Euthyroid sick syndrome

Background

Euthyroid sick syndrome can be described as abnormal findings on thyroid function tests that occur in the setting of a nonthyroidal illness (NTI) without preexisting hypothalamic-pituitary and thyroid gland dysfunction. After recovery from an NTI, these thyroid function test result abnormalities should be completely reversible.

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of NTI without evidence of preexisting thyroid or hypothalamic-pituitary disease. The most prominent alterations are low serum triiodothyronine (T3) and elevated reverse T3 (rT3), leading to the general term low T3 syndrome. Thyroid-stimulating hormone (TSH), thyroxine (T4), free T4, and free T4 index (FTI) also are affected in variable degrees based on the severity and duration of the NTI. As the severity of the NTI increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers.

TSH is affected in variable degrees, but, in the overwhelming majority of patients, TSH is above 0.05 µIU/mL. In severe, critical illness, most patients have reduced T4 levels. In patients hospitalized for NTI, about 10% have abnormally low TSH values; the highest incidence occurs in the most severely ill group. In the sickest patients who manifest low T4, TSH elevates to hypothyroid levels at the recovery phase, returning to reference range levels with complete recovery. These changes in thyroid function test results are observed in most of the acute and chronic illnesses. Examples of illness include the following:

- Gastrointestinal diseases
- Pulmonary diseases
- Cardiovascular diseases
- Renal diseases
- Infiltrative and metabolic disorders
- Inflammatory conditions
- Myocardial infarction
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation

Alterations in thyroid function test findings may reflect changes in production of thyroid hormone by effects on the thyroid itself, on the hypothalamic-pituitary-thyroid axis, on peripheral tissue metabolism of the hormones, or a combination of these effects.

A general conviction exists that patients with thyroid function test result abnormalities do not have hypothyroidism despite the low serum hormone levels in blood and low T3 in most of the tissues. Many patients with NTI also receive drugs that affect thyroid hormone regulation and metabolism. This discussion does not consider pharmacological interference an intrinsic part of the spectrum of changes in hypothalamic-pituitary-thyroid function that occur in NTI. Consider pharmacological interferences as part of the evaluation of a patient with thyroid function test result abnormalities.

Pathophysiology

Proposed mechanisms explaining abnormalities in thyroid hormone levels

Accuracy of test assays in nonthyroidal illness

Abnormalities of thyroid function test results might represent test artifacts or true abnormalities. According to one proposition, the assays would indicate reference range thyroid hormone levels in the blood if appropriate tests were applied.

Inhibition of thyroid hormone binding to thyroid-binding proteins and tissues

Some authors propose that serum thyroid hormone abnormalities are due to inhibition of thyroid hormone binding to proteins, thus preventing tests from appropriately reflecting free hormone levels. This binding inhibitor can be present both in the serum and in body tissues and might inhibit uptake of thyroid hormones by cells or prevent binding to nuclear T3 receptors, thus inhibiting the action of the hormone. This inhibitor is associated with the nonesterified fatty acid (NEFA) fraction in the serum.

Contrary to this proposition, substantial evidence indicates that, in an in vivo state, the levels of binding inhibitors do not reach levels sufficient to influence the circulating levels of free T4, even in patients who are severely ill. Also, some studies have failed to demonstrate an existing binding inhibitor.

Cytokines

Cytokines are thought to play a role in NTI—particularly interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, and interferon-beta. Cytokines are thought to affect the hypothalamus, the pituitary, or other tissues, inhibiting production of TSH, thyroid-releasing hormone (TRH), thyroglobulin, T3, and thyroid-binding globulins. Cytokines are also thought to decrease the activity of type I deiodinase and to decrease the binding capacity of T3 nuclear receptors.

Deiodination

Peripheral deiodination of T4 to T3 is impaired, largely secondary to decreased activity of type I deiodinase enzyme, which deiodinates T4 to T3. Diminished enzyme activity accounts for decreased deiodination of T4 to T3.

