

# Thyroid-function test abnormalities are common in elderly people taking thyroid hormone–replacement medications

Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab* 2009;94:1342-5.

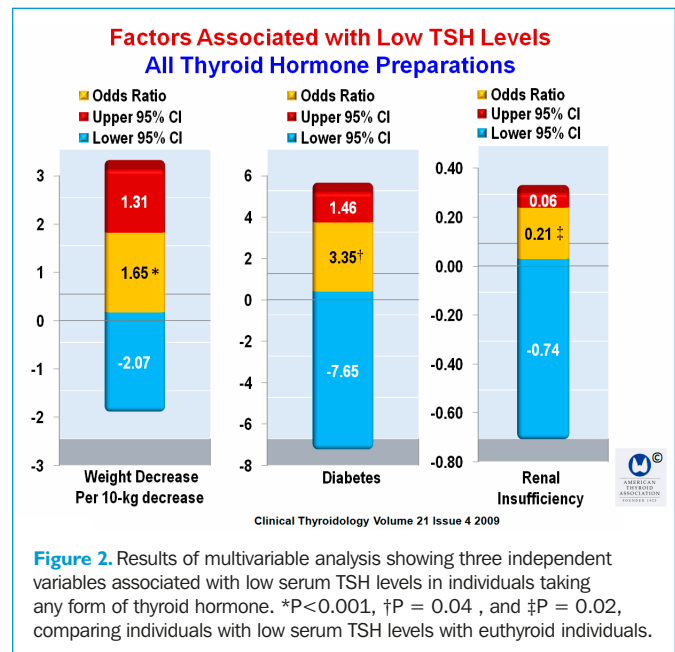
**SUMMARY**

**BACKGROUND** Hypothyroidism requiring levothyroxine replacement therapy is common in the elderly population and not infrequently results in overtreatment or undertreatment. The aim of this study was to assess the frequency of and factors associated with thyroid hormone overtreatment and underreplacement.

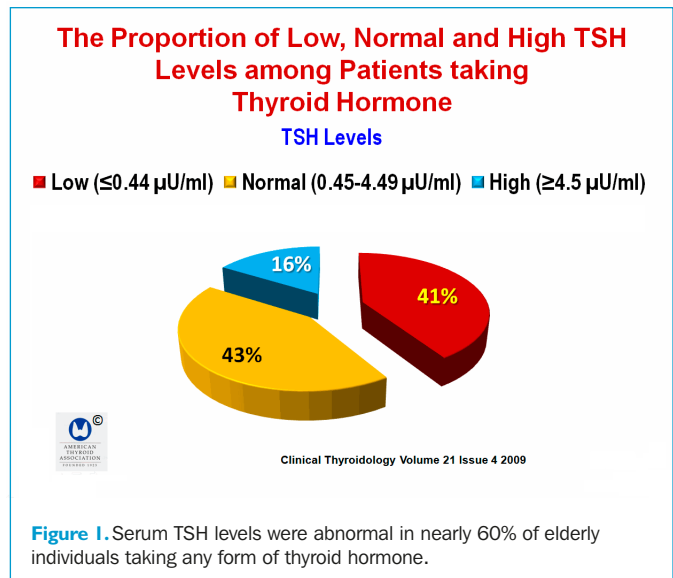
**METHODS** The study subjects were from a cohort of 5201 adults enrolled from 1989 through 1990 in the Cardiovascular Health Study, which at baseline obtained a medical history, physical examination, assessment of health status and blood tests, including thyrotropin (TSH) and free thyroxine (FT<sub>4</sub>). Among the original cohort, a subgroup of 3678 individuals had thyroid-function tests, and of this group, 339 (9.2%) were taking various thyroid hormone preparations. Those taking thyroid hormones were stratified into one of three groups: low TSH (TSH, ≤0.44 μIU/ml), euthyroid (TSH, 0.45 to 4.49 μIU/ml), and high TSH (≥4.5 μIU/ml). In addition, 321 of the 339 individuals taking thyroid hormones were stratified into five other groups: overt hyperthyroidism (TSH, ≤0.10 μIU/ml plus high serum FT<sub>4</sub>); subclinical hyperthyroidism (TSH, 0.11 to 0.44 or ≤0.10 μIU/ml plus normal FT<sub>4</sub>); euthyroid (TSH, 0.45 to 4.50 μIU/ml); subclinical hypothyroidism (TSH, 4.51 to 19.9 μIU/ml plus normal FT<sub>4</sub>); or overt hypothyroidism (TSH, ≥20 μIU/ml or >4.50 μIU/ml plus low free FT<sub>4</sub>). An additional 18 subjects were excluded because they did not fit into any of the categories.

