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CLIABook II

Know more about the thyroid

Content

Know more about the thyroid

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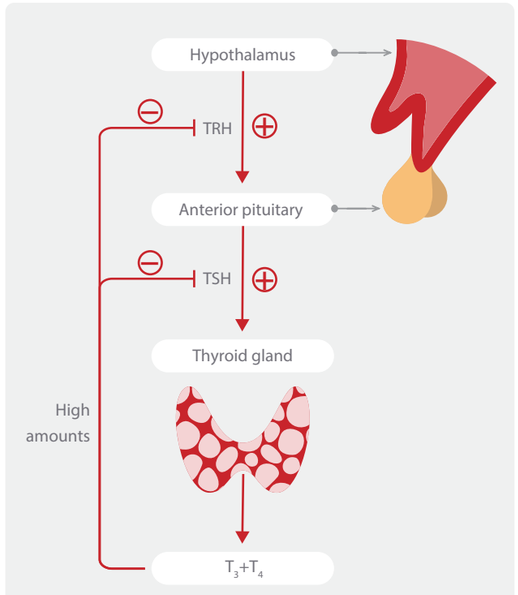
The thyroid gland is a butterfly-shaped endocrine gland and located anterior and inferior to the larynx. It produces two types of hormones, i.e., tri-iodothyronine or T3, thyroxine or T4, and calcitonin. T3 and T4 are tyrosine-based iodine-containing hormones that help regulate our body's metabolism.

T3 helps to speed up the basal metabolic rate, especially when we have to adapt to the environment. Thyroid hormones help activate the sympathetic nervous system, which is responsible for the fight or flight response. This increases cardiac output, respiratory rate, and mental alertness. And hyroid hormones also play a part in increasing sebaceous and sweat gland secretion, and promoting hair follicle growth. Moreover, they play a very important developmental role by working synergistically with growth hormone to promote long bone growth, and they also are necessary for normal brain development.

Production and secretion of thyroid hormones is under control of the hypothalamus-pituitary axis. The following figure illustrates the negative feedback loop which regulates thyroid hormone secretion.



In order to work properly, the levels of thyroid hormones must be kept within the normal range. To that end, the body uses negative feedback, which means that high levels of thyroid hormones tell the hypothalamus and anterior pituitary gland to stop their secretion of TRH and TSH, respectively, lowering thyroid hormone secretion from the thyroid gland.

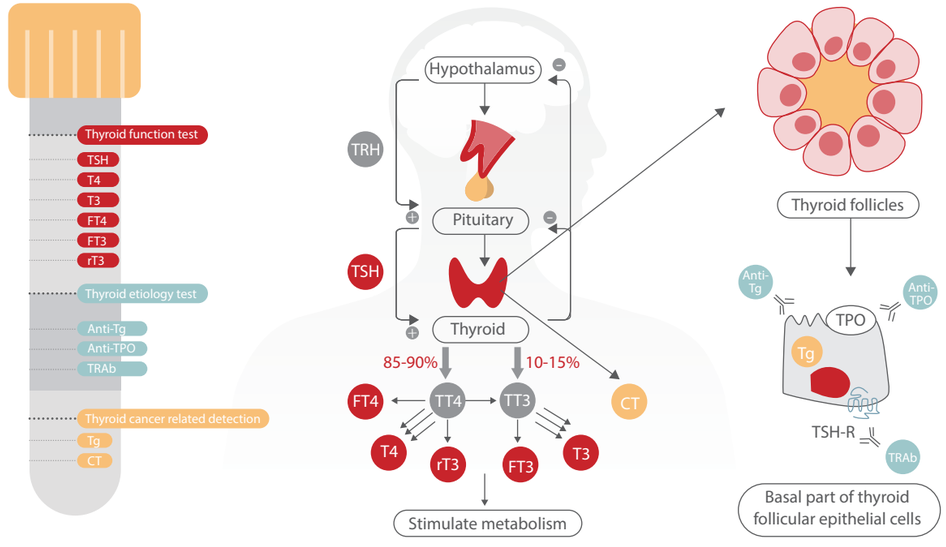
Thyroid disorders are conditions that affect the thyroid gland. Different types of thyroid disorders can affect the structure or function of the thyroid gland. Since the thyroid gland is controlled by the pituitary gland and hypothalamus, disorders of these tissues can also affect thyroid function and cause thyroid problems.

