

CONTENTS

1 Editorial

2 Disease
Diagnosis

6 Interpretation

7 Troubleshooting

10 Bouquet

11 Tulip News

Editorial

Hashimoto's thyroiditis, also known as **chronic lymphocytic thyroiditis** and **Hashimoto's disease**, is an autoimmune disease in which the thyroid gland is gradually destroyed. Early on there may be no symptoms. Over time the thyroid may enlarge, forming a painless goiter. Some people eventually develop hypothyroidism with accompanying weight gain, feeling tired, constipation, depression, and general pains. After many years the thyroid typically shrinks in size. Potential complications include thyroid lymphoma.

Hashimoto's thyroiditis is thought to be due to a combination of genetic and environmental factors. Risk factors include a family history of the condition and having another autoimmune disease. Diagnosis is confirmed with blood tests for TSH, T4, and anti-thyroid autoantibodies. Other conditions that can produce similar symptoms include Graves' disease and nontoxic nodular goiter.

Hashimoto's thyroiditis is typically treated with levothyroxine. If hypothyroidism is not present, some may recommend no treatment, while others may treat to try to reduce the size of the goiter. Those affected should avoid eating large amounts of iodine; however, sufficient iodine is required especially during pregnancy. Surgery is rarely required to treat the goiter. **"DISEASE DIAGNOSIS"** segment outlines this Thyroidal autoimmune disease for you.

In order to understand the Thyroid gland, one must know everything about the hormones that relate to it. Hence **"INTERPRETATION"** part of this issue outlines, in details, the process of synthesis of the Thyroid hormones.

"TROUBLE SHOOTING" completes the issue by detailing all Thyroid related hormonal investigations. It also highlights various hormones along with their expected altered values in different disorders of the Thyroid Gland.

Little fun and frolic amidst all this serious stuff hasn't been omitted.

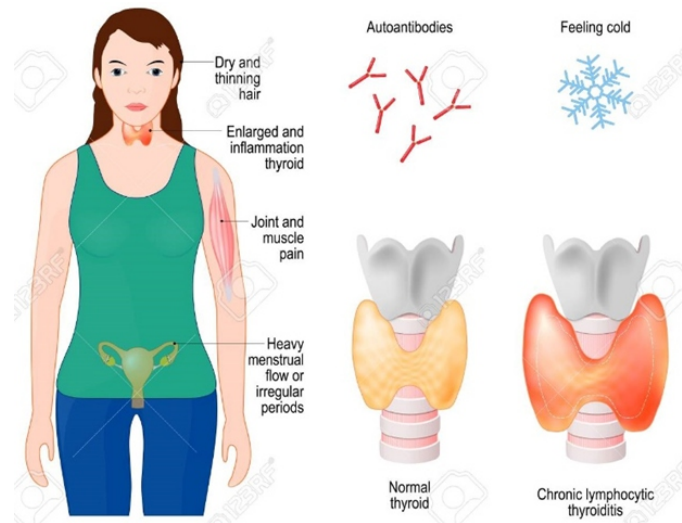
Tulip Group takes pride in introducing its COMPLETE THYROID HORMONES RANGE in Elisa and Clia formats.

Happy Reading!



DISEASE DIAGNOSIS

HASHIMOTO THYROIDITIS (Autoimmune disease)



Background

Hashimoto thyroiditis (or Hashimoto's thyroiditis) is characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes. It is the most common cause of hypothyroidism in the United States after age 6 years. Hashimoto thyroiditis is part of the spectrum of autoimmune thyroid diseases (AITDs). By strict criteria, Hashimoto thyroiditis is a histologic diagnosis first described by Hakaru Hashimoto, a Japanese surgeon working in Berlin, Germany. His report, published in 1912, was based on the examination of 4 postoperative cases. He is also credited with introducing the term struma lymphomatosa in reference to the syndrome.

Other variants of AITD include the following conditions:

- Atrophic thyroiditis
- Juvenile thyroiditis
- Postpartum thyroiditis
- Silent thyroiditis
- Focal thyroiditis

Etiology

The initiating process in Hashimoto thyroiditis is not well understood. The thyroid gland is typically goitrous but may be atrophic or normal in size. Antibodies binding to and blocking the thyroid-stimulating hormone (TSH) receptor, thyrotropin receptor blocking antibodies (TBII) have also been described and may contribute to impairment in thyroid function. The result is inadequate thyroid hormone production and secretion, although initially, preformed thyroxine (T4) and triiodothyronine (T3) may "leak" into the circulation from damaged cells. **Patients with Hashimoto thyroiditis have antibodies** to various thyroid antigens, the most frequently detected of which include anti-thyroid peroxidase (anti-TPO), antithyroglobulin (anti-Tg), and to a lesser extent, TSH receptor-blocking antibodies (TBII). Nevertheless, a small percentage of patients with Hashimoto thyroiditis (approximately 10-15%) may be serum antibody negative. **Other antithyroid antibodies found in AITD** (including

Hashimoto thyroiditis) include thyroid-stimulating antibody and cytotoxic antibody. **Hashimoto thyroiditis has a markedly higher clustering** of other autoimmune diseases, including pernicious anemia, adrenal insufficiency, celiac disease, and type 1 diabetes mellitus. A study by Ruggeri et al of patients with Hashimoto thyroiditis indicated that the disease is associated with different nonthyroidal autoimmune diseases (NTADs) at different ages. Associated NTADs were significantly more prevalent in adults than children/adolescents in the study, and more adults than children/adolescents suffered from two or more associated NTADs, with the frequency of arthropathies and connective tissue diseases being greater in adults and the frequency of type 1 diabetes and celiac disease being higher in children/adolescents. **A study by Mazokopakis et al indicated** that an association may exist between vitamin D deficiency and the development of Hashimoto thyroiditis. The study, which included 218 patients with Hashimoto thyroiditis, found serum 25-hydroxy vitamin D levels to be negatively correlated with anti-TPO levels in all patients, with the anti-TPO levels being significantly greater in the 186 patients who were vitamin D deficient. After receiving oral vitamin D3 supplementation of 1200-4000 IU daily for 4 months, serum anti-TPO levels in the vitamin D deficient patients were determined to be significantly reduced. **In a study of 830 patients with Hashimoto thyroiditis**, Tagami et al reported slight, but significant, increases in TSH serum levels and decreases in free T4 serum levels, with increasing patient age. In addition, TSH levels were positively correlated with levels of total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and non-HDL, as well as with the ratio of LDL to HDL. Free T4 levels, on the other hand, were negatively correlated with these lipid parameters. **A study by Bothra et al reported that, compared with the general population**, first-degree relatives of persons with Hashimoto thyroiditis have a nine-fold greater risk of developing the disease.

