

New Dimensions in TSH Control

Summaries of 3 Lectures Presented at the 12th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) in San Diego, California on May 14, 2003

This newsletter provides background information and summaries of 3 lectures presented at the 12th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) in San Diego, California on May 14, 2003. The first lecture, presented by Stephanie L. Lee, MD, associate professor of medicine at Boston University School of Medicine and director of the Thyroid Disease Center at Boston Medical Center, discussed the reassessment of the thyroid stimulating hormone (TSH) reference range as a clinical measure for the diagnosis and treatment of thyroid disease. Bryan R. Haugen, MD, associate professor of medicine and pathology at University of Colorado School of Medicine and assistant chief of the Division of Endocrinology, Metabolism, and Diabetes at University of Colorado Health Sciences Center in Denver, Colorado, discussed the implications of using a narrower TSH reference range for thyroid function screening and management of thyroid disease. Peter A. Singer, MD, professor of clinical medicine at Keck School of Medicine of the University of Southern California and chief of clinical endocrinology and director of the Thyroid Diagnostic Center at University of Southern California Medical Center, Los Angeles, California, concluded the program by presenting a case study that described the utility of TSH measurements in the treatment and management of hypothyroidism in an elderly patient.

When Is the TSH Normal? New Criteria for Diagnosis and Management

Stephanie L. Lee, MD

Recommendation for a new normal TSH reference range. The TSH reference range of 0.4 to 4.0 mIU/L is considered normal based on the results of general cross-sectional population studies lacking well-defined reference populations.¹ In contrast, the third National Health and Nutrition Examination Survey (NHANES III) screened 17 353 subjects and excluded those with a history of thyroid disease, goiter, pregnancy, or biochemical hypo- or hyperthyroidism, and those taking thyroid medication, androgens or estrogens.² In the resulting “normal” reference population of 13 344 subjects, 95% had TSH levels that fell between 0.3 and 2.5 mIU/L (Figure 1). Though TSH levels increased slightly with age, the highest mean TSH level of the normal population was slightly higher than 2 mIU/L, and the average level across all ages was only 1.49 mIU/L (Figure 2). These data were consistent with those of the smaller Andersen study, in which TSH levels measured in 16 normal men fell between 0.16 and 2.4 mIU/L with a mean of 1.27 mIU/L (Figure 3).³ Taken together, these findings support the establishment of a new normal reference TSH range from 0.5 to 2.5 mIU/L, with subclinical hypothyroidism defined as a TSH level between 2.5 and 10 mIU/L with a normal free thyroxine (FT₄) level, and overt hypothyroidism as TSH greater than 10 mIU/L with a suppressed FT₄ level.

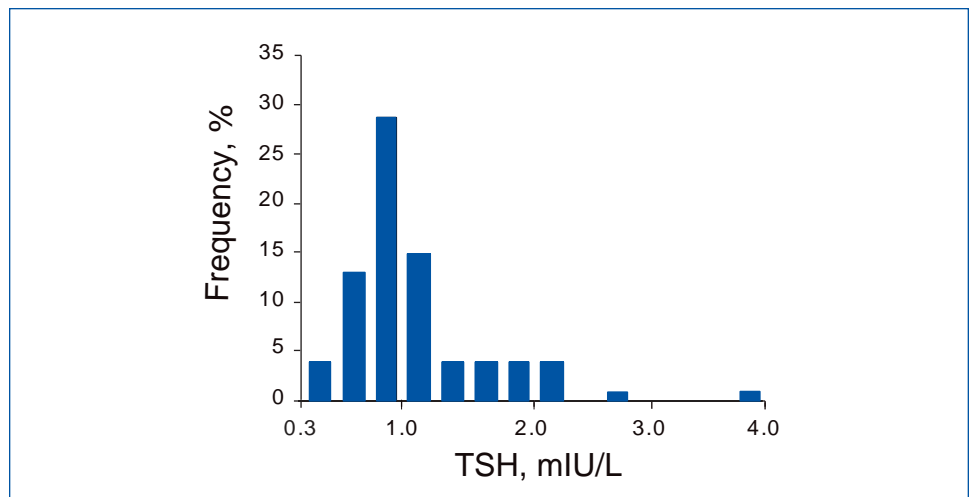


Figure 1. Approximately 95% of normal reference subjects in the NHANES III study had TSH levels between 0.3 and 2.5 mIU/L.²

