



C. Thyrotropin/Thyroid Stimulating Hormone (TSH)

For more than twenty-five years, TSH methods have been able to detect the TSH elevations that are characteristic of primary hypothyroidism. Modern-day TSH methods however, with their enhanced sensitivity are also capable of detecting the low TSH values typical of hyperthyroidism. These new methods are often based on non-isotopic immunometric assay (IMA) principles and are available on a variety of automated immunoassay analyzer platforms. Most of the current methods are capable of achieving a functional sensitivity of 0.02 mIU/L or less, which is a necessary detection limit for the full range of TSH values observed between hypo- and hyperthyroidism. With this level of sensitivity, it is possible to distinguish the profound TSH suppression typical of severe Graves' thyrotoxicosis (TSH < 0.01 mIU/L) from the TSH suppression (0.01 – 0.1 mIU/L) observed with mild (subclinical) hyperthyroidism and in some patients with a non-thyroidal illness (NTI).

In the last decade the diagnostic strategy for using TSH measurements has changed as a result of the sensitivity improvements in these assays. It is now recognized that the TSH measurement is a more sensitive test than FT4 for detecting both hypo- and hyperthyroidism. As a result, some countries now promote a TSH-first strategy for diagnosing thyroid dysfunction in ambulatory patients (provided that the TSH method has a functional sensitivity ≤ 0.02 mIU/L). Other countries still favor the TSH + FT4 panel approach, because the TSH-first strategy can miss patients with central hypothyroidism [Section-3 C4(f)] or TSH-secreting pituitary tumors [Section-3 C4(g)] (19,195-197). An additional disadvantage of the TSH-centered strategy is that the TSH-FT4 relationship cannot be used as a "sanity check" for interferences or detection of unusual conditions characterized by discordance in the ratio of TSH/FT4 (Table 1).

1. Specificity

(a) TSH Heterogeneity

TSH is a heterogeneous molecule and different TSH isoforms circulate in the blood and are present in the pituitary extracts used for assay standardization (Medical Research Council (MRC) 80/558). In the future, recombinant human TSH (rhTSH) preparations might be used as primary standards for standardizing TSH immunoassays (198). Current TSH IMA methods use TSH monoclonal antibodies that virtually eliminate cross-reactivity with other glycoprotein hormones. These methods however, may detect different epitopes of abnormal TSH isoforms secreted by some euthyroid individuals, as well as some patients with abnormal pituitary conditions. For example, patients with central hypothyroidism caused by pituitary or hypothalamic dysfunction, secrete TSH isoforms with abnormal amounts of glycosylation and reduced biological activity. These isoforms are measured as paradoxically normal or even elevated serum TSH concentrations by most methods (195,197,199). Likewise, paradoxically normal serum TSH levels may be seen in patients with hyperthyroidism due to a TSH-secreting pituitary tumor, that appears to secrete TSH isoforms with enhanced biologic activity (196,200,201).

(b) Technical Problems

Technical problems, especially with the washing step, may result in falsely high TSH values (202). Additionally, any interfering substance in the specimen (eg heterophilic antibodies, HAMA) that produces a high background or a false bridge between the capture and signal antibodies will create a high signal on the solid support that will be read out as a falsely high result [see Section-2C3] (203,202).

(c) Methods for Detecting Interference with a TSH Result

The conventional laboratory approach to verifying an analyte concentration such as dilution may not always detect an interference problem. Since methods vary in their susceptibility to most interfering substances, the most practical way to test for interference is to measure the TSH concentration in the specimen using a different manufacturer's method, and to check for a significant discordance between the TSH values. When the

variability of TSH measurements made on the same specimen with different methods exceeds expectations (>50% difference), interference may be present. Biologic checks may also be useful to verify an unexpected result. Inappropriately low TSH values could be checked by a TRH-stimulation test, which is expected to elevate TSH more than 2-fold (≥ 4.0 mIU/L increment) in normal individuals (204). In cases where TSH appears inappropriately elevated, a thyroid hormone suppression test (1 mg L-T4 or 200 μ g L-T3, po) would be expected to suppress serum TSH more than 90 % by 48 hours in normal individuals.

Guideline 18. Investigation of Discordant Serum TSH Values in Ambulatory Patients

A discordant TSH result in an ambulatory patient with stable thyroid status may be a technical error. Specificity loss can result from laboratory error, interfering substances (i.e. heterophilic antibodies), or the presence of an unusual TSH isoform (see Guideline 7 and Table 1). Physicians can request that their laboratory perform the following checks:

- Confirm specimen identity (i.e. have laboratory check for a switched specimen in the run).
- When TSH is unexpectedly high, ask the laboratory to re-measure the specimen diluted, preferably in thyrotoxic serum, to check for parallelism.
- Request that the laboratory analyze the specimen by a different manufacturer's method (send to a different laboratory if necessary). If the between-method variability for a sample is > 50%, an interfering substance may be present.
- Once a technical problem has been excluded, biologic checks may be useful:
 - Use a TRH stimulation test for investigating a discordant low TSH result, expect a 2-fold (≥ 4.0 mIU/L increment) response in TSH in normal individuals.
 - Use a thyroid hormone suppression test to verify a discordant high TSH level. Normal response to 1mg of L-T4 or 200 μ g L-T3 administered p.o. is a suppressed serum TSH of more than 90 % by 48 hours.