Epidemiology

International occurrence

Worldwide, the most common cause of hypothyroidism is iodine deficiency. However, Hashimoto thyroiditis remains the most common cause of spontaneous hypothyroidism in areas of adequate iodine intake. The annual incidence of Hashimoto thyroiditis worldwide is estimated to be 0.3-1.5 cases per 1000 persons.

Sex- and age-related demographics

The incidence of Hashimoto thyroiditis is estimated to be 10-15 times higher in females. The most commonly affected age range in Hashimoto thyroiditis is 30-50 years, with the peak incidence in men occurring 10-15 years later. The overall incidence of hypothyroidism increases with age in men and women.

Prognosis

With early diagnosis, timely institution of levothyroxine replacement therapy, informed patient follow-up care, and attention to other attendant complications, the prognosis in Hashimoto thyroiditis is excellent, with patients leading a normal life. Untreated myxedema coma has a poor prognosis and a high mortality rate. **Morbidity related to Hashimoto thyroiditis** typically results from failure to make the diagnosis of hypothyroidism or to institute L-thyroxine replacement therapy in adequate doses, or from failure on the part of the patient to take the replacement medication. **The increased prevalence of lipid disorders** in association with untreated hypothyroidism has the potential to increase morbidity from coronary artery disease. **The risk for papillary thyroid**

carcinoma is increased in patients with Hashimoto thyroiditis. (Indeed, a prospective study by Silva de Moraes et al indicated that any patient with Hashimoto thyroiditis presenting for thyroid nodule evaluation has a greater risk of malignancy than do patients without Hashimoto thyroiditis who present with nodules [23.3% vs 15.9%, respectively].) These cancers are not clearly more aggressive than other papillary thyroid carcinomas. In fact, a study by Liang et al suggested that in patients with papillary thyroid carcinoma, those with concurrent Hashimoto thyroiditis have a better prognosis than do patients without it. Subjects with both papillary thyroid carcinoma and Hashimoto thyroiditis tended to have a smaller tumor size, a less advanced TNM stage, and a decreased lymph node metastasis rate. **A study by Kahaly et al indicated that a strong link exists** between the presence of TSH receptor-stimulating antibodies (TSABs) in patients with Hashimoto thyroiditis and the development of thyroid-associated orbitopathy (TAO). The study, which included 700 patients with Hashimoto thyroiditis, found higher serum levels of TSABs in those with TAO than in those without this condition, while patients with active and severe TAO had higher TSAB levels than did patients with mild and inactive TAO. Healthy controls were negative for TSABs.

Therapeutic complications

Complications of overreplacement with levothyroxine sodium include the following:

- Accelerated bone loss
- Reduction in bone mineral density
- Osteoporosis
- Increased heart rate
- Increased cardiac wall thickness
- Increased contractility

The last three problems above increase the risk of cardiac arrhythmias (especially atrial fibrillation), particularly in the elderly population.

Patient Education

Patients should know that thyroid replacement therapy in Hashimoto thyroiditis is, except in very rare cases, lifelong. Patients must be informed about the importance of compliance with their replacement therapy and must be instructed to report any symptoms suggestive of hyperthyroidism caused by overreplacement. **Patients must be instructed to separate**—by at least 4 hours—ingestion of levothyroxine from ingestion of cholestyramine, ferrous sulfate, sucralfate, calcium carbonate, aluminum hydroxide (and other antacids), and iron-containing multivitamins, all of which impair the absorption of levothyroxine. **For patient education information**, see the Thyroid and Metabolism Center, as well as Thyroid Problems.

Clinical Presentation

History

Hypothyroidism is usually insidious in onset, with signs and symptoms slowly progressing over months to years. Most commonly, patients do not relate a history suggestive of transient hyperthyroidism secondary to increased T4 and T3 levels resulting from thyrocyte destruction. The time course is influenced by the rapidity of onset and the severity of the clinical state of hypothyroidism. The history may be suggestive of other autoimmune associations. **The presentation of patients with hypothyroidism may be subclinical**, without any symptoms, and may be found simply from routine screening of thyroid function. The usual finding is an elevated TSH level. The early compensatory increase in TSH tends to maintain a nearly normal thyroid function and keeps the patient in a euthyroid state. **Patients most commonly present with nonspecific**

symptoms suggestive of overt hypothyroidism. Patients with longstanding, severe hypothyroidism could present in myxedema coma, precipitated by some major stress or infection. **Common, early presenting symptoms of hypothyroidism**, such as fatigue, constipation, dry skin, and weight gain, are nonspecific. Weight gain due to hypothyroidism is usually no greater than 10% of the baseline euthyroid weight and is mostly attributable to fluid accumulation in interstitial tissues.

Other symptoms of hypothyroidism include the following:

- Cold intolerance
- Voice hoarseness and pressure symptoms in the neck from thyroid enlargement
- Slowed movement and loss of energy
- Decreased sweating
- Mild nerve deafness
- Peripheral neuropathy
- Galactorrhea - This may occur because of the increased prolactin levels.
- Depression, dementia, and other psychiatric disturbances
- Memory loss
- Joint pains and muscle cramps
- Hair loss from an autoimmune process directed against the hair follicles
- Menstrual irregularities (typically menorrhagia, infertility, and loss of libido) - Increased prolactin secondary to increased thyrotropin-releasing hormone (TRH) leads to decreased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and to decreased response to gonadotropin-releasing hormone (GnRH); the result is anovulatory cycles with menstrual irregularities.

