A Retrospective Study of the Natural History of Endogenous Subclinical Hyperthyroidism

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ABSTRACT

Objective: The treatment of subclinical hyperthyroidism is controversial because the natural history is uncertain. We undertook a retrospective study to examine the natural history of endogenous subclinical hyperthyroidism.

Methods: Between 2002 and 2006, we identified 116 patients with thyroid-stimulating hormone (TSH) concentrations <0.4 µIU/mL but normal free thyroxin and triiodothyronine or free triiodothyronine levels and >6 months of follow-up. The medical records of these subclinical hyperthyroid patients were reviewed for demographic data, clinical outcomes, and thyroid function test results. Because the etiology of hyperthyroidism could not be identified in 57 (49%) patients, we compared patients with normal-sized or diffusely enlarged thyroid glands with patients with nodular thyroid glands. We also compared the results of patients with initial TSH levels <0.1 µIU/mL to patients with TSH levels between 0.1 and 0.39 µIU/mL, and patients age <65 years to older patients.

Results: Of 116 patients with subclinical hyperthyroidism, 88 (76%) were women and 28 (24%) were men. They ranged in age from 19 to 98 years (mean = 55 years). Ninety-eight patients did not have thyroid nodules, and 18 had thyroid nodules. Follow-up ranged from 6 months to 6.5 years (median, 3.2 years). TSH reverted to normal in 58 (59%) patients without nodules; we treated only 4 (4%) of these patients for hyperthyroidism. In contrast, TSH levels in only 3 (17%) patients with nodules reverted to normal and 7 (39%) received antithyroid treatment. Atrial fibrillation was present in 8 (8%) patients without thyroid nodules and in 3 patients (17%) with thyroid nodules (*P*=.373). There were no significant outcome differences based on initial TSH levels or age.

Conclusion: We conclude that most patients with subclinical hyperthyroidism who do not have thyroid nodules rarely require antithyroid therapy but should be followed carefully.

INTRODUCTION

Subclinical hyperthyroidism is defined as a low or undetectable thyroid-stimulating hormone (TSH) and normal free thyroxin (FT_4) and free triiodothyronine (FT_3) concentrations.[1]

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Patients with subclinical hyperthyroidism usually do not display clinical features of hyperthyroidism. Endogenous hyperthyroidism results from the usual thyroid disorders that cause overt hyperthyroidism (eg, Graves disease, silent thyroiditis, toxic nodular goiter, and toxic nodule), whereas exogenous subclinical hyperthyroidism is caused by the ingestion of thyroid hormone. Endogenous subclinical hyperthyroidism affects approximately 1% of the general population. The treatment of subclinical hyperthyroidism is controversial because the frequency of progression to overt hyperthyroidism is unknown.[2] Therefore we undertook a retrospective study to examine the natural history of endogenous subclinical hyperthyroidism in our patient population.

PATIENTS AND METHODS

After approval of the Gundersen Lutheran Human Subjects Committee, we performed a retrospective review of TSH test results recorded between 2002 and 2006; 1463 patients with TSH levels below the normal range were identified. Patients were excluded from further analysis if they had elevated FT_4, triiodothyronine (T_3), or FT_3 levels. Also excluded were patients with nonthyroidal illnesses who were acutely ill when TSH was measured; patients ingesting thyroid supplements, glucocorticoids, or amiodarone; pregnant women; patients without at least 1 follow-up TSH measurement; and patients with <6 months follow-up. The final study group consisted of 116 patients with low TSH levels but normal FT_4 and T_3 or FT_3 concentrations and at least 6 months of follow-up.

A technician trained in data collection reviewed the medical records of subclinical hyperthyroid patients. The cause of hyperthyroidism was identified, if possible, and the clinical outcome and thyroid function test results were tabulated. Also

recorded was the frequency of atrial fibrillation. When the etiology of hyperthyroidism could not be determined or the data was unclear, the medical records were reviewed by 1 or 2 of us (RP, RHC).

Radionuclide uptake and/or scans were performed by standard techniques in 14 of 18 (78%) patients with palpable thyroid nodules, but in only 13 of 98 (13%) patients without thyroid nodules. Thyroid-stimulating immunoglobulins (TSI), thyroid peroxidase antibody measurements, and thyroid ultrasonography were performed in only a few patients.