Some of the common types of thyroid disorders are:

1. Hypothyroidism: Hypothyroidism is a result of the thyroid gland producing an insufficient amount of thyroid hormone. It can develop from problems within the thyroid gland, pituitary gland, or hypothalamus. Some common causes of hypothyroidism include: Hashimoto's thyroiditis, thyroid hormone resistance and other types of thyroiditis, such as acute thyroiditis and postpartum thyroiditis.
2. Hyperthyroidism: Hyperthyroidism describes excessive production of thyroid hormone, a less common condition than hypothyroidism. Some of the most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, excessive iodine consumption and thyroid nodules that overexpress thyroid hormone (known as "hot" nodules).
3. Goiters: A goiter simply describe enlargement of the thyroid gland, regardless of cause. A goiter is not a specific disease. It may be associated with hypothyroidism, hyperthyroidism, or normal thyroid function.
4. Thyroid nodules: A thyroid nodule is lump or abnormal mass within the thyroid. Nodules can be caused by benign cysts, benign tumors, or, less commonly, by cancers of the thyroid. Nodules may be single or multiple and can vary in size.
5. Thyroid cancer: Thyroid cancer is far more common in adult women than in men or youth. There are different kinds of thyroid cancer, depending upon the specific cell type within the thyroid that has become cancerous.

How are thyroid disorders diagnosed? In addition to thorough medical history and physical exams, several specialized tests, like blood tests, imaging tests, thyroid scans, fine needle aspiration and biopsy, are used to diagnose thyroid disorders. Blood tests are typically and essentially done to measure levels of thyroid hormones and TSH. Blood tests to identify antibodies against thyroid tissue may also be ordered by your doctors, such as titers of anti-thyroglobulin, anti-thyroperoxidase, or TSH receptor stimulating antibodies (TRAb).

Mindray provides a complete package of thyroid blood tests for patients, including TSH, T3, T4, FT3, FT4, reverse T3, anti-TPO, anti-Tg, Tg and TRAb (coming soon). It provides a discussion of the role of thyroid blood tests in patients with autoimmune thyroid diseases or thyroid cancers and an analysis of the reference ranges of thyroid hormones in different populations. Meanwhile, the book also discusses the value of reverse T3 (rT3) for Euthyroid Sick Syndrome (ESS) and lists some of the articles published by Mindray in recent years. I hope you find this book a useful tool for diagnosing thyroid disorders.



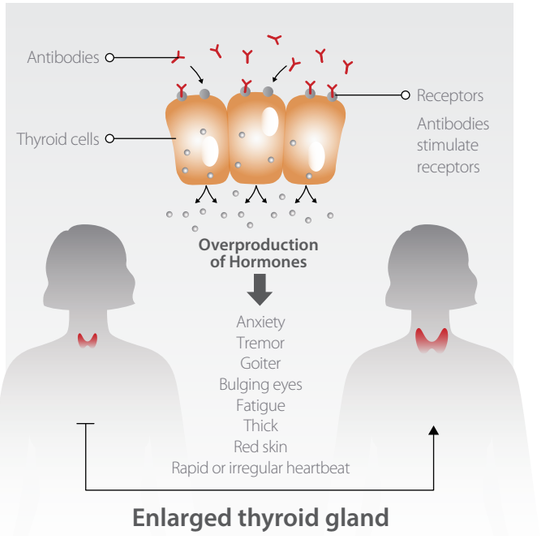
Two main types of autoimmune thyroid disease and roles of serological tests

Autoimmune thyroid disease (AITD), which includes Graves' disease (GD) and Hashimoto's thyroiditis (HT), affects an estimated 5% of the general population, making it one of the most prevalent autoimmune diseases[1].

Graves' disease

What is Graves' disease ?

Graves' disease is an immune system disorder that is the most common cause of hyperthyroidism.