Sleep apnea and daytime somnolence - Obstructive sleep apnea in hypothyroidism is thought to be partly caused by hypofunction of upper airway muscles and weakness

Physical Examination

Physical findings are variable and depend on the extent of hypothyroidism and other factors such as age. Findings include the following:

- Puffy face and periorbital edema typical of hypothyroid facies
- Cold, dry skin, which may be rough and scaly - Skin may appear yellow but does not involve the sclera, which distinguishes it from the yellowing of jaundice due to hypercarotenemia
- Peripheral edema of hands and feet, typically nonpitting
- Thickened and brittle nails (may appear ridged)
- Hair loss involving the scalp, the lateral third of the eyebrows, and possibly skin, genital, and facial hair
- Bradycardia
- Elevated blood pressure (typically diastolic hypertension) - Most often, blood pressure is normal or even low
- Diminished deep tendon reflexes and the classic prolonged relaxation phase, most notable and initially described at the Achilles tendon (although it may be present in other deep tendon reflexes as well)
- Macroglossia
- The thyroid gland is typically enlarged, firm, and rubbery, without any tenderness or bruit; it may be normal in size or not palpable at all.
- Voice hoarseness
- Slow speech
- Impairment in memory function
- Peripheral neuropathy - This may be a mononeuropathy (as

exemplified by carpal tunnel syndrome) or a polyneuropathy resulting from the involvement of several peripheral nerves, manifesting as paresthesia

- Ataxia - Ataxia from cerebellar dysfunction has been documented in hypothyroidism.

Differential Diagnoses

Diagnostic Considerations

The following autoimmune phenomena may occur or be found in association with Hashimoto thyroiditis:

- Addison disease
- Alopecia areata, totalis, and universalis
- Autoimmune gastritis (pernicious anemia)
- Chronic active hepatitis
- Idiopathic hypoparathyroidism
- Polymyalgia rheumatica and giant cell arteritis
- Primary biliary cirrhosis
- Primary ovarian or testicular failure
- Rheumatoid arthritis
- Sjögren syndrome
- Systemic lupus erythematosus (SLE)
- Systemic sclerosis (scleroderma)
- Type 1 diabetes mellitus
- Vitiligo

A study by Posselt et al found the prevalence of Hashimoto thyroiditis to be 12.6% in patients with SLE, compared with 5.6% in controls. The investigators also found a higher level of anti-Smith antibodies in patients with Hashimoto thyroiditis, but a lower prevalence of malar rash. No relation was found between the presence of Hashimoto disease and cumulative damage from SLE.

Differential Diagnoses

- Diffuse Toxic Goiter (Graves Disease)
- Euthyroid Sick Syndrome
- Goiter
- Hypopituitarism (Panhypopituitarism)
- Lithium-Induced Goiter
- Nontoxic Goiter
- Thyroid Lymphoma
- Toxic Nodular Goiter
- Type I Polyglandular Autoimmune Syndrome
- Type II Polyglandular Autoimmune Syndrome

Workup

Approach Considerations

Up to 15% of patients aged 65 years or older may have subclinical hypothyroidism (mild thyroid failure, as evidenced by an elevated TSH above 4.0 μ IU/mL and normal free T4 levels), with few if any symptoms suggestive of hypothyroidism. These patients have a decreased thyroid reserve. **The best marker of progression to overt hypothyroidism** is a combination of an elevated TSH level with the presence of thyroid autoantibodies, namely anti-TPO and anti-Tg antibodies. The rate of progression to overt hypothyroidism is estimated to be about 5% per year. **Patients with positive thyroid autoantibodies** but a normal TSH level should be followed up periodically to monitor for symptoms of hypothyroidism and to detect any rise in their TSH or cholesterol levels. Checks can usually be performed every 6-12 months. These patients should be treated if the TSH level continues to rise, even if the level is at the upper limit of the reference range.

Iodine uptake and scan

Iodine uptake and scan usually are not indicated for the diagnosis of Hashimoto thyroiditis. The usefulness of radioactive iodine and scan is in classifying a nodule as either hot or cold. A cold thyroid nodule would indicate a higher risk for malignancy and therefore a need for fine-needle aspiration.

Fine-needle aspiration

Perform fine-needle aspiration of any dominant or suspicious thyroid nodules to exclude malignancy or the presence of a thyroid lymphoma in fast-growing goiters. **A literature review by Travaglino et al** found that with regard to evidence of the presence of Hashimoto thyroiditis, the pooled prevalence was 78.9% in patients with primary thyroid lymphoma. A significantly higher prevalence of Hashimoto thyroiditis was found in patients with mucosa-associated lymphoid tissue (MALT) lymphoma or with mixed MALT/diffuse large B-cell lymphoma (DLBCL) than in those with DLBCL alone.

Histologic findings

Hashimoto thyroiditis is a histologic diagnosis. Typically, the thyroid gland shows diffuse lymphocytic and plasma cell infiltration with formation of lymphoid follicles from follicular hyperplasia and damage to the follicular basement membrane. Atrophy of the thyroid parenchyma is usually evident. Correlation with the presence of thyroid autoantibodies, namely anti-TPO and anti-Tg, is helpful in confirming the diagnosis.

Serum TSH Test and Other Studies

In the presence of suggestive symptoms and physical findings, a serum TSH test is needed for the diagnosis of primary hypothyroidism, and it serves to assess the functional status of the thyroid. **This is a sensitive test of thyroid function**; levels are invariably raised in hypothyroidism due to Hashimoto thyroiditis and in primary hypothyroidism from any cause. **The TSH level is also elevated in subclinical hypothyroidism** and is usually the initial laboratory abnormality detected as the pituitary gland attempts to increase thyroid hormone production from the failing thyroid gland. The total T4 or free T4 usually remain within reference ranges in subclinical hypothyroidism. The TSH level may also be elevated in the recovery phase of euthyroid sick syndrome. **In the outpatient setting, when there is no cause to suspect hypothalamic or pituitary disease** and in the absence of nonthyroidal illness and of medications that suppress TSH production in the inpatient setting, a normal TSH level excludes primary hypothyroidism from any cause. **Medications that suppress TSH production include** steroids, dopamine, dobutamine, and octreotide.

