

## **What's a Normal TSH?**

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### ***Introduction:***

Serum thyrotrophin hormone (TSH) measurement is the most sensitive test for screening for thyroid dysfunction. Because serum TSH has a log-linear relationship with circulating thyroid hormone levels (a two fold change in FT4 will produce a 100-fold change in TSH) it is the determining test for diagnosis of subclinical hypothyroidism and subclinical hyperthyroidism when the peripheral thyroid hormone levels are within normal laboratory range.

The normal or reference range for any parameter should provide a framework for physicians to categorize patients as 1) normal, 2) those who may require closer observation or intervention to detect and then treat a specific adverse health outcome, and 3), those with disease who might benefit from treatment. Defining a normal range for serum TSH implies that anyone outside of this range must be abnormal, and by inference, is a candidate for some type of intervention. However because reference range is determined by choosing 95% confidence limits of a population of individuals free of thyroid dysfunction, there may be overlap and 2.5% of normals may have higher and 2.5% may have lower values.

The importance of having a consensus on normal TSH levels is that some societies have recommended routine screening for thyroid disease after age 35 and some for women above age 50. Screening of pregnant women and women anticipating pregnancy has also been proposed.

### **Subclinical hypothyroidism**

Subclinical hypothyroidism or mild thyroid failure is a very common problem with a prevalence in the United States adult population of 4–8.5% in patients without known thyroid disease. The prevalence increases with increasing age and is higher in the female population. Some studies, including our own, show that the prevalence in men approaches that of women with a combined prevalence over 10% after the sixth decade of life. In mild thyroid failure, 75% have TSH values less than 10 mIU/L. The issues of screening and treatment of subclinical hypothyroidism and normal levels of TSH is subject of intense debate among the thyroid community. Treatment of minimally elevated TSH between 4.5 and 10 has been suggested by several national societies and yet a consensus panel has found no evidence in favor of routine therapy of patients at these levels of TSH.

## Proposed consequences of subclinical hypothyroidism

### 1) *High rate of progression to clinically overt hypothyroidism:*

There is consensus on this point and available data is sufficient. (2.6% /year if TPO negative, 4.3% if TPO positive).

### 2) *Systemic symptoms of hypothyroidism:*

At least 5 randomized studies of effect of Thyroxine therapy on a total of 185 patients are available. Only one was limited to patients with TSH 5-10 mIU/L that did not show any benefit. Three other studies (TSH ranging 3-50) showed improved symptom scores. One study (TSH range 6-32) showed improved memory. The data was considered insufficient by a recent review.

### 3) *Lipid abnormalities and other cardiac risk factors:*

Colorado health fair study showed that a mean total cholesterol was 216 mg d/L for euthyroid patients and 224 for subclinical hypothyroid patients. Several randomized studies show reduction of LDL by therapy. However the studies showing benefit were not categorized for serum TSH level 5-10 mIU/L. A meta-analysis of 13 studies concluded that there were benefits from therapy. My assessment is that there is a fair possibility of benefit on lipid levels if TSH is above 10 and no benefit if TSH is less than 10 mIU/L. Although, homocysteine levels are elevated in overt hypothyroidism, recent data, and our own unpublished data shows no elevation in subclinical hypothyroidism.

### 4) *Adverse cardiac end points:*

Rotterdam cross sectional study shows association with myocardial infarction and aortic calcification. Wickham study shows no increased cardiac mortality in a 20-year follow up. The subject remains controversial and the data insufficient.

### 5) *Cardiac dysfunction:*

Several studies have shown slowed LV relaxation time, increased vascular tone at rest, and LV systolic dysfunction effort. Some studies have shown improvement of cardiac contractibility and systolic time interval with therapy. These studies were not categorized for various levels of TSH, and the data remains insufficient but suggestive for TSH levels above 10.0 mIU/L.

### 6) *Adverse fetal effects:*

Haddow study showed that offspring of mothers who had subclinical hypothyroidism at second trimester of pregnancy when tested at 7-9 years of age had 7 points reduced IQ compared to offspring of euthyroid mothers. Although this is a single study, it has nevertheless influenced the practice regarding screening of the pregnant women and therapy of mild thyroid failure in pregnancy and when there is anticipation of pregnancy.