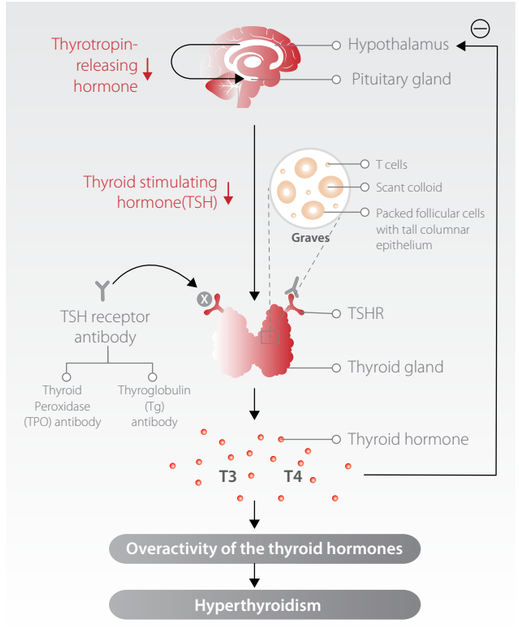
Overview

Graves' disease is characterized by abnormal goiter and hyperthyroidism. With Graves' disease, the immune system attacks the thyroid gland, causing it to produce more thyroid hormones than that is needed by the body and thereby speeding up many body functions. Overproduction of thyroid hormones can affect many body systems, causing signs and symptoms that can vary widely from one person to another. Common symptoms of Graves' disease include hyperthyroidism, eye disease and skin disease. Although Graves' disease may affect anyone, it occurs more common in women and younger age groups.

The hallmark of GD is the presence of the stimulating Thyroid Stimulating Hormone Receptor (TSHR) antibodies.

An eye-catching hypothesis is that Graves' disease is triggered by a defect in negative selection of autoreactive T cells to the TSHR. A number of genetic variants associated with Graves' disease were shown to impact central tolerance (TSHR) or peripheral tolerance (FOXP3 and CD25)[2]. TSHR antibodies are currently classified further into stimulating, blocking and neutral antibodies, depending on their ability to bind with different types of epitopes and the diversity of their biological actions. Stimulating TSHR antibodies cause the hyperthyroidism of Graves' disease.

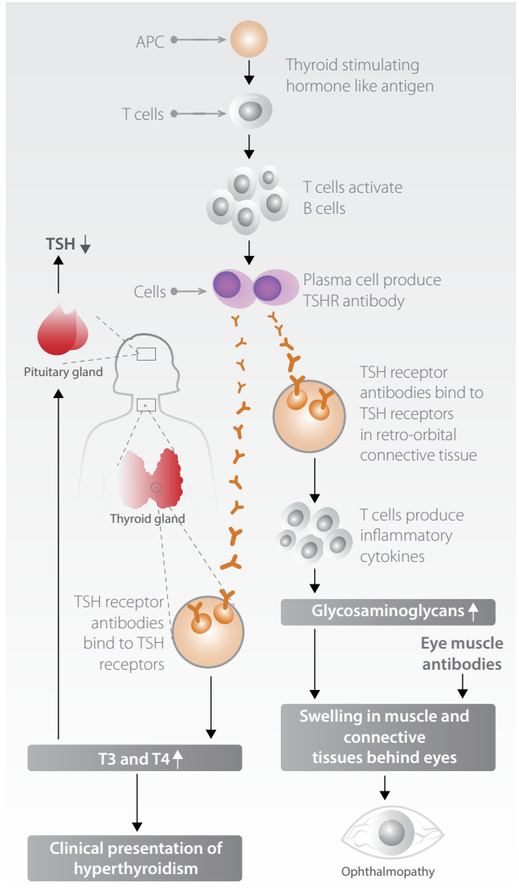
Pathophysiology process of Graves' disease



A normal thyroid gland is made up of follicular cells which form the inner colloid where thyroid hormone is produced. In Graves' disease, follicular cells are packed and squeezed together to become tall cells. This subsequently causes a scant colloid. Furthermore, lymphocytic infiltration is present in Graves' disease.

Where do these autoantibodies come from?

The Antigen-presenting Cell (APC) in this context may present TSHR like antigen, which will activate plasma cells to produce TSHR autoantibodies. Actually, these autoantibodies act similarly to thyroid stimulating hormones but limited to thyroid ones only. Due to the presence of stimulating hormones like receptors all around our body, particularly the eyes and the legs, cross reactivity may occur to cause ophthalmopathy or dermopathy.