2. Sensitivity

Historically, the "quality" of a serum TSH method has been determined from a clinical benchmark - the assay's ability to discriminate euthyroid levels (~ 0.4 to 4.0 mIU/L) from the profoundly low (<0.01 mIU/L) TSH concentration typical of overt Graves' thyrotoxicosis. Most TSH methods now claim a detection limit of 0.02 mIU/L or less ("third generation" assays) (202).

Guideline 19. Definition of Functional Sensitivity

Functional Sensitivity should be used to determine the Lowest Detection Limit of the assay.

- TSH assay functional sensitivity is defined as a 20 % between-run coefficient of variation (CV) determined by the recommended protocol (see Guideline 20).

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Guideline 20. Protocol for TSH Functional Sensitivity & Between-Run Precision

Measure human serum pools covering the assay range in at least 10 different runs. The lowest pool value should be 10% above the detection limit and the highest pool value should be 90% of the upper assay limit.

- Carry-over should be assessed by analyzing the highest pool followed by the lowest pool.
- Use the same test mode as for patient specimens (i.e. singlicate or duplicate).
- The instrument operator should be blinded to the presence of test pools in the run.
- Runs should be spaced over a clinically representative interval (i.e. 6 to 8 weeks for TSH in an outpatient setting).
- Use at least two different lots of reagents and two different instrument calibrations during the testing period.
- When running the same assay on two similar instruments, blind duplicates should be run on each instrument periodically to verify correlation.

Manufacturers have largely abandoned the use of the “analytical sensitivity” parameter for determining the sensitivity of a TSH assay because it is calculated from the within-run precision of the zero calibrator which does not reflect the sensitivity of the test in clinical practice (126,127). Instead, a “functional sensitivity” parameter has been adopted (202). Functional sensitivity is calculated from the 20% between-run coefficient of variation (CV) for the method and is used to establish the lowest reportable limit for the test (202).

Functional sensitivity should be determined by strictly adhering to the recommended protocol (Guideline 20) that is designed to assess the minimum detection limit of the assay in clinical practice and ensure that the parameter realistically represents the lowest detection limit of the assay. The protocol is designed to take into account a variety of factors that can influence TSH method imprecision in clinical practice. These include:

- Matrix differences between patient serum and the standard diluent
- Erosion of precision over time
- Lot-to-lot variability in the reagents supplied by the manufacturer
- Differences between instrument calibration and technical operators
- Carry-over from high to low specimens (205)

The use of the functional sensitivity limit as the lowest detection limit is a conservative approach to ensure that any TSH result reported is not merely assay “noise”. Further, the 20% between-run CV approximates the maximum imprecision required for diagnostic testing (Table 5).

Guideline 21. For Laboratories Performing TSH Testing

Functional sensitivity is the most important performance criterion that should influence the selection of a TSH method. Practical factors such as instrumentation, incubation time, cost, and technical support though important, should be secondary considerations. Laboratories should use calibration intervals that optimize functional sensitivity, even if re-calibration needs to be more frequent than recommended by the manufacturer:

- Select a TSH method that has a functional sensitivity ≤ 0.02 mIU/L
- Establish functional sensitivity independent of the manufacturer by using Guideline 20
- There is no scientific justification to reflex from a less sensitive to a more sensitive test. (Insensitivity causes falsely high, not falsely low, values that are missed by reflex testing!)

3. TSH Reference Intervals

Despite some gender, age and ethnicity-related differences in TSH levels revealed by the recently published NHANES III US survey, it is not considered necessary to adjust the reference interval for these factors in clinical practice (18). Serum TSH levels exhibit a diurnal variation with the peak occurring during the night and the nadir, which approximates to 50% of the peak value, occurring between 1000 and 1600 hours (123,124).

This biologic variation does not influence the diagnostic interpretation of the test result since most clinical TSH measurements are performed on ambulatory patients between 0800 and 1800 hours and TSH reference intervals are more commonly established from specimens collected during this time period. Serum TSH reference intervals should be established using specimens from TPOAb-negative, ambulatory, euthyroid subjects who have no personal or family history of thyroid dysfunction and no visible goiter. The variation in the reference intervals for different methods reflects differences in antibody epitope recognition by the different kit reagents and the rigor applied to the selection of appropriate normal subjects.

Serum TSH concentrations determined in normal euthyroid subjects are skewed with a relatively long "tail" towards the higher values of the distribution. The values become more normally distributed when log-transformed. For reference range calculations, it is customary to log-transform the TSH results to calculate the 95% reference interval (typical population mean value ~1.5 mIU/L, range 0.4 to 4.0 mIU/L in iodide-sufficient populations) (202,206). However, given the high prevalence of mild (subclinical) hypothyroidism in the general population, it is likely that the current upper limit of the population reference range is skewed by the inclusion of persons with occult thyroid dysfunction (18).

Guideline 22. TSH Reference Intervals

TSH reference intervals should be established from the 95 % confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers who have:

- No detectable thyroid autoantibodies, TPOAb or TgAb (measured by sensitive immunoassay)
- No personal or family history of thyroid dysfunction
- No visible or palpable goiter
- No medications (except estrogen).