### 7) *Neuromuscular dysfunction:*

There is some soft data, not conclusive, to indicate association of subclinical hypothyroidism with abnormalities of muscle metabolism and nerve conduction in

subclinical hypothyroidism. More studies with categorization for TSH less than and above 10 mIU/L are needed for conclusion.

8) *Psychiatric dysfunction, cognitive dysfunction:*

There is some data available but it is not conclusive on this subject.

### **Subclinical hyperthyroidism**

Subclinical hyperthyroidism is diagnosed when serum free thyroxine (T<sub>4</sub>) and free triiodothyronine (T<sub>3</sub>) are normal and serum TSH is below lower limit of normal and other causes of abnormal TSH such as euthyroid sick effect of medications such as dopamine and corticosteroids and dobutamine, pituitary disease, and recovery from hyperthyroidism, and first trimester of pregnancy are excluded. For diagnosis, 2 abnormal TSH few weeks apart are needed especially in the absence of nodular thyroid disease. NHANES study showed that the prevalence of subclinical hyperthyroidism in the cross sectional US population is 3.2%, if lower limit of TSH is considered 0.4.0 mIU/L (2% if prior thyroid disease is excluded). For TSH level <0.1 mIU/L the incidence is 0.7%. However among the patients who are on thyroxine therapy 14-21% have exogenous subclinical hyperthyroidism. Therapy of persistent suppression of TSH below 0.1 is accepted by most authors.

### **Proposed consequences of subclinical hyperthyroidism**

1. *Progression to clinical hyperthyroidism:*

In autoimmune thyroid disease early stages may present with subclinical state and in few months overt hypothyroidism may develop. In cases of nodular thyroid disease progression to overt hyperthyroidism may occur over period of several years. In cases of transient thyroiditis patients may become euthyroid after few months, occasionally after a transient hypothyroid phase. In general the outcome of subclinical hyperthyroidism is similar to clinical hyperthyroidism depending on the cause. In the absence of nodular thyroid disease the likelihood of normalization of TSH will be as high as 50%.

2. *Hyperthyroid symptoms*

Patients who have serum TSH level in the undetectable range or less than 0.1 mIU/L may have some hyperthyroid symptoms. The boundary between definition of subclinical and clinical hypothyroidism is defined by normal reference laboratory range for peripheral thyroid hormone levels. In the process of development of hyperthyroidism individual T<sub>4</sub> or T<sub>3</sub> set point may increase significantly enough to create mild symptoms yet still be in the normal laboratory reference range.

3. *Cardiac end points*

Parle et. al. have reported on increased cardiovascular mortality in the first 5 year in a 10 year follow-up of British cohort for patients with serum TSH level <0.5 (age older than 60 and not on T<sub>4</sub> therapy). This study needs confirmation, and the effect of confounding factors needs to be considered.

#### 4. *Cardiac dysfunction*

Increased LV mass index and decreased LV filling time have been reported by Biondi and colleagues. Clinical significance of these findings needs to be clarified.

#### 5. *Cardiac arrhythmia*

In patients with serum TSH levels  $<0.1$  mIU/L 3 times higher rate of AF has been reported. Also, patients with subclinical hyperthyroidism may have increased heart rate and higher frequency of atrial premature contractions.

#### 6. *Bone loss and musculoskeletal adverse effects*

Reduces BMD in postmenopausal women, not in men or premenopausal women, and increased fracture rate in postmenopausal women with subclinical hyperthyroidism has been reported. This effect is more documented in serum TSH level  $<0.1$  than TSH above 0.1 and below normal range.

#### 7. *Dementia*

Prospective study of a random sample of Rotterdam epidemiological study showed that TSH  $<0.4$  mIU/L at baseline was associated with a relative risk for dementia of 3.5. The risk was higher TPO antibody was positive. This single study also needs confirmation.

### **What is a normal TSH?**

Strong argument to lower the upper limit of TSH to 3.0 mIU/L and possibly 2.5 mIU/L has been published. However others have argued for leaving the upper limit at the present 4.5 mIU/L level.

For lower limit of TSH, a level of 0.3 or 0.4 mIU/L is acceptable to all thyroidologists. Most of the controversy thus lies for the exact upper limit of normal TSH and therapy of elevated TSH between that level and 10.0 mIU/L. There is consensus for therapy of TSH levels above 10.0 mIU/L.

