Risk factors predicting hypothyroidism with autoimmune thyroid disease are female sex and baseline TSH levels combined with thyroid antibodies

Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010; January 22 [Epub ahead of print].

SUMMARY

BACKGROUND

Autoimmune hypothyroidism is a common disorder that is largely defined by the population being studied. The most sensitive diagnostic marker of the disease is a high serum thyrotropin (TSH) concentration. However, there is an ongoing debate concerning the upper reference limit for TSH. It is generally based on the 95% confidence interval of log-transformed TSH concentrations in healthy individuals, which usually places the upper TSH reference limit at approximately 4.0 to 4.5 mU/L, although some believe that this should be lowered to 2.5 to 3 mU/L. The authors of this study suggest that the main arguments in favor of maintaining the upper reference limit around 4.0 to 4.5 are the increased prevalence of antibodies and the risk for hypothyroidism in people with TSH levels in the upper reference range and that longitudinal studies of risk factors for hypothyroidism are required to address the debate regarding the upper TSH range, including the predictive value of thyroid antibodies measured by automated immunoassay, as compared with using older semiquantitative methods.

METHODS

In surveys conducted in 1981 and 1994, sera were analyzed for TSH, free thyroxine (FT_4), antithyroid peroxidase antibodies (TPOAb), and antithyroglobulin antibodies (TgAb) using the Immulite platform on sera from the 1184 participants. The two surveys were conducted in Busselton, Western Australia, an iodine-sufficient area with a predominantly white population. The main outcome in the 1994 survey was hypothyroidism, defined as a serum TSH level greater than 4.0 mU/L or treatment with levothyroxine ($L\text{-}T_4$). The following were excluded from the study: subjects with raised serum TSH with low FT_4, treatment with $L\text{-}T_4$ or antithyroid drugs, hyperthyroidism, missing serum TSH values, and discordant thyroid-function test results suggesting pituitary disease or antibody interference and subjects on amiodarone or lithium. As the rationale for routine $L\text{-}T_4$ replacement is uncertain for individuals with mildly elevated TSH concentrations up to 10 mU/L, this large group was also excluded from the study. Receiver-operating-characteristic (ROC) curve analysis was used to determine optimal cutoffs for baseline TSH, TPOAb, and TgAb as predictors of hypothyroidism. The characteristics of the study cohort at baseline (1981) and follow-up (1994) surveys were compared.

RESULTS

A total of 1804 of the 1981 subjects (86%) were alive in 1994, but some chose not participate in the follow-up study; however, those who died before the 1994 survey were significantly older than those in the 1994 follow-up survey. After exclusions, 1184 subjects met the criteria for the study. The mean time between the two study visits was 13 years (range, 12.3 to 14.0)

The Baseline Demographics of the Study Cohort in 1981 and 1994 (Figure 1)

The original 1981 survey cohort and those in the 1994 follow-up survey had serum TPOAb concentrations that increased

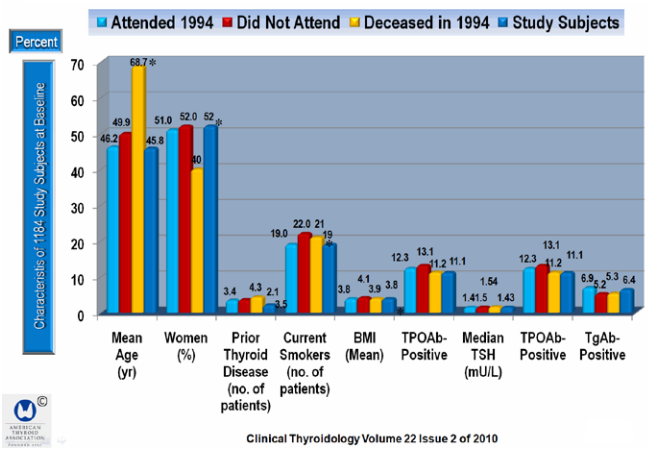

Figure 1. This figure shows the baseline characteristics of the original 1981 cohort of 1184 subjects compared with the group studied 13 years later in 1994. *P<0.001. Data for this figure are derived from Table 1 of Walsh et al.