**RESULTS** Of the 339 individuals taking thyroid hormones, 41% had a low serum TSH, 16% had a high TSH, and 43% were euthyroid (Figure 1). Among this group, 26% were taking thyroid hormone products with both levothyroxine (L-T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) and the rest were taking L-T<sub>4</sub> alone. The mean age of the latter group was 72.9 years, which was the

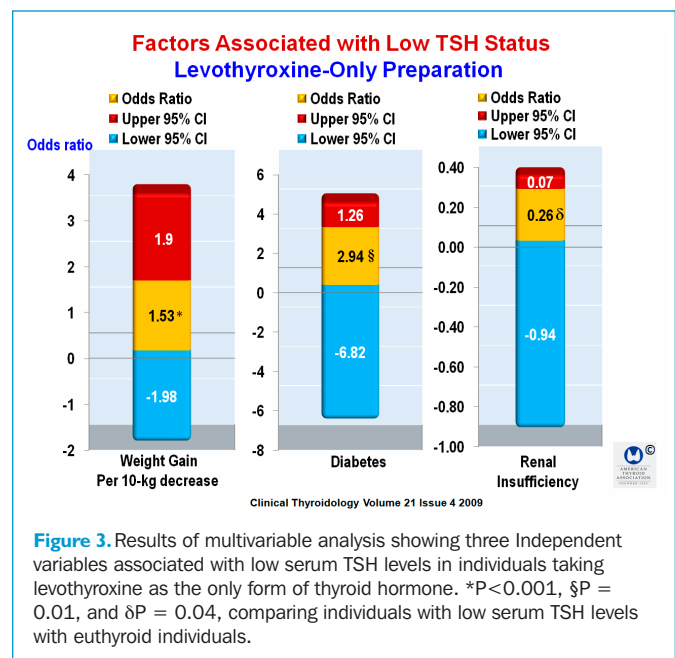
same among all the thyroid status categories. More women were in the low TSH group than the euthyroid group (87.8 vs.72.9%; P = 0.03). Individuals with low serum TSH levels had lower weight (65.3 vs. 72.2 kg; P<0.001) and lower body-mass index (25.5 vs. 27.1 kg/m<sup>2</sup>; P<0.006), and fewer had a medical diagnosis (P<0.05) and were taking fewer medications (P = 0.02) as compared with the euthyroid group. Serum TSH levels increased