NHANES III provides data on the distribution of TSH, thyroid hormones, and antithyroid antibodies in 17,353 people over the age of 12 years designed to represent the United States population. Individuals who reported thyroid disease, goiter, or taking thyroid medication were excluded from the total population, leaving 16,533 people classified as the disease-free population. A third group of 13,334 people (the reference population) further were selected by exclusion of people who had antithyroid antibodies; were pregnant, were taking estrogens, androgens, or lithium; and were without laboratory evidence of overt hypothyroidism or hyperthyroidism. The normal reference range from this study was 0.45-4.12 mIU/L.

The National Academy of Clinical Biochemistry (NACB) guidelines suggests establishing TSH reference range from 120 normal euthyroid volunteers after exclusion of goiter, medications (except estrogen), and antithyroid antibodies detected by a sensitive immunoassay. The suggested lower limit is 0.4 mIU/L. They suggest with the mean value of 1.3 mIU/L if the values were normally distributed the upper limit would be

2.5 mIU/L. This value obtained by rigorous selection of small group of volunteers is less than NHANES value of 4.1 mIU/L from a large population study.

The argument is that the distribution of TSH from large population is not Gaussian and the mean normal TSH is 1.3 mIU/L and the individuals at the tail end of upper limit of normal above 3.0 mIU/L have early form of thyroid dysfunction with a higher prevalence of goiter and positive antithyroid antibodies. Indeed, Wickham study has shown that this group has high frequency of developing clinical thyroid disease in future. When serum TSH was between 3.0 and 5.0 mIU/liter in adults 20–40 years of age, the probability of developing hypothyroidism in 20 years was less than 10%, whereas in adults 50–70 years old, the 20-year probability increased to 5–15%. When antithyroid antibodies were present as well, the 20-year prevalence increased to 15–30% in the younger adults and to 25–50% in the older age group.

**Impact of lowering upper limit of TSH:** A total of 22–28 million additional individuals in US would be diagnosed with hypothyroidism if the upper limit of the TSH range were decreased to 2.5–3.0 mIU/liter. By comparison, 2.3–4.3% of the population (4.6–8.6 million individuals) has hypothyroidism when defined as a serum TSH level of 5–10 mIU/liter. Lowering the upper limit to 2.5–3.0 mIU/liter in these populations would result in a 300–400% increase in individuals considered hypothyroid. This decrease in the upper limit of normal will increase sensitivity of diagnosing subclinical thyroid disease but will decrease its specificity. These projections are supported by an analysis of TSH values in patients without a history of thyroid disease in a tertiary care practice (Mayo Clinic). Decreasing the upper limit of the TSH reference range to 3.0 mIU/liter resulted in more than a 4-fold increase in patients classified as hypothyroid.

**Variability of serum TSH:** There may also be day to day variability of TSH some repeated TSH measurements would be expected to exceed the newly proposed upper limits of normal for TSH (2.5–3.0 mIU/liter). Those values could classify patients incorrectly as abnormal, although, the mean concentration over time is quite normal. However, some studies have shown little variability of TSH in each individual over a year's time.

There is also a diurnal variation of serum TSH. Serum TSH peaks around midnight and is higher in the early morning compared to afternoon. The average decline between 0730 and 0900 and 1030 and 1200 hours is 26.4%. Some patients classified as having subclinical hypothyroidism based on the fasting sample, are reclassified as normal based on the late morning sample. In one study, 10 of 15 individuals with fasting early morning TSH between 3.0 and 4.5 mIU/liter had a late morning of fasting TSH level below 3.0 mIU/liter. Also because of diurnal variation, 3 million night shift workers may have abnormal values with the new narrower reference range.

### **Physiologic variation in serum TSH level**

1. Upper limit of normal for new born cord is 15-20 mIU/L.
2. Values are highest at early morning and lowest in the afternoon. There is a diurnal variation.
3. Diurnal variation may be affected by alcohol.
4. Diurnal variation may be affected in depression and bipolar disorder
5. In the first trimester of pregnancy serum TSH may be partially suppressed and lower TSH levels are normal.
6. In the very old TSH levels may be slightly lower than normal.
7. Reduction of TSH may occur after glucose load and slight increase few hours later.
8. Serum TSH may be slightly higher in obesity and may be reduced after weight loss.