(a) TSH Upper Reference Limits

Over the last two decades, the upper reference limit for TSH has steadily declined from ~10 to approximately ~4.0-4.5 mIU/L. This decrease reflects a number of factors including the improved sensitivity and specificity of current monoclonal antibody based immunometric assays, the recognition that normal TSH values are log-distributed and importantly, improvements in the sensitivity and specificity of the thyroid antibody tests that are used to pre-screen subjects. The recent follow-up study of the Whickham cohort has found that individuals with a serum TSH >2.0 mIU/L at their primary evaluation had an increased odds ratio of developing hypothyroidism over the next 20 years, especially if thyroid antibodies were elevated (35). An increased odds-ratio for hypothyroidism was even seen in antibody-negative subjects. It is likely that such subjects had low levels of thyroid antibodies that could not be detected by the insensitive microsomal antibody agglutination tests used in the initial study (207). Even the current sensitive TPOAb immunoassays may not identify all individuals with occult thyroid insufficiency. In the future, it is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 mIU/L because >95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L.

(b) TSH Lower Reference Limits

Before the immunometric assay era, TSH methods were too insensitive to detect values in the lower end of the reference range (209). Current methods however, are capable of measuring TSH at the lower end and now cite lower limits between 0.2 and 0.4 mIU/L (202). As the sensitivity of the methods has improved, there has been an increased interest in defining the true lower limit of normal to better determine the presence of mild (subclinical) hyperthyroidism. Current studies suggest that TSH values in the 0.1 to 0.4 mIU/L range may represent thyroid hormone excess and in elderly patients might be associated with an increased risk of atrial fibrillation, and cardiovascular mortality (36,37). It is therefore important to carefully exclude subjects with a goiter and any illness or stress in the normal cohort selected for reference range study.

4. Clinical Use of Serum TSH Measurements

(a) Screening for Thyroid Dysfunction in Ambulatory Patients

Most professional societies recommend that TSH be used for case finding or screening for thyroid dysfunction in ambulatory patients, provided that the TSH assay used has a functional sensitivity at or below 0.02 mIU/L (4,10,210). The TSH assay sensitivity stipulation is critical for the reliable detection of subnormal values, since less sensitive TSH assays are prone to produce false negative (normal range) results on specimens with subnormal TSH concentrations (202). The log/linear relationship between TSH and FT4 dictates that serum TSH is the preferred test, since only TSH can detect mild (subclinical) degrees of thyroid hormone excess or deficiency (Figure 1) [Section-2 A1]. Mild (subclinical) thyroid dysfunction, characterized by an abnormal TSH associated with a normal range FT4 have reported prevalences in population surveys of ~10% and 2%, for subclinical hypo- and hyperthyroidism, respectively (10,18,25,211). Despite the clinical sensitivity of TSH, a TSH-centered strategy has inherently two primary limitations. First, it assumes that hypothalamic-pituitary function is intact and normal. Second, it assumes that the patients thyroid status is stable, i.e. the patient has had no recent therapy for hypo- or hyperthyroidism [Section-2 A1 and Figure 2] (19). If either of these criteria is not met, serum TSH results can be diagnostically misleading (Table 1).

When investigating the cause of an abnormal serum TSH in the presence of normal FT4 and FT3, it is important to recognize that TSH is a labile hormone and subject to nonthyroidal pituitary influences (glucocorticoids, somatostatin, dopamine etc) that can disrupt the TSH/FT4 relationship (69,70,71,212). It is important to confirm any TSH abnormality in a fresh specimen drawn after ~3 weeks before assigning a diagnosis of mild (subclinical) thyroid dysfunction as the cause of an isolated TSH abnormality. After confirming a high TSH abnormality, a TPOAb measurement is a useful test for establishing the presence of thyroid autoimmunity as the cause of mild (subclinical) hypothyroidism. The higher the TPOAb concentration, the more rapid the development of thyroid failure. After confirming a low TSH abnormality it can be difficult to unequivocally establish a diagnosis of mild (subclinical) hyperthyroidism, especially if the patient is elderly and not receiving L-T4 therapy (34). If a multinodular goiter is present, thyroid autonomy is the likely cause of mild (subclinical) hyperthyroidism (213).

There is no consensus regarding the optimal age to begin the screening process. The American Thyroid Association guidelines recommend screening at age 35 and every 5 years thereafter (10). Decision analysis appears to support the cost-effectiveness of this strategy, especially for women (215). The strategy for using TSH to screen for mild (subclinical) hypo- and hyperthyroidism will remain in dispute until there is more agreement on the clinical consequences and outcome of having a chronically abnormal TSH. Also there needs to be agreement as to the level of the TSH abnormality that should indicate the need for treatment (216,217).

There is mounting evidence to suggest that patients with a persistent TSH abnormality may be exposed to greater risk if left untreated. Specifically, a recent study reported a higher cardiovascular mortality rate when patients had a chronically low serum TSH (37). Further, there are an increasing number of reports that indicate that mild hypothyroidism in early pregnancy increases fetal wastage and impairs the IQ of the offspring (63-65)). Such studies support the efficacy of early thyroid function screening, especially in women during their childbearing years.