An alternative explanation is that reduced tissue uptake of T4 secondary to deficiency of cytosolic cofactors (eg, nicotinamide adenine dinucleotide phosphate [NADPH], glutathione) results in decreased substrate for type I deiodinase enzyme. Type I deiodinase is a selenoprotein; because selenium deficiency is common in critically ill patients, some propose that selenium deficiency may contribute to type I deiodinase malfunction. Cytokines (eg, IL-1 beta, TNF-alpha, interferon-gamma) decrease type I deiodinase messenger RNA (mRNA) in vitro. Type I deiodinase does not exist in the pituitary, where T3 levels are within the reference range, because of enhanced local deiodination. This indicates that an enhancement of intrapituitary T4 to T3 conversion exists due to pituitary-specific and brain-specific type II deiodinase.

Inhibition of thyroid-releasing hormone and thyroid-stimulating hormone secretion

Cytokines, cortisol, and leptin, as well as changes in brain thyroid hormone metabolism, affect inhibition and secretion of TRH and TSH.

Inhibition of plasma membrane transport of iodothyronines

Serum factors, such as bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, which are present in various NTIs, have been shown to inhibit transport of thyroid hormones.

Thyroxine-binding globulin decrease and desialation

T4-binding globulin (TBG) is a member of the serine protease inhibitors. Diminished T4 in NTI has been proposed to be due to low TBG caused by protease cleavage at inflammatory sites in acute inflammatory conditions. One other hypothesis for the cause of disproportionately low serum T4 concentrations in patients with NTI is the presence of abnormal serum binding due to desialation of TBG.

The effects of nonthyroidal illness

Triiodothyronine and reverse triiodothyronine

In healthy people, 20% of T3 production comes from thyroidal secretion and 80% from peripheral deiodination from T4. In NTI, thyroidal production of T3 is normal, but the peripheral production of T3 is decreased. The fractional rate of transport of T3 to tissues is unaltered. Production of T3 is decreased, but its clearance is unchanged. Production of rT3 is unchanged, while its clearance is diminished.

In rat hepatocytes, rT3 and T4 have been demonstrated to be transported in the same mechanism, which implies that a diminished transport of rT3 to the liver would accompany inhibition of transport of T4 to the liver (eg, as in during calorie deprivation). Because the liver is the main site of disposal of T3, this leads to a diminished metabolic clearance rate of rT3 and T4.

Another explanation could be reduced 5'-deiodinase tissue activity, resulting in decreased T3 production from T4 and reduced breakdown of rT3. The decreased production of T3 during early and late starvation has been explained as either a diminished activity of the enzyme (deiodinase) itself or a deficiency of cytosolic cofactors, such as NADPH or glutathione. Specific deiodinative enzymes, 3 of which have been identified, affect deiodination of iodothyronines. Type I deiodinase is present in the liver, kidney, and thyroid and affects both 5 and 5' deiodination of T3. Type II deiodinase is present in the brain, pituitary, and brown adipose tissue and is active only in 5' deiodination. Type III deiodinase is found particularly in the brain, skin, and placenta, and it deiodinates iodothyronines at the 5 locations.

Both type II and type III enzymes are insensitive to 6-propylthiouracil (PTU). Alterations of serum thyroid hormone parameters in cases of calorie deprivation exhibit similarities to the changes observed in NTI. Fasted animals had decreased 5'-deiodinase activity. The activity of type I deiodinase is inhibited by 6-PTU. Because it is a selenoprotein and selenium deficiency is common in critically ill patients, selenium deficiency also may contribute to its malfunction.

Cytokines, such as IL-1 beta, TNF-alpha, and interferon-gamma, decrease type I deiodinase mRNA in vitro. Infusion of TNF-alpha decreases serum T3 and increases rT3. Soluble TNF-alpha, soluble TNF-alpha receptor, soluble IL-2 receptor antagonist, and IL-6 are inversely correlated with serum T3 levels. The elevations of soluble TNF-alpha receptor and IL-6 were independent determinants of serum T3 and accounted for 35% and 14%, respectively, of the change in T3. These cytokine changes can be concluded to occur concomitantly with changes in T3 and may play a pathogenic role through mechanisms that are not clearly defined. The increase of endogenous cortisol during illness apparently is not involved in inhibition of type I deiodinase.