Free T4 test

A free T4 is usually needed to correctly interpret the TSH in some clinical settings. A low total T4 or free T4 level in the presence of an elevated TSH level further confirms the diagnosis of primary hypothyroidism. **When a total T4 study, rather than a free T4 study, is performed**, a T3 resin uptake helps to correct the total T4 and T3 values for protein binding, especially thyroid hormone-binding globulin (TBG) abnormalities, but the free T4 is typically the test of choice. **When the serum TSH and the free T4 levels are low** in the outpatient setting, the case for central hypothyroidism is strengthened. However, in the acutely ill patient, nonthyroidal illness (euthyroid sick syndrome) is the more likely possibility. The TSH level cannot be reliably used in some clinical settings to distinguish central hypothyroidism from nonthyroidal illness. Physical findings suggestive of thyroid disease, as well as the presence of obvious or subtle clinical features of hypothyroidism, become pivotal in establishing the correct diagnosis.

T3 test

A low T3 level and a high reverse T3 level may be of additional help in the diagnosis of nonthyroidal illness. **T3 levels are most often maintained within reference ranges** (even in the very late stages of hypothyroidism), and T3 measurement has little value in the diagnosis of hypothyroidism. Furthermore, T3 levels may be low in up to 70% of hospitalized patients without hypothyroidism or any thyroid disease, as is the case with nonthyroidal illness.

Thyroid autoantibodies

The presence of thyroid autoantibodies, typically anti-TPO and also anti-Tg antibodies, delineates the cause of hypothyroidism as Hashimoto thyroiditis or its variant. However, 10-15% of patients with Hashimoto thyroiditis may be antibody negative.

Ultrasonography

Although features of Hashimoto thyroiditis are usually identifiable on an ultrasonogram, a thyroid ultrasonogram is usually not necessary for diagnosing the condition. However, it is useful for assessing thyroid size, echotexture, and, most importantly, whether thyroid nodules are present. Ultrasonographic study aids in confirming the presence of a thyroid nodule, in defining a nodule as solid or cystic, and in defining features suggestive of malignancy, such as irregular margins, a poorly defined halo, microcalcification, and increased vascularity on Doppler interrogation. **Ultrasonography is useful in facilitating fine-needle aspiration of nodules** in general and, in particular, small or poorly defined nodules when indicated and in patients with distorted neck anatomy. A definite diagnosis of benign versus malignant thyroid lesion can be confirmed only by cytologic or histologic examination of thyroid tissue.

Evaluating Complications of Hypothyroidism

The following tests are not necessary for the diagnosis of primary hypothyroidism but may be performed to evaluate complications of hypothyroidism in some patients, when clearly indicated.

Complete blood count

Up to 30-40% of patients with hypothyroidism have anemia, usually from decreased erythropoiesis. In 15% of patients, the anemia is of the iron deficiency type, with microcytosis and hypochromia. Although this can be a normocytic normochromic anemia, the most common morphologic abnormality is a macrocytic anemia that may be partially due to insufficient vitamin B-12 and folate intake.

Total and fractionated lipid profile

Total cholesterol, LDL, and triglyceride levels may be elevated in hypothyroidism and may be responsive to levothyroxine replacement.

Basic metabolic panel

Glomerular filtration rate, renal plasma flow, and renal free water clearance are all decreased in hypothyroidism and may result in hyponatremia.

Creatine kinase

Creatine kinase levels, predominantly the MM isoenzyme from skeletal muscle and the aldolase enzyme, are frequently elevated in severe hypothyroidism.

Prolactin

Prolactin may be elevated in primary hypothyroidism. This is thought to be caused by overlap secretion due to stimulation of the lactotroph by the elevated TRH level. The decreased clearance of prolactin in hypothyroidism may also play a contributory role. The elevated prolactin level leads to decreased gonadotropin secretion and decreased responsiveness to GnRH. The result of this is anovulatory cycles with menstrual abnormalities, galactorrhea, and infertility in some patients.

Additional studies

Other studies may be performed in the evaluation of complications of primary hypothyroidism (when indicated). These tests are usually not performed and are not necessary in routine diagnosis or evaluation of hypothyroid patients.

- Chest radiograph - May show small pleural effusions
- Electrocardiogram (ECG) - May show low-voltage QRS tracing, nonspecific ST-wave changes, and premature ventricular contractions; prolongation of the QT interval with torsade de pointes and ventricular tachycardia may be noted
- Echocardiogram - May show some pericardial effusion in severe cases of hypothyroidism

Management

Pharmacotherapy

The treatment of choice for Hashimoto thyroiditis (or hypothyroidism from any cause) is thyroid hormone replacement. The drug of choice is individually tailored and titrated levothyroxine sodium administered orally, usually for life.

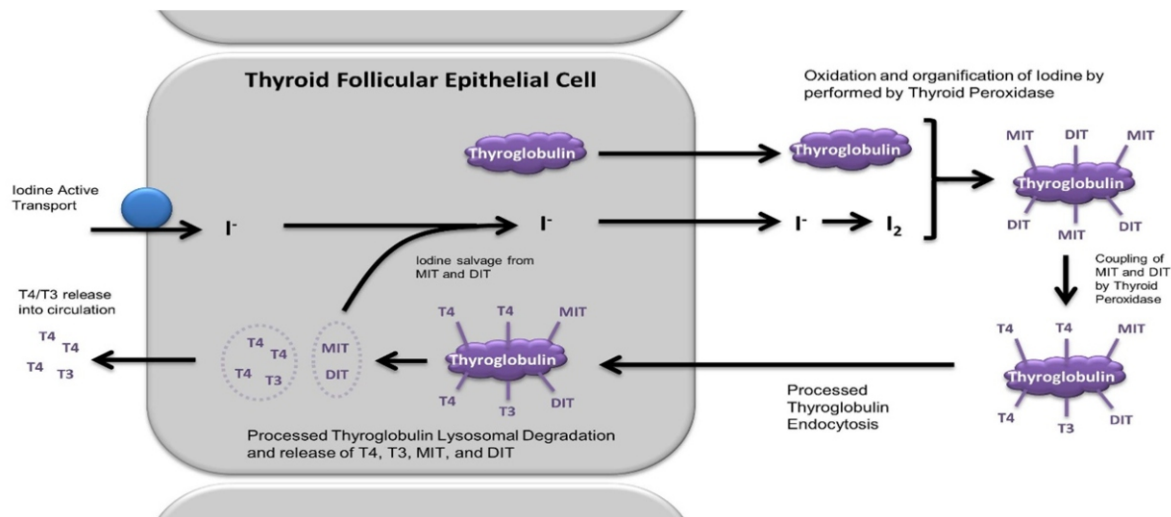
Surgery

Indications for surgery include the following:

