

The Relationship between Serum TSH and Free T₄ Is Not Log-Linear and Varies by Age and Sex

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Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EM, Walsh JP. The relationship between TSH and free T₄ in a large population is complex, non-linear and differs by age and gender. *J Clin Endocrinol Metab*. May 13, 2013 [Epub ahead of print].

SUMMARY • • • • • • • • • • • • • • • •

Background

In older studies, the relationship between serum TSH and free T₄ appeared to be log-linear (1,2). However, in a more recent study, a complex and nonlinear relationship was seen (3). This had not previously been assessed in a very large population sample. In addition, there have been conflicting reports regarding the effects of age and sex on the relationship between TSH and free T₄ (4-6).

Methods

This cross-sectional study assessed relationships between TSH and free T₄ values using thyroid-function tests measured during 2000 and 2011 at a single statewide private laboratory in Western Australia. Individuals with concurrent TSH and free T₄ measurements were included. Individuals who were hospitalized, pregnant, less than 1 year of age, being treated by endocrinologists, with unknown sample-collection times, with unknown ages, or with samples collected outside of usual office hours were excluded. In addition, patients with a history of thyrotoxicosis, thyroid cancer, thyroidectomy, or hypopituitarism and those treated with radioactive iodine or with drugs that might affect thyroid function were also excluded. In all, 15% of the records initially identified were excluded from analyses. Individuals taking levothyroxine (L-T₄) were included, but were analyzed separately.

The median value for every TSH concentration associated with a given integer free T₄ value was calculated, with upper and lower quartiles. Because they were

nonnormally distributed, serum TSH values were log-transformed. Nonlinear quantile regression models were used to assess relationships between serum TSH and free T₄ values, with age and sex as covariates.

Results

A total of 445,994 TSH-free T₄ pairs from 152,261 individual subjects were analyzed. Most study subjects (75%) were women, and 21% were taking L-T₄. Among individuals not taking L-T₄, median log TSH and free T₄ values were inversely related. The relationship was not linear, but rather was best described by two negative sigmoid curves. Among patients taking L-T₄, the relationship was similar. Median serum TSH values were higher for males than for females (3.8 mIU/L vs. 3.3 mIU/L; P<0.001) and serum free T₄ values were slightly higher in males (14.0 vs. 13.7 pmol/L; P<0.001). Median TSH was higher in men than in women at almost every free T₄ value, with more extreme differences in the upper part of the reference range. Among those with normal serum free T₄ values who were not treated with L-T₄, median TSH increased with age. Among the 4403 patients with untreated overt hypothyroidism (elevated TSH and free T₄ <10 pmol/L), median TSH was lower in older than in younger adults.

Conclusions

The relationship between serum T₄ and serum TSH was not log-linear. Among euthyroid individuals, TSH was higher in men and increased with advancing age. The rise in TSH with overt hypothyroidism is attenuated in older adults.

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ANALYSIS AND COMMENTARY ● ● ● ● ●

Strengths of this study include the very large sample size, which allowed the investigators ample power to study sex and age subgroups and both treated and untreated hypothyroidism. Information about some potentially important covariates, such as race/ethnicity, body-mass index, and smoking status, was not ascertained. Importantly, it is possible that the lack of a log-linear relationship between TSH and free T₄ was merely an artifact due to inadequacies of the free T₄ assay used. Future studies could conduct similar analyses using different free T₄ assay methods, in particular the gold standard methods of equilibrium dialysis or isotope-dilution liquid chromatography with tandem mass spectroscopy.

What relevance do these results have for clinical practice? These data suggest that TSH reference ranges are not one-size-fits-all, and the use of a single TSH range for all subpopulations might result in misclassification of thyroid status in some cases, in particular the inappropriate diagnosis of subclinical hypothyroidism. The age-associated increase in serum TSH among euthyroid individuals seen in this and previous studies (4) argues against routine treatment of mild TSH elevations in elderly patients. Age- and sex-specific TSH reference ranges might be used to more accurately classify thyroid status (5). Although race and ethnicity were not examined by Hadlow and colleagues, racial and ethnic variability in serum TSH values have been described previously (5) and racial/ethnic subpopulation-specific TSH values might also be helpful in some regions.

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