Using an adenovirus model in mice hepatocyte primary cultures, it was demonstrated that forced expression of steroid receptor co-activator 1 (SRC-1) prevented the cytokine induced inhibition of type 1 deiodinase activity, suggesting the involvement of receptor co-activators in the nonthyroidal illness.[1]

Free triiodothyronine

Most studies have found free T3 hormones to be depressed.

Thyroxine

The decrease in the T4 binding of TBG has been used as an explanation for the low plasma T4 concentration in patients with NTI. The existence of a binding inhibitor could explain the observed alterations in T4 and free T4 fraction. TBG levels usually are within the reference range in patients with NTI and are somewhat lower in critically ill patients with low serum T4. Low TBG levels can be explained, according to some proposals, by rapid protease cleavage at inflammatory sites, particularly in acute inflammatory states (in which the decrease in TBG is too rapid to be accounted for by inhibition of synthesis).

In patients with NTI, serum T4 concentration has been demonstrated to be low because much of the circulating TBG in these patients is desialated. In NTI, the fractional rate of T4 transport from serum to tissues is reduced to 50% of the reference range value. This decrement in fractional rate of T4 transport is not related to the serum levels of total or free T4. Because in illness the reduction in the fractional rate of T4 transport from serum to tissues cannot be attributed to alterations in serum T4 binding, consider other causes such as an impairment of transport into tissues. In nonuremic critical illness, it has been demonstrated that elevated bilirubin or elevated NEFA and low albumin concentration may be at least partially responsible for the T4 transport inhibition in T3-producing tissues (eg, the liver).

A correlation exists between the probability of death and the levels of total T4. When serum T4 levels drop below 4 mcg/dL, the probability of death is about 50%; with serum T4 levels below 2 mcg/dL, the probability of death reaches 80%.

Free thyroxine

Evaluating thyroid function in patients with NTI has considerable challenges. No consensus exists as to whether free T4 levels are within the reference range, low, or high. Free T4 is believed to represent the hormone available to tissues. Measurement of total serum T4 has only limited value because nearly all (99.97%) of the circulating T4 is bound to TBG, T4-binding prealbumin (TBPA), and albumin. The rest of the circulating T4 (0.2-0.03%) is free T4. The circulating concentration of these binding proteins is understood to affect the total T4 concentration without necessarily changing the amount of free T4. Usually, TBG levels are within the reference range in patients with NTI and somewhat lower in critically ill patients with low serum T4. Decreased concentrations of one or more of the binding proteins would explain low levels of total T4 but does not explain a significant increase in free T4 fraction, which some patients with NTI exhibit.

Various explanations for the existence of inhibitors of T4 binding have been reported. Although low levels of TBPA and albumin may occur in patients with NTI, even complete inhibition of T4 binding to these proteins has been demonstrated to produce only about a 30% increase in free T4 fraction. Because free T4 fraction is increased above this level in many patients, other

factors must be present. The observations of reduced total T4 and free T4 have been explained alternatively as either a fall in TBG levels or an inhibition of thyroid hormone binding to TBG. Some studies have shown a decrease in the T4 binding of TBG, which has been used as an explanation for the low plasma T4 concentration and, perhaps, the high free T4 fractions, in patients with NTI. Other studies postulate the existence of a binding inhibitor that could explain the observed alterations in free T4 fraction.

The inhibitor also has been demonstrated to interfere with the binding of iodothyronines to solid matrices, thus interfering with the T3 resin uptake and explaining the low FTI found in patients with NTI. The inhibitor appears to be extractable with ether and was associated with the NEFA fraction in the serum. Furthermore, the extracted inhibitor from sera of patients with NTI reduced conversion of T4 to T3 in rat liver homogenates. The inhibitor could be extracted from extrathyroidal tissues as well.