Serum TSH was measured by an electrochemiluminescense sandwich immunoassay. The assay had a functional sensitivity of 0.02 µIU/mL and an adult reference range of 0.4 to 5.5 µIU/mL. Serum FT_4 was measured by an electrochemiluminescense competition immunoassay and had a normal range of 0.9 to 1.7 ng/dL. Serum T_3 was measured by an electrochemiluminescense competition immunoassay and had a normal range of 60 to 181 ng/dL. The Mayo Medical Laboratory measured FT_3 by an immunoenzymatic assay that had a normal range of 2.0 to 3.5 pg/mL. The Mayo Medical Laboratory also measured TSI by recombinant bioassay. The normal range was ≤1.3 TSI index. Statistical comparisons were made using χ^2 and Fisher exact tests. All statistics were calculated using SAS 9.2 (Cary, North Carolina) software. An alpha level of 0.05 was considered statistically significant.

RESULTS

Of the 116 patients with subclinical hyperthyroidism, 88 were women and 28 were men. They ranged in age from 19 to 98 years (mean=55 years). The causes of hyperthyroidism were as follows: Graves disease, 15 (13%); silent thyroiditis, 26 (22%); toxic multinodular goiter, 15 (13%); and toxic thyroid nodule, 3 (3%). Because of incomplete clinical and laboratory data, the etiology of subclinical hyperthyroidism could not be accurately assessed in 57 (49%) patients. Therefore, we classified all patients based on clinical examination and/or radionuclide imaging. The nonnodular group consisted of patients with normal-sized or diffusely enlarged thyroid glands; the nodular group was composed of patients with thyroid nodules, as documented by clinical examination or thyroid scintigraphy. Ninety-eight patients had normal-sized or diffusely enlarged thyroid glands; 18 had nodular thyroid glands. The duration of follow-up was 6 months to 6.5 years (median, 3.2 years).

Comparison of clinical status during follow-up of patients in both groups is displayed in Figure 1. Four (4%) of the patients in the nonnodular group and 7 (39%) of the patients in the nodular group were treated for hyperthyroidism (P=<.001). The treatments were as follows: antithyroid drug therapy, 6; radioactive I-131, 4; and antithyroid drug followed by radioac-

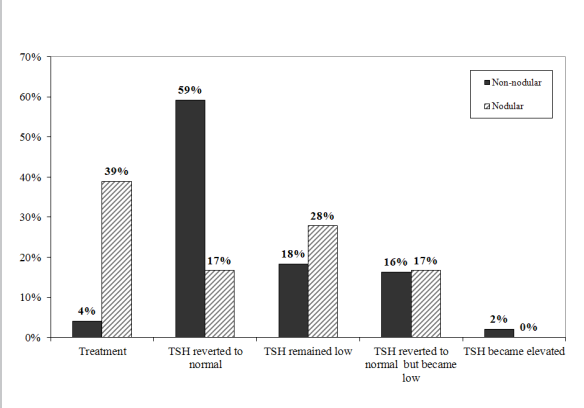

Figure 1. Change in clinical status between nonnodular and nodular patients, median follow-up period of 3.2 years.
TSH = thyroid-stimulating hormone.

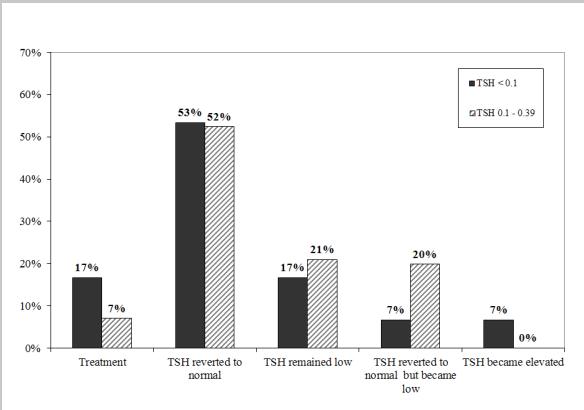

Figure 2. Change in clinical status in patients with initial TSH levels <0.1 µIU/mL and patients with TSH levels between <0.1 and 0.39 µIU/mL.
TSH = thyroid-stimulating hormone.

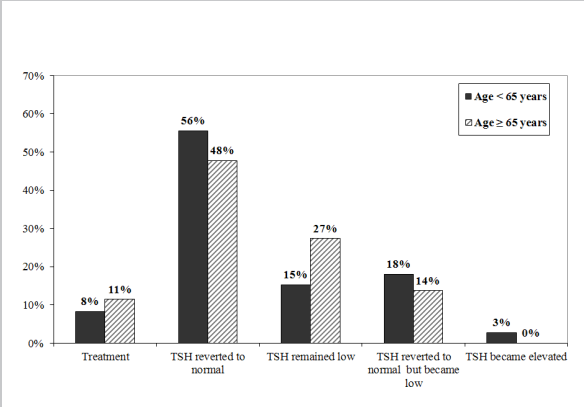

Figure 3. Change in clinical status in patients <65 years of age and older patients.
TSH = thyroid-stimulating hormone.

tive I-131 and metoprolol,1. The reasons for therapy were as follows: development of hyperthyroid symptoms, 6; elevated FT_4, 2; osteoporosis and goiter, 1; and clinician's decision, 2. Fifty-nine percent of nonnodular patients reverted to normal TSH levels without therapy, compared to only 17% of nodular patients ($P = <.001$; Figure 1).