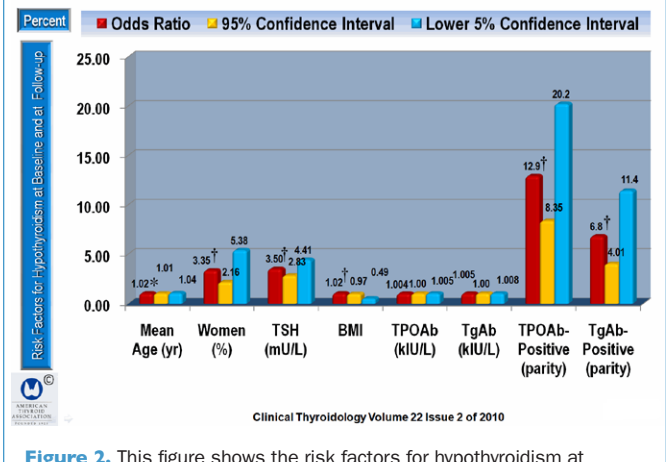

Figure 2. This figure shows the risk factors for hypothyroidism at baseline and follow-up results of logistic-regression age-adjusted analysis of potential risk factors at baseline for the presence of hypothyroidism at follow-up. *P = 0.002. †P < 0.001. BMI = body-mass index, which is the weight in kilograms divided by the square of the height in meters. Data for this figure are derived from Table 3 of Walsh et al.

from 11.1% in 1981 to 15.1% in 1994 (P<0.001), and the TPOAb status changed from negative to positive in 5.2% and from positive to negative in 1.3% of the participants. The baseline group of 1110 subjects (93.7%) had serum TSH concentrations between 0.1 and 4.0 mU/L, and none were taking L-T_4; however, 13 years later, 29 subjects (2.4%) were taking L-T_4 and another 81 (6.8%) had elevated serum TSH concentrations, 3 of whom also had low FT_4 concentrations. Thus, of the 1110 subjects in the 1981 cohort with normal serum TSH concentrations, 110 (9.3%) had overt hypothyroidism, defined as a TSH >4 mU/L, or were on L-T_4 therapy; 84 of these were women (76%). Thus, of the 1110 subjects with normal TSH levels, 42 (3.5%) had overt hypothyroidism, 38 of whom (91%) were women

Univariate Analysis (Figure 2)

The baseline variables associated with overt hypothyroidism were age; female sex; TSH, TgAb, and TPOAb concentrations; TPOAb-positive status; and TgAb-positive status. Of the 76 subjects with positive TgAb, 26 (34%) were TPOAb-negative, 4 of whom (15.4%) had overt hypothyroidism at follow-up. Thus, TgAb was not a significant risk factor for hypothyroidism as compared with TPOAb-negative and TgAb-negative subjects (odds ratio, 1.80; 95% confidence interval, 0.52 to 4.82).

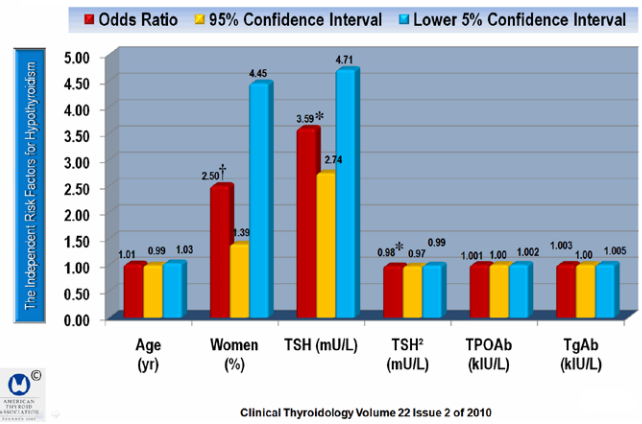

Figure 3. This figure shows that the independent risk factors for hypothyroidism, are a TSH above 2.5 mU/L and a TPOAb above 29 kIU/L in women positive for thyroid antibodies. The prevalence of hypothyroidism at follow-up was 12%, with a baseline TSH of 2.5 mU/L, and 87.5% for TSH above 4.0 mU/L. *P<0.001 for odds ratio. †P = 0.002 for the odds ratio. Data for this figure are derived from Table 3 of Walsh et al. Functional forms of covariates (e.g. TSH2, in case of a quadratic relationship) and interactions were explored, and TSH2 was included because it significantly improved goodness of fig.