(b) Elderly Patients

Most studies support screening for thyroid dysfunction in the elderly (10,35,214). The prevalence of both a low and high TSH (associated with normal FT4) is increased in the elderly compared with younger patients. Hashimotos' thyroiditis, associated with a high TSH and detectable TPOAb, is encountered with increasing prevalence as we get older. (35). The incidence of a low TSH is also increased in the elderly (35). A low TSH may be transient but is a persistent finding in approximately 2 % of elderly individuals, with no other apparent evidence of thyroid dysfunction (36,214). This could be due to a change in the FT4/TSH set-point, a change in TSH bioactivity or mild thyroid hormone excess (218). A recent study by Parle et al showed a higher cardiovascular mortality rate in such patients (37). This suggests that the cause of a persistently low TSH level

should be actively investigated (37). Multinodular goiter should be ruled out as the cause especially in areas of iodide deficiency (213). Medication history should be thoroughly reviewed (including over-the-counter preparations, some of which contain T3). If a goiter is absent and the medication history negative, a serum TSH should be rechecked together with TPOAb measurements after 4 to 6 weeks. If the TSH is still low and TPOAb is positive, the possibility of autoimmune thyroid dysfunction should be considered. Treatment of low TSH should be made on a case-by-case basis.

(c) L-T4 Replacement Therapy

It is now well documented that hypothyroid patients have serum FT4 values in the upper third of the reference interval when the L-T4 replacement dose is titrated to bring the serum TSH into the therapeutic target range (0.5-2.0 mIU/L) (219,220).

Levothyroxine (L-T4) and not desiccated thyroid, is the preferred long-term replacement medication for hypothyroidism.

A euthyroid state is usually achieved in adults with a L-T4 dose averaging 1.6 µg/kg body weight/day. Children require higher doses (up to 4.0 µg/kg bw/day) and older individuals require lower doses (1.0 µg/kg bw/day) (221,222). The initial dose and the optimal time needed to establish the full replacement dose should be individualized relative to age, weight and cardiac status. The requirements for an increase in thyroxine during pregnancy [Section-2 A3] and in post-menopausal women just starting hormone replacement therapy (223) may also be increased.

A serum TSH result between 0.5 and 2.0 mIU/L is generally considered the therapeutic target for a standard L-T4 replacement dose for primary hypothyroidism.

A serum FT4 concentration in the upper third of the reference interval is the therapeutic target for L-T4 replacement therapy when patients have central hypothyroidism due to pituitary and/or hypothalamic dysfunction.

A typical schedule for gradually titrating to a full replacement dose involves giving L-T4 in 25 µg increments each 6–8 weeks until the full replacement dose is achieved (serum TSH 0.5-2.0 mIU/L). As shown in figure 2, TSH is slow to re-equilibrate to a new thyroxine level. Patients with chronic, severe hypothyroidism may develop pituitary thyrotroph hyperplasia which can mimic a pituitary adenoma, but which resolves after several months of L-T4 replacement therapy (224). Patients taking Rifampin and anticonvulsants that influence the metabolism of L-T4 may also need an increase in their dose of L-T4 to maintain the TSH within the therapeutic target range.

Both free T4 and TSH should be used for monitoring hypothyroid patients suspected of intermittent or non-compliance with their L-T4 therapy. The paradoxical association of a high FT4 + high TSH is often an indication that compliance may be an issue. Specifically, acute ingestion of missed L-T4 doses before a clinic visit will raise the FT4 but fail to normalize the serum TSH because of the “lag effect” (Figure 2). In essence, the serum TSH is analogous to the hemoglobin A1c as a long-term free T4 sensor! At least 6 weeks is needed before retesting TSH following a change in the dose of L-T4 or brand of thyroid medication. Annual TSH testing of patients receiving a stable dose of L-T4 is recommended. The optimal time for TSH testing is not influenced by the time of day the L-T4 dose is ingested (133). However, the daily dose should be withheld when FT4 is used as the therapeutic endpoint, since serum FT4 is significantly increased (~13%) above baseline for 9 hours after ingesting the last dose (225).

Ideally L-T4 should be taken before eating; at the same time of day and at least 4 hours apart from any other medications or vitamins. Many medications can influence T4 absorption/metabolism (especially Cholestyramine, Ferrous Sulfate, Soy Protein, Sucralfate, antacids containing Aluminum Hydroxide, anticonvulsants or Rifampin) (4,226).

(d) L-T4 Suppression Therapy

L-T4 administration designed to suppress serum TSH levels to subnormal values is typically reserved for patients with well-differentiated thyroid carcinoma for which thyrotropin is considered a trophic factor (227). The efficacy of L-T4 suppression therapy has been determined from uncontrolled retrospective studies that have yielded conflicting results (228,229).

It is important to individualize the degree of TSH suppression by weighing patient factors such as age, clinical status including cardiac factors and DTC recurrence risk against the potentially deleterious effects of iatrogenic mild (subclinical) hyperthyroidism on the heart and bone (36). Many physicians use a serum TSH target of 0.05-0.1 mIU/L for low-risk patients and a TSH of <0.01 mIU/L for high-risk patients. Some physicians reduce the L-T4 dose to give low-normal TSH values when patients have undetectable serum thyroglobulin (Tg) levels and no recurrences 5-10 years after thyroidectomy. Suppression therapy for non-endemic goiters is generally considered ineffective (230). Furthermore, patients with nodular goiters often already have suppressed TSH concentrations as a result of thyroid gland autonomy (213).

