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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Hypothyroidism, also called **underactive thyroid** or **low thyroid**, is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain. Occasionally there may be swelling of the front part of the neck due to goiter. Untreated hypothyroidism during pregnancy can lead to delays in growth and intellectual development in the baby, which is called cretinism.

Worldwide, too little iodine in the diet is the most common cause of hypothyroidism. In countries with enough iodine in the diet, the most common cause of hypothyroidism is the autoimmune condition Hashimoto's thyroiditis. Less common causes include: previous treatment with radioactive iodine, injury to the hypothalamus or the anterior pituitary gland, certain medications, a lack of a functioning thyroid at birth, or previous thyroid surgery. The diagnosis of hypothyroidism, when suspected, can be confirmed with blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine levels.

Prevention at the population level has been with the universal salt iodization. Hypothyroidism can be treated with levothyroxine. The dose is adjusted according to symptoms and normalization of the thyroxine and TSH levels. Thyroid medication is safe in pregnancy. While a certain amount of dietary iodine is important, excessive amounts can worsen certain types of hypothyroidism.

Worldwide about one billion people are estimated to be iodine deficient; however, it is unknown how often this results in hypothyroidism. In Western countries, hypothyroidism occurs in 0.3–0.4% of people. Subclinical hypothyroidism, a milder form of hypothyroidism characterized by normal thyroxine levels and an elevated TSH level, is thought to occur in 4.3–8.5% of people. Hypothyroidism is more common in women than men. People over the age of 60 are more commonly affected. Dogs are also known to develop hypothyroidism and in rare cases cats and horses can also have the disorder. The word "hypothyroidism" is from Greek *hypo-* meaning "reduced", *thyreos* for "shield", and *eidos* for "form." The **DISEASE DIAGNOSIS** segment of this issue delves deep into all aspects of hypothyroidism.

INTERPRETATION, interprets thyroid function tests and **TROUBLE SHOOTING** simplifies 5 atypical patterns of TFTs for you.

DISEASE DIAGNOSIS

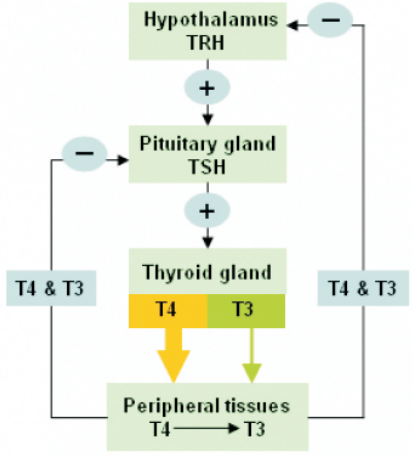
HYPOTHYROIDISM

Background

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. It usually is a primary process in which the thyroid gland is unable to produce sufficient amounts of thyroid hormone. Hypothyroidism can also be secondary—that is, the thyroid gland itself is normal, but it receives insufficient stimulation because of low secretion of thyrotropin (ie, thyroid-stimulating hormone [TSH]) from the pituitary gland. In tertiary hypothyroidism, inadequate secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus leads to insufficient release of TSH, which in turn causes inadequate thyroid stimulation. Worldwide, iodine deficiency remains the foremost cause of hypothyroidism. In the United States and other areas of adequate iodine intake, autoimmune thyroid disease (Hashimoto disease) is the most common cause. Hypothyroidism may also be drug-induced or otherwise iatrogenic. The patient's presentation may vary from asymptomatic to myxedema coma with multisystem organ failure. Because nearly all metabolically active cells require thyroid hormone, deficiency of the hormone has a wide range of effects. Classic signs and symptoms, such as cold intolerance, puffiness, decreased sweating, and coarse skin, may not be present, especially in younger patients. Third-generation TSH assays are readily available and are generally the most sensitive screening tool for primary hypothyroidism. The generally accepted reference range for normal serum TSH is 0.40-4.2 mIU/L. If TSH levels are above the reference range, the next step would be to measure free thyroxine (T4). Subclinical hypothyroidism, also referred to as mild hypothyroidism, is defined as normal serum levels of free T4 and triiodothyronine (T3) with a slightly high serum TSH concentration. For hypothyroidism, thyroid hormone is administered to supplement or replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT4). Congenital hypothyroidism, which affects 1 of every 4000 newborns, is due to congenital maldevelopment of the thyroid. This disorder is included in the newborn screening panel in the United States and many other countries, and it is readily treatable once detected. Cretinism refers to severe hypothyroidism in an infant or child. This is classically the result of maternal iodine deficiency, and thankfully is increasingly rare.

Pathophysiology

The hypothalamic-pituitary-thyroid axis governs thyroid hormone secretion (see the image below).



The hypothalamic-pituitary-thyroid axis. Levels of circulating thyroid hormones are regulated by a complex feedback system involving the hypothalamus and pituitary gland. Although hypothalamic or pituitary disorders can affect thyroid function, localized disease of the thyroid gland that results in decreased thyroid hormone production is the most common cause of hypothyroidism. Under normal circumstances, the thyroid releases 100-125 nmol of T4 daily and only small amounts of T3. The half-life of T4 is approximately 7-10 days. T4, a prohormone, is converted to T3, the active form of thyroid hormone, in the peripheral tissues by 5'-deiodination. Early in the disease process, compensatory mechanisms maintain T3 levels. Decreased production of T4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and 5'-deiodinase activity, thereby increasing T3 production. Deficiency of thyroid hormone has a wide range of effects. Systemic effects are the result of either derangements in metabolic processes or direct effects by myxedematous infiltration (ie, accumulation of glucosaminoglycans in the tissues). The hypothyroid changes in the heart result in decreased contractility, cardiac enlargement, pericardial effusion, decreased pulse, and decreased cardiac output. In the gastrointestinal (GI) tract, achlorhydria and prolonged intestinal transit time with gastric stasis can occur. Delayed puberty, anovulation, menstrual irregularities, and infertility are common. TSH screening should be a routine part of any investigation into menstrual irregularities or infertility. Decreased thyroid hormone effect can cause increased levels of total cholesterol and low-density lipoprotein (LDL) cholesterol and a possible change in high-density lipoprotein (HDL) cholesterol because of a change in metabolic clearance. In addition, hypothyroidism may result in an increase in insulin resistance.

Etiology

Wherever adequate iodine intake is seen, autoimmune thyroid disease (Hashimoto disease) is the most common cause of hypothyroidism. The prevalence of antibodies is higher in women and increases with age.

Primary hypothyroidism

Types of primary hypothyroidism include the following:

- Chronic lymphocytic (autoimmune) thyroiditis
- Postpartum thyroiditis
- Subacute (granulomatous) thyroiditis
- Drug-induced hypothyroidism
- Iatrogenic hypothyroidism

Chronic lymphocytic (autoimmune) thyroiditis

The most frequent cause of acquired hypothyroidism is chronic lymphocytic (autoimmune) thyroiditis (Hashimoto thyroiditis). The body considers the thyroid antigens as foreign, and a chronic immune reaction ensues, resulting in lymphocytic infiltration of the gland and progressive destruction of functional thyroid tissue. The majority of affected individuals will have circulating antibodies to thyroid tissue. Anti–thyroid peroxidase (anti-TPO) antibodies are the hallmark of this disease. It should be noted that antibody levels can vary over time, may not be present early in the disease process, and usually disappear over time. Given this change in antibody concentration, it should be understood that the absence of antibodies does not exclude the diagnosis of chronic lymphocytic (autoimmune) thyroiditis.