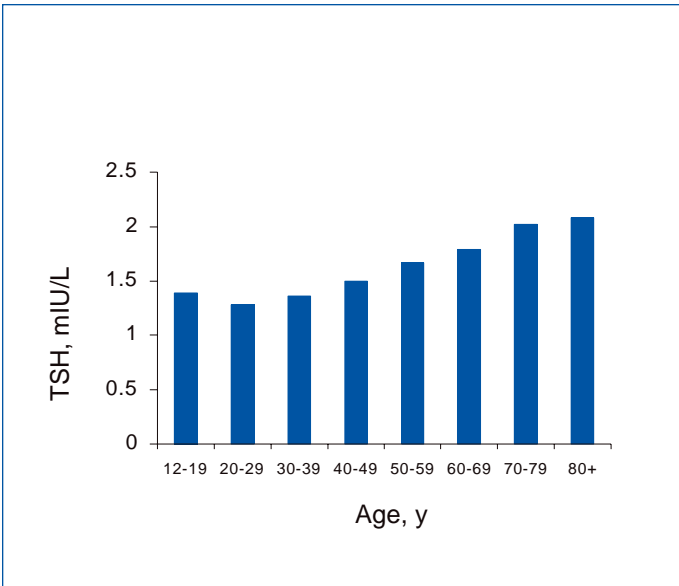


Figure 2. Though the reference TSH range increased with age in normal subjects, the average TSH level was 1.49 mIU/L.²

TSH and TPOab as predictors of hypothyroidism.

Positive thyroid peroxidase antibodies (TPOab) are the primary indicators of autoimmune thyroid disease, and they positively correlate with elevated TSH. In the NHANES III study, 80% to 90% of subjects with a TSH level over 10 mIU/L also were positive for TPOab, whereas only about 5% of subjects with TSH levels from 0.4 to 1.5 mIU/L were positive for the antibody (Figure 4).² The results of the NHANES III study also indicated that a significant increase in TPOab levels occurred at TSH levels

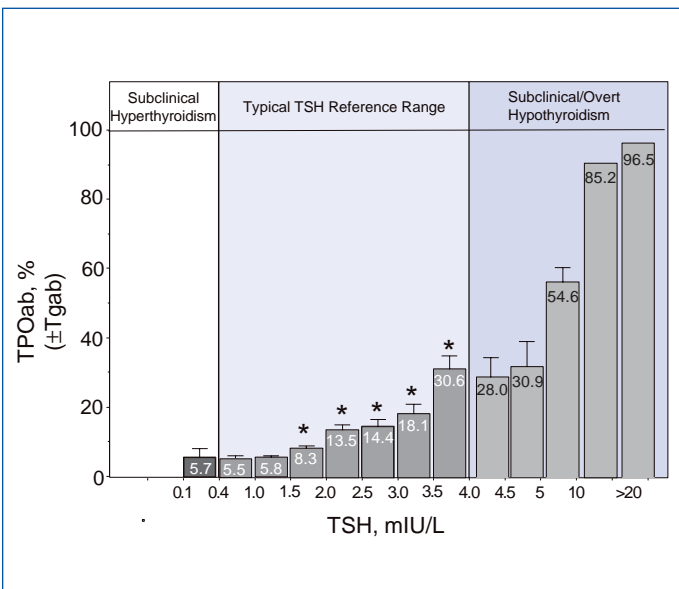


Figure 4. TPOab positivity correlates with elevated TSH. TPOab frequency increased at TSH levels greater than 2.0 mIU/L.

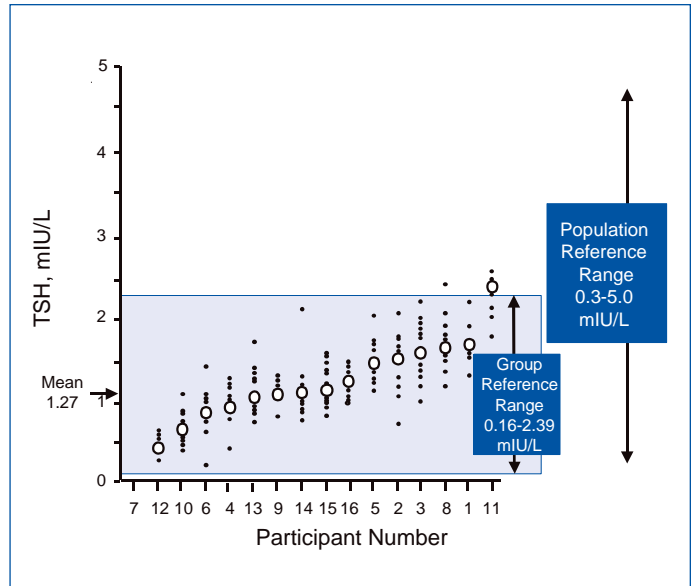


Figure 3. The Andersen study established a TSH normal reference range between 0.16 and 2.4 mIU/L. Individual TSH levels vary within the normal reference range.³

above 2.0 mIU/L.² Further, a 20-year follow-up to the Wickham study, which measured the TSH levels and progression of hypothyroidism in 1700 subjects, demonstrated that the risk of developing hypothyroidism increased with TSH levels greater than 2.0 mIU/L (Figure 5).⁴ Thus, patients with slightly elevated TSH (≥ 2.0 mIU/L) who were positive for TPOab had a higher risk of progressing from subclinical to overt hypothyroidism than did subjects who were TPOab negative.⁴