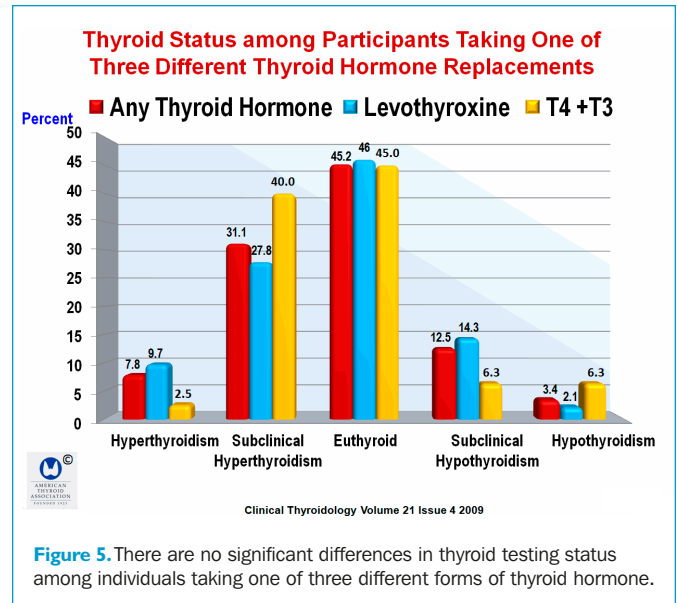
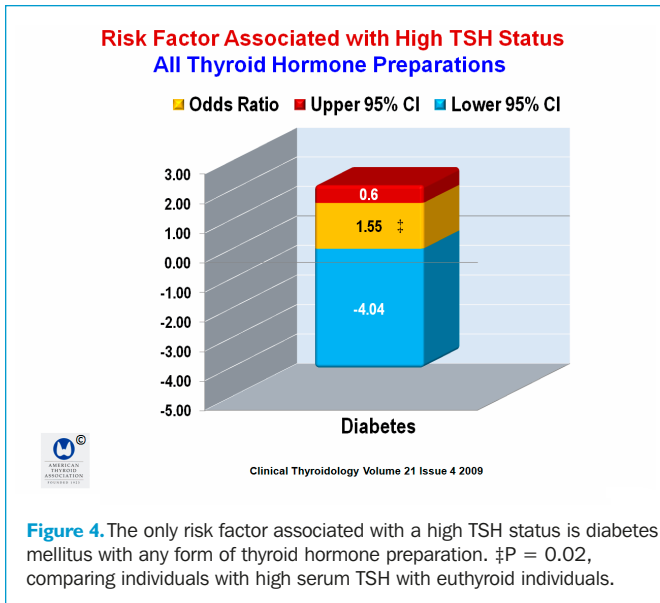
**Figure 2.** Results of multivariable analysis showing three independent variables associated with low serum TSH levels in individuals taking any form of thyroid hormone. \*P<0.001, †P = 0.04, and ‡P = 0.02, comparing individuals with low serum TSH levels with euthyroid individuals.



**Figure 1.** Serum TSH levels were abnormal in nearly 60% of elderly individuals taking any form of thyroid hormone.



**Figure 3.** Results of multivariable analysis showing three independent variables associated with low serum TSH levels in individuals taking levothyroxine as the only form of thyroid hormone. \*P<0.001, §P = 0.01, and δP = 0.04, comparing individuals with low serum TSH levels with euthyroid individuals.



65% for every 10-kg decrease in weight. Individuals with diabetes mellitus were more likely and those with renal insufficiency were less likely to have low TSH levels (P = 0.02).

Multivariable-adjusted models found weight, diabetes mellitus, and renal insufficiency to be independently and significantly associated with low TSH status. Serum TSH levels decreased 65% for every 10-kg decrease in weight, and those with diabetes were more likely to have low TSH levels, although low TSH levels were less likely with renal insufficiency (Figure 2). The results

were similar when levothyroxine alone was taken (Figure 3). The prevalence of euthyroidism was the same among all thyroid hormone preparations (Figures 2 to 4). Diabetes mellitus was the only statistically significant predictor of a high TSH both for all thyroid hormone preparations (P = 0.004) and for levothyroxine alone (P = 0.02) (Figure 4). The prevalence of euthyroidism was similar among all thyroid hormone preparations (Figure 5).

**CONCLUSION** Thyroid-function test abnormalities are common in elderly people taking thyroid hormone-replacement therapy.

**COMMENTARY**

Somwaru et al. have performed an interesting and important study that assessed the frequency of abnormal serum TSH concentrations in a large cohort of older individuals. Using baseline serum samples stored between 1989 and 1990 from the Cardiovascular Health Study, they measured serum TSH in 339 subjects who were taking exogenous thyroid hormone(s) (9.2% of the entire study population) and divided the results into separate groups. Surprisingly, only 43% of the serum TSH concentrations fell within the normal range, with 41% having decreased serum TSH values and 16% having elevated serum TSH values. There were more women who had a low serum TSH than had a normal TSH. Using further statistical analyses, they observed that lower body weight, renal insufficiency, and diabetes mellitus were independently associated with lower serum TSH values. Curiously, diabetes mellitus was also associated with an increased likelihood of having an elevated serum TSH. The authors appropriately conclude that this high frequency of abnormal TSH values stresses the importance of close monitoring of patients receiving exogenous thyroid hormone(s), especially individuals with diabetes, renal insufficiency and low body weight. It is important to normalize serum TSH concentrations to decrease the risks of cardiovascular and osseous abnormalities; it is assumed that the goal TSH in these patients taking thyroid hormone-replacement preparations is within the normal reference range (1).