Postpartum thyroiditis

Up to 10% of postpartum women may develop lymphocytic thyroiditis (postpartum thyroiditis) in the 2-12 months after delivery. The frequency may be as high as 25% in women with type 1 diabetes mellitus. Although a short course of treatment with levothyroxine (LT4) may be necessary, the condition is usually transient (2-4 months). However, patients with

postpartum thyroiditis (anti-TPO–positive) are at increased risk of permanent hypothyroidism or recurrence of postpartum thyroiditis with future pregnancies. The hypothyroid state can be preceded by a short thyrotoxic state. High titers of anti-TPO antibodies during pregnancy have been reported to have high sensitive and specificity for postpartum autoimmune thyroid disease. In a 12-year longitudinal study, Stuckey et al found that hypothyroidism developed in 27 of 71 women (38%) who had a past history of postpartum thyroid dysfunction (PPTD). In comparison, only 14 of 338 women (4%) who had not had PPTD developed hypothyroidism.

Subacute granulomatous thyroiditis

Also known as de Quervain disease, subacute granulomatous thyroiditis is a relatively uncommon disease that occurs most frequently in middle-aged women. Disease features include low grade fever, thyroid pain, dysphagia, and elevated erythrocyte sedimentation rate (ESR). The disease is usually self-limited and does not normally result in longstanding thyroid dysfunction. It is important to note that inflammatory conditions or viral syndromes may be associated with transient hyperthyroidism followed by transient hypothyroidism (ie, de Quervain or painful thyroiditis and subacute thyroiditis).

Drug-induced and iatrogenic hypothyroidism

The following medications reportedly have the potential to cause hypothyroidism:

- Amiodarone
- Thalidomide
- Stavudine
- Perchlorate
- Ethionamide
- Phenytoin
- Phenobarbital
- Sulfisoxazole
- Ipilimumab
- Interferon alfa
- Lithium
- Bexarotene
- Interleukin (IL)-2
- Rifampin
- Carbamazepine
- Aminoglutethimide
- *p*-Aminosalicylic acid
- Oral tyrosine kinase inhibitors – Sunitinib, imatinib

Use of radioactive iodine (I-131) for treatment of Graves disease generally results in permanent hypothyroidism within 3-6 months after therapy. The frequency of hypothyroidism after I-131 treatment is much lower in patients with toxic nodular goiters and those with autonomously functioning thyroid nodules. Patients treated with radioiodine should be monitored for clinical and biochemical evidence of hypothyroidism. External neck irradiation (for head and neck neoplasms, breast cancer, or Hodgkin disease) may result in hypothyroidism. Patients who have received these treatments require monitoring of thyroid function. Thyroidectomy of course results in hypothyroidism. Patients who undergo a thyroid lobectomy, with or without isthmectomy, have an approximately 15-30% chance of developing thyroid insufficiency.

Genetics

Genome-wide association studies have suggested that a single-nucleotide polymorphism located near the *FOXE1* gene is associated with risk of developing thyroid disease and that the strongest association is with hypothyroidism. Persons found to have GG at the described location had an odds ratio (OR) of 1.35 for development of hypothyroidism, whereas persons found to have AG at the location had an OR of 1.00, and persons found to have AA at the location had an OR of 0.74. Approximately 10% of patients with congenital hypothyroidism have an error in thyroid hormone synthesis. Mutations in the *TPO* gene appear to be the most common error of hormone synthesis, causing failure to produce adequate amounts of TPO. Mutations in the *TSHR* and *PAX8* genes are known to cause congenital hypothyroidism without goiter. Mutations in the *TSHR* gene can cause hypothyroidism due to insensitivity to TSH, though most cases are notable for a clinically euthyroid state despite abnormal laboratory test results (elevated TSH with normal serum thyroid hormone concentrations). Mutations in the *PAX8* gene cause hypothyroidism due to dysgenesis or agenesis of the gland. Syndromic forms of hypothyroidism are also well described. Pendred syndrome is caused by a mutation in the *SLC26A4* gene, which causes a defect in the organification of iodine (ie, incorporation into thyroid hormone), congenital sensorineural hearing loss, and, usually, an enlarged thyroid gland. It is inherited in an autosomal recessive manner. Autoimmune polyendocrinopathy type I is caused by a mutation in the *AIRE* gene and is characterized by the presence of Addison disease, hypoparathyroidism, and mucocutaneous candidiasis. A subset of patients with this disease also have a high prevalence of autoimmune thyroiditis and hypothyroidism and a novel mutation in the *AIRE* gene that is inherited in an autosomal dominant fashion. Autoimmune polyendocrinopathy type 2 (Schmidt syndrome) is associated with adrenal insufficiency and hypothyroidism.

Iodine deficiency or excess

Worldwide, iodine deficiency is the most common cause of hypothyroidism. Excess iodine, as in radiocontrast dyes, amiodarone, health tonics (herbal and dietary supplements), and seaweed, can transiently inhibit iodide organification and thyroid hormone synthesis (the Wolff-Chiakoff effect). Most healthy individuals have a physiologic escape from this effect. In patients with iodine overload, the sodium-iodide symporter shuts down, and this allows intracellular iodine levels to drop and hormone secretion to resume. The Wolff-Chiakoff effect is short-lived because the sodium-iodide symporter is capable of rapidly downregulation. However, exposure to excess iodine can produce more profound and sustained hypothyroidism in individuals with abnormal thyroid glands (eg, from autoimmune thyroiditis, subtotal thyroidectomy, or prior radioiodine therapy).

Central hypothyroidism

Central hypothyroidism (secondary or tertiary) results when the hypothalamic-pituitary axis is damaged. The following potential causes should be considered:

- Pituitary adenoma
- Tumors impinging on the hypothalamus
- Lymphocytic hypophysitis
- Sheehan syndrome
- History of brain or pituitary irradiation
- Drugs (eg, dopamine, prednisone, or opioids)
- Congenital nongoiterous hypothyroidism type 4
- TRH resistance
- TRH deficiency

Tumors in or around the pituitary cause impaired pituitary function by exerting pressure on normal pituitary cells and thereby affect the secretion of TRH, TSH, or both. Radiation, hypophysitis, and Sheehan syndrome cause death of these cells. Drugs such as dopamine and corticosteroids result in decreased TSH secretion. Congenital nongoiterous hypothyroidism type 4 is caused by a mutation in the *TSHB* gene and is inherited in an autosomal recessive pattern. Patients have hypothyroidism and a low TSH level that does not rise with administration of TRH. Many patients with this condition were the products of consanguineous unions. TRH resistance is caused by a mutation in the *TRHR* gene and is inherited in an autosomal recessive manner. Patients with this condition have hypothyroidism and, unsurprisingly, have insensitivity to thyrotropin secretion. That only a handful of cases of TRH resistance have been reported in the literature suggests that this is a rare condition. TRH deficiency is caused by mutation in the *TRH* gene and is inherited in an autosomal recessive

manner. The index case was a girl evaluated for short stature who was found to have an isolated deficiency of TRH.

Epidemiology

Hypothyroidism is more common in women with small body size at birth and low body mass index during childhood. Iodine deficiency as a cause of hypothyroidism is more common in less-developed countries. Routine supplementation of salt, flour, and other food staples with iodine has decreased the rates of iodine deficiency. World Health Organization (WHO) data from 130 countries taken from January 1994 through December 2006 found inadequate iodine nutrition in 30.6% of the population. The WHO recommends urinary iodine concentrations between 100 and 199 µg/L in the general population and a range of 150-249 µg/L in pregnant women. In developed countries, death caused by hypothyroidism is uncommon.