The addition of NEFA to normal serum is able to raise the free T4 fraction only if total NEFA concentration is higher than 3 millimoles in normal serum, representing a NEFA-to-albumin molar ratio greater than 5:1. Because this high NEFA-to-albumin ratio is not reached even in severely ill patients, NEFA is unlikely to influence the circulating free T4 concentration in vivo. Inhibitors of binding were also observed during equilibrium dialysis assay in patients treated with heparin. This is due to an in vitro artifact that is not present in vivo.

Cytokines also can elevate free T4. When TNF-alpha was infused, it was observed that free T4 could elevate transiently in association with a significant rise in free fatty acids. However, other studies question the role of NEFA inhibition or whether any thyroid hormone–binding inhibitor exists at all.

Thyroid hormone receptor expression and DNA binding

In experimental mouse liver models, infection decreased thyroid hormone receptor (TR) expression as well as retinoid X receptor (RXR)–TR DNA binding. TR-alpha and TR-beta protein levels were both decreased when lipopolysaccharide was administered, particularly at 16 hours. Lipopolysaccharide exposure was also shown to reduce RXR protein levels in the liver.[2]

Methods used to measure free thyroxine and their comparison

An ongoing controversy concerns true free T4 levels in NTI. Various studies use different techniques to measure free T4 in NTI, but all methods have been challenged. Using these methods, free T4 has been found to be within the reference range, low, and high. The results of free T4 assays in NTI are method dependent and may be influenced by many variables.

Several methods can be used to measure free T4 directly, including equilibrium dialysis, a 2-step immunoextraction technique, a 1-step (analog) method, FTI (T3 resin-binding ratio), and ultrafiltration. Equilibrium dialysis

usually is the reference method. In equilibrium dialysis, a small amount of radioactive tracer T4 and the unknown sample are placed in a dialysis membrane, which limits the diffusion of bound T4. The proportion of the hormone that is dialyzable (ie, free) is determined. The dialyzable hormone–to–total hormone ratio is used, with the concentration of T4 determined in a standard assay and then used to calculate the concentration of free T4.

A second type of assay is the 2-step radioimmunoassay (RIA). The patient's serum is equilibrated with a solid phase antibody to T4. The unoccupied antibody binding sites are quantified in a second step in which labeled hormone is added to the solid phase system. The 2-step assay appears to have the best correlation with equilibrium dialysis results.

The 1-step (analog) assay uses an analog, usually an alanine substitution for T4. The analog does not bind to proteins in the serum but does compete for binding with antibody to T4. The analog also binds to albumin, which has a low affinity but high capacity; therefore, if albumin concentration changes, then free T4 measurements change (ie, if albumin increases, free T4 decreases and vice versa). Such changes can produce spurious results. This technique is not used widely.

An FTI is calculated by multiplying the total T4 concentration by the T3 uptake (T3U). The T3U is an indirect estimate free T4 fraction, which is obtained by adding labeled T3 to serum and estimating how much of it remains free for binding to a secondary binder (eg, charcoal, talc, ion-exchange resin, anti-T3 antibody, immobilized albumin) added to the serum. In this way, the FTI reflects the actual free T4 concentration, although this appears to be less accurate in cases of very low or high TBG concentrations. The use of FTI had poor reliability in patients with NTI; both artificially low and high FTI values were encountered frequently. This discrepancy in reported results probably is attributable to differences in patient selection (eg, the severity of illness and drugs used that interfere with serum T4 binding). These findings seriously limit the usefulness of the FTI tests in patients with NTI.

The ultrafiltration method is a research assay in which ultrafiltrates of undiluted serum are used to measure free T4. In a study by Docter et al (1993) of 504 patients, free T4 was elevated in 54% of the patients with mild-to-severe NTI, according to measurements using equilibrium dialysis, and free T4 was elevated in about 24% of patients in the most severely ill group (see Image 1).[3] Another study by Melmed et al (1982) demonstrated that free T4 was reduced in ICU patients as measured by 6 different methods, including equilibrium dialysis.[4] Free T4 was found to be uniformly reduced as measured by all methods, but patients with liver disease and chronic renal failure exhibited more variable results. This study demonstrated that, overall, patients with NTI who have serum total T4 levels within the reference range typically do not have reduced free T4 by most assay methods.