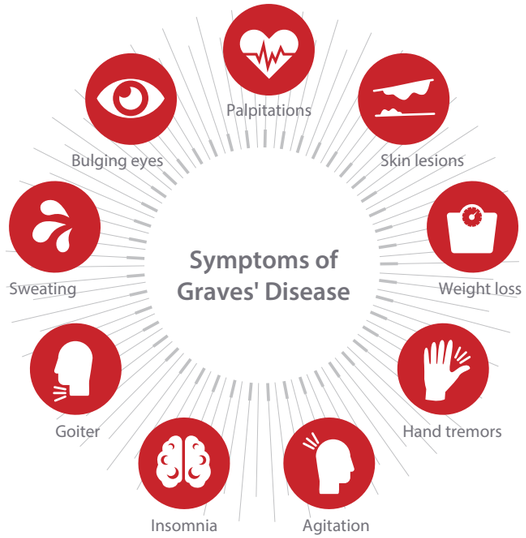


Who is more likely to have Graves' disease?

AITD is much more common in women than in men, with a female: male ratio ranging from 5:1 to 10:1[3]. Graves' disease is more common in women, those older than age 30[4], and those with a family history of Graves' or Hashimoto's disease. Other autoimmune disorders, such as vitiligo, autoimmune gastritis, type 1 diabetes and rheumatoid arthritis, are associated with the use of nicotine products[5,6].

What are the symptoms and complications of Graves' disease?

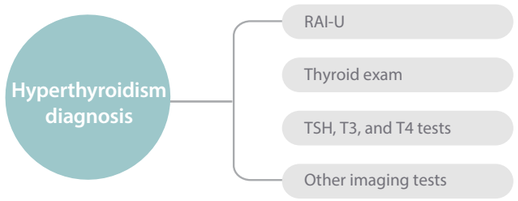
Graves' disease can cause hyperthyroidism and is characterized by increase in metabolic rate and increase in sympathetic activity[7,8].



How do doctors diagnose Graves' disease?

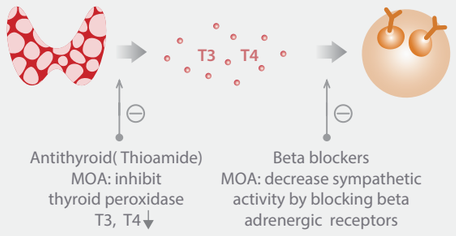
The diagnosis of hyperthyroidism is performed based on symptoms and physical signs and confirmed by a laboratory test. First, the levels of thyroid hormones (thyroxine/T4, and triiodothyronine/T3) and thyroid-stimulating hormone (TSH) in blood are measured, and then the levels of thyrotropin receptor antibodies (TRAbs) which are antibodies directed against the TSH receptor are measured, the elevation of which confirms the diagnosis of Graves' disease.

A TRAb test helps to diagnose Graves' disease, but may confirm the diagnosis of toxic multinodular goiter. The test is also performed during the last three months of pregnancy to check a baby's risk of being born with Graves' disease or an overactive thyroid.

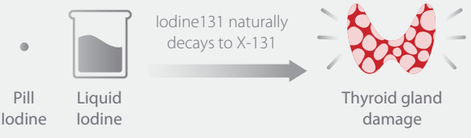


Graves' disease management

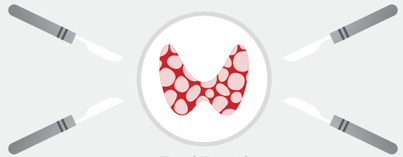
Pharmaceutical therapy



Radioiodine therapy



Surgery- thyroidectomy



- Thionamide drugs
- Beta blockers
- Recurrence/no response to meds → surgery
- Radioactive iodine therapy

Some preanalytical factors should be considered when interpreting thyroid function results as they might be influenced by these factors[9].