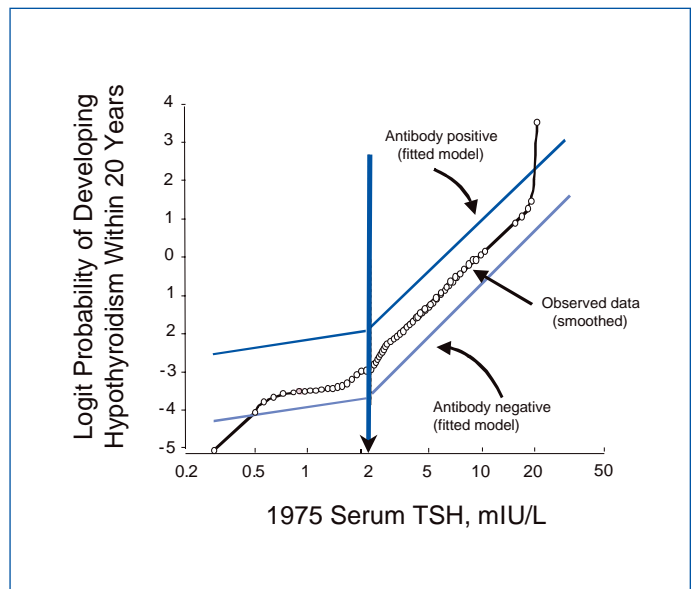


Figure 5. TPOab positivity and elevated TSH predicted an increased risk of developing hypothyroidism in a 20-year follow-up to the Wickham study.⁴

Individual TSH ranges. When compared with the normal reference TSH range established by the NHANES III and Colorado studies,^{2,5} TSH levels within the general population vary widely, with 95% falling between 0.45 and 4.0 mIU/L (Figure 6). This variation is probably due to age, gender, and comorbidities or drugs that interfere with normal thyroid function. Individual TSH and thyroxine (T₄) levels vary within the wide population range (Figures 3 and 7). Of note, small nonpersistent increases in TSH may result in a misdiagnosis of mild thyroid failure in

some individuals with TSH levels near the upper edge of the normal range. In addition, TSH is secreted from the pituitary in a periodic, diurnal manner, with TSH levels generally higher in the morning and lower in the late afternoon and evening hours. Thus, a single TSH measurement may not provide an accurate representation of a patient's TSH range. Repeat TSH testing should be carried out consistently, with measurements taken at the same time of day, in order to determine an individual's TSH range and to properly diagnose thyroid dysfunction.

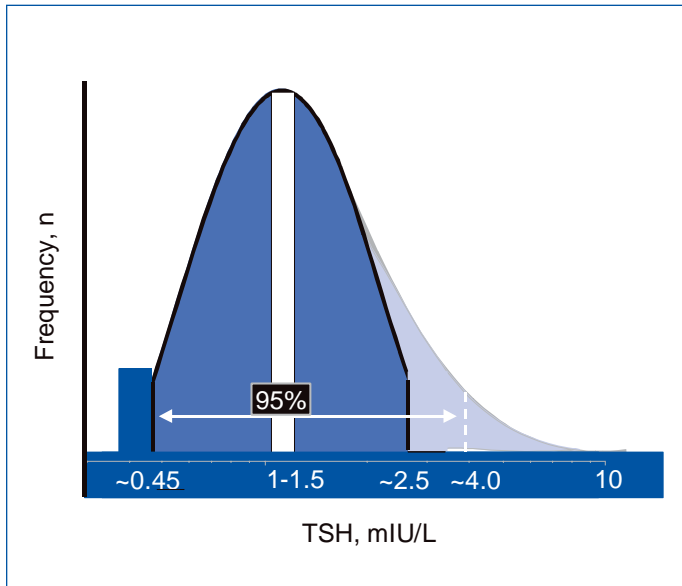


Figure 6. The general population TSH levels ranged from 0.45 to 4.0 mIU/L in the NHANES III and Colorado studies due to age, gender, and comorbidities that interfere with normal thyroid function. Given the high prevalence of mild hypothyroidism in the general population, the upper limit of the population TSH range is skewed by inclusion of individuals with overt thyroid dysfunction.^{2,5}