- A large goiter with obstructive symptoms, such as dysphagia, voice hoarseness, and stridor, caused by extrinsic obstruction of airflow
- Presence of a malignant nodule, as demonstrated by cytologic examination
- Presence of a lymphoma diagnosed on fine-needle aspiration
- Cosmetic reasons (eg, large, unsightly goiters).

INTERPRETATION

THYROID HORMONES SYNTHESIS



THYROID HORMONES SYNTHESIS/ PATHWAY

- Thyroid Hormones are amine hormones and so their synthesis is based on the amino acid tyrosine. The primary synthetic organ of Thyroid Hormones is the thyroid gland which produces about twenty times more T₄ compared to T₃. T₄ is then converted to either T₃ or rT₃ by the enzyme 'Iodinase' which is present throughout the body's tissues.
- The thyroid gland is full of thyroid follicles which are the basic units of thyroid hormone synthesis (For detailed histology see Thyroid Histology). The thyroid follicles are surrounded by a lining of follicular epithelial cells and contain an acellular lumen full of proteinacious material termed the *Thyroid Colloid*. Synthesis of thyroid hormones is a complex multi-step process which possesses steps that occur within the follicular epithelial cells and also within the acellular follicular lumen.

Thyroid Hormones Synthesis Mechanism

- **Iodine Transport**
 - Large amounts of iodine are required for synthesis of physiological levels of thyroid hormones. To generate sufficient concentrations of iodine, the ionic form of the atom, Iodide (I⁻) is actively transported from the blood stream into the follicular lumen by the Follicular Epithelial Cells. Consequently, Iodide is highly concentrated in the thyroid gland compared to the rest of the body.
- **Thyroglobulin Synthesis**
 - Thyroglobulin is a protein that contains large numbers of tyrosine amino acids that go on to become individual thyroid hormone molecules. Thyroglobulin is synthesized within the follicular epithelial cell and secreted into the follicular lumen.
- **Thyroid Peroxidase**
 - Thyroid Peroxidase is an enzyme present in the acellular colloid of the follicular lumen and performs several key reactions. Thyroid Peroxidase first generates I₂ by oxidizing I⁻ ions present in the follicular lumen. Thyroid Peroxidase then "organifies" the generated I₂ by covalently linking it with the tyrosine residues present in Thyroglobulin. This generates either single or doubly-

iodinated species of tyrosine, termed "Monoiodotyrosine (MIT)" and "Diiodotyrosine (DIT)", respectively

- Peroxidase then combines MIT and DIT residues to generate T₄ or T₃ species within the thyroglobulin protein, a process termed "Coupling". T₄ is generated by combining two DIT residues while T₃ is generated by combining one DIT residue with one MIT residue. Importantly, peroxidase is much more efficient at combining of two DIT residues and thus generation of T₄ occurs much more readily, explaining why the thyroid gland primarily produces T₄ rather than T₃. Notably, some MIT and DIT residues do not get coupled and so peroxidase-processed thyroglobulin will retain some MIT and DIT residues.
- **Endocytosis of Peroxidase-processed Thyroglobulin**
 - Peroxidase-processed thyroglobulin is then endocytosed by follicular epithelial cells on a regulated basis whenever the thyroid gland is stimulated to release thyroid hormone into the circulation. Importantly, peroxidase-processed thyroglobulin within the follicle can act as a reservoir for thyroid hormones in the absence of stimulation for hormone release. Importantly, this reservoir of peroxidase-processed thyroglobulin is usually enough for months of use explaining why defects in thyroid hormone synthesis often take months to become clinically apparent.
- **Release of T₄ and T₃ from Thyroglobulin**
 - Once endocytosed into the follicular epithelial Cell, the thyroglobulin is broken down by lysosomes, thus releasing attached T₄, T₃, MIT, and DIT. T₄ and T₃ are then transported out of the follicular epithelial cells and into the circulation. The iodine atoms of MIT and DIT are salvaged and transported back into the follicular lumen as I⁻.

Name of Marker	Normal Range
TSH	0.4 to 7.0 µU/ml
T4	5-13.0 µg/dL
T3	0.5 to 2.0 ng/ml
FT3	1.52 to 4.21 pg/ml
FT4	0.65 to 1.97 µg/dL

TROUBLESHOOTING

TROUBLESHOOTING THYROID HORMONE RESULTS

What are Normal Thyroid Hormone Levels?

What is thyroid hormone?

Thyroid hormone is made by the thyroid gland, a butterfly-shaped endocrine gland normally located in the lower front of the neck. Thyroid hormone is released into the blood where it is carried to all the tissues in the body. It helps the body use energy, stay warm and keeps the brain, heart, muscles, and other organs working as they should. **Thyroid hormone exists in two main forms: thyroxine (T4) and triiodothyronine (T3).** T4 is the primary form of thyroid hormone circulating in the blood (about 95%). To exert its effects, T4 is converted to T3 by the removal of an iodine atom; this occurs mainly in the liver and in certain tissues where T3 acts, such as in the brain. T3 normally accounts for about 5% of thyroid hormone circulating in the blood. **Most thyroid hormone in the blood is bound by protein**, while only a small fraction is “free” to enter tissues and have a biologic effect. Thyroid tests may measure total (protein bound and free) or free hormone levels. **Production of thyroid hormone by the thyroid gland** is controlled by the pituitary, another endocrine gland in the brain. The pituitary releases Thyroid Stimulating Hormone (abbreviated TSH) into the blood to stimulate the thyroid to make more thyroid hormone. The amount of TSH that the pituitary sends into the bloodstream depends on the amount of thyroid hormone in the body. Like a thermostat, if the pituitary sense low thyroid hormone, then it produces more TSH to tell the thyroid gland to produce more. Once the T4 in the bloodstream goes above a certain level, the pituitary's production of TSH is shut off. In this way, the pituitary senses and controls thyroid gland production of thyroid hormone. Endocrinologists use a combination of thyroid hormone and TSH testing to understand thyroid hormone levels in the body.