Multivariate Analysis (Figures 3 to 5)

The strongest independent predictors of hypothyroidism were female sex and baseline TSH, whereas the predictive value of thyroid antibodies was not significant in the multivariate model, although TgAb as a continuous variable remained significant. The odds ratios for baseline TPOAb and TgAb are shown in Figures 3 to 5.

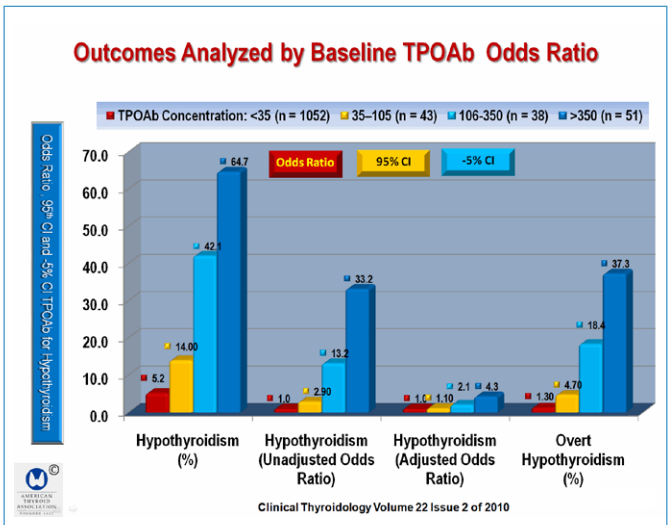

Figure 4. This figure shows the outcomes analyzed by baseline TPOAb concentration. The data for this figure are derived from Table 5 of Walsh et al, which shows odds ratio (red) 95% Ci = confidence interval (gold), and -5% CI (light blue).

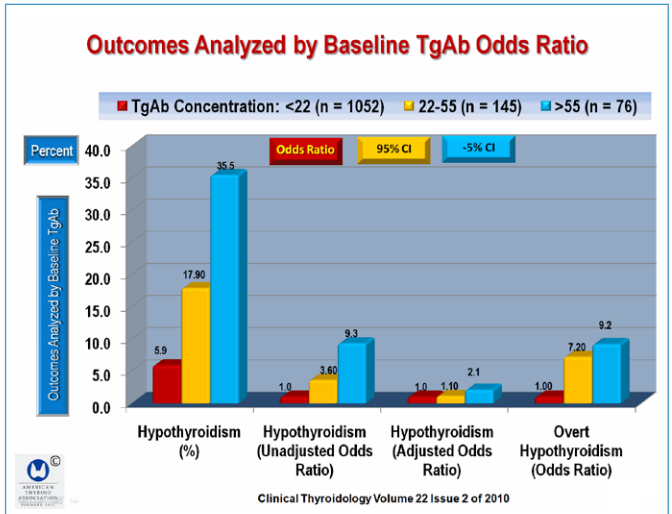

Figure 5. This figure shows the outcomes analyzed by baseline TgAb concentration. The data for this figure are derived from Table 5 of Walsh et al. See Figure 4 legend.

Optimal Cutoffs for TSH, TPOAb, and TgAb (Figures 6 and 7)

The best predictor of hypothyroidism was associated with a baseline TSH of 2.6 mU/L, with a sensitivity of 76% and a specificity of 90% using a ROC curve analysis. Using these data, the sensitivity, specificity, positive predictive value, and negative predictive value of baseline serum TSH of 2.5 mU/L versus 4 mU/L is shown in Figure 6. The study outcomes analyzed by baseline TSH and antibody concentrations are shown in Figure 7.