Atrial fibrillation was detected before or at the time of diagnosis of subclinical hyperthyroidism in 8 (8%) non-nodular patients and developed after the diagnosis of subclinical hyperthyroidism in 3 (17%) nodular patients ($P = .373$).

Thirty patients had initial TSH values of <0.1 μIU/mL; 86 patients had initial TSH concentrations between 0.1 and 0.39 μIU/mL. TSH levels reverted to normal in 16 (53%) patients with TSH levels <0.1 μIU/mL; 5 (17%) received antithyroid drug treatment (Figure 2). Thyrotropin reverted to normal in 45 (52%) patients with initial TSH levels between 0.1 and 0.39 μIU/mL; 6 (7%) of these received antithyroid drug treatment ($P = .044$; Figure 2). Atrial fibrillation was present in 3 (10%) patients with initial TSH levels <0.1 μIU/mL and 8 (9%) patients with TSH levels between 0.1 and 0.39 μIU/mL ($P = .999$).

Seventy-two patients were <65 years; 44 patients were ≥65 years old. Of the younger group, 6 (8%) received antithyroid therapy, whereas 5 (11%) patients >65 years were treated; (Figure 3). Thyrotropin reverted to normal in 40 (56%) patients <65 years of age and 21 (48%) older patients, respectively ($P = .435$). Atrial fibrillation was present only in patients 65 years of age or older.

DISCUSSION

The frequency in which subclinical hyperthyroidism progresses to overt thyrotoxicosis is uncertain[1,2] but it has been reported to range from 2% to 45% per year.[3] The progression may depend on the cause of endogenous hyperthyroidism,[3-6] the initial serum TSH concentration,[7-9] or the age of the patient.[5] Our study indicates that subclinical hyperthyroidism associated with nodular thyroid glands frequently required antithyroid drug treatment, whereas only 4% of patients with normal-sized or diffusely enlarged thyroid glands were treated. Thyrotropin levels reverted to normal without treatment in only 17% of patients with nodular thyroid glands, in contrast to normalization of TSH in 59% of patients without thyroid nodules (Figure 1). We did not find differences in the clinical outcome related to initial TSH levels (Figure 2) or age (Figure 3).

Previous studies have examined the natural history of subclinical hyperthyroidism. In a study by Sawin et al, persons >60 years of age with TSH levels <0.1 μIU/mL were followed for 4 years.[10] Only 6 of 50 patients developed overt hyperthyroidism during the follow-up period.

During 4 to 12 months of observation, Stott et al noted that TSH reverted to normal in 7 of 15 patients with subclinical hyperthyroidism.[11] Although thyroid hormone concentrations rose above normal in 4 patients, only 2 were treated.

Tenerz et al reported 33 elderly patients with subclinical hyperthyroidism had a 68% prevalence of multinodular goiter, whereas matched controls had a 29% prevalence.[3] The patients were followed for 2 years. Serum TSH levels remained low or borderline low in 17 patients and reverted to normal in 4. Patients with subclinical hyperthyroidism were more likely than control subjects to develop overt hyperthyroidism.[3] Twelve patients were treated for goiter or hyperthyroidism during the 2-year follow-up period.

Woeber retrospectively reviewed 16 patients with subclinical hyperthyroidism followed for 11 to 36 months.[4] TSH returned to normal in 5 of 7 patients with subclinical Graves disease, but remained abnormal in all 9 patients with multinodular goiter. One of the patients with Graves disease and none of the patients with multinodular goiter progressed to overt hyperthyroidism.

Recently, Schouten et al determined that the etiology of subclinical hyperthyroidism is the major factor influencing the progression to overt hyperthyroidism.[6] On the basis of clinical evaluation and thyroid scintigraphy, they identified and followed for 5 years 12 patients with subclinical Graves disease, 70 with multinodular goiter, and 14 with autonomous thyroid nodules. Progression to overt hyperthyroidism occurred in 8%, 16%, 21%, and 26% at 1, 2, 3, and 5 years, respectively. During the 5 years of follow-up, the progression to overt hyperthyroidism was 9% for the group with subclinical Graves disease, 21% for 3 with multinodular goiter, and 61% for those with autonomous nodules.[6]

Our findings are consistent with those of Woeber[4] and Schouten.[6] In contrast, Rosario noted patients with subclinical Graves disease who were <65 years of age progressed to overt hyperthyroidism 40% of the time, whereas only 20% of patients <65 years of age with subclinical hyperthyroidism due to nodular thyroid disease progressed to overt thyrotoxicosis.[5] Serum TSH returned to normal in 13% of patients with Graves disease and 20% of patients with nodular disease.

