

Subclinical thyrotoxicosis progresses to overt hyperthyroidism more often in Graves' disease than with toxic nodular goiter

Rosario PW. The natural history of subclinical hyperthyroidism in patients below the age of 65 years. *Clin Endocrinol (Oxf)* 2008;68:491-2.

SUMMARY

BACKGROUND Subclinical hyperthyroidism (SCH) is characterized by persistently reduced serum thyrotropin (TSH) levels in the range of 0.01 to 0.4 mIU/L, and normal serum thyroxine (T₄) and triiodothyronine (T₃) concentrations. Although it usually does not progress to overt hyperthyroidism, it is more common with serum TSH levels <0.1 mIU/L. It has been suggested that the course of SCH is influenced by its etiology, with a higher rate of spontaneous cessation in Graves' disease, but most such studies have been conducted on individuals over 60 years of age. This is a study in a younger patient cohort.

METHODS Sixty women younger than 65 years old were enrolled in the study if their serum TSH was <0.1 mIU/L and they had no elevations of serum FT₄ or T₃, or a history of thyroid disease. Also excluded were those who were pregnant and those who were taking medication, or had conditions known to affect serum TSH levels, or had resting tachycardia, or an unintentional weight loss greater than 5%. Six to 8 weeks after enrollment, serum TSH, FT₄, and T₃ concentrations were remeasured and four patients with elevations in serum FT₄ or T₃ or both, and eight with a TSH >0.1 mIU/L (0.22 to 1.9 mIU/L) were excluded from the study. The remaining 48 patients who continued to have a serum TSH <0.1 mIU/L with normal serum FT₄ and T₃ levels underwent follow-up for 2 years without therapeutic intervention. Clinical and laboratory follow-up (TSH, FT₄, and T₃) was performed, respectively, at 3- and 6-month intervals.

RESULTS Fifteen of 48 patients (31%) had Graves' disease verified by diffuse uptake on scans and ophthalmopathy, with or without positive TSH-receptor antibodies (TRAb), and 24 (50%) had toxic multinodular goiter or a single toxic nodule without TRAb, and the cause was uncertain in 3 (6%). The average age was 56 years in those with nodular disease, 48 in those with Graves' disease, and 47 in those with SCH of undefined cause (Figure 1). The serum TSH was <0.05 mIU/L in 24 (50%) of the patients with nodular disease and 8 (53%) with Graves' disease, and serum FT₄ and T₃ levels were within the upper limit of normal (≥ 14.16 ng/dl and ≥ 2.16 pmol/L). Two patients were lost to follow-up after 9 and 12 months and a 59-year-old patient with a toxic thyroid nodule and persistent SCH had atrial fibrillation. Overt hyperthyroidism developed in 6 of 30 patients (20%) with toxic nodular disease and in 6 of 15 (40%) with Graves' disease (Figure 2). Serum TSH spontaneously returned to normal in 6 of 30 (20%) patients with

nodular disease and in 2 of 15 (13%) with Graves' disease, and TSH improved (0.14 to 0.3 mIU/L) in 8 of 30 (26.6%) patients with nodular disease and 3 of 15 (20%) with Graves' disease. Subclinical hyperthyroidism persisted in 10 of 30 (33.3%) with nodular disease and 4 of 15 (26.6%) with Graves' disease (Figure 2). Among 8 patients (33%) with serum TSH <0.05 mIU/L, 4 of 15 (26.2%) with nodular disease and 4 of 8 (50%) with Graves' disease progressed to overt hyperthyroidism (Figure 3). In comparison, overt hyperthyroidism developed in 4 patients with TSH levels ranging from 0.05 to 0.1 mIU/L—2 of 15 (13.3%) who had nodular goiter and 2 of 7 (28%) with Graves' disease (Figure 3).

Age and Laboratory Findings in Patients with Subclinical Hyperthyroidism

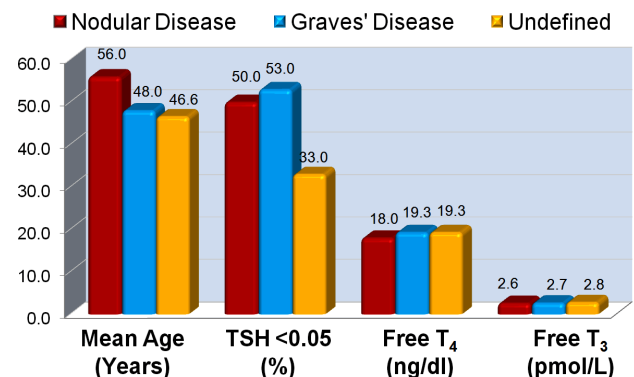


Figure 1. The initial clinical and laboratory findings are summarized according to cause of thyrotoxicosis in 48 patients. All figures are drawn from the data of Rosario et al. None of the differences are statistically significant.