Physiological differences

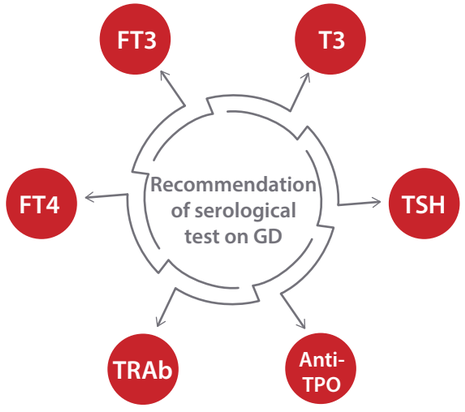
- TSH/FT4 relation
- Age
- Pregnancy
- Biological differences

Pathological differences

- Thyroid dysfunction
- Liver or kidney insufficiency
- Medical treatment
- Systemic disease

Sample-related differences

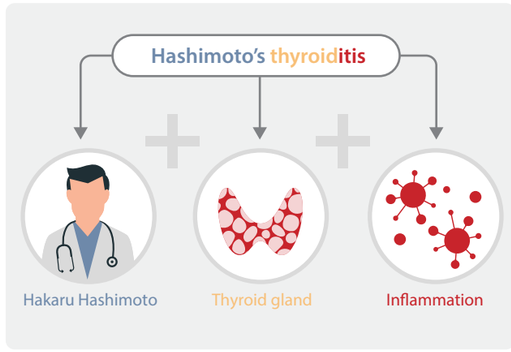
- Interfering factors



Hashimoto's thyroiditis

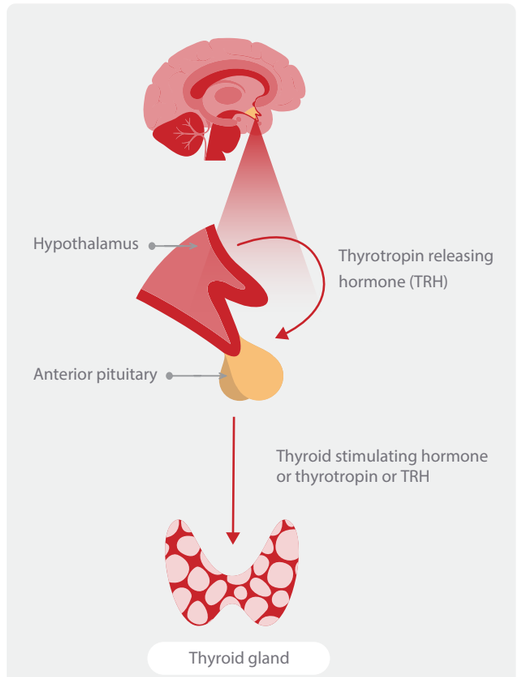
What is Hashimoto's thyroiditis?[10-13]

Hashimoto's thyroiditis, named after the Japanese physician Hakaru Hashimoto who first described it, belongs to a group of disorders where there is some form of inflammation "-itis" of the thyroid gland. It is basically an autoimmune destruction of the thyroid gland, which typically progresses gradually to hypothyroidism, or state of too low "hypo-" thyroid hormones. In fact, Hashimoto's thyroiditis is the most common cause of hypothyroidism in areas of the world where dietary iodine, the basic structural element of thyroid hormones, is sufficient.



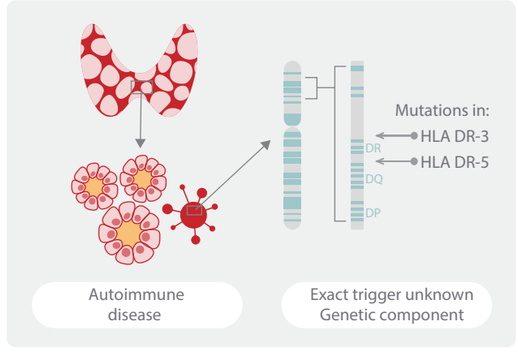
Normally, the hypothalamus, which is located at the base of the brain, secretes thyrotropin-releasing hormone, or TRH, into the hypophyseal portal system - which is a network of capillaries linking the hypothalamus to the anterior pituitary. The anterior pituitary then releases a hormone of its own, called thyroid-stimulating hormone, thyrotropin or simply TSH. TSH stimulates the thyroid gland which is a gland located in the neck that looks like two thumbs hooked together in the shape of a "V".

Thyroid hormones are also involved in a number of other activities, like controlling sebaceous and sweat gland secretion, hair follicle growth, and regulating proteins and mucopolysaccharide synthesis by skin fibroblasts. For all this to work properly, the levels of thyroid hormones have to be kept within the normal range. The body uses negative feedback to achieve that end which means that low levels of thyroid hormones tell the hypothalamus and pituitary gland to increase their secretion of TRH and TSH, respectively.