There are additional issues, however, that should be mentioned, many of which are also noted by the authors. The underlying cause for hypothyroidism was not mentioned except to indicate that none of the patients had thyroid cancer. However, it is not noted whether any patients were taking exogenous levothyroxine for suppressive purposes for thyroid nodule(s), a process that has largely become obsolete (2, 3). TSH was also measured only once, and it is not known whether the TSH values remained abnormal in patients for the duration of the study. Further, 26% of the patients taking exogenous thyroid hormone(s) were taking a combination of levothyroxine and triiodothyronine. It is now recommended that only exogenous levothyroxine be used for replacement purposes (<http://hyper.thyroidguidelines.net/hormone>). The inclusion of patients who ingest a combination of levothyroxine and triiodothyronine makes it difficult to interpret the TSH values, since the triiodothyronine component has a shorter half-life and can suppress the TSH for several hours following its ingestion, whereas during the remainder of the day the TSH may not be as suppressed or could even be normal. The timing of the ingestion of thyroid hormones in relationship to the measurement of serum levels is not reported. The associations noted above for decreased serum TSH concentrations with the presence of lower weight, renal insufficiency and diabetes mellitus still held when users of only levothyroxine (not with triiodothyronine) were reanalyzed. However, the relationship of elevated serum TSH with ingestion of exogenous levothyroxine now became statistically

nonsignificant. The authors also could not comment on whether nonthyroidal illness was contributing to the presence of perturbed thyroid-function tests, especially in patients with renal insufficiency and diabetes mellitus, although this seems relatively unlikely to affect a substantial number of individuals, given the outpatient nature of the study.

It is also worthwhile to comment that the normal TSH range they chose is 0.45 to 4.49  $\mu\text{IU/ml}$  and the NHANES study has now suggested that the normal TSH reference range is approximately 0.45 to 4.12  $\mu\text{IU/ml}$  (median, 1.39) (4), implying that an even higher percentage of subjects (in the Somwaru et al. study) may have elevated TSH values. It appears that free  $T_4$  levels were measured only in subjects with serum TSH less than 0.1  $\mu\text{IU/ml}$  or higher than 4.5  $\mu\text{IU/ml}$ , and it is possible individuals with TSH values outside these parameters may have had abnormal serum  $\text{FT}_4$  values. Serum  $T_3$  or  $\text{FT}_3$  levels and thyroid antibodies were not analyzed in this study.

The issue of age and thyroid-function tests also requires comment. Participants in this study were 65 years or older. The mean age was 72.9, but a further breakdown of age categorization is not given. However, it is now believed that the TSH reference range is higher in elderly subjects. Perhaps an elevated serum TSH, in approximately the 5 to 10  $\mu\text{IU/ml}$  range, may be beneficial rather than harmful in individuals over age 85 and should not be treated with levothyroxine, with the implication that perhaps in patients taking thyroid hormone-replacement preparations a serum TSH in this level would not require an increase in levothyroxine dosage (5, 6).

In summary, Somwaru et al. have advanced our understanding of patients taking exogenous levothyroxine by emphasizing that goal serum TSH values are achieved in only approximately 43% of these patients. They correlated decreased serum TSH with lower body weight, renal insufficiency, and diabetes mellitus and an elevated TSH with diabetes mellitus (only in patients taking a combination of levothyroxine and triiodothyronine). The ATA guidelines suggest that serum TSH should be measured in patients taking thyroid hormone-replacement preparations on a periodic basis, and specifically when there has been a change in weight or in older individuals (<http://hyper.thyroidguidelines.net/care>). Following equilibration and normalization of serum TSH, periods between visits and serum measurements can be lengthened to every 6 to 12 months, unless clinical circumstances change. When the levothyroxine dose or brand of levothyroxine is changed, TSH measurements should be repeated in 6 to 8 weeks. The explanation for the high frequency of perturbed TSH concentrations in the population studied by Somwaru et al. is not known, but previous clinical studies have suggested a similarly high frequency (4, 7). The importance of periodic assessment of serum TSH in patients with hypothyroidism who are taking levothyroxine cannot be overemphasized.

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