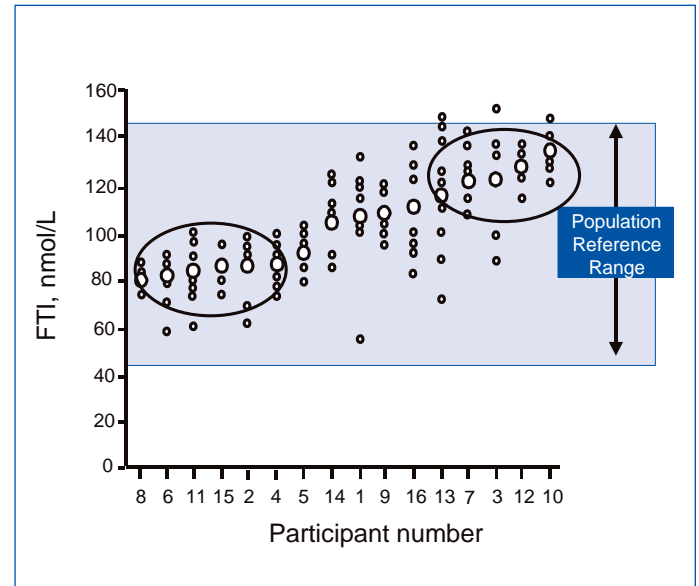


Figure 7. Individual FTI varied within the general population TSH range.³

When Isn't the TSH Normal and Why? Clinical Implications and Causes

Bryan R. Haugen, MD

Who should be screened? The American Thyroid Association suggested in 2000 that all adults over 35 years of age should undergo TSH testing every 5 years.⁶ This opinion differs from that of the American College of Physicians, whose guidelines state that general screening to detect mild thyroid failure is not cost-effective, primarily because of insufficient evidence from clinical trials to support any benefit from LT_4 treatment of asymptomatic individuals.^{7,8}

After presenting with symptoms, most patients undergo laboratory testing for TSH and thyroid hormone levels to confirm a diagnosis of hypothyroidism. The Colorado study, which screened 25 862 individuals at a statewide health fair for elevated TSH, demonstrated a clear positive correlation between the type and number of symptoms and elevated TSH (Figures 8 and 9).⁵ However, mild thyroid failure is defined by elevated serum TSH with normal FT_4 levels and is often asymptomatic. Some authors have suggested that many asymptomatic individuals with mild thyroid failure will remain undiagnosed and untreated if patients with observable symptoms are the only individuals routinely tested.⁹

About 10% of the population is estimated to have mild thyroid failure.¹⁰ Results from the Colorado study found that 9.5% of subjects had a TSH level higher than the laboratory range upper limit at the time of the study (5.1 mIU/L).⁵ Approximately 74% of those subjects had TSH levels between 5.0 and 10 mIU/L. An extrapolation of these data to the United States population leads to an estimate of 13 million people who may have subclinical hypothyroidism and have not been diagnosed.

It is also unclear whether clinicians should measure TPOAb in all individuals with elevated TSH to verify a diagnosis of autoimmune thyroid disease. The Whickham study showed that 87% of subjects with elevated TSH (>10 mIU/L) and 68% of subjects with TSH between 5.3 and 10 mIU/L were positive for TPOAb, so testing for antibodies in these populations is probably not necessary for diagnosing hypothyroidism. By contrast, only 14% of subjects with TSH between 0.5 and 5.2 mIU/L were TPOAb positive. Because both positive TPOAb and TSH levels between 2.5 and 5.0 mIU/L are highly predictive of the development of hypothyroidism, it may be worthwhile to test for antibodies in individuals with borderline TSH levels (between 3.0 and 5.0 mIU/L).

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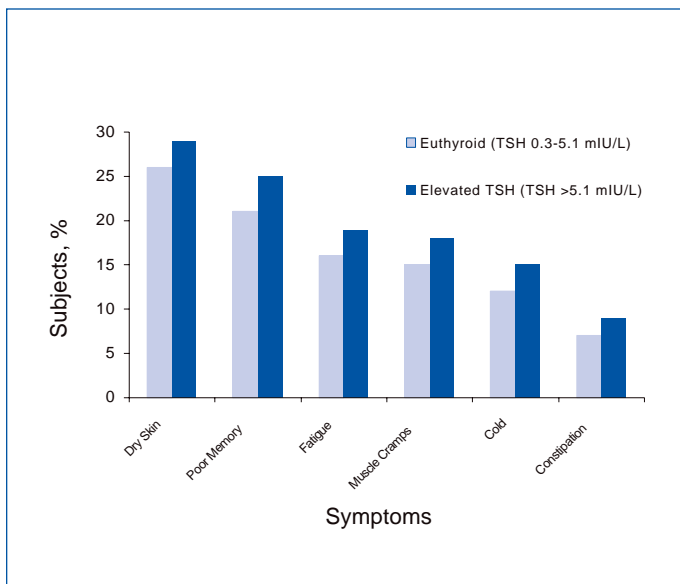