In an extensive comparison of 5 measurement methods, free T4 was extremely low in patients with NTI who had a serum level of total T4 less than 3 mcg/dL. Results obtained using ultrafiltration also are variable. Thus,

although extensively studied, the question remains whether free T4 in patients with NTI actually is low, within the reference range, or even high.

Thyroid-stimulating hormone and thyroid-releasing hormone

Serum TSH is measured with immunometric assays. In describing a serum TSH assay, referring to its sensitivity in µU/L is preferable to using terms such as ultrasensitive or supersensitive.

Immunometric assays in general perform well, but the sensitivity of the same commercial kit assay in different laboratories can vary substantially. In this method, 2 monoclonal antibodies are used, between which TSH becomes "sandwiched." Usually, the antibody to which TSH first is bound is immobilized on a solid surface. After separation of the solid phase, the bound TSH is quantified with a second anti-TSH antibody labeled with iodine-125, an enzyme, a fluorescent probe, or a chemiluminescent tag. In general, the assays using a chemiluminescent principle seem to perform best. Serum TSH in NTI typically is within the reference range or reduced. Serum TSH may be markedly low, although it usually is not less than 0.05 µIU/mL. These low TSH levels are often observed without significant decrease in T4.

Some patients with NTI have slightly elevated serum TSH, which is thought to have reduced biological activity. After recovery from severe NTI, transient elevation of TSH to above-normal limits commonly occurs. Some authors interpret this TSH elevation as a sign of recovery from a hypothyroid state. Despite the distortion of TSH in some euthyroid patients with NTI, patients with NTI who have significant elevation of TSH usually have underlying primary hypothyroidism.

Responsiveness of the pituitary to TRH during NTI varies; some patients respond normally, while many have a less-than-normal response. Normal responsiveness in the presence of low TSH may suggest that a hypothalamic abnormality is causing the low TSH and low T4. The down-regulation at the hypothalamus-pituitary level provides an explanation for the decreased sensitivity of TSH secretion to low serum T3 and T4 concentrations in patients with NTI. A diminution, or loss, of the diurnal rhythm of TSH also occurs, and some studies have produced evidence for a reduction of TSH glycosylation with lower TSH bioactivity.

That TSH is not elevated in the presence of low T4 indicates that the patients are not hypothyroid. Diminished release of TRH also is thought perhaps to result in low TSH and, thus, low output of thyroid hormones by the thyroid. Low TRH mRNA in hypothalamic paraventricular nuclei also has been demonstrated.

The role of cytokines, especially IL-1 beta, in the activity of the hypothalamic-pituitary-adrenal axis is well known. Cytokines also affect TRH in rats. IL-1 beta decreases the release of TSH in cultured rat anterior pituitary cells, but the role of TNF-alpha on TSH release is disputed. IL-6 decreases TSH secretion. In rodents, leptin has been demonstrated as a major mediator of

changes in hypothalamic-pituitary-thyroid function during fasting. However, TSH secretion and thyroid gland function are less affected during NTI in humans than they are in animals. The role of leptin in patients with NTI is unclear. Leptin concentrations often are elevated during critical illness and increase acutely in response to administration of TNF-alpha or IL-1; however, the leptin increase is not related to changes in serum T3 and T4 concentrations.

Frequency

The frequency of thyroid function abnormalities is related to the magnitude of the illness. The most common abnormality is a T3 reduction, occurring in about 40-100% of cases of NTI, which parallels the increase of rT3. As the disease severity increases, T4 levels also decrease. Most patients who are critically ill have reduced T4 levels. In patients who are hospitalized with an NTI, about 10% have abnormally low TSH values. The highest incidence occurs among the most severely ill group.

