**Topic:** THE UPPER REFERENCE LIMIT OF SERUM TSH IN THE HEALTHY U.S. POPULATION

**Title:** National Health & Nutrition Examination Survey III (NHANES III) thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction.

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**SUMMARY**

**Context:** The setting of the TSH upper reference limit impacts the diagnosis of mild hypothyroidism and is currently controversial.

**Methodology:** The objective was to evaluate factors influencing the TSH reference range.

**Design:** Nonpregnant subjects aged 12 yr and older from NHANES III were used to study the relationships between TSH, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies in different ethnic groups.

**Results:** TPO-Ab prevalence was lowest (<3%) when TSH was between 0.1 & 1.5 mU/L in women and between 0.1 & 2.0 mU/L in men and progressively increased to above 50% when TSH exceeded 20 mU/L. TSH reference range parameters (2.5th, 50th, & 97.5th percentiles) were analyzed according to thyroid antibody status, race/ethnicity, and age for the 14.202 subjects made up of non-Hispanic Blacks (B), non-Hispanic whites (W), and Mexican-Americans (M) who did not report thyroid disease or taking thyroid-altering medications and whose total T4 was within the reference range. For each age group of each ethnicity, the inclusion of antibody-positive subjects increased TSH medians and upper limits (97.5th percentile). The TSH upper limit was lower for the entire B cohort vs W or M. However, this difference was lost when age cohorts with a similar prevalence of TPO-Ab (B 40-49 years vs W and M 20-29 years) were compared.

**Conclusion:** Ethnic differences in TSH were not present when populations with the same relative frequency of thyroid antibodies were compared. TSH upper reference limits may be skewed by TPO-Ab negative individuals with occult autoimmune thyroid dysfunction.

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**COMMENT**

Reference limits for serum TSH are calculated from the 95% confidence intervals of cohorts of individuals considered to be healthy subjects, i.e. without evidence of thyroid disorders, medications known to interfere with thyroid function, or presence of thyroid auto-antibodies. Most epidemiologic studies report that the lower serum TSH limit lies between 0.2 and 0.4 µU/ml, but the upper TSH limit varies between 2.4 and 4.2 µU/ml, depending upon ethnicity or geographical location. When TSH reference ranges are extrapolated from rigorously selected small cohorts of strictly normal individuals (as compared to large but less-defined populations), the upper serum TSH limit is typically much...
narrower than the classical 4.0 µU/ml accepted by most laboratories. In the recent NHANES III survey, a large cohort of non-pregnant healthy subjects was investigated nationally to represent the U.S. population (see Hollowell, JCEM 87:489, 2002). In the disease-free fraction of the population, mean serum TSH was 1.50 µU/ml with reference limits between 0.44 (2.5th perc.) and 5.52 µU/ml (97.5th perc.). The study showed also that serum TSH was greater in women, increased with age, and differed with regard to ethnicity.

In present work, the authors showed that the prevalence of thyroid antibodies increased significantly with increasing age (in all ethnic groups). Even though the prevalence of positive thyroid antibody approached 80% when serum TSH was > 20 µU/ml, 31% of men and 11% of women with a serum TSH >10 µU/ml had no detectable thyroid antibodies. Inclusion of antibody-positive subjects had no effect on the lower TSH reference limit, while it had a clear impact on the upper reference limit. Thus in the absence of thyroid antibodies, the calculated 97.5th percentile for TSH was lowered from 5.52 µU/ml in the entire population to 3.50 µU/ml (and did not differ among the U.S. ethnic subgroups).

The authors concluded that TSH reference intervals calculated from population data may be skewed (to the right) by including individuals whose underlying mild thyroid dysfunction cannot be detected by thyroid antibody testing alone, since these may remain undetectable as the result of occult thyroid autoimmunity.

Setting the upper limit of serum TSH at different levels has an impact on the controversy concerning the diagnosis and efficacy of thyroxine treatment in subjects with mild preclinical hypothyroidism. The American Association of Clinical Endocrinologists (AACE) recommends to adopt an upper TSH limit set at 3 µU/ml, a value close to the TSH limit observed for populations with a low prevalence of thyroid autoimmunity.

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See Figure below (prevalence of thyroid antibodies in men and women across TSH intervals, between 0.001 and 20 mU/L)