What is a TSH test?

Thyroid tests

Blood tests to measure thyroid hormones are readily available and widely used. Not all thyroid tests are useful in all situations.

TSH Test

The best way to initially test thyroid function is to measure the TSH (Thyroid Stimulating Hormone) level in a blood sample. Changes in TSH can serve as an “early warning system” – often occurring before the actual level of thyroid hormones in the body becomes too high or too low. **A high TSH level indicates** that the thyroid gland is not making enough thyroid hormone (primary hypothyroidism). On the other hand, a low TSH level usually indicates that the thyroid is producing too much thyroid hormone (hyperthyroidism). Occasionally, a low TSH may result from an abnormality in the pituitary gland, which prevents it from making enough TSH to stimulate the thyroid (central hypothyroidism). In most healthy individuals, a normal TSH value means that the thyroid is functioning properly.

What is a T4 test?

T4 Tests

A **Total T4** test measures the bound and free thyroxine (T4) hormone in the blood. A **Free T4** measures what is not bound and able to freely enter and affect the body tissues.

What does it mean if T4 levels are abnormal?

Importantly, Total T4 levels are affected by medications and medical conditions that change thyroid hormone binding proteins. Estrogen, oral contraceptive pills, pregnancy, liver disease, and hepatitis C virus infection are common causes of *increased* thyroid hormone binding proteins and will result in a high Total T4. Testosterone or androgens and anabolic steroids are common causes of *decreased* thyroid hormone binding proteins and will result in a low Total T4. **In some circumstances, like pregnancy**, a person may have normal thyroid function but Total T4 levels outside of the normal reference range. Tests measuring free T4 – either a free T4 (FT4) or free T4 index (FTI) – may more accurately reflect how the thyroid gland is functioning in these circumstances. An endocrinologist can determine when thyroid disease is present in the context of abnormal thyroid binding proteins.

What is a T3 test?

T3 Tests

T3 tests measure triiodothyronine (T3) levels in the blood. A Total T3 test measures the bound and free fractions of triiodothyronine. Hyperthyroid patients typically have an elevated Total T3 level. T3 tests can be used to support a diagnosis of hyperthyroidism and can determine the severity hyperthyroidism. **In some thyroid diseases**, the proportions of T3 and T4 in the blood change and can provide diagnostic information. A pattern of increased T3 vs T4 is characteristic of Graves' disease. On the other hand, medications like steroids and amiodarone, and severe illness can decrease the amount of thyroid hormone the body converts from T4 to T3 (active form) resulting in a lower proportion of T3. **T3 levels fall late in the course of hypothyroidism** and therefore are not routinely used to evaluate patients with underactive or surgically absent thyroid glands. **Measurement of Free T3 is possible**, but is often not reliable and therefore may not be helpful.

What is reverse T3?

REVERSE T3

Reverse T3 is a biologically inactive protein that is structurally very similar to T3, but the iodine atoms are placed in different locations, which makes it inactive. Some reverse T3 is produced normally in the body, but is then rapidly degraded. In healthy, non-hospitalized people, measurement of reverse T3 does not help determine whether hypothyroidism exists or not, and is not clinically useful.

What is a normal thyroid (hormone) level?

Tests often used to assess thyroid hormone status include TSH and FT4 tests. The normal value for a laboratory test is determined by measuring the hormone in a large population of healthy individuals and finding the normal reference range. Normal ranges for thyroid tests may vary slightly among different laboratories, and typical ranges for common tests are given below. **TSH normal values are 0.5 to 5.0 mIU/L.** Pregnancy, a history of thyroid cancer, history of pituitary gland disease, and older age are some situations when TSH is optimally maintained in different range as guided by an endocrinologist. **FT4 normal values are 0.7 to 1.9ng/dL.** Individuals taking medications that modify thyroid hormone metabolism and those with a history of thyroid cancer or pituitary disease may be optimally managed with a different normal FT4 range. **Total T4 and Total T3 levels measure bound and free thyroid hormone** in the blood. These levels are influenced by many factors that affect protein levels in the body, including medications, sex hormones, and liver disease.

A normal Total T4 level in adults ranges from 5.0 to 12.0 µg/dL.

A normal Total T3 level in adults ranges from 80-220 ng/dL.

Free T3 assays are often unreliable and not routinely used to assess thyroid function.

What does it mean if my thyroid levels are abnormal?

Lab results	Consider...
High TSH, low thyroid hormone level	Primary hypothyroidism
High TSH, normal thyroid hormone level	Subclinical hypothyroidism
Low TSH, high thyroid hormone level	Primary hyperthyroidism
Low TSH, normal thyroid hormone level	Early or mild hyperthyroidism
Low TSH, high thyroid hormone level Followed by... High TSH, low thyroid hormone level	Thyroiditis (Thyroid Inflammation)
Low TSH, low thyroid hormone level	Pituitary disease

Patterns of thyroid tests associated with thyroid disease

Primary Hypothyroidism

A high TSH and low thyroid hormone level (e.g. low FT4) can indicate primary hypothyroidism. Primary hypothyroidism occurs when the thyroid gland makes too little thyroid hormone. Symptoms of hyperthyroidism can include feeling cold, constipation, weight gain, slowed thinking, and decreased energy.