Figure 8. The prevalence of several symptoms of hypothyroidism was higher in patients with elevated TSH (≥ 5 mIU/L) compared to euthyroid patients.⁵

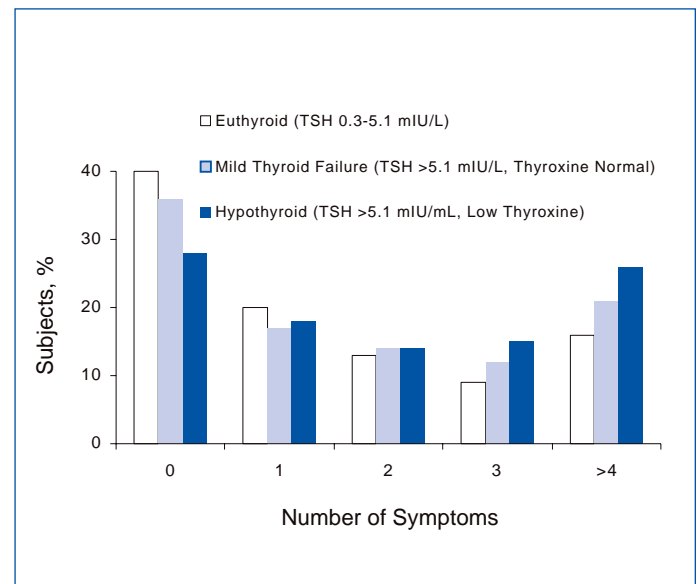


Figure 9. The number of symptoms reported by patients also correlated with elevated TSH (≥ 5 mIU/L) and low T_4 .⁵

Thyroid Disease - Epidemiology and Treatment: Overview

Primary hypothyroidism in the adult population of the United States is most commonly caused by autoimmune thyroid disease, in which thyroid tissue is attacked by the immune system.¹¹ Autoimmune thyroid disease is initiated by T-cell intolerance, which is influenced by both genetic and nongenetic factors (Figure 10).⁹ The first evidence of autoimmune thyroid disease is the appearance of antibodies against TPOab.⁹ Hypothyroidism can also be triggered during pregnancy and can arise from iodide intake deficiency or following radioactive or surgical treatment for hyperthyroidism.⁹ Certain drugs can also reduce thyroid hormone levels. The risk of developing autoimmune thyroid disease increases with age, and women are 15 to 20 times more likely than men to develop the disease.¹¹

Under the influence of TSH secreted from the pituitary, the thyroid produces the thyroid hormones T₄ and triiodothyronine (T₃). These hormones normally exert feedback inhibition on the pituitary to negatively regulate TSH release. In the early stages of hypothyroidism, a reduction in thyroid hormone levels leads to the decrease of negative feedback to the pituitary and to an increase in serum TSH levels.¹² Thyroxine levels may remain normal as TSH rises and compensates for the loss in thyroid function. If a patient has elevated TSH with relatively normal FT₄ levels and few, if any, symptoms, he or she is said to have mild thyroid failure.⁹ Because patients with elevated TSH levels often do not show symptoms, mild thyroid failure is also referred to as subclinical hypothyroidism.⁶ It is estimated that 20% of women over 60 have mild thyroid failure.¹¹ As the disease progresses, FT₄ levels drop, TSH levels continue to rise, and symptoms begin to appear.⁹

There are several signs and symptoms commonly associated with hypothyroidism (Table 1). A tentative diagnosis of hypothyroidism based on the appearance of these signs and symptoms can be verified with laboratory tests that measure the levels of total and free thyroid hormones, TSH, and TPOab.¹² The measurement of TSH is considered to be the most reliable test to diagnose all forms of hypothyroidism.⁶ The diagnosis of subclinical or overt thyroid disease is based on the presence of TPOab, measurement of T₄ levels, and the comparison of an individual's TSH levels with a reference normal TSH range.

Though the laboratory TSH range is currently 0.4 to 4.0 mIU/L for a normal (euthyroid) individual,¹ recent population studies have suggested that this range should be reset to 0.5 to 2.5 mIU/L when evaluating patients for hypothyroidism.^{2,5} This change would alter the current diagnosis of hypothyroidism because patients with TSH levels that are currently considered normal would be diagnosed as having mild thyroid failure. These findings particularly affect the diagnosis and treatment of patients with mild thyroid failure who are at risk for progressing to overt hypothyroidism and developing associated cardiovascular complications.

Hypothyroidism is treated with levothyroxine sodium (LT₄), and the dosage is tailored to the individual depending upon age, comorbidities, and confounding drugs.¹¹ Follow-up testing and monitoring are essential to establish and maintain the correct dose of LT₄.