Guideline 23. Levothyroxine (L-T4) Replacement Therapy for Primary Hypothyroidism

- L-T4, not desiccated thyroid, is the preferred medication for long-term replacement therapy for hypothyroidism.
- A euthyroid state is usually achieved with an average L-T4 dose of 1.6 µg/kg body weight/day. The initial dose and time to achieve full replacement should be individualized relative to age, weight and cardiac status. An initial L-T4 dose is normally 50-100 µg daily. Serum TSH measurement after six weeks will indicate the need for dose adjustment by 25-50 µg increments.
- Children require higher doses of L-T4, up to 4.0µg/kg bw/day, due to rapid metabolism. Serum TSH and FT4 values should be assessed using age-specific and method-specific reference ranges (Table 3).
- A serum TSH level between 0.5 and 2.0 mIU/L is generally considered the optimal therapeutic target for the L-T4 replacement dose for primary hypothyroidism.
- TSH is slow to re-equilibrate to a new thyroxine status (Guideline 2). Six to 8 weeks is needed before retesting TSH after changing the L-T4 dose or brand of thyroid medication.
- Intermittent or non-compliance with levothyroxine (L-T4) replacement therapy will result in discordant serum TSH and FT4 values (high TSH/high FT4) because of a persistently unstable thyroid state (Guideline 2). Both TSH and FT4 should be used for monitoring such patients.
- Thyroxine requirements decline with age. Older individuals may require less than 1.0 µg/kg bw/day and may need to be titrated slowly. Some physicians prefer to gradually titrate such patients. An initial dose of 25 µg is recommended for patients with evidence of ischemic heart disease followed by dose increments of 25 µg every 3-4 weeks until the full replacement dose is achieved. Some believe that a higher target TSH (0.5-3.0 mIU/L) value may be appropriate for the elderly patient.
- In severe hypothyroidism an initial L-T4 loading dose is the most rapid means for restoring a therapeutic FT4 level because the excess of unoccupied binding sites may blunt the FT4 response to treatment.
- Thyroxine requirements increase during pregnancy. Thyroid status should be checked with TSH + FT4 during each trimester of pregnancy. The L-T4 dose should be increased (usually by 50 µg/day) to maintain a serum TSH between 0.5 and 2.0 mIU/L and a serum FT4 in the upper third of the normal reference interval.
- Post-menopausal women starting hormone replacement therapy may need an increase in their L-T4 dose to keep the serum TSH within the therapeutic target.
- TSH testing of patients receiving a stable L-T4 dose is recommended on an annual basis. The ideal time for TSH testing is not influenced by the time of day the L-T4 dose is ingested.
- Ideally L-T4 should be taken before eating, at the same time of day, and at least 4 hours apart from any other medications or vitamins. Bedtime dosing should be 2 hours after the last meal.
- Patients beginning chronic therapy with cholestyramine, ferrous sulfate, calcium carbonate, soy protein, sucralfate and antacids containing aluminum hydroxide that influence L-T4 absorption may require a larger L-T4 dose to maintain TSH within the therapeutic target range.
- Patients taking Rifampin and anticonvulsants that influence the metabolism of L-T4 may also need an increased L-T4 dose to maintain the TSH within the therapeutic target range.

Guideline 24. Levothyroxine (L-T4) Suppression Therapy

- ❑ Serum TSH is considered a growth factor for differentiated thyroid cancer (DTC). The typical L-T4 dose used to suppress serum TSH in DTC patients is 2.1µg/kg body weight/day.
- ❑ The target serum TSH level for L-T4 suppression therapy for DTC should be individualized relative to the patient's age and clinical status including cardiac factors and DTC recurrence risk.
- ❑ Many physicians use a serum TSH target value of 0.05-0.1 mIU/L for low-risk patients and a TSH of <0.01 mIU/L for high-risk patients.
- ❑ Some physicians use a low-normal range therapeutic target for TSH when patients have undetectable serum Tg levels and have had no recurrence 5-10 years after thyroidectomy.
- ❑ If iodide intake is sufficient, L-T4 suppression therapy is rarely an effective treatment strategy for reducing the size of goiters.
- ❑ Over time, multi-nodular goiters typically develop autonomy that is characterized by a subnormal serum TSH level. Serum TSH should be checked before initiating L-T4 suppression therapy in such patients.