Age-related demographics

The frequency of hypothyroidism, goiters, and thyroid nodules increases with age. Hypothyroidism is most prevalent in elderly populations, with 2-20% of older age groups having some form of hypothyroidism. The Framingham study found hypothyroidism (TSH > 10 mIU/L) in 5.9% of women and 2.4% of men older than 60 years. In NHANES 1999-2002, the odds of having hypothyroidism were 5 times greater in persons aged 80 years and older than in individuals aged 12-49 years.

Sex-related demographics

Community studies use slightly different criteria for determining hypothyroidism; therefore, female-to-male ratios vary. Generally, thyroid disease is much more common in females than in males, with reported prevalences ranging from 2 to 8 times higher in females.

History

Hypothyroidism commonly manifests as a slowing in physical and mental activity but may be asymptomatic. Symptoms and signs of this disease are often subtle and neither sensitive nor specific. Classic signs and symptoms (eg, cold intolerance, puffiness, decreased sweating, and coarse skin) may not be present as commonly as was once believed. Many of the more common symptoms are nonspecific and difficult to attribute to a particular cause. Individuals can also present with obstructive sleep apnea (secondary to macroglossia) or carpal tunnel syndrome. Women can present with galactorrhea and menstrual disturbances. Consequently, the diagnosis of hypothyroidism is based on clinical suspicion and confirmed by laboratory testing. Myxedema coma is a severe form of hypothyroidism that results in an altered mental status, hypothermia, bradycardia, hypercarbia, and hyponatremia. Cardiomegaly, pericardial effusion, cardiogenic shock, and ascites may be present. Myxedema coma most commonly occurs in individuals with undiagnosed or untreated hypothyroidism who are subjected to an external stress, such as low temperature, infection, myocardial infarction, stroke, or medical intervention (eg, surgery or hypnotic drugs).

The following are symptoms of hypothyroidism:

- Fatigue, loss of energy, lethargy
- Weight gain
- Decreased appetite
- Cold intolerance
- Dry skin
- Hair loss
- Sleepiness
- Muscle pain, joint pain, weakness in the extremities
- Depression
- Emotional lability, mental impairment
- Forgetfulness, impaired memory, inability to concentrate
- Constipation
- Menstrual disturbances, impaired fertility
- Decreased perspiration
- Paresthesias, nerve entrapment syndromes
- Blurred vision
- Decreased hearing
- Fullness in the throat, hoarseness

Hashimoto thyroiditis is difficult to distinguish clinically, but the following symptoms are more specific to this condition:

- Feeling of fullness in the throat
- Painless thyroid enlargement
- Exhaustion
- Transient neck pain, sore throat, or both.

Physical Examination

Signs found in hypothyroidism are usually subtle, and their detection requires a careful physical examination. Moreover, such signs are often dismissed as part of aging; however, clinicians should consider a diagnosis of hypothyroidism when they are present.

Physical signs of hypothyroidism include the following:

- Weight gain
- Slowed speech and movements
- Dry skin
- Jaundice
- Pallor
- Coarse, brittle, straw-like hair
- Loss of scalp hair, axillary hair, pubic hair, or a combination
- Dull facial expression
- Coarse facial features
- Periorbital puffiness
- Macroglossia
- Goiter (simple or nodular)
- Hoarseness
- Decreased systolic blood pressure and increased diastolic blood pressure
- Bradycardia
- Pericardial effusion
- Abdominal distention, ascites (uncommon)
- Hypothermia (only in severe hypothyroid states)
- Nonpitting edema (myxedema)
- Pitting edema of lower extremities
- Hyporeflexia with delayed relaxation, ataxia, or both

Additional signs specific to different causes of hypothyroidism, such as diffuse or nodular goiter and pituitary enlargement or tumor, can occur.

Diagnostic Considerations

Because the most frequent presenting symptoms of hypothyroidism are nonspecific, the list of differential diagnoses is long. In addition to diseases of other organ systems, the following thyroid disorders may deserve consideration:

- Anemia
- Autoimmune Thyroid Disease and Pregnancy
- Euthyroid Sick Syndrome
- Goiter
- Myxedema Coma or Crisis
- Riedel Thyroiditis
- Subacute (granulomatous, De Quervain) Thyroiditis
- Thyroid Lymphoma
- Thyroiditis, Subacute
- Thyroxine-Binding Globulin Deficiency
- Iodine Deficiency

Differential Diagnoses

- Addison Disease
- Anovulation
- Autoimmune Thyroid Disease and Pregnancy
- Cardiac Tamponade
- Chronic Fatigue Syndrome
- Chronic Megacolon
- Constipation
- De Quervain Thyroiditis
- Depression
- Dysmenorrhea
- Eosinophilia
- Eosinophilia-Myalgia Syndrome
- Erectile Dysfunction
- Euthyroid Sick Syndrome
- Familial Hypercholesterolemia
- Geriatric Sleep Disorder
- Goiter
- Hypoalbuminemia
- Hypochondriasis
- Hypopituitarism (Panhypopituitarism)
- Hypothermia
- Ileus
- Infectious Mononucleosis
- Infertility
- Iodine Deficiency
- Lithium Nephropathy
- Lithium-Induced Goiter
- Lymphomas, Endocrine, Mesenchymal, and Other Rare Tumors of the Mediastinum
- Male Infertility
- Menopause
- Myxedema Coma or Crisis
- Nontoxic Goiter
- Obesity
- Obstructive Sleep Apnea
- Ovarian Insufficiency
- Pericardial Effusion
- Pituitary Macroadenomas
- Polygenic Hypercholesterolemia
- Prolactin Deficiency
- Rehabilitation and Fibromyalgia
- Riedel Thyroiditis
- Sleep Disorders
- Surgery for Craniopharyngiomas
- Syndrome of Inappropriate Antidiuretic Hormone Secretion
- Thyroid Lymphoma
- Thyroiditis, Subacute
- Thyroxine-Binding Globulin Deficiency
- Type I Polyglandular Autoimmune Syndrome
- Type II Polyglandular Autoimmune Syndrome
- Type III Polyglandular Autoimmune Syndrome