Causes of primary **hypothyroidism** include:

- Autoimmune thyroid disease, including Hashimoto's thyroiditis
- Thyroid gland dysfunction due to a medication (e.g. amiodarone, tyrosine kinase inhibitors, or cancer immunotherapy)
- Removal of all or part of the thyroid gland
- Radiation injury to the thyroid (e.g. external beam radiation, radioactive iodine ablation treatment)
- Excess treatment with anti-thyroid medications (e.g. methimazole, propylthiouracil)

Early or mild hypothyroidism may present as a persistently elevated TSH and a normal FT4 hormone level. This pattern is called subclinical hypothyroidism and your doctor may recommend treatment. Over time, untreated subclinical hypothyroidism can contribute to heart disease. **It is important to remember that** normal TSH levels in older individuals (ages 70 and above) are higher than the normal ranges for younger individuals.

Primary Hyperthyroidism

A low TSH and a high thyroid hormone level (e.g. high FT4) can indicate primary hyperthyroidism. Primary **hyperthyroidism** occurs when the thyroid gland makes or releases too much thyroid hormone. Symptoms of hyperthyroidism can include tremors, palpitations, restlessness, feeling too warm, frequent bowel movements, disrupted sleep, and unintentional weight loss.

Causes of primary **hyperthyroidism** include:

- Graves' disease
- Toxic or autonomously functioning thyroid nodule
- Multinodular goiter
- Thyroid inflammation (called thyroiditis) early in the course of disease

- Thyroid gland dysfunction due to a medication (e.g. amiodarone or cancer immunotherapy)
- Excess thyroid hormone therapy

Early or mild hyperthyroidism may present as a persistently low TSH and a normal FT4 hormone level. This pattern is called **subclinical hyperthyroidism** and your doctor may recommend treatment. Over time, untreated subclinical hyperthyroidism can worsen osteoporosis and contribute to abnormal heart rhythms.

Thyroiditis

Thyroid inflammation, also called thyroiditis, causes injury to the thyroid gland and release of thyroid hormone. Individuals with thyroiditis usually have a brief period of hyperthyroidism (low TSH and high FT4 or Total T4) followed by development of hypothyroidism (high TSH and low FT4 or Total T4) or resolution. **Some forms of thyroiditis are transient**, like post-partum thyroiditis or thyroiditis following an infection, and often resolve on their own without need for medication. **Other forms of thyroiditis, like thyroiditis resulting from cancer immunotherapy, interferon alpha, or tyrosine kinase inhibitors, usually result in permanent hypothyroidism and require long term treatment with thyroid hormone replacement. Your endocrinologist will monitor your thyroid tests** during thyroiditis and can help determine if you need short and long term medications to balance your thyroid function and control any symptoms.

Central Hypothyroidism

A low TSH and a low FT4 may indicate pituitary disease. Detection of central hypothyroidism should prompt your doctor to check for problems in other pituitary hormones, an underlying cause, and you may need imaging tests to look at the pituitary gland. **Central hypothyroidism is treated with thyroid hormone replacement.** Importantly, adequacy of thyroid replacement in central hyperthyroidism is assessed with FT4 and Total T4 tests not TSH as in primary hyperthyroidism, and deficiency in stress hormone cortisol should be assessed before starting thyroid treatment to prevent an adrenal crisis. **Causes of central hypothyroidism include** pituitary gland disease, such as a pituitary mass or tumor, history of pituitary surgery or radiation, pituitary inflammation (called hypophysitis) resulting from autoimmune disease or cancer immunotherapy, and infiltrative diseases.

Rare causes of abnormal thyroid function

- Thyroid hormone resistance
- Iodine induced hyperthyroidism
- TSH-secreting tumor (TSH-oma)
- Germ cell tumors
- Trophoblastic disease
- Infiltrative diseases, such as systemic scleroderma, hemochromatosis, or amyloidosis

What to do if thyroid tests are abnormal, but patient feels fine.

Or...

When thyroid tests are abnormal, but clinician says there is no thyroid problem.

What does it mean?

While blood tests to measure thyroid hormones and thyroid stimulating hormone (TSH) are widely available, it is important to remember that not all tests are useful in all circumstances and many factors including medications, supplements, and non-thyroid medical conditions can affect thyroid test results. **An endocrinologist can help you make sense of thyroid test results** when there is a discrepancy between your results and how you feel. A good first step is often to repeat the test and ensure there

are no medications that might interfere with the test results. Below are some common reasons for mismatch between thyroid tests and thyroid disease.

When abnormal thyroid function tests are not due to thyroid disease

Non-thyroidal illness

Significant illness, such as an infection, cancer, heart failure, or kidney disease, or recent recovery from an illness can cause changes transient changes in the TSH. Fasting or starvation can also cause a low TSH. An endocrinologist can help to interpret changes in thyroid function tests in these circumstances to distinguish non-thyroid illness from true thyroid dysfunction.

Test interference

Biotin, a common supplement for hair and nail growth, interferes with many thyroid function tests and can lead to inaccurate results. Endocrinologists recommend stopping biotin supplements for 3 days before having a blood test for thyroid function. **Individuals who have exposure to mice**, like laboratory researchers and veterinarians, may develop antibodies against mouse proteins in their blood. These antibodies cross react with reagents in multiple thyroid function tests and cause unpredictable results. A specialized assay can accurately measure thyroid hormone levels and TSH in this circumstance.

Hypothyroidism Treatment

What is thyroid medication?

Thyroid Hormone Treatment

Levothyroxine is the standard of care in thyroid hormone replacement therapy and treatment of hypothyroidism. Levothyroxine (also called LT4) is equivalent to the T4 form of naturally occurring thyroid hormone and is available in generic and brand name forms.

How to take levothyroxine?

To optimize absorption of your thyroid medication, it should be taken with water at a regular time each day. Multiple medications and supplements decrease absorption of thyroid hormone and should be taken 3-4 hours apart, including calcium and iron supplements, proton pump inhibitors, soy, and multivitamins with minerals. Because of the way levothyroxine is metabolized by the body, your doctor may ask you to take an extra pill or skip a pill on some days of the week. This helps us to fine tune your medication dose for your body and should be guided by an endocrinologist. **For patients with celiac disease** (autoimmune disease against gluten) or gluten sensitivity, a gluten free formulation of levothyroxine is available. **Some individuals may have genetic variant** that affects how the body converts T4 to T3 and these individuals may benefit from the addition of a small dose of triiodothyronine.