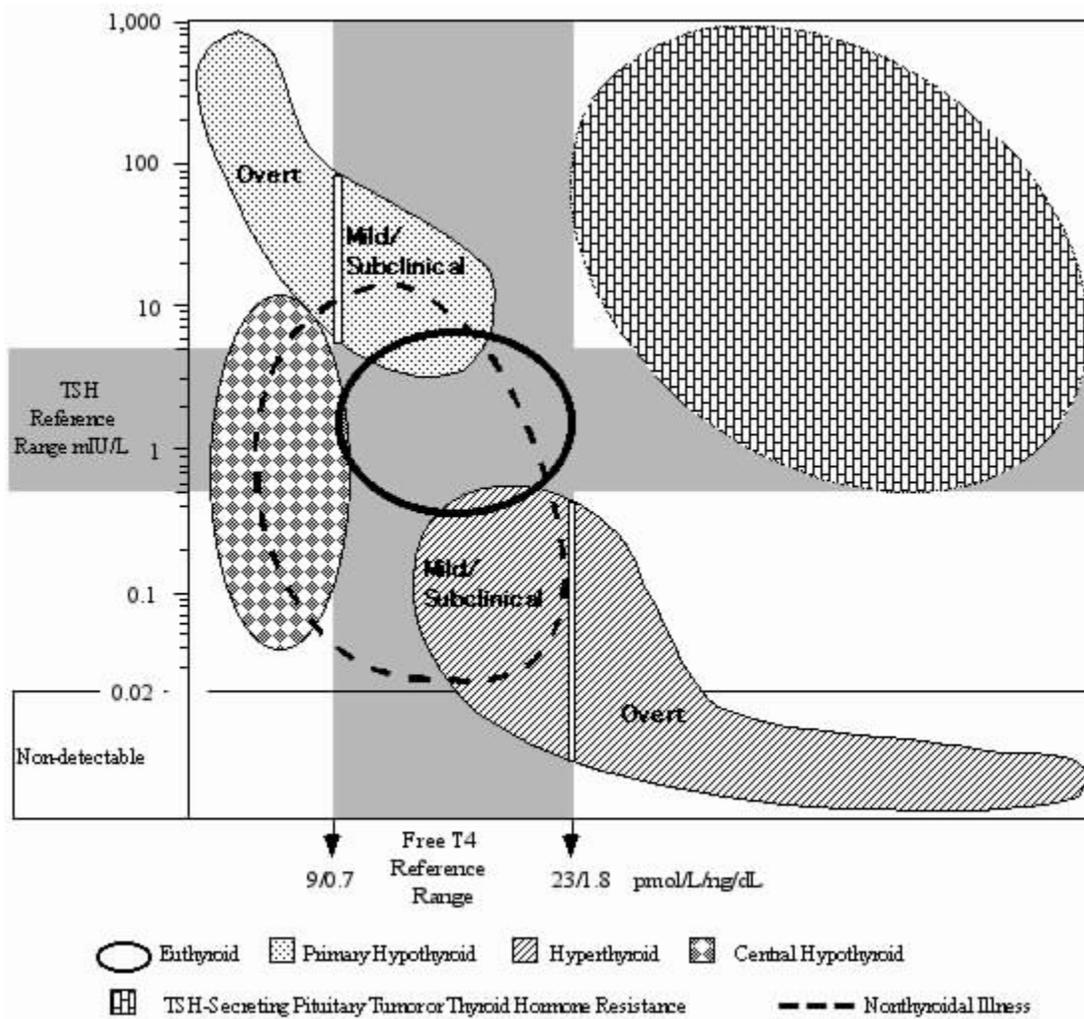


Fig 4. The serum TSH/FT4 relationship typical of different clinical conditions

(e) Serum TSH Measurement in Hospitalized Patients with NTI

Although most hospitalized patients with NTI have normal serum TSH concentrations, transient TSH abnormalities in the 0.02 – 20 mIU/L range are commonly encountered in the absence of thyroid dysfunction (20,87,92,93). It has been suggested that the use of a wider reference range (0.02 –10 mIU/L) would improve the positive predictive value of TSH measurements for evaluating the sick hospitalized patient (20,92,93,231). TSH should be used in conjunction with a FT4 estimate (or TT4) test for evaluating hospitalized patients with clinical symptoms or patients with a history of thyroid dysfunction (Guidelines 6 and 25).

Sometimes the cause of the TSH abnormality in a hospitalized patient is obvious, such as in the case of dopamine or glucocorticoid-therapy (87,92). In other cases the TSH abnormality is transient and appears to be caused by NTI per se, and resolves with recovery from the illness. It is common to see a transient minor suppression of TSH into the 0.02-0.2 mIU/L range during the acute phase of an illness, followed by a rebound to mildly elevated values during recovery (103). It is important to use a TSH assay with a functional sensitivity ≤ 0.02 mIU/L in the hospital setting in order to be able to reliably determine the degree of TSH suppression. Specifically, the extent of TSH suppression can be used to discriminate sick hyperthyroid patients with profoundly low serum TSH values (< 0.02 mIU/L) from patients with a mild transient suppression of NTI (20).

Guideline 25. TSH Measurement in Hospitalized Patients

- TSH + T4 (FT4 or TT4) is the most useful test combination to detect thyroid dysfunction in a sick hospitalized patient.
- It is more appropriate to use a widened TSH reference interval (0.05 to 10.0 mIU/L) in the hospitalized setting. Serum TSH levels may become subnormal transiently in the acute phase and become elevated in the recovery phase of an illness.
- A serum TSH value between 0.05 and 10.0 mIU/L is usually consistent with a euthyroid state, or only a minor thyroid abnormality that can be evaluated by retesting after the illness subsides. (This only applies to patients not receiving medications such as dopamine that directly inhibit pituitary TSH secretion.)
- A low-normal TSH level in the presence of a low TT4 and low TT3 may reflect central hypothyroidism as a result of a prolonged illness; whether or not this condition requires immediate treatment remains uncertain and is currently controversial.
- When thyroid dysfunction is suspected, a thyroid peroxidase antibody (TPOAb) test may be useful to differentiate autoimmune thyroid disease from NTI.