Laboratory Studies

Third-generation thyroid-stimulating hormone (TSH) assays are readily available and are generally the most sensitive screening tool for primary hypothyroidism. The generally accepted reference range for normal serum TSH is 0.40-4.2 mIU/L. In one of the studies, of 17,353 people evaluated, 80.8% had a serum TSH below 2.5 mIU/L; TSH concentrations rose with advancing age. Certain physiologic conditions, such as illness, psychiatric disorders, and significant physical stress (eg. running a marathon), exposure to extremes in temperature, negative energy balance), can produce marked variations in TSH levels. If TSH levels are above the reference range, the next step is measure free thyroxine (T4). Another option is to measure total T4 and binding proteins. T4 is highly protein-bound (99.97%), with approximately 85% bound to thyroid-binding globulin (TBG), approximately 10% bound to transthyretin or thyroid-binding prealbumin, and the remainder bound loosely to albumin. The levels of these binding proteins can vary by hormonal status, inheritance, and in various disease states. Hence, free T4 assays, which measure unbound (ie, free) hormone, are becoming popular. However, free T4 assays can be unreliable in the setting of severe illness or pregnancy. Free T4 can be directly measured via equilibrium dialysis. Results are independent of binding protein concentrations. However, this test is more costly and generally takes longer to return. Free thyroid hormone levels can be estimated by calculating the percentage of available thyroid hormone-binding sites (triiodothyronine [T3] resin uptake, or thyroid hormone binding ratio [THBR]) or by measuring the TBG concentration. A free T4 index (FTI) serves as a surrogate of the free hormone level. The FTI is the product of T3 resin uptake and total T4 levels. In pregnancy, the variation in the results of commercially available free T4 assays has led the American Thyroid Association to recommend using method-specific and trimester-specific reference ranges for serum free T4. If these specific ranges are not available, TSH, total T4, and FTI can be used to monitor the pregnant patient. Patients with primary hypothyroidism have elevated TSH levels and decreased free hormone levels. Patients with elevated TSH levels (usually 4.5-10.0 mIU/L) but normal free hormone levels or estimates are considered to have mild or subclinical hypothyroidism. Primary hypothyroidism is virtually the only disease that is characterized by sustained rises in TSH levels. As the TSH level increases early in the disease, conversion of T4 to T3 increases, maintaining T3 levels. In early hypothyroidism, TSH levels are elevated, T4 levels are normal to low, and T3 levels are normal. Given this early protection of the T3 level, routine checking of T3 is not recommended if one suspects that a patient is hypothyroid. Drawing a reverse T3 is also not recommended as a routine part of the hypothyroidism workup. Assays for anti–thyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) antibodies may be helpful in determining the etiology of hypothyroidism or in predicting future hypothyroidism. However, once a patient has been found to be antibody positive, repeated antibody testing adds little to the clinical picture and thus is not recommended. In addition, anti-TPO antibodies have been associated with increased risk of infertility and miscarriage; levothyroxine (LT4) treatment may lower this risk. In patients with nonthyroidal disease, TSH secretion is normal or decreased, total T4 levels are normal or decreased, and total T3 levels are decreased to markedly decreased. This scenario can be confused with secondary hypothyroidism. In these patients, the primary abnormality is decreased peripheral production of T3 from T4. They have an increased reverse T3, which can be measured. Other abnormalities seen in patients who are critically ill include decreased TBG levels and abnormalities in the hypothalamic-pituitary axis. During recovery, some patients have transient elevations in serum TSH concentrations (up to 20 mIU/L). Hence, thyroid function should not be evaluated in a critically ill person unless thyroid dysfunction is strongly suspected, and if evaluation is warranted, screening with TSH alone is insufficient. When needed, however, multiple thyroid hormone measurements over time may assist with interpretation. In patients with hypothalamic or pituitary dysfunction, TSH levels do not increase in appropriate relation to the low free T4

levels. The absolute levels may be in the reference range or even slightly elevated while still being inappropriately low for the severity of the hypothyroid state. Hence, when secondary or tertiary hypothyroidism is suspected, measurement of serum TSH alone is inadequate; free T4 should also be measured. The TRH stimulation test is an older and rarely needed test for helping to assess pituitary and hypothalamic dysfunction. With the improvements in TSH and free T4 assays, TRH stimulation has become outmoded. In the United States, this medication is available only at the National Institutes of Health (NIH). The complete blood count and metabolic profile may show abnormalities in patients with hypothyroidism. These include anemia, dilutional hyponatremia, hyperlipidemia, and reversible increases in serum creatinine. Elevations in transaminases and creatinine kinase have also been found. Primary hypothyroidism causes an elevation of TRH, which can cause an elevation of prolactin along with TSH. Prolactin levels in patients with hypothyroidism tend to be lower than those usually seen with prolactinomas (the latter are usually 150-200 ng/mL or higher).

Imaging Studies

Ultrasonography of the neck and thyroid can be used to detect nodules and infiltrative disease. It has little use in hypothyroidism per se unless a secondary anatomic lesion in the gland is of clinical concern. Hashimoto thyroiditis is usually associated with a diffusely heterogeneous ultrasonographic image. In rare cases, it may be associated with lymphoma of the thyroid. Serial images with fine-needle aspiration (FNA) of suspicious nodules may be useful. The use of color flow Doppler scanning allows assessment of vascularity, which can help to distinguish thyroiditis from Graves disease. Glands with the former will have decreased flow, whereas glands with the latter will have increased flow. Any thyroid nodules noted on imaging studies should undergo standard evaluation. Radioactive iodine uptake (RAIU) and thyroid scanning are not useful in hypothyroidism, because these tests require some level of endogenous thyroid function if they are to provide useful information. Patients with Hashimoto thyroiditis may have relatively high early uptake (after 4 hours) but do not have the usual doubling of uptake at 24 hours consistent with an organification defect. Patients undergoing whole-body F18-fluorodeoxyglucose positron emission tomography (FDG-PET) for nonthyroid disease often show significant thyroid uptake as an incidental finding. In general, diffuse uptake by the thyroid on FDG-PET is considered a benign finding and is typical of thyroiditis.

Screening

Governmental bodies frequently mandate screening of neonates for hypothyroidism so as to prevent delay in the recognition and treatment of cretinism. No universal screening recommendations exist for thyroid disease for adults. The American Thyroid Association recommends screening at age 35 years and every 5 years thereafter, with closer attention to patients who are at high risk, such as the following:

- Pregnant women
- Women older than 60 years
- Patients with type 1 diabetes or other autoimmune disease
- Patients with a history of neck irradiation

Fine-Needle Aspiration Biopsy

Thyroid nodules are often found incidentally during physical examination or on chest radiography, computed tomography (CT), or magnetic resonance imaging (MRI). Thyroid nodules can be found in patients who are hypothyroid, euthyroid, or hyperthyroid. FNA biopsy is the procedure of choice for evaluating suspicious nodules, usually with ultrasound guidance. Risk factors for thyroid nodules include age greater than 60 years, history of head or neck irradiation, and a family history of thyroid cancer. About 5-15% of solitary nodules are malignant. Suspicious nodules are those with sonographic features such as irregular margins, hypoechoic parenchyma, or microcalcifications.

Histologic Findings

Autoimmune thyroiditis causes a decrease in intrathyroidal iodine stores, increased iodine turnover, and defective organification. Chronic inflammation of the gland causes progressive destruction of the functional tissue with widespread infiltration by lymphocytes and plasma cells with epithelial cell abnormalities. In time, dense fibrosis and atrophic thyroid follicles replace the initial lymphocytic hyperplasia and vacuoles.

Other causes of functional tissue destruction and infiltration include the following:

- Previous administration of radioiodine
- Surgical removal
- Metastasis
- Lymphoma
- Sarcoidosis
- Tuberculosis
- Amyloidosis
- Cystinosis
- Thalassemia
- Riedel thyroiditis
- Hemochromatosis

Approach Considerations

The treatment goals for hypothyroidism are to reverse clinical progression and correct metabolic derangements, as evidenced by normal blood levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4). Thyroid hormone is administered to supplement or replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT4). Thyroid hormone can be started at anticipated full replacement doses in individuals who are young and otherwise healthy. In elderly patients and those with known ischemic heart disease, treatment should begin with one fourth to one half the expected dosage, and the dosage should be adjusted in small increments after no less than 4-6 weeks. For most cases of mild to moderate hypothyroidism, a starting levothyroxine dosage of 50-75 µg/day will suffice. Clinical benefits begin in 3-5 days and level off after 4-6 weeks. Achieving a TSH level within the reference range may take several months because of delayed readaptation of the hypothalamic-pituitary axis. In patients receiving treatment with LT4, dosing changes should be made every 6-8 weeks until the patient's TSH is in target range. In patients with central (ie, pituitary or hypothalamic) hypothyroidism, T4 levels rather than TSH levels are used to guide treatment. In most cases, the free T4 level should be kept in the upper third of the reference range. After dosage stabilization, patients can be monitored with annual or semiannual clinical evaluations and TSH monitoring.