In a 12-month follow-up study of 66 patients with subclinical hyperthyroidism, Parle et al reported that serum TSH reverted to normal in 38 of 50 patients with subnormal but detectable TSH levels, but remained subnormal in 14 of 16 patients with undetectable serum TSH concentrations.[7] Only 1 patient progressed to overt hyperthyroidism. In a retrospective study of 75 subclinical hyperthyroid patients, Diez and Iglesias found that 34 (45.3%) developed overt hyperthyroidism and 15 (20%) reverted to normal TSH levels.[8] Eighty percent of the

study population had toxic multinodular goiter, 10% had toxic nodules, and 5% had Graves disease. The degree of TSH suppression was a significant factor for progression to overt hyperthyroidism. Patients with TSH levels <0.1 µIU/mL had the highest probability of progression to overt hyperthyroidism.[8]

In a recent prospective study, Rosario followed 102 women with a median age of 68 years who had TSH levels between 0.1 and 0.4 µIU/mL for 12 to 70 weeks.[9] Seven patients had Graves disease, 91 had nodular disease, and 4 had subclinical hyperthyroidism without a defined cause. Seven patients were treated for overt hyperthyroidism or progressive abnormalities of thyroid function tests. TSH levels in 24 women reverted to normal. Subclinical hyperthyroidism with TSH levels remaining between 0.1 and 0.4 µIU/mL persisted in 71 patients, 4 of whom were treated because of the development of atrial fibrillation or heart disease. Rosario concluded that elderly patients with endogenous subclinical hyperthyroidism who had TSH levels between 0.1 and 0.4 µIU/mL progressed to overt hyperthyroidism at a low rate (approximately 1% per year).[9] He further concluded that although spontaneous normalization of TSH may occur, persistence of subclinical hyperthyroidism was the most likely outcome. In our study, initial TSH levels did not predict overt hyperthyroidism.

Vadiveloo et al used record-linkage technology to retrospectively identify 2024 patients with subclinical hyperthyroidism.[12] At 2, 5, and 7 years after diagnosis, 81.8%, 67.5%, and 63%, respectively, remained subclinically hyperthyroid. Only 0.5%-0.7% of patients developed overt hyperthyroidism at the 2-, 5-, and 7-year observation periods. Seventeen percent, 31.5%, and 35.6%, respectively, of patients reverted to normal TSH levels at the 3 observation periods. Reversion to normal thyroid function was most common in subclinical hyperthyroid patients with TSH levels between 0.1 and 0.4 µIU/mL. The authors concluded that very few patients developed overt hyperthyroidism; more reverted to normal thyroid function, but many remained subclinically hyperthyroid.

The frequency of atrial fibrillation is increased in patients with subclinical hyperthyroidism[1,2] Sawin et al studied people >60 years of age for 10 years.[13] The authors noted a relative risk of atrial fibrillation of 3.1 among individuals with TSH levels <0.1 µIU/mL and a relative risk of 1.6 for people with TSH levels between 0.1 and 0.4 µIU/mL. The frequency of atrial fibrillation increases with age in euthyroid and hyperthyroid patients. In our study, atrial fibrillation was present before or at the time of diagnosis of subclinical hyperthyroidism in 8 patients and developed during observation in 3 additional patients. All 11 patients with atrial fibrillation were 65 years of age or older, which is 9% in this group. Prevalence of atrial fibrillation in euthyroid patients is 1.7% in women and 3% in men.[14]

CONCLUSIONS

Although the retrospective nature of our relatively small study limited the completeness of clinical and laboratory data and prevented an accurate determination of the cause and indication for treatment of subclinical hyperthyroidism, we believe the following conclusions are warranted: most patients with subclinical hyperthyroidism associated with normal-sized or diffuse thyroid enlargement rarely progress to overt hyperthyroidism and can be followed safely. On the other hand, patients with subclinical hyperthyroidism associated with thyroid nodules should have thyroid scintigraphy performed to document the cause of their thyroid dysfunction and should be strongly considered for treatment. All patients with subclinical hyperthyroidism should be followed carefully regardless of the initial TSH level. Finally, patients >65 years of age should be carefully observed for the development of atrial fibrillation.

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