Diagnosing hyperthyroidism in NTI patients can be a challenge because current FT4 methods can give both inappropriately low and high values in euthyroid NTI patients (101,232). Serum TT4 and TT3 measurements may be useful for confirming a diagnosis of hyperthyroidism if assessed relative to the severity of the illness (Guideline 6). A suppressed serum TSH below 0.02mIU/L is less specific for hyperthyroidism in hospitalized individuals, compared with ambulatory patients. One study found that 14% of hospitalized patients with TSH < 0.005 mIU/L were euthyroid. However, such patients had a detectable TRH-stimulated TSH response whereas patients who were truly hyperthyroid with NTI did not (20).

Mild (subclinical) hypothyroidism cannot be easily diagnosed during a hospitalization, because of the frequency of high TSH abnormalities associated with NTI. Provided that the thyroid hormone (FT4 or TT4) concentration is within normal limits, any minor abnormality in serum TSH (0.02-20.0 mIU/L) arising from a mild (subclinical) thyroid condition is unlikely to affect the outcome of the hospitalization, and can be deferred for evaluation 2-3 months after discharge. In contrast, sick hypothyroid patients typically exhibit the combination of low FT4 and elevated TSH (>20 mIU/L) (92).

(f) Central Hypothyroidism

The log/linear relationship between TSH and FT4 dictates that patients with primary hypothyroidism and a subnormal FT4 should have a serum TSH value > 10 mIU/L (Figure 1) [Section-2 A1]. When the degree of TSH elevation in response to a low thyroid hormone level appears inappropriately low, pituitary insufficiency should be excluded. A diagnosis of central hypothyroidism will usually be missed using a “TSH first” strategy (19).

Guideline 26. Levothyroxine (L-T4) Replacement Therapy for Central Hypothyroidism

- A serum FT4 level in the upper third of the reference interval is the therapeutic target for the L-T4 replacement dose used to treat central hypothyroidism due to pituitary or hypothalamic dysfunction.
- When using FT4 as the therapeutic endpoint for central hypothyroidism, the daily dose of L-T4 should be withheld on the day of the FT4 measurement. (Serum FT4 is increased (~13 %) above baseline for 9 hours after ingesting L-T4).

Central hypothyroid conditions are characterized by paradoxically normal or slightly elevated serum TSH in the majority of cases (29). In one study of central hypothyroid patients, 35% had subnormal TSH values but 41% and 25% had inappropriately normal and elevated TSH values, respectively (233). It is now well documented that the paradoxically elevated serum TSH levels seen in central hypothyroid conditions is caused by the measurement of biologically inert TSH isoforms that are secreted when the pituitary is damaged or when hypothalamic TRH stimulation is deficient (197). The inappropriate TSH values arise because the monoclonal antibodies used in current TSH assays cannot distinguish between TSH isoforms of different biological activity, since TSH biological activity is determined not by the protein backbone but by the degree of glycosylation, specifically the sialylation of the TSH molecule. It appears that normal TRH secretion is essential for producing normal TSH sialylation and association of the TSH subunits to form mature, biologically active TSH molecules (29,197,234). The biological activity of TSH in central hypothyroid conditions appears to be inversely related to the degree of TSH sialylation as well as the FT4 level in the circulation (29). TRH-stimulation testing may be useful for specifically diagnosing central hypothyroidism (235). Typical TSH-responses in such conditions are blunted (<2-fold rise/ ≤4.0 mIU/L increment) and may be delayed (197,204,235,236). In addition, the T3-responses to TRH-stimulated TSH are blunted and correlate with TSH biological activity (197,237,238).

Guideline 27. Clinical Utility of TSH Assays (Functional Sensitivity ≤ 0.02 mIU/L)

- Serum TSH measurement is the most diagnostically sensitive test for detecting mild (subclinical), as well as overt, primary hypo- or hyperthyroidism in ambulatory patients.
- The majority (>95%) of healthy euthyroid subjects have a serum TSH concentration below 2.5 mIU/L. Ambulatory patients with a serum TSH above 2.5 mIU/L when confirmed by a repeat TSH measurement made after 3-4 weeks, may be in the early stages of thyroid failure, especially if TPOAb is detected.
- A serum TSH measurement is the therapeutic endpoint for titrating the L-T4 replacement dose for primary hypothyroidism (see Guideline 23) and for monitoring L-T4 suppression therapy for differentiated thyroid carcinoma (see Guideline 24).
- Serum TSH measurements are more reliable than FT4 in hospitalized patients with non-thyroidal illness not receiving dopamine. Serum TSH should be used in conjunction with T4 (TT4 or FT4) testing for hospitalized patients (Guidelines 6 and 26).
- TSH cannot be used to diagnose central hypothyroidism because current TSH assays measure biologically inactive TSH isoforms.
- Central hypothyroidism is characterized by an inappropriately normal or slightly elevated serum TSH level and a blunted (<2-fold rise/ ≤4.0 mIU/L increment) TRH response.
- When the serum FT4 is low and yet the serum TSH is only minimally elevated (<10 mIU/L), a diagnosis of central hypothyroidism should be considered.
- Serum TSH measurements are an important pre-natal and first trimester screening test to detect mild (subclinical) hypothyroidism in the mother (see Guideline 4).
- A low TSH in the setting of a multinodular goiter suggests the presence of mild (subclinical) hyperthyroidism due to thyroid autonomy.
- A serum TSH measurement is required for confirming that an elevated thyroid hormone level is due to hyperthyroidism and not a thyroid hormone binding protein abnormality (such as FDH).
- A serum TSH measurement is the primary test for detecting amiodarone – induced thyroid dysfunction (see Guideline 5).