Patients should be monitored for symptoms and signs of overtreatment, which include the following:

- Tachycardia
- Palpitations
- Atrial fibrillation
- Nervousness
- Tiredness
- Headache
- Increased excitability
- Sleeplessness
- Tremors
- Possible angina

The updated guidelines on hypothyroidism issued by the American Thyroid Association in 2014 maintain the recommendation of levothyroxine as the preparation of choice for hypothyroidism, with the following considerations:

- If levothyroxine dose requirements are much higher than expected, consider evaluating for gastrointestinal disorders such as *Helicobacter pylori* –related gastritis, atrophic gastritis, or celiac disease; if such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended.
- Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum TSH at steady state, since such medications may alter levothyroxine requirement.
- Serum TSH should be reassessed upon initiation of agents such as tyrosine kinase inhibitors that affect thyroxine metabolism and thyroxine or triiodothyronine deiodination.
- Serum TSH monitoring is advisable when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are started.
- When deciding on a starting dose of levothyroxine, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should be considered. The serum TSH goal appropriate for the clinical situation should also be considered.
- Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal.
- Dose adjustments should be made upon significant changes in body weight, with aging, and with pregnancy; TSH assessment should be performed 4-6 weeks after any dosage change.
- Reference ranges of serum TSH levels are higher in older populations (eg, >65 years), so higher serum TSH targets may be appropriate.

In Most patients with hypothyroidism can be treated in an ambulatory care setting. Patients who require long-term continuous tube feeding routinely require intravenous (IV) LT4 replacement because the absorption of oral agents is impaired by the contents of tube feeds. Alternatively, tube feeds can be withheld for 1 hour while the patient receives an oral preparation of LT4. It should be noted that oral and IV preparations of LT4 are not equivalent; consequently, great care must be taken in switching between these formulations. Patients with severe hypothyroidism requiring hospitalization (eg, myxedema) may require aggressive management. Overreplacement or aggressive replacement with any thyroid hormone may precipitate tachyarrhythmias or, very rarely, thyroid storm and should be balanced against the need for urgent replacement. Risk is higher with T3 therapy. Surgery is rarely needed in patients with hypothyroidism; it is more commonly required in the treatment of hyperthyroidism. However, surgery is indicated for large goiters that compromise tracheoesophageal function.

Hypothyroidism in Pregnancy

The updated guidelines on hypothyroidism issued by the American Thyroid Association in 2014 concerning hypothyroidism treatment in pregnant women are as follows:

- Pregnant women with overt hypothyroidism should receive levothyroxine replacement therapy with the dose titrated to achieve a TSH concentration within the trimester-specific reference range.
- Serial serum TSH levels should be assessed every 4 weeks during the first half of pregnancy to adjust levothyroxine dosing to maintain TSH within the trimester-specific range.
- Serum TSH should be reassessed during the second half of pregnancy.
- In women already taking levothyroxine, 2 additional doses per week of the current levothyroxine dose, given as one extra dose twice weekly with several days' separation, may be started as soon as pregnancy is confirmed.

Hypothyroidism in pregnancy can produce an array of obstetric complications. Even mild disease may have adverse effects on the offspring. Adverse effects of hypothyroidism in pregnancy include the following:

- Preeclampsia
- Anemia
- Postpartum hemorrhage
- Cardiac ventricular dysfunction
- Increased risk of spontaneous abortion
- Low birth weight
- Impaired cognitive development in the fetus
- Fetal mortality

Increased thyroid hormone dosage requirements should be anticipated during pregnancy, especially in the first and second trimesters. Studies have suggested that in pregnant women with hypothyroidism, the LT4 dose should be increased by 30% at the confirmation of pregnancy and subsequently adjusted in accordance with TSH levels. In addition, iodine demands are higher with pregnancy and lactation. Iodine needs rise from approximately 150 µg/day in the nonpregnant woman to 240-290 µg/day with pregnancy and lactation. Guidelines from the American Thyroid Association recommend that all pregnant and lactating women ingest a minimum of 250 mg iodine daily—optimally, in the form of potassium iodide, to ensure consistent delivery.

Subclinical Hypothyroidism

Significant controversy persists regarding the treatment of patients with mild hypothyroidism. Some have argued that treatment of these patients improves symptoms, prevents progression to overt hypothyroidism, and may have cardioprotective benefits. Ultrasonography may have prognostic value in subclinical hypothyroidism. In an Italian study, progression to overt hypothyroidism occurred more often in patients whose ultrasonographic thyroid scan showed diffuse hypoechogenicity (an indication of chronic thyroiditis). In nonpregnant patients, following subclinical hypothyroidism and treating on a case-by-case basis is reasonable. Treatment of subclinical hypothyroidism has been shown to reduce total cholesterol, non-HDL cholesterol, and apolipoprotein B levels and to decrease arterial stiffness and systolic blood pressure. In patients with concomitant subclinical hypothyroidism and iron deficiency anemia, iron supplementation may be ineffective if LT4 is not given. Guidelines from the American Association of Clinical Endocrinologists (AACE) recommend treatment in patients with TSH levels higher than 10 mIU/L and in patients with TSH levels of 5-10 mIU/L in conjunction with goiter or positive anti-TPO antibodies; these patients have the highest rates of progression to overt hypothyroidism. An initial LT4 dosage of 50-75 µg/day can be used, which can be titrated every 6-8 weeks to achieve a target TSH of between 0.3 and 3 mIU/L.

Myxedema Coma

In patients with myxedema coma, an effective approach consists of the following:

- Give 4 µg of LT4 per kilogram of lean body weight (approximately 200-250 µg) as an IV bolus in a single or divided dose, depending on the patient's risk of cardiac disease
- 24 hours later, give 100 µg IV

- Subsequently, give 50 µg/day IV, along with stress doses of IV glucocorticoids
- Adjust the dosage on the basis of clinical and laboratory findings

If adrenal insufficiency is suspected (eg, in a patient with hypothyroidism secondary to panhypopituitarism), that diagnosis should be investigated. If adrenal insufficiency is confirmed, stress doses of IV glucocorticoids should be given before hypothyroidism is treated. If the patient's condition is critical and there is no time to complete the workup for adrenal insufficiency before the necessary use of IV LT4, the patient must be given stress-dose glucocorticoids to prevent the catastrophic complication of adrenal crisis. Use of IV LT3 is controversial and based on expert opinion. It is associated with a higher frequency of adverse cardiac events and is generally reserved for patients who are not improving clinically on LT4. LT3 can be given initially as a 10 µg IV bolus, which is repeated every 8-12 hours until the patient can take maintenance oral doses of T4. Advanced age, high-dose T4 therapy, and cardiac complications have the highest associations with mortality in myxedema coma.

