normalize serum TSH. There was no significant difference in bone mineral density and bone turnover markers at baseline or follow-up in any of the groups of women on thyroxine or a euthyroid control group. However, the lumbar spine and femoral neck bone mineral density increased significantly over 2 years in the group which had the thyroxine dose lowered, and the levels of 3 markers of bone turnover decreased significantly. Overall, in the patients the serum TSH at baseline was negatively correlated with serum levels of osteocalcin, bone alkaline phosphatase, and urinary cross-linked N-telopeptide (73).

There is no disagreement about the lack of adverse effect in men of thyroxine suppression of serum TSH in regard to bone density (68,74). A recent study has concluded that there is no evidence for a decreased bone mineral density in hypothyroid postmenopausal women given replacement (not suppressive) thyroxine therapy, even if they had prior overt hyperthyroidism (75). Finally in regard to an adverse effect of thyroxine suppression in postmenopausal women, estrogen therapy appears to be protective (76). In 196 women taking thyroxine at greater than 1.6 μg/kg body weight,

bone mineral density was decreased at four sites. Women taking both thyroxine and estrogen had bone mineral density levels comparable to those observed in women taking only estrogen (Fig. 8) (76).

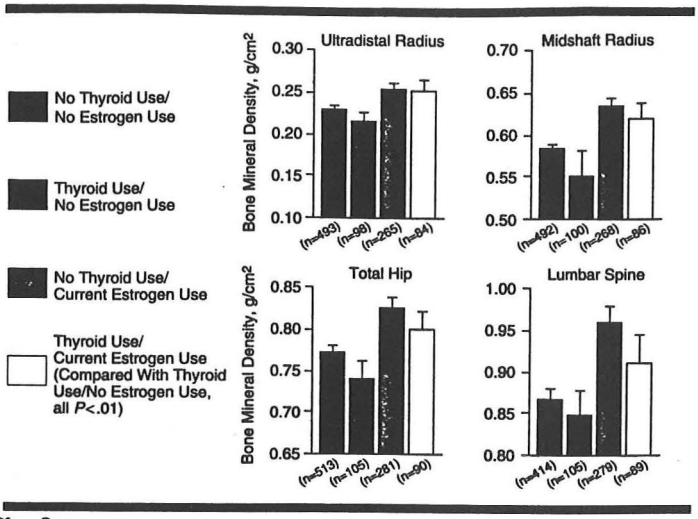

Fig. 8 Mean bone mineral densities (95% confidence intervals) by current thyroid hormone use and estrogen use adjusted for age, body mass index, smoking, and use of thiazide diuretics and oral corticosteroids in women, Rancho Bernardo, Calif, 1988 to 1991.

Bone turnover markers might be a useful additional indicator of an adverse effect of thyroxine on bone. A study mentioned above noted a decrease in bone turnover markers when the thyroxine dose was lowered (73). In addition, another study found significantly increased urinary excretion of bone collagen-derived pyridinium pyridinoline and deoxypyridinoline in postmenopausal women on thyroxine with suppressed TSH (77). Serum carboxy-terminal-1-telopeptide significantly increased in postmenopausal women with suppressed serum TSH on thyroxine therapy (78). And a significant negative correlation between serum TSH and fasting urinary total hydroxyproline-creatine excretion was found in patients with serum TSH concentration in the range of 0.1 to 1.0 μU/ml (79).

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Treatment Decisions

It is not clear that all patients unexpectedly found to have an undetectable serum TSH concentration and normal T_4 and T_3 require treatment. First it is important to rule out a transient TSH abnormality either due to nonthyroidal illness or a self-limited condition such as thyroiditis. Repeating the thyroid function tests in several weeks or months will help assess whether the TSH is chronically suppressed. If subclinical hyperthyroidism persists, look for possibly related symptoms or signs, existing cardiac problems, or predisposition to adverse cardiac or skeletal effects based on age and/or gender including menopausal status. As mentioned, the possible causes of persistent subclinical hyperthyroidism include early Graves' disease, a solitary autonomous nodule, and a multinodular goiter. Thyroid nuclear scans may be useful in detecting a multinodular goiter or the activity of a palpable nodule, and the finding of an increased radioiodine uptake may signal Graves' disease. In patients at risk for adverse effects of mild thyroid excess or with large goiters, treatment should be instituted if the TSH is < 0.1 μU/ml. If the TSH is 0.1 to 0.5 μU/ml, treatment should be considered if the thyroid scan is abnormal or bone density is low. In younger patients lacking any risk factors or even mild symptoms or signs (e.g. slightly increased resting heart rate) with TSH <0.1 μU/ml, treatment should be considered if the thyroid scan is abnormal or bone density is low. If the TSH is 0.1 to 0.5 μU/ml, observation seems appropriate. In patients with prior treatment of Graves' disease, retreatment or alternate treatment should be considered if they have symptoms or signs or are at risk because of age or gender.

In those hypothyroid patients overmedicated with thyroxine who do not have a history of thyroid cancer, the thyroxine dose should be lowered until the steady state TSH increases to the normal range. For patients who have been significantly overmedicated

for a long time and who are not clinically toxic, this may require a gradual reduction in thyroxine dose to avoid the patient having severe fatigue on too abrupt a decrease. For patients being treated with thyroxine for suppression of a benign goiter, the lowest dose that is effective should be used, and it is probably unreasonable to lower the serum TSH to the undetectable range in light of the controversial status of this therapy. In patients with thyroid cancer who require suppression of TSH to undetectable levels, periodic reassessment should be made to ensure that the thyroxine dose is the lowest required for suppression. This is the group of patients in whom β-blocker therapy should be considered if increased resting heart rate or hyperadrenergic symptoms develop.

Finally, in Case 2 a small multinodular goiter with autonomy appears likely. Her fatigue may be a symptom of mild thyroid excess, and her resting heart rate remains in the mid-80's. I would recommend treatment with radioiodine or low dose methimazole.