CONCLUSION

Female sex and baseline TSH levels, combined with thyroid antibodies are the strongest risk factors predicting the development of hypothyroidism during an extended follow-up.

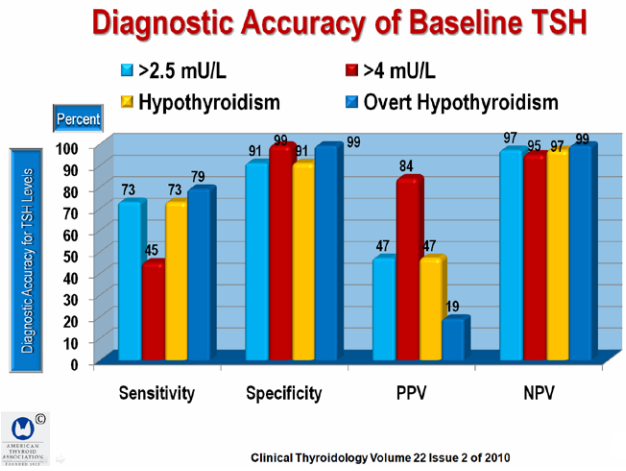

Figure 6. This figure shows the diagnostic accuracy for baseline TSH levels for hypothyroidism. The data for this figure are derived from Table 4 of Walsh et al. NPV = negative predictive value; PPV = positive predictive value.

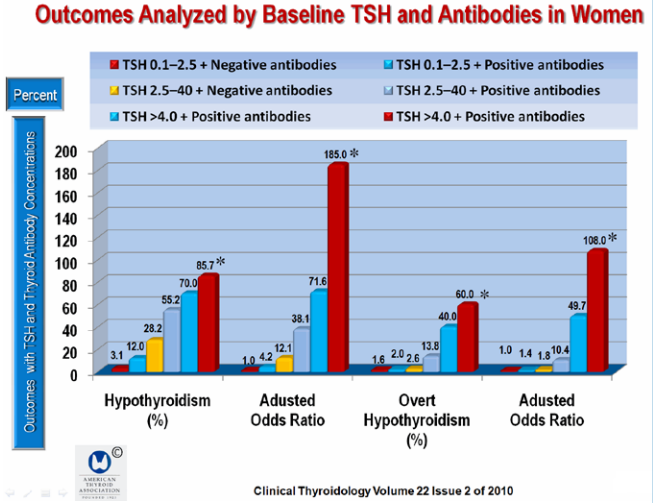

Figure 7. This figure shows the study outcomes analyzed by various baselines of TSH and thyroid antibodies in women.*P<0.001 for trend. The data for males are not shown. The data for this figure are derived from Table 7 by Walsh et al.

COMMENTARY

This study provides data concerning hypothyroidism over a 13-year period, using current methods for the determination of TSH and thyroid antibodies. The authors opine that the results will provide information concerning the upper reference range for TSH that provides a means for clinicians to estimate the long-term risk for hypothyroidism, based on sex, TSH, and thyroid antibody status. Still, multivariate analysis found that female sex and TSH were the strongest independent predictors of hypothyroidism, while age was of no significance and thyroid antibodies were of borderline importance. The ROC analysis identified a TSH threshold of 2.5 mU/L as the optimal cutoff for predicting hypothyroidism, which was associated with optimal diagnostic sensitivity and specificity. The authors suggest that this finding is broadly consistent with several other studies. The Whickham study (1) found that increasing values of serum TSH above 2 mU/L at the first survey increased the probability of hypothyroidism developing, which was further increased in the presence of antithyroid antibodies. Other studies, by Teng et al. (2) and Li et al. (3), found that subjects who were TPOAb- and TgAb-positive at baseline had thyroid dysfunction more frequently than seronegative subjects. The authors concluded that patients with TSH concentrations of 2.5 to 4 mU/L are at increased risk for hypothyroidism; however, the risk is small at 12% (range, 3 to 21%) over 13 years. For this reason, the authors do not support lowering the upper limit of the TSH reference range, but suggest that these individuals be regarded as being at intermediate risk for developing hypothyroidism. However, the role of antithyroid antibodies altered this risk. For example, with a baseline TSH less than 2.5 mU/L, the risk for hypothyroidism was approximately 1% per year and the risk of overt hypothyroidism was 0.2% per year, whereas in women who were antibody-positive with a baseline TSH between 2.5 and 4.0 mU/L, the risks were much higher, at 4 and 1% per year, respectively. The strength of this study is based on its duration and large number of participants, and probably is one of the largest of its kind. However, there are a few weaknesses in the study, such as the attrition rate due to death and failure to attend the 1994 survey; still, 81% of the survivors participated in the study. The Walsh study essentially confirms the 20-year follow-up study by Vanderpump et al. (1) of the Whickham cohort that provides 20-year risks for the development of hypothyroidism as a function of age, antibody status, and initial TSH in 1-ml increments of TSH from 1 to 5 mU/L.