Complications of Treatment

Thyroid hormone replacement can precipitate adrenal crises in patients with untreated adrenal insufficiency by enhancing hepatic corticosteroid metabolism. If adrenal insufficiency is suspected, it should be confirmed or ruled out; if confirmed, it should be treated before treatment of hypothyroidism. Aggressive replacement of thyroid hormone may compromise cardiac function in patients with existing cardiac disease. In these patients, administer smaller initial doses of LT4, and titrate the dosage upward in small increments. Subclinical hyperthyroidism is a more common complication of treatment with LT4. The relationship of overtreatment to osteoporosis and fracture is not consistent and is best studied in postmenopausal women. A large population-based nested case-control study demonstrated a 2-fold to 3-fold increase in fractures in LT4 users older than 70 years; the increase was dose-related. Because thyroid function studies were not performed, the relation between subclinical hyperthyroidism and osteoporosis requires further evaluation. However, this study does support careful dose titration, especially in elderly patients. Nonetheless, patients at risk for osteoporosis (eg, women who are estrogen-deficient) and individuals receiving a long-term suppressive dose of LT4 (eg, patients with differentiated thyroid cancer) should be closely monitored. It should be noted that patients with thyroid cancer are usually on a higher dose of LT4. The desired TSH depends on the staging of the cancer and on the evidence (or lack of evidence) of active disease. In patients with stage IV thyroid cancer, it is desirable to keep the TSH below 0.1 mIU/L in the long term. Patients should be advised that in rare cases, vision may temporarily worsen when hormone therapy is initiated. Pseudotumor cerebri may occur, albeit uncommonly. Patients with depression may develop mania, and psychosis may be exacerbated in patients with severe psychological illness. Because most brain growth occurs in the first 2 years of life, untreated hypothyroidism in infants can cause irreversible mental retardation. Older infants are spared nervous system damage but continue to have slowed physical and linear bone growth. They also have delayed dental development.

Diet and Activity

No specific diets are required for hypothyroidism. Subclinical hypothyroidism has been seen in increased frequency in patients with greater iodine intake. The World Health Organization (WHO) recommends a daily dietary iodine intake of 150 µg for adults, 200 µg for pregnant and lactating women, and 50-120 µg for children. Patients who have hypothyroidism have generalized hypotonia and may be at risk for ligamentous injury, particularly from excessive force across joints. Thus, patients should exercise caution with certain activities, such as contact sports and heavy physical labor. Patients with uncontrolled hypothyroidism may have difficulty maintaining concentration in low-stimulus activities and may have slowed reaction times. Patients should use caution when engaging in an activity that poses a risk of injury (eg. operating presses or heavy equipment and driving).

Consultations

Indications for referral to an endocrinologist include any of the following:

- A nodular thyroid, suspicious thyroid nodules, or compressive symptoms (eg, dysphagia)
- Pregnancy (or planned pregnancy)
- Underlying cardiac disorders or other endocrine disorders
- Age younger than 18 years
- Secondary or tertiary hypothyroidism
- Unusual constellation of thyroid function test results
- Inability to maintain TSH in the target range
- Unresponsiveness to treatment

Some patients with subacute or postpartum thyroiditis can develop thyrotoxicosis (or symptoms consistent with hyperthyroidism) before developing hypothyroidism. These patients also may benefit from consultation with an endocrinologist. Suspected myxedema coma is a medical emergency with a high risk of mortality, and it necessitates requires initiation of IV LT4 and glucocorticoid therapy before laboratory confirmation. An urgent endocrinology consultation should be obtained.
Rarely, an increase in size of a goiter in a patient with autoimmune thyroid disease could indicate a lymphoma. These patients should be evaluated by an endocrinologist.

Long-Term Monitoring

Once an appropriate therapeutic dosage is arrived at, patients can be monitored annually or semiannually with laboratory evaluation and physical examination. In addition, monitor patients for signs of excess dosing (eg, nervousness, palpitations, diarrhea, excessive sweating, heat intolerance, chest pain, or insomnia). Monitor pulse rate, blood pressure, and vital signs. In children, sleeping pulse rate and basal temperature can be used as guides to the adequacy of the clinical response to treatment.

Prognosis

Undertreatment of hypothyroidism leads to disease progression, with gradual worsening of symptoms and further metabolic derangements. Ultimately, untreated hypothyroidism can cause profound coma or even death. Untreated hypothyroidism in infants can cause irreversible mental retardation. In most patients, fortunately, thyroid hormone treatment reverses the signs and symptoms of hypothyroidism. With treatment, other secondarily affected laboratory values (eg, circulating lipid levels and elevated prolactin levels) should improve.

Patient Education

Emphasize proper compliance at each visit. Clearly discuss the lifelong nature of hypothyroidism, the need for lifelong levothyroxine therapy, the proper way to take medicine, and the need for TSH testing at least annually. Patients should take thyroid hormone as a single daily dose. Thyroid hormone is better absorbed in the small bowel; therefore, absorption can be affected by malabsorptive states, small bowel disease (eg, celiac sprue), and the patient's age. Many drugs (eg, iron, calcium carbonate, calcium acetate aluminum hydroxide, sucralfate, raloxifene, and proton pump inhibitors) can interfere with absorption and therefore should not be taken within 2-4 hours of LT4 administration. Estrogen/progestin oral contraceptives and pregnancy are associated with changes in thyroid-binding globulin. These changes may impact thyroid hormone dosing.

INTERPRETATION

THYROID FUNCTION TESTS

Reference Ranges

It should be remembered that different testing laboratories may have different reference ranges. These are the reference ranges used by the Leeds and Bradford Department of Chemical Pathology & Immunology.

TSH	0.2 - 4.0 miu/L
free T4	10 - 20 pmol/L
total T3	0.9 - 2.5 nmol/L

These references ranges are used in all the evaluations shown above.

The Euthyroid Patient

In the Euthyroid patient the free T4 is within the range 10 - 20 pmol/L and the TSH is within the range 0.2 - 4.0 miu/L . However in sick euthyroidism T4 and or TSH may be lowered during the non-thyroidal illness. TSH may be transiently elevated during recovery from non-thyroidal illness but almost any combination of thyroid tests can be seen in sick patients.

Hypothyroidism

TSH Low or Normal	TSH Elevated
If T4 is normal then Thyroid status is Normal	● If T4 is normal, sublinical hypothyroidism exists. ● Consider T4 replacement if TSH > 12 miu/L. ● When the TSH is mildly elevated ie 4 - 12 miu/L, positive TPO antibodies indicate an increased risk of future hypothyroidism of 5% per year.
If T4 is low consider secondary hypothyroidism (but more commonly Sick Euthyroid)	● If T4 is low, primary hypothyrodism.

- A normal or low TSH level usually excludes primary hypothyroidism. However, the rare diagnosis of secondary (pituitary) hypothyroidism should be considered if T4 is also low. The commonest cause of this pattern is sick euthyroid syndrome.
- A TSH level between 10-16 miu/L indicates hypothyroidism, and usually indicates that replacement therapy should be commenced.
- A TSH level between 6-12 miu/L with normal T4 may represent subclinical or compensated hypothyroidism.
- Anti-thyroid peroxidase autoantibodies (TPO Ab) are recommended as their presence predicts the development of hypothyroidism at va rate of approx 5% per year.