Mortality/Morbidity

Mortality and morbidity depend on the underlying NTI, the severity, and, possibly, the duration of the illness. The magnitude of the thyroid function test result abnormalities seems to depend on the severity, rather than the type, of illness. T4 is believed to fall in proportion to severity of illness.

The probability of death correlates with the levels of T4. When serum total T4 levels drop below 4 mcg/dL, the probability of death is about 50%; with serum T4 levels below 2 mcg/dL, the probability of death reaches 80%.

Causes

- Multiple explanations have been proposed for the causes of NTI.
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    - Accuracy of test assays in NTI
    - Cytokines
    - Deiodination
    - Inhibition of TRH and TSH secretion
    - Inhibition of plasma membrane transport of iodothyronines
    - Thyroid-binding globulin decrease/desialation
    - Reduction in TR expression as well as DNA binding
- Drugs that influence thyroid function

Other Problems to be Considered

Drugs that influence thyroid function include the following:

Drugs that decrease thyroid-stimulating hormone secretion

Dopamine
Glucocorticoids
Octreotide

Drugs that decrease thyroid hormone secretion

Lithium
Iodide
Amiodarone
Aminoglutethimide

Drugs that increase thyroid hormone secretion

Iodide
Amiodarone

Drugs that decrease thyroxine absorption

Colestipol
Cholestyramine
Aluminum hydroxide
Ferrous sulphate
Sucralfate

Drugs that alter thyroxine and triiodothyronine transport in serum (increased serum thyroxine-binding globulin concentration)

Estrogens
Tamoxifen
Heroin
Methadone
Mitotane
Fluorouracil

Drugs that alter thyroxine and triiodothyronine transport in serum (decreased serum thyroxine-binding globulin concentration)

Androgens
Anabolic steroids
Slow-release nicotinic acid
Glucocorticoids

Drugs that alter thyroxine and triiodothyronine transport in serum (displacement from protein-binding sites)

Furosemide
Fenclofenac
Mefenamic acid
Salicylates

Drugs that alter thyroxine and triiodothyronine metabolism (increased hepatic metabolism)

Phenobarbital
Rifampin
Phenytoin
Carbamazepine

Drugs that alter thyroxine and triiodothyronine metabolism (decreased thyroxine 5'-deiodinase activity)

Propylthiouracil
Amiodarone
Beta-adrenergic antagonist drugs

Conditions that affect thyroid function tests

Certain thyroid function test result abnormalities also have been characterized in the conditions and NTIs discussed as follows:

- Effect of heat: Induction of increased temperature in patients with primary hypothyroidism results in demonstrable decreases in serum TSH, and thyroid hormone secretion may be less in summer than winter. Acute exposure to heat decreases serum T3 and causes reciprocal elevation of rT3. Both total T3 and free T3 commonly are decreased in patients who are hyperpyrexic.
- Thermal injury: Patients with significant burns exhibit typical euthyroid sick profile values, ie, low T3 and FT3 with increased rT3; total T4 and free T4 levels may be slightly decreased acutely but normalize after a few days. Basal TSH secretion is unchanged.
- Effects of cold: After acute cold exposure, rats have demonstrated increased serum levels of TSH and thyroid hormone; similar changes have been more difficult to demonstrate in humans. Cold exposure is associated with increased rates of deiodination of T4 and T3, enhanced hepatic binding and biliary and fecal clearance of the iodothyronines, and increased conversion of T4 to T3. A transient increase in TSH also occurs after exposure to cold.
- Fasting and/or starvation: Total T4 usually remains unchanged, but thyroidal secretion might be diminished. Free T4 may remain unchanged, or it may elevate due to decreased binding of T4 secondary to an increase in free fatty acids, which elevate during starvation. Serum total T3 and free T3 levels decrease dramatically. rT3 generally is elevated, and basal TSH secretion is diminished. TSH response to TRH also is diminished.
- Protein/calorie malnutrition: Starvation alters the results of thyroid function tests. Total T4 is reduced, free T4 is unchanged, total T3 is reduced significantly, free T3 is reduced, and rT3 is elevated significantly. Basal TSH either is unchanged or elevated. A delay of TSH to TRH stimulation is exaggerated.