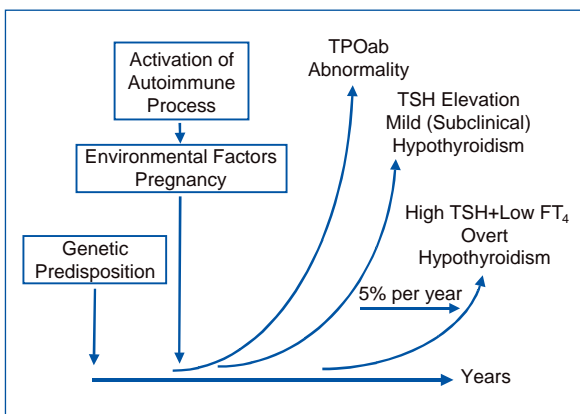


Figure 10. Autoimmune thyroid dysfunction can be triggered by genetic and nongenetic factors and develops from mild to overt hypothyroidism at the rate of 5% per year.⁹

Table 1. The common signs and symptoms of hypothyroidism.⁹

Common Signs/Symptoms

- Lethargy, fatigue
- Weight gain
- Cold intolerance
- Dry skin
- Constipation
- Bradycardia
- Goiter

Associated Signs/Symptoms

- Menstrual irregularities
- Infertility
- Elevated cholesterol
- Sleep apnea
- Carpal tunnel syndrome
- Hypertension
- Depression

When Isn't the TSH Normal and Why? Clinical Implications and Causes

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Who should be treated? While most physicians agree that patients with TSH levels exceeding 10 mIU/L with low T_4 will benefit from LT_4 treatment, evidence supporting the efficacy of treating patients who have TSH levels between 5.0 and 10 mIU/L, or between 2.0 and 5.0 mIU/L, is not conclusive. Yet, elevated TSH levels, despite normal T_4 levels, represents mild thyroid failure¹⁰ and has been associated with hypertension, elevated cholesterol, and cardiac abnormalities.^{9,12} If not treated, 2% of all patients and 17% of women with mild thyroid failure are at risk for developing overt hypothyroidism per year.¹¹ There are contradicting studies on whether the symptoms of mild thyroid failure can be improved with LT_4 treatment.¹³ However, LT_4 therapy has been demonstrated to prevent progression from subclinical to overt hypothyroidism^{4,14} and to alleviate adverse effects on the cardiovascular system¹² and during pregnancy.¹⁵ Although it may not be necessary to treat all individuals who have TSH levels in the 2.0 to 5.0 mIU/L range, treatment may be beneficial to those whose TSH levels exceed 3.0 mIU/L and who are positive for TPOab.

Is there a clinical benefit to giving LT_4 to patients with symptoms of hypothyroidism, but whose TSH levels are within the reference range? In a study by Pollock et al,¹⁶ 22 subjects who had 3 or more symptoms but normal TSH levels (1.9 ± 1.1 mIU/L), and 19 control subjects with no symptoms were treated with 100 μ g LT_4 or placebo in a double-blind, placebo-controlled crossover trial with a 6-week wash-out period. Clinical, cognitive, and psychological effects were measured. As expected, TSH levels dropped and the free thyroxine index (FTI) increased with LT_4 treatment. However, there was no significant change in 8 of 9 cognitive tests ($P > .1$), the anxiety/depression scale ($P = .874$), or any of the 5 components of the standardized SF-36 health summary ($P > .2$). The results of this study underscored the difficulty of diagnosing hypothyroidism solely based on symptoms, and suggested that symptoms should be used as a guide to direct further testing of TSH.

Cardiovascular effects of mild thyroid failure.

Hypothyroidism has been associated with increased cholesterol, premature coronary artery disease, and hypertension (Figure 11).^{12,17} A recent review by Biondi et al discussing the effects of subclinical hypothyroidism on cardiovascular function described that neither resting heart rate nor left ventricular systolic function changed with mild hypothyroidism.¹⁸ However, left ventricular diastolic function in patients with mild thyroid failure was

abnormal, and cardiac output was impaired during exercise.¹⁸ Levothyroxine replacement improved both resting and exertional ventricular function.¹⁹ There are conflicting data regarding the link between mild thyroid failure and high cholesterol levels, and the benefit of LT_4 treatment remains unclear.^{12,20} Only preliminary studies linking hypothyroidism and low-density lipoprotein (LDL) oxidation, lipoprotein levels, and homocysteine levels have been carried out. The effects of mild thyroid failure on coronary artery disease are similarly unclear, though one large study reported a link between mild thyroid failure and aortic atherosclerosis and myocardial infarction in elderly women.²¹