Sick Euthyroid Syndrome

During severe illness or starvation, the metabolic drive on the human body by the thyroid is reduced. The term 'sick euthyroid' is used in this condition since it represents a state of thyroid function appropriate for a sick individual; and it returns to normal with the return of good health. The most active thyroid hormone tri-iodothyronine, T3, is largely produced by peripheral ie non-thyroidal conversion of thyroxine, T4. In the typical sick euthyroid, circulating T3 is usually low but the total T4 may be normal or even raised since there is reduced conversion to T3. Conversely, T4 may be low since the majority is carried on serum binding proteins and their synthesis may be suppressed by severe illness. The absence of a raised TSH excludes primary hypothyroidism. However, almost any pattern of thyroid hormones may be seen in an unwell patient!! Suppressed TSH may be seen in elderly patients who do not have thyrotoxicosis (since the T3 is low or normal). TSH may also be suppressed in depression.

Interference with TFT interpretation due to committant drug therapy

Amiodarone interferes both with the synthesis of TSH, with iodine uptake by the thyroid gland and with conversion of T4 to T3. It may be impossible to interpret TFTs in isolation and decisions may need to be taken on clinical grounds or on the pattern of change in TFTs over a period of time. Overt hypo- or hyperthyroidism probably occurs in 4% (2% each) of patients treated with amiodarone but the exact proportion is strongly affected by iodine intake. Minor abnormalities may be seen in approximately 50% of patients.

Beta-blockers interfere with conversion of T4 to T3 but this does not cause hypothyroidism.

Lithium interferes with thyroid hormone synthesis and inhibits their release from the gland. Long term lithium treatment results in goitre in up to 50% of patients, subclinical hypothyroidism occurs in 20% and overt hypo-thyroidism in a further 20%. The presence of thyroid peroxidase antibodies may be useful to predict the future development of hypothyroidism in long- term treated patients.

Cortisol (or hydrocortisone or prednisolone) given orally transiently suppresses TSH secretion for a few hours. Patients taking corticosteroids should have blood taken for TFTs before the morning steroid medication is taken.

Antiepileptics, NSAIDS & aspirin all interfere with the binding of thyroxine and its binding proteins resulting in lowish free T4 in the presence of normal thyroid binding globulin. It is most marked with carbamazepine; there appears to be no interference by valproate.

Hyperthyroidism

- TSH is the most useful parameter in screening for thyroid dysfunction in most non critically ill patients since TSH is almost always suppressed in hyperthyroidism.
- A raised T4 and T3 with suppressed TSH and an elevated TSH receptor antibody level confirms the diagnosis of Grave's disease.
- A proportion of cases have normal T4 with suppressed TSH and represent T3 toxicosis and T3 measurements may be necessary. This is usually performed automatically by the laboratory.
- A raised T4 with normal or raised TSH usually indicates T4 -> T3 conversion defect, or analytical artefacts.
- A rare cause is secondary hyperthyroidism (TSH resistance or secreting pituitary tumours).

Thyroxine Replacement Therapy in Primary Hypothyroidism

Replacement Therapy	
TSH Level	This Indicates
< 0.05 miu/L	Over Replacement
0.05 - 0.2 miu/L	Indicates Possible Over Replacement
0.2 - 2.0 miu/L	Sufficient Replacement
> 2.0 miu/L	Likely under Replacement

- Clinical symptomatology and TSH are the major parameters used in assessing the adequacy of replacement therapy.
- T4 level is an index of recent patient compliance.
- TSH may take up to 4-6 weeks to stabilise. Thus, repeat TFT following alteration of dose should only be performed after this period.
- PAtients with Throid Cncer should have their TSH suppressed to inhibit regrowth of malignant thyroid cells.

Medications interfering with thyroxine replacement

Treatment with iron and calcium salts, proton pump inhibitors and oestrogens is associated with reduced therapeutic efficacy and rises in TSH. The effect with iron and calcium is due to impaired absorption and these agents should be taken at a different time of day than the thyroxine.

Thyroxine Replacement Therapy for Secondary Hypothyroidism

Replacement Therapy	
freeT4 Level	This Indicates
< 17 pmol/L	Likely under replacement
17-25 pmol/L	Sufficient replacement
>25 nmol/L	Likely over replacement

- Clinical symptoms and T4 are used to monitor the adequacy of therapy in hypopituitarism as TSH is not representative of thyroid function.
- Results should always be interpreted in combination with clinical status.

Suggested monitoring schemes

Thyroxine Therapy

Newly commenced

- Measure TFT ~ 6-8 weeks post commencement of thyroxine therapy and adjust the dose accordingly in order to bring TSH into the range of 0.2 - 2.0 miu/L
- Repeat TFT ~ 6 months after normalisation as metabolic clearance of T4 may increase with correction of hypothyroidism.
- Note that TFT should not be repeated until at least 4-6 weeks post alteration of thyroxine dose.

On Thyroxine

- Repeat TFT only if suspected alteration in thyroid function.
- Perform TFT 4-6 weeks after alteration of dose.
- Yearly TFT is recommended unless earlier measurement is indicated clinically.
- Secondary Hypothyroidism
- Repeat T4 4 weeks after changing the dosage is recommended.

Grave's Disease on Antithyroid Drug Therapy

- Both T4 and TSH are used to assess thyroid function (occasionally T3).
- Clinical status of patient should take precedence over TFT in evaluating the adequacy of treatment as TSH may take months to normalise following commencement of therapy.

Repeating TFT measurements

- Repeat TFT is only indicated in appropriate medical conditions, eg recurrent AF.
- TFT performed more than 3 times a year is usually inappropriate providing previous TFTs are normal.

How to request TFTs

Efficient management of patients requires accurate results from investigations. However, in order for the laboratory to correctly interpret TFT results and provide accurate reports, relevant clinical history on the request forms is essential.

The following points serve as a guide as to what should be included with TFT requests:

- Current diagnosis (in particular, indicate if patient is ill).
- Purpose for which TFT was requested.
- Previous TFT findings and when.
- Current or recent drug therapy (in particular, antiepileptics, NSAIDS, aspirin, amiodarone and lithium).
- Any known thyroid abnormalities or pathologies.
- Antithyroid drug therapy (including when commenced or dose altered).
- Any known thyroid abnormalities or pathologies.
- Thyroxine therapy (including when commenced or dose altered).Any other forms of treatment related to the thyroid dysfunction.
- Other endocrinological pathologies.

For patients taking T4 replacement, then requests for TSH alone are adequate unless the patient has pituitary disease.

BOUQUET

In Lighter Vein

There was an elderly couple who in their old age noticed that they were getting a lot more forgetful, so they decided to go to the doctor. The doctor told them that they should start writing things down so they don't forget. They went home and the old lady told her husband to get her a bowl of ice cream. "You might want to write it down," she said. The husband said, "No, I can remember that you want a bowl of ice cream." She then told her husband she wanted a bowl of ice cream with whipped cream. "Write it down," she told him, and again he said, "No, no, I can remember: you want a bowl of ice cream with whipped cream." Then the old lady said she wants a bowl of ice cream with whipped cream and a cherry on top. "Write it down," she told her husband and again he said, "No, I got it. You want a bowl of ice cream with whipped cream and a cherry on top." So he goes to get the ice cream and spends an unusually long time in the kitchen, over 30 minutes. He comes out to his wife and hands her a plate of eggs and bacon. The old wife stares at the plate for a moment, then looks at her husband and asks, "Where's the toast?"