- Obesity: Obesity affects thyroid function only minimally. Total T3 might be elevated.
- Surgery: Total T3 falls dramatically on the day of surgery and remains significantly decreased postoperatively. The degree of the fall is related to the severity of surgical trauma. An absolute percent increase of free T3 also occurs on the day of the surgery. The free T3 concentration rapidly falls to low levels postoperatively, paralleling the decline in total T3. T4 usually is not altered on the day of surgery. One study demonstrated that total T4 decreased during surgery with epidural anesthesia but increased with general anesthesia. The percent of free T4 increases during surgery and decreases postoperatively.

  TSH has been found to be unchanged during surgery, except with hypothermic surgery, where TSH increased. In a 2001 study by Michalaki, in patients who underwent abdominal surgery, the decline of serum T3 was not correlated with the increase of serum IL-6 or TNF-alpha levels; rather, brisk cortisol response to surgery was postulated to explain, in part, the early decrease in serum T3 levels in sick euthyroid syndrome.[5]
- Myocardial infarction: In 1-3 days postinfarction, total T3 is low, rT3 is elevated, and basal TSH might be elevated.
- Renal disease: The thyroid hormones may be affected by renal function in a variety of ways considering the heterogeneity of renal dysfunction and variations in renal function, which may have profound effects on thyroidal economy. Variation in thyroid function test findings also depends on the severity and duration of the disease. In chronic renal failure, total T4 and free T4 can be either normal or elevated, total T3 is reduced significantly, free T3 is reduced, rT3 is unchanged, basal TSH can be unchanged or elevated, and TSH response to TRH stimulation is decreased or delayed. Many of these abnormalities are reversed with kidney transplantation.

  In nephrotic syndrome, clinical presentation and thyroid function test findings mimic hypothyroidism. Total T4 and free T4 levels can be normal or reduced (significant proteinuria or loss of TBG and concomitant steroid administration can explain reduced T4). Total T3 is reduced significantly, free T3 is reduced, and rT3 is unchanged. In contrast to primary hypothyroidism, basal TSH either is unchanged or increased slightly, while TSH response to TRH is decreased and delayed.
- Liver disease: Abnormalities of thyroid function test results are common in patients with liver disease. These abnormalities vary depending on the type and severity of the liver disease. The liver probably is the most important site for conversion of T4 to T3; decreases in T3 generation may reflect a direct effect of liver disease on the deiodinative process rather than an indirect effect of systemic illness. Liver disease affects thyroid hormone transport in blood significantly because synthesis of all 3 of the binding proteins, ie, TBG, TBPA, and albumin, occurs in the liver. In cirrhosis, thyroid function test result abnormalities depend on the amount of residual functional liver

tissue. Generally, total T4 is unchanged or reduced, free T4 is unchanged or elevated, free T3 is reduced or unchanged, and rT3 is elevated. In contrast to most of the other low T3 syndrome categories, basal TSH may be elevated.