(g) Inappropriate TSH Secretion Syndromes

As shown in Table 1, binding protein abnormalities or assay technical problems are the most common causes for a discordant FT4/TSH relationship. The apparent paradoxical dissociation between high levels of thyroid hormone and a non-suppressed serum TSH has led to the widespread use of the term “inappropriate TSH secretion syndromes” to describe these conditions. Specimens that display a discordant TSH/FT4 relationship are increasingly being identified now that sensitive TSH assays that can reliably detect subnormal TSH concentrations are available and in widespread use [Section-3 C2]. As shown in Table 1, it is critical to first exclude likely causes of a discordant TSH/FT4 ratio, i.e technical interference and/or binding protein abnormality. This confirmatory testing should be performed on a fresh specimen by measuring TSH together with free and total thyroid hormone with a different manufacturer’s method. Only after the more common causes of discordance have been eliminated should rare conditions such as a TSH-secreting pituitary tumor or thyroid hormone resistance be considered.

When the abnormal biochemical profile has been confirmed, the possibility that a TSH-secreting pituitary tumor is the cause of the paradoxical TSH should first be eliminated before assigning the diagnosis of thyroid hormone resistance (THR). It should be noted that both conditions can coexist (247). TSH-secreting pituitary tumors have similar biochemical profiles to THR but can be distinguished from THR by TSH-alpha subunit testing and radiographic imaging. Additionally, TRH-stimulation testing may occasionally be useful in developing the differential diagnosis. Specifically, a blunted TRH-stimulation test and T3-suppression test is characteristic of most TSH-secreting pituitary tumors whereas a normal response is seen in most cases of THR (245).

(i) TSH-Secreting Pituitary Tumors

Pituitary tumors that hypersecrete TSH are rare, representing <1% of cases of inappropriate TSH secretion (27,28). These tumors often present as a macroadenoma with symptoms of hyperthyroidism associated with a non-suppressed serum TSH and MRI evidence of a pituitary mass (28).

After excluding a technical reason for the paradoxically elevated TSH level (i.e. HAMA), the diagnosis of TSH-secreting pituitary tumor is usually made on the basis of:

- A lack of TSH response to TRH stimulation
- An elevated serum TSH alpha subunit
- A high alpha subunit/TSH ratio
- The demonstration of a pituitary mass on MRI

Guideline 28. For Manufacturers of TSH Tests

- Manufacturers that market TSH tests with differing sensitivities are urged to discontinue marketing the less sensitive product.
- There is no justification for the pricing of TSH assays to be based on sensitivity!
- There is no scientific justification for reflexing from a less sensitive to a more sensitive TSH test.
- Manufacturers should help laboratories independently establish functional sensitivity by providing appropriately low TSH human serum pools when requested.
- Manufacturers should indicate the use of calibration factors, especially if calibration factors are country-dependent.
- Manufacturers should quote the recovery of the TSH Reference Preparation at the claimed functional sensitivity.
- Kit Package Inserts should:
 - Document the realistic functional sensitivity of the method using the Guideline 20 protocol
 - Cite the functional sensitivity that can be achieved across a range of clinical laboratories
 - Display the typical between-run precision profile expected for a clinical laboratory
 - Recommend the use of functional sensitivity not analytical sensitivity to determine the lowest reporting limit. (Analytical sensitivity prompts laboratories to adopt an unrealistic detection limit.)

(ii) Thyroid Hormone Resistance

Thyroid hormone resistance (THR) is usually caused by a mutation of the thyroid hormone (TR), TR-beta receptor gene that occurs in 1: 50,000 live births (239-242). Although the clinical presentation can be variable, patients have a similar biochemical profile. Specifically, serum FT4 and FT3 are typically elevated (from a minimal degree to a 2-3-fold elevation above the upper normal limit) and associated with a normal or slightly elevated serum TSH that responds to TRH stimulation (242,243). However, it should be recognized that TSH secretion is not inappropriate given the fact that the tissue response to thyroid hormone is reduced, requiring higher thyroid hormone levels to maintain a normal metabolic state. THR patients typically have a goiter as a result of chronic hypersecretion of a hybrid TSH isoform that has increased increased biologic potency (199,244). The clinical manifestation of thyroid hormone excess covers a wide spectrum. Some patients appear to have a normal metabolism with a near-normal serum TSH and whose receptor defect appears to be compensated for by high levels of thyroid hormone (Generalized THR). Other patients appear to be hypermetabolic and to have a defect that selectively affects the pituitary (Pituitary THR).

The distinctive features of THR are the presence of a non-suppressed TSH, together with an appropriate response to TRH despite elevated thyroid hormone levels (242,245). Although rare, it is important to consider the diagnosis of THR when encountering a patient with elevated thyroid hormone levels associated with a paradoxically normal or elevated TSH (242,246). Such patients have often been misdiagnosed as having hyperthyroidism and have been subjected to inappropriate thyroid surgery or radioiodide gland ablation (242).