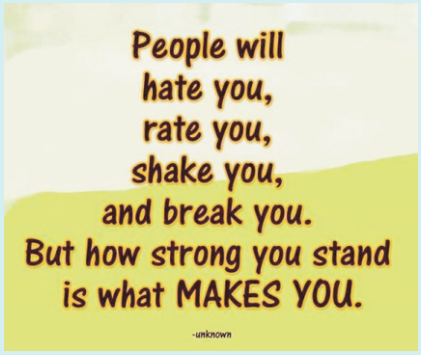
A boy asks his father, "Dad, are bugs good to eat?" "That's disgusting. Don't talk about things like that over dinner," the dad replies. After dinner the father asks, "Now, son, what did you want to ask me?" "Oh, nothing," the boy says. "There was a bug in your soup, but now it's gone."

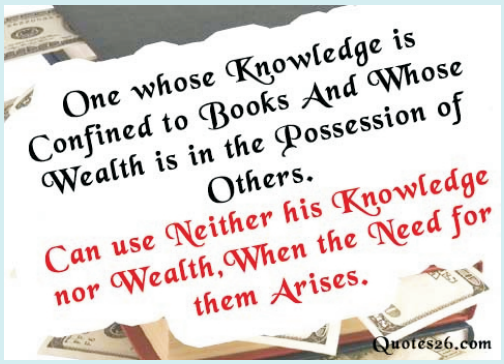
Dad: "Can I see your report card, son?"
Son: "I don't have it."
Dad: "Why?"
Son: "I gave it to my friend. He wanted to scare his parents."

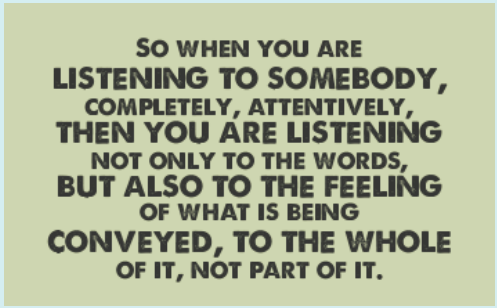
A little girl comes back home from school and tells her mom:
"Mommy, today I got punished for something I didn't even do!"
"What?! What do you mean?" Her mother says, angry, "I'm going to call your teacher right now! What is it you didn't do?"
"**My homework.**"

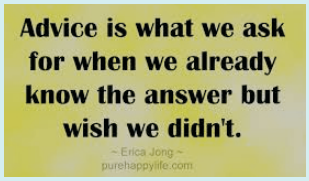
Teacher: "Daniel, if you had a dollar in your hand and you asked your dad for another dollar, how many dollars would you have in your hand?"
Daniel: "A dollar."
Teacher: "Daniel, apparently you don't know math..."
Daniel: "**Apparently you don't know my dad.**"

Wisdom Whispers









Brain Teasers

1. **The characteristics of a useful antigen that can be used in immunological assays are:**
   A. Should have large molecular size
   B. Should be complex
   C. Should be structurally stable
   D. All of the above.
2. **Which of the following statements regarding an epitope are true?**
   A. An epitope is an antigen determinant
   B. Antibodies are directed against epitopes
   C. A molecule may have several epitopes
   D. All of the above.
3. **Which of the following antibodies is found in body secretions?**
   A. IgG B. IgA C. IgM D. IgE.
4. **Which of the following antibodies is related to allergic reactions?**
   A. IgG B. IgA C. IgM D. IgE.
5. **Which of the following antibodies is present in highest concentration in blood?**
   A. IgG B. IgA C. IgM D. IgE.

ANSWERS: 1.D 2.D 3.B 4.D 5.A

TROUBLESHOOTING

ATYPICAL THYROID PATTERNS

The five thyroid patterns

1. **Hypothyroidism caused by pituitary dysfunction**
   This pattern is caused by elevated cortisol, which is in turn caused by active infection, blood sugar imbalances, chronic stress, pregnancy, hypoglycemia or insulin resistance. These stressors fatigue the pituitary gland at the base of the brain so that it can no longer signal the thyroid to release enough thyroid hormone. There may be nothing wrong with the thyroid gland itself. The pituitary isn't sending it the right messages. With this pattern, you'll have hypothyroid symptoms and a TSH **below** the functional range (1.8 – 3.0) but within the standard range (0.5 – 5.0). The T4 will be low in the functional range (and possibly the lab range too).

2. **Under-conversion of T4 to T3**
   T4 is the inactive form of thyroid hormone. It must be converted to T3 before the body can use it. More than 90% of thyroid hormone produced is T4. This common pattern is caused by inflammation and elevated cortisol levels. T4 to T3 conversion happens in cell membranes. Inflammatory cytokines damage cell membranes and impair the body's ability to convert T4 to T3. High cortisol also suppresses the conversion of T4 to T3. With this pattern you'll have hypothyroid symptoms, but your TSH and T4 will be normal. If you have your T3 tested, which it rarely is in conventional settings, it will be **low**.

3. **Hypothyroidism caused by elevated TBG**
   Thyroid binding globulin (TBG) is the protein that transports thyroid hormone through the blood. When thyroid hormone is bound to TBG, it is inactive and unavailable to the tissues. When TBG levels are high, levels of unbound (free) thyroid hormone will be low, leading to hypothyroid symptoms. With this pattern, TSH and T4 will be normal. If tested, T3 will be **low**, and T3 uptake and TBG will be **high**. Elevated TBG is caused by high estrogen levels, which are often often associated with birth control pills or estrogen replacement (i.e. Premarin or estrogen creams). To treat this pattern, excess estrogen must be cleared from the body.

4. **Hypothyroidism caused by decreased TBG**
   This is the mirror image of the pattern above. When TBG levels are low, levels of free thyroid hormone will be high. You might think this would cause hyperthyroid symptoms. But too much free thyroid hormone in the bloodstream causes the cells to develop resistance to it. So, even though there's more than enough thyroid hormone, the cells can't use it and you'll have hypothyroid – not hyperthyroid – symptoms. With this pattern, TSH and T4 will be normal. If tested, T3 will be **high**, and T3 uptake and TBG will be **low**. Decreased TBG is caused by high testosterone levels. In women, it is commonly associated with PCOS and insulin resistance. Reversing insulin resistance and restoring blood sugar balance is the key to treating this pattern.

5. **Thyroid resistance**
   In this pattern, both the thyroid and pituitary glands are functioning normally, but the hormones aren't getting into the cells where they're needed. This causes hypothyroid symptoms. Note that **all lab test markers will be normal** in this pattern, because we don't have a way to test the function of cellular receptors directly. Thyroid resistance is usually caused by chronic stress and high cortisol levels. It can also be caused by high homocysteine and genetic factors.

Conclusion

The five patterns above are only a partial list. Several others also cause hypothyroid symptoms and don't show up on standard lab tests. If you have hypothyroid symptoms, but your lab tests are normal, it's likely you have one of them.

Not only do these patterns fail to show up on standard lab work, they **don't respond well** to conventional thyroid hormone replacement. If your body can't convert T4 to T3, or you have too much thyroid binding protein, or your cells are resistant, it doesn't matter how much T4 you take; you won't be able to use it. Unfortunately, if you have one of these patterns and tell your doctor your medication isn't working, all too often the doctor's response is to simply increase the dose. When that doesn't work, the doctor increases it yet again. As I said at the beginning of this article, the key to a successful treatment is an accurate diagnosis. The reason the conventional approach fails is that it skips this step and gives the same treatment to everyone, regardless of the cause of their problem. The good news is that, once the correct diagnosis is made, patients respond very well to treatment.

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