Recent recommendations to decrease the upper reference range of the TSH from 4.5 to 2.5 mIU/liter, based on the high proportion of healthy people whose serum TSH is less than 2.5 mIU/liter and the observation that those with a serum TSH between 2.5 and 4.5 mIU/L (upper reference range) have an increased risk of progression to overt hypothyroidism.

A study by Surks, Goswami, and Daniels (4) challenged the notion of lowering the TSH upper reference range from 4.5 to

2.5 mU/L. Using the reference group of the National Health and Nutrition Examination Survey (NHANES) III, the authors found that 85% of 14,333 people 12 years of age or older without thyroid disease or antithyroid antibodies had TSH levels below 2.5 mIU/liter and that 2.3% had subclinical hypothyroidism. They also found that if the upper TSH limit were decreased, an additional 9.7% had an upper reference range for TSH, representing 20.6 million Americans who would also be identified as having subclinical hypothyroidism, many of whom do not have thyroid disease. They opined that about half of those with a TSH at upper reference range probably have thyroid disease, but most with thyroid disease and antithyroid peroxidase antibodies have a TSH below 2.5 mIU/liter.

The distribution of serum TSH shifts progressively to higher concentrations with age. A study by Atzmon et al. (5) found that serum TSH was significantly higher in Ashkenazi centenarians than in Ashkenazi and NHANES controls (median, 2.5th and 97.5th centiles)—1.97 mIU/L (0.42 and 7.15), 1.55 (0.46 and 4.55), and 1.61 (0.39 and 6.29), respectively ($P<0.001$). The TSH distribution curve of the NHANES control group was superimposable on and not significantly different from the Ashkenazi controls. This is of some importance in the Welsh study. The mean age at follow-up was 58.8±14.4 years. Thus, there were many people in the study 70 years of age or older, suggesting that this group would have higher TSH levels due to advancing age, which might increase the number of individuals with a diagnosis of hypothyroidism.

The Walsh study has one relatively important shortcoming: the definition of hypothyroidism included physician-prescribed L-T_4 replacement, and the authors had no access to serum TSH concentrations at the time of diagnosis for independent verification, which is a potentially serious shortcoming insofar as it relates to the serum TSH level, the standard for the diagnosis of hypothyroidism. A study from Israel by Meyerovitch et al. (6) found that nearly 5000 patients with normal TSH levels were treated with L-T_4 for reasons that could not be determined. Thus, the authors have no idea how many of those treated with L-T_4 actually had hypothyroidism.

The Walsh study thus will likely join the debate concerning the optimal upper reference range to establish a diagnosis of hypothyroidism with or without antithyroid antibodies.

— Ernest L. Mazzaferri, MD, MACP

References

1. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995;43:55-68.

2. Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006;354:2783-93.

3. Li Y, Teng D, Shan Z, et al. Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 2008;93:1751-7.

4. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab 2005;90:5489-96.

5. Atzmon G, Barzilai N, Hollowell JG, et al. Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 2009;94:1251-4.

6. Meyerovitch J, Rotman-Pikielny P, Sherf M, et al. Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. Arch Intern Med 2007;167:1533-8.