Hypothyroid management practices. In 2000, a survey was given to members of the American Thyroid Association and to primary care providers who were members of the American Medical Association.²² The survey presented 2 patients: a 26-year-old woman with TSH levels of 9.1 and 8.2 mIU/L, and a 71-year-old woman with TSH levels of 8.7 and 8.1 mIU/L. Both women presented with mild fatigue but normal T_4 levels. The respondents were asked whether they would measure TPOab, how they would treat these patients based on the TPOab test results, and to state their target TSH therapeutic goal. Fewer primary care physicians than endocrinologists or thyroid specialists said they would test for antibodies or use the outcome of the antibody test in their treatment decision. Further, primary care physicians responded that they were more likely to use the TSH range of 0.5 to 5.0 mIU/L as their therapeutic goal. Given the new normal TSH range, these practices will need to change in order to more effectively screen and treat patients with mild thyroid failure.

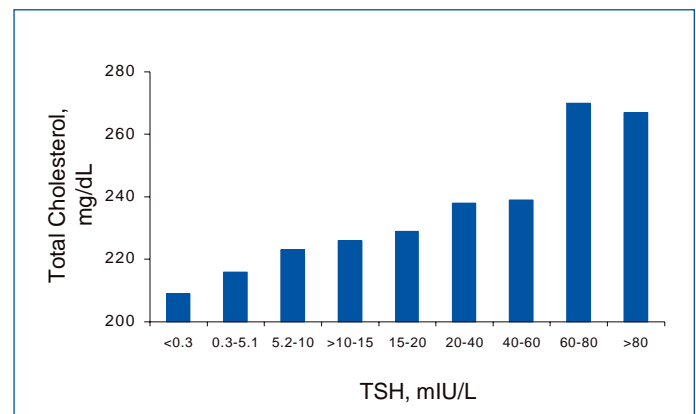


Figure 11. Total cholesterol levels generally increased as TSH levels increased.⁵

Now It's Normal – Now It's Not: Food for Thought From a Complex Case

Peter A. Singer, MD

A Discussion with Drs. Lee and Haugen

The patient. A 72-year-old woman presented with fatigue, chest pain, exertional shortness of breath, decreased appetite, weight loss, symptoms of depression, and slight hypertension. The patient also had elevated cholesterol and LDL levels. The diagnosis given by her doctor was hyperlipidemia, anemia, and mild depression. The patient was put on a low-fat diet and given a psychiatry referral.

Depression and hypothyroidism. There are many similarities between patients who are depressed and those who are hypothyroid,²³ underscoring the need to carry out TSH screening on patients who have depression (Figure 12). Knowing this, the psychiatrist in the present case noted that the patient had elevated TSH (16.2 mIU/L), but a normal FTI of 5.2, and diagnosed hypothyroidism. The patient was referred back to her doctor for treatment.

Dr. Lee: She has mild thyroid failure as defined by an elevated TSH and a normal FTI, but generally I think TSH levels above 15 mIU/L are abnormal. A thyroid antibody test is warranted, but I would treat her based on the symptoms she had. I would repeat the TSH test to confirm it is elevated.

Dr. Haugen: I agree. You could repeat the TSH test, but a patient with a TSH of greater than 10 or 15 mIU/L is probably going to be elevated after a second test and I reserve a test for TPOab for those who are under 10 mIU/L. However, I think measuring antibodies is not unreasonable for this patient.

Treatment and management. The patient was diagnosed with mild thyroid failure, as evidenced by the high TSH

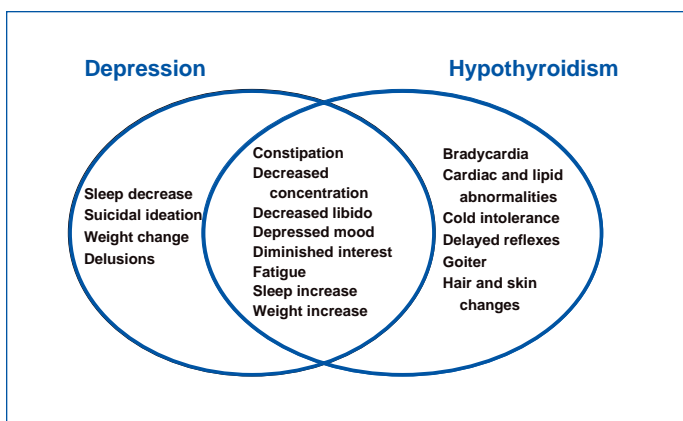


Figure 12. Depression and hypothyroidism share a number of symptoms.²³

levels with a normal FTI. Because the patient was 72-years-old, there was concern regarding underlying cardiac disease that could be impacted by thyroid hormone treatment. The patient was started at 25 µg of LT₄ per day. After 2 months, the patient reported feeling better, but her TSH levels were 5.6 mIU/L, above the 0.5 to 2.0 mIU/L therapeutic target range. The LT₄ dose was increased to 50 µg per day.