- Infectious hepatitis: In infectious hepatitis, the abnormalities are not the common ones. Total T4 often is unchanged. Total T4 is elevated when TBG is increased. Free T4 may be reduced, total T3 is increased, free T3 is decreased, rT3 is unchanged, and basal TSH is increased. TSH response to TRH is exaggerated.
- Chronic active hepatitis and primary biliary cirrhosis: In these cases, serum levels of TBG are increased, resulting in increased levels of total T4 and T3 and decreased T3 resin uptake. In contrast to patients with cirrhosis, decreased free T4 and free T3 levels, elevated basal TSH, and unchanged rT3 levels are present. TSH response to TRH stimulation is exaggerated.
- Infection: In humans, serum T4 and T3 levels fall shortly after the onset of clinical infection. This reflects decreased TSH stimulation of the thyroid, decreased thyroidal secretion, accelerated T4 disappearance, and inhibited hormone binding to transport proteins. With recovery, TSH release resumes, and T4 and T3 levels progressively rise.
- Human immunodeficiency virus infection: Patients with asymptomatic HIV infection, or AIDS, and without opportunistic infections or hepatic dysfunction have serum T4 and T3 concentrations within the reference range. Their FTI values and free T4 concentrations also are within the reference range or are slightly low. Some patients may have slightly elevated TBG concentrations, which tend to be inversely related to the percentage of CD4 cells. Some patients may have small increases in serum TSH concentrations. Patients with AIDS complicated with *Pneumocystis carinii* infection or other serious infections have thyroid function alterations typical of other severe NTI.
- Bone marrow transplantation: Thyroid dysfunction is observed usually as a late complication after bone marrow transplantation. In an interesting 2001 study by Kami, transient thyrotoxicosis was observed in 7 of 52 patients at a median time of 111 days. Six months after bone marrow transplantation, 24 patients had developed euthyroid sick syndrome. After 1 year, 8 patients were diagnosed with hypothyroidism and 9 patients were diagnosed with euthyroid sick syndrome.[6]
- Malignancy: The severity, the type, and the stage of malignancy affect a thyroid function test in various ways. Effects on thyroid function test results also are associated with nutritional status, medications, and treatment types. Generally, total T4 is unchanged, free T4 is increased or unchanged, total T3 is decreased, free T3 is unchanged, rT3 is elevated, basal TSH is unchanged, and TSH response to TRH is unchanged.
- Subarachnoid hemorrhage: In a study in Brazil, subarachnoid hemorrhage due to ruptured intracranial aneurysm was demonstrated to cause changes in the thyroid hormone profile, particularly causing a reduction in serum T3 and free T4. No significant difference was noted in the serum levels of total T4 and TSH levels. The control group included patients who underwent surgery for benign spine disease.[7]

- Psychiatric illness: The alterations in thyroid function test results are varied and confusing. The factors that cause alterations in thyroid function test results, such as the specific psychiatric illness, age of the patient, stage of the patient's illness, concomitant medications, and the presence of other thyroidal illnesses and NTIs, are variable. In primary depression, total T4 can be elevated or unchanged, free T4 can be elevated or unchanged, total T3 is unchanged, free T3 is unchanged, rT3 is elevated, basal TSH is unchanged, and TSH response to TRH is decreased. One of the most common abnormalities in thyroid function test findings in acute psychiatric admissions is an elevation of FTI (7-9% of patients). This is secondary to a transient increase in T4, which is rare in other diseases. Elevated total T4 and FTI normalize after treatment.

  The TRH response is blunted in depression but not in schizophrenia. In a 2006 study, out of 250 subjects with major psychiatric depression, 6.4% exhibited low T3 syndrome and these were not ascribed to malnutrition or any other illness and the metabolic parameters were all normal.[8]
- Anorexia nervosa: This disease has aspects similar to starvation and hypothyroidism. Dry skin, bradycardia, hypothermia, constipation, and amenorrhea can be signs and symptoms. A hypothalamic defect in TRH release is present. In this disorder, total T4 is decreased, and free T4 usually is not changed. Total T3 is reduced significantly, but free T3 usually is unchanged. rT3 is elevated, and basal TSH is not changed, but a late peak of TSH in response to TRH occurs.

Lab Studies

- Typical NTI findings are T4 level within the reference range, low T3 level, slightly reduced or reference range level of TSH, elevated rT3 level, and a free T4 level that is within the reference range or is elevated.
- In severe NTI, the findings are low T4, low T3, reduced TSH, elevated rT3, and free T4 that is within the reference range or is diminished.
- Recommended tests include the following:
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    - Total T4
    - Total T3
    - TSH
    - Free T4
    - rT3
    - Free T3
- Refer to specific nonthyroidal diseases for particular alterations in thyroid function test results.