Liothyronine is replacement T3 (triiodothyronine) thyroid hormone. This medication has a short half-life and is taken twice per day or in combination with levothyroxine. Liothyronine alone is not used for treatment of hypothyroidism long term.

Other formulations of thyroid hormone replacement include **natural or desiccated thyroid hormone extracts** from animal sources. Natural or desiccated thyroid extract preparations have greater variability in the dose of thyroid hormone between batches and imbalanced ratios of T4 vs T3. Natural or animal sources of thyroid hormone typically contain 75% T4 and 25% T3, compared to the normal human balance of 95% T4 and 5% T3. Treatment with a correct balance of T4 and T3 is important to replicate normal thyroid function and prevent adverse effects of excess T3, including osteoporosis, heart problems, and mood and sleep disturbance. An endocrinologist can evaluate symptoms and thyroid tests to help balance thyroid hormone medications.

How to verify if the thyroid dose is correct?

Monitoring thyroid levels on medication

Correct dosing of thyroid hormone is usually assessed using the same tests for diagnosis of thyroid disease, including TSH and FT4. Thyroid tests are typically checked every 4-6 weeks initially and then every 6 to 12 months once stable. In special circumstances, such as pregnancy, a history of thyroid cancer, central hypothyroidism, amiodarone therapy, or use of combination T4 and T3 thyroid hormone replacement, your endocrinologist may check different thyroid tests. Additionally, your endocrinologist will evaluate for symptoms of hyperthyroidism and hypothyroidism and perform a physical exam. **Women who are pregnant and women who may become pregnant** should only be treated with levothyroxine (T4). Only T4 efficiently crosses the placenta to provide thyroid hormone to the developing fetus. Thyroid hormone is critical in early pregnancy for brain development. Normal ranges for thyroid tests in pregnancy are different and change by trimester. Women with thyroid disease in pregnancy or who are considering pregnancy should be under the care of an endocrinologist to guide therapy. **Individuals with a history of thyroid cancer**, even if only a portion of the thyroid was removed, also have different target ranges for TSH and FT4 tests. Thyroid hormone replacement in these individuals is closely tied to ongoing thyroid cancer surveillance, monitoring of thyroid cancer tumor markers, and dynamic assessment of recurrence risk. These patients are optimally managed by a multidisciplinary team including an endocrinologist and endocrine surgeon.

BOUQUET

Wisdom Whispers



In Lighter Vein

The police pulled me over and asked me 'you know how fast you were going?' I said obviously not fast enough because you caught me.



Police: Where do u live?
 Me: With my parents.
 Police: Where do your parents live?
 Me: With Me.
 Police: Where do you all live?
 Me: Together.
 Police: Where is your house?
 Me: Next to my neighbors house.
 Police: Where is your neighbors house?
 Me: You won't believe me if I tell you.
 Police: Tell Me!
 Me: Next to my house.



So the cops came to my house today and said your dog was chasing someone on a bike i said "My dog doesn't have a bike!"



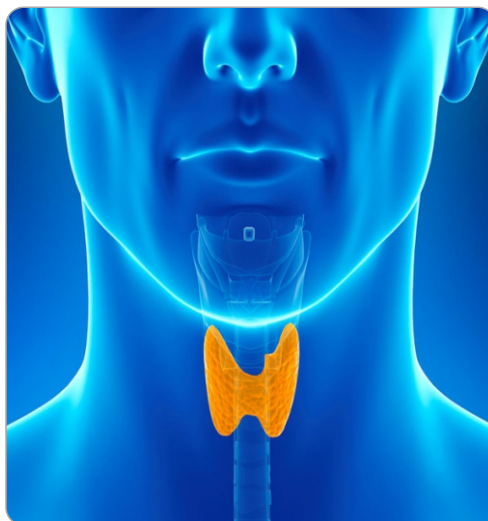
Rabbits jump and they live for 8 years.
 Dogs run and they live for 15 years.
 Turtles do nothing and live for 150 years.
 Lesson learned.



Brain Teasers

- What are the features of hypothyroidism?
 - A. Constipation
 - B. Bradycardia
 - C. Weight gain
 - D. All of the above.
- What are the indications for ordering thyroid function tests?
 - A. Abnormal weight loss or gain
 - B. Tiredness, lethargy, intolerance to cold
 - C. Constipation, bradycardia, increased menstruation
 - D. All of the above.
- If needed which is the single test from amongst the TFTs that can be ordered?
 - A. T3
 - B. T4
 - C. TSH
 - D. FT3
- FT3 is reduced in.
 - A. Primary hypothyroidism
 - B. Hyperthyroidism
 - C. Graves disease
 - D. Hashimotos thyroiditis.

ANSWER: 1:D; 2:D; 3:C; 4:A

Tulip Introduces**Thyroid Immunoassays****ELISA****Qualisa T3****Qualisa T4****Qualisa TSH****Qualisa fT3****Qualisa fT4****Qualisa U-TSH****MICROWELL CLIA****Electra T3****Electra T4****Electra TSH****Electra fT3****Electra fT4****Electra U-TSH****Tulip's Thyroid Immunoassays offers...**

- **CAPS - Common Assay Protocol Strategy**
CAP of all Thyroid Assays facilitates the user to perform multiple tests simultaneously & increase throughput.
- **Turn Around Time (TAT)**
Shortest turn around time with accurate & reliable results.
- **Stable Calibration**
Calibration stability up to 45 days.
- **Ease of Use**
*Ready to use Substrate in Elisa.
Electra workstation for organised & faster pipetting.*

**Better Testing System For Better Diagnostics**

Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA.
E-mail: sales@tulipgroup.com Website: www.tulipgroup.com

orchid



Microexpress®

Coral Clinical Systems

BioShields®



Viola