Cardiovascular complications. A month later, the patient complained of shortness of breath and chest discomfort. An examination revealed an irregular-irregular pulse, fine bi-basilar rales, and a third heart sound. She was admitted to the hospital with chronic heart failure, atrial fibrillation, and chest pain. Her TSH level was tested and was extremely low, 0.09 mIU/L. Both FT₄ levels (0.9 ng/dL) and total T₃ levels (83 ng/dL) were normal. The decision was made to discontinue LT₄ for a few days.

Dr. Lee: If you go back to Clark Sawin's data from the Framingham study,²⁴ we see the increased incidence of atrial fibrillation in the elderly with suppressed TSH. If you look at those data carefully, there is actually an increased risk of atrial fibrillation with high TSH, and there is no evidence here suggesting that this patient has an elevation in thyroid hormone causing her atrial fibrillation. I would have waited to take her off LT₄ until I had the rest of the tests back. She is not hyperthyroid with these test results, and I would have continued her dose.

An echocardiogram revealed an ejection fraction of 42% with wall motion abnormality, and a cardiac catheterization was performed. A stent was placed and the atrial fibrillation was treated. LT₄ treatment was resumed at 25 µg per day and the patient was discharged.

Follow-up. A month later, the patient returned fatigued and depressed, with poor appetite. Her TSH level was elevated to 26 mIU/L, with an FTI of 3.6. The possible reasons for these findings were delayed recovery from nonthyroid illness affecting thyroid function (sick euthyroid), a further reduction in the LT₄ dose from the original 25 µg per day, iodine-induced hypothyroidism caused by the iodine-based contrast dye used in the cardiac catheterization, or progression of autoimmune thyroid disease that would cause further reduction in thyroid hormone output.

Dr. Lee: Patients recovering from sick euthyroid rarely have a TSH level up to 26 mIU/L. I do not think that the elevation in TSH is simply from the recovery of sick euthyroid, so I would assume along with the low FTI that she really does need an increase in thyroid hormone. Therefore, I would increase her dose back to 50 µg per day.

Dr. Haugen: I agree. I think that a component of it is recovery, but the TSH level is too high and I would be fairly certain that if you continued treating her with 25 µg per day and waited 4, 5, or 6 weeks, it would probably be reduced to 20 mIU/L. I would increase the dosage of her thyroid medication.

Two months later, the patient reported that she was feeling well, but that she had moved away from the area and could not come in for follow-up. She was instead tested at a local clinic. The result was a TSH level of 1.2 mIU/L, within the target TSH range, and the patient was told to have a repeat clinical examination within 6 months.

The problem with bioequivalence. The patient called after 6 months, and said she had found a provider within a large medical group, but she no longer felt well. She was using the same dose of LT₄, but her TSH levels were again elevated to 7.2 mIU/L. The patient was not taking any new medications, and was taking the LT₄ as prescribed. She mentioned that her pill looked different.

Dr. Lee: Any time a patient changes hormone brand, you always have to consider that there is a difference in the actual therapeutic equivalence of different brands.

The present case demonstrated the difficulty in controlling TSH levels as a result of unauthorized pharmacy switching to alternate LT₄ products. The Food and Drug Administration (FDA) determines bioequivalence between

2 or more preparations of LT₄ by comparing the pharmacokinetic profile of the generic product to that of the reference (branded) drug product.²⁵ The test is not based on the measurement of TSH, which is the best indicator of the bioactivity of thyroid hormone. A recent study demonstrated that the FDA's method of determining bioequivalence is not able to distinguish between a 400 µg and a 450 µg dose of thyroid hormone, a difference of 12.5%.²⁶ Thus, bioequivalence of 2 LT₄ preparations as defined by the FDA does not necessarily translate to therapeutic equivalence.

Conclusion. The patient was put back on the original LT₄ preparation. Two months later, her TSH levels were at 1.4 mIU/L.

SUMMARY

- The laboratory TSH reference range needs to be re-evaluated and reset to 0.5 to 2.5 mIU/L in order to reflect TSH levels of the normal reference population.
- The TSH therapeutic goal should be re-established at 0.5 to 2.0 mIU/L, and LT₄ therapy tailored to patients based on their individual health conditions and by frequent monitoring of TSH levels.
- Under the new reference standard, a TSH level above 3.0 mIU/L should not be considered normal.
- Patients with TSH levels from 5.0 to 10 mIU/L would likely benefit from LT₄ therapy.
- Patients diagnosed with depression should be routinely tested for hypothyroidism.
- Because the bioequivalence of different LT₄ preparations does not necessarily equal therapeutic equivalence, patients should consistently use a single LT₄ preparation.

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