Change in Clinical Status during Follow-up

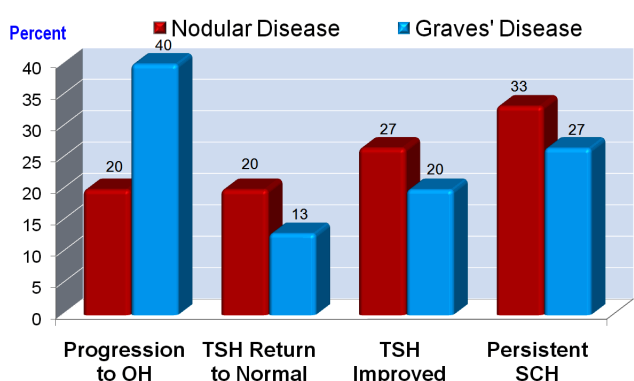
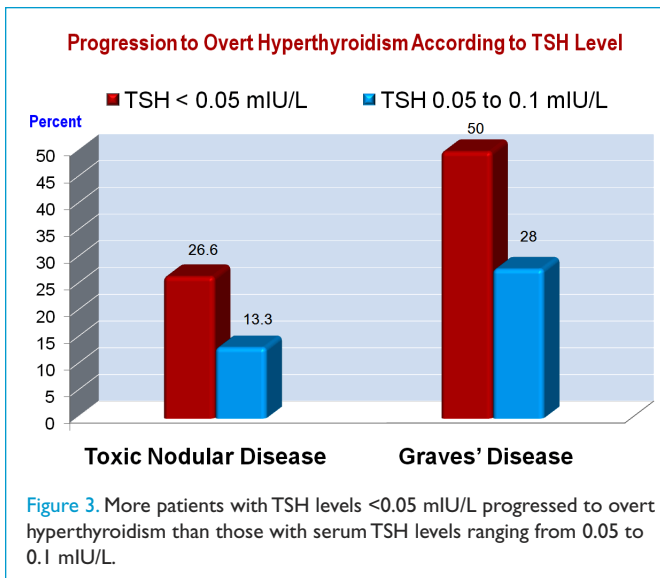


Figure 2. During follow-up, more patients with Graves' disease had progression to overt hyperthyroidism (OH) and fewer had TSH levels that returned to normal as compared with patients with toxic nodular disease.



CONCLUSION Patients younger than 65 years of age who have subclinical hyperthyroidism have a somewhat different outcome than older patients, depending on the cause of the disease. After a 2-year follow-up, the progression rate to overt hyperthyroidism was about 10% per year for toxic nodular disease and about 20% for Graves' disease. Serum TSH levels spontaneously returned to normal in more patients with toxic nodular disease than it did in patients with Graves' disease.

COMMENTARY

The natural history of SCH is uncertain, and the influence thereon of the cause of subclinical hyperthyroidism is even more uncertain. Earlier studies that have addressed this question involved elderly patients of whom most had subclinical hyperthyroidism associated with multinodular goiter. These studies collectively indicated that a subnormal serum TSH is more likely to persist in patients with goiter or when the initial serum TSH value is <0.1 mIU/L and that only a minority of patients progress to overt hyperthyroidism (1–3). A more recent retrospective analysis examined the natural history of subclinical hyperthyroidism in 7 patients with Graves' disease and 9 patients with multinodular goiter (4). In the patients with Graves' disease, serum TSH returned to normal in 5 patients (71%) within 3 to 19 months and persisted in 2 patients, 1 of whom had overt hyperthyroidism at 36 months. By contrast, in the patients with multinodular goiter, subnormal serum TSH persisted without progression

to overt hyperthyroidism during a cumulative follow-up period of 11 to 36 months.

The study by Rosario represents a significant contribution to our understanding of the natural history of subclinical hyperthyroidism. It provides convincing evidence that progression to overt hyperthyroidism is more common in patients with Graves' disease than in patients with nodular goiter, while persistence of subclinical hyperthyroidism appears to be more common in nodular goiter. The cardinal difference from the small retrospective study lies in the finding of a greater likelihood of spontaneous remission in nodular disease than in Graves' disease, a difference that can be resolved only by additional study.

Kenneth A. Woeber, MD, F.R.C.P.E.
University of California San Francisco
San Francisco, CA

References

1. Tenerz A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *J Intern Med* 1990;228:229-33.
2. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med* 1991;151:165-8.
3. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotropin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol* 1991;34:77-83.
4. Woeber K. Observations concerning the natural history of subclinical hyperthyroidism. *Thyroid* 2005;15:687-91.