### **Causes of elevated TSH not related to primary hypothyroidism**

1. Presence of heterophile antibodies.
2. Recovery from non-thyroidal illness.
3. Thyroid hormone resistance.
4. TSH producing pituitary tumor.
5. TSH with lower biologic activity.
6. Certain cases of hypothalamic-pituitary disorder.
7. Recovery from silent or subacute thyroiditis.
8. TSH receptor mutations.

### **Suggested normal values for serum TSH**

- |                                 |                          |
|---------------------------------|--------------------------|
| 1. Mayo lab normal range        | 0.3-5.0 mIU/L            |
| 2. NHANES III                   | 0.45-4.12 mIU/L          |
| 3. NACB                         | 0.4-3.0 or 0.4-2.5 mIU/L |
| 4. AACE                         | 0.3- 3.0 mIU/L           |
| 5. First trimester of pregnancy | 0.02 -2.5 mIU/L          |
| 6. Cord blood of infant         | <20 or <15 mIU/L         |
| 7. Recent Danish study          | 0 .68-4.07 mIU/L         |

### **Arguments in Favor of lowering upper limit of Normal TSH**

1. Individuals with family history of thyroid disease, with positive antithyroid antibodies, with abnormal thyroid exam and with abnormal ultrasound of thyroid should be excluded when determining normal values (NHANES III).
2. The distribution for previous normal values is not Gaussian and is skewed with the tale in the upper limit.
3. The mean in normal s is 1.3 mIU/L.
4. Within person variability of serum TSH is very narrow.

5. Higher prevalence of thyroid antibodies in individuals with TSH 2.5-5 mIU/L
6. Epidemiologic studies show higher prevalence of progression to clinical hypothyroidism for values 2.5-5mIU/L.
7. There may be adverse consequences of minimal thyroid failure.

### **Arguments against lowering upper limit of normal TSH**

1. There is diurnal variation of TSH and the level of TSH depends on the time of the day.
2. 3 million night shift workers may have higher values and may be marked as abnormal.
3. Reproducibility of TSH assay may not be exact.
4. TSH values may not be stable in on individual over time.
5. TSH 3-5 mIU/L may not be specific for hypothyroidism.
6. Significant number of individuals returns to lower values of TSH with time.
7. There is no evidence to show that therapy of TSH levels between 3-5 mIU/L is beneficial.
8. Benefits of therapy of TSH levels between 4.5 and 10 are controversial.
9. Some studies have shown that in the extreme older age higher TSH is associated with better outcomes.
10. With lowering of normal TSH levels unusually large number of population will be classified as hypothyroid.
11. In patients aged 50-70 in a tertiary care center, by lowering upper limit of normal 25% of males and 29% of females will be classified as hypothyroid.
12. Therapy of minimally elevated TSH may result in inadvertent subclinical hyperthyroidism with adverse effects.
13. Measurement of bio-inactive form of TSH may explain some of 3-5 mIU/L values.
14. In rare cases because of inactivating polymorphism of TSH receptor higher level of TSH is needed to maintain euthyroidism.

### **What are the points of agreement?**

1. Minimal elevation of TSH is very common.
2. Individuals at the upper range of standard normal range (2.5-5) have higher likelihood of developing thyroid failure in future.
3. Individuals at the higher end of present normal require monitoring for thyroid failure.
4. For younger patients requiring thyroxine therapy optimal serum TSH goal is 0.4-3.0 mIU/L.
5. For first trimester of pregnancy both lower limit of normal and upper limit of normal should be lowered significantly.

### ***Conclusion:***

Individuals with serum TSH levels at higher end of standard serum TSH values of 2.5-5 mIU/L have higher likelihood of progression to clinical hypothyroidism. However, there

is absence of evidence for benefits of therapy for this group. This change in normal values will result in categorizing millions more as hypothyroid which may result in therapies with unproven efficacy and hence possible adverse consequences and expense of such therapies.

The best approach would be to educate physicians to consider appropriate follow up of individuals at the higher upper end of normal TSH. My personal opinion is that a TSH reference range of 0.4-4 mIU/L is more clinically relevant.

Also it is reasonable to aim for a serum TSH level of 0.4-3.0 mIU/L for young patients that are under thyroxine therapy and in particular for pregnant women. For very old, slightly higher TSH levels should be allowed.

It is reasonable to accept a different normal value for the first trimester of pregnancy from non pregnant state with a range of 0.02 -2.5 mIU/L.

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