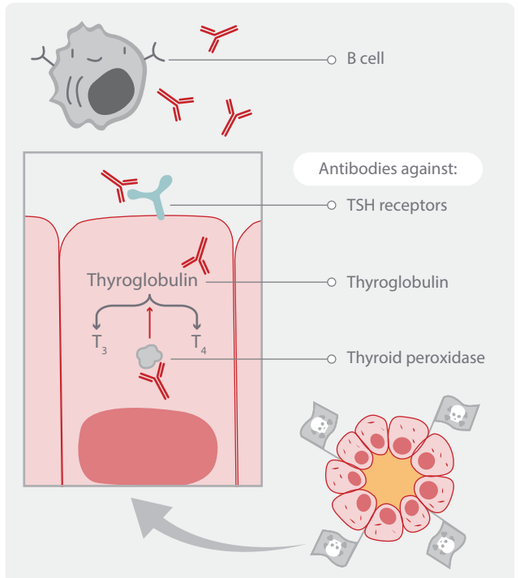
Pathophysiology process of Hashimoto's Disease[14-17]

Now, Hashimoto's thyroiditis is an autoimmune disease, meaning that the immune system goes rogue and starts attacking our own follicular cells in the thyroid. The exact trigger for this response is unknown, but there does seem to be a genetic component. For example, mutations in specific human leukocyte antigen genes called HLA-DR3 and HLA-DR5 are associated with developing Hashimoto's thyroiditis.



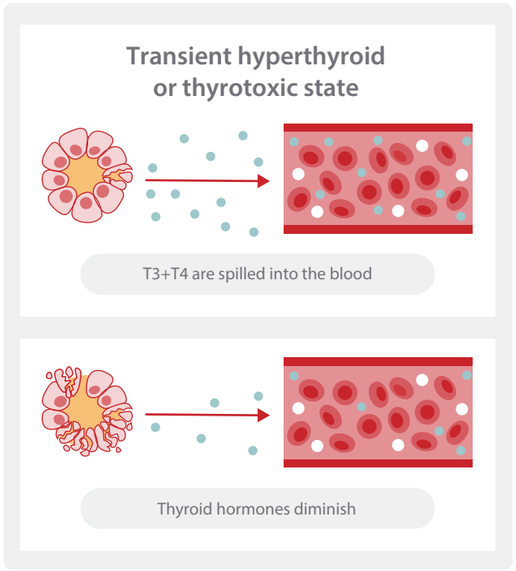
Pathophysiology process of Hashimoto's Disease

When an immune response is triggered by a protein of our own, that protein is called an autoantigen. In Hashimoto's thyroiditis, autoantibodies against thyroid peroxidase, thyroglobulin, or TSH receptors are produced by the activated B cells. These autoantibodies bind to and block those targets to impede normal thyroid function. Meanwhile, CD4+ T-helper cells produce inflammatory cytokines, like interferon-γ, which attract macrophages into the thyroid gland which then cause damage to the follicles. These cytokines also attract another type of T- lymphocytes, called CD8+ cytotoxic T-cells. CD8+ cytotoxic T-cells directly target and destroy thyroid follicular cells.



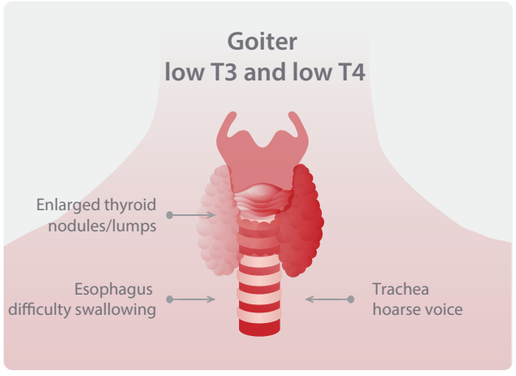
Stages of Hashimoto's Disease[18-19]

The hypothalamus and pituitary gland respond by increasing their TRH and TSH production, but eventually, the thyroid becomes too damaged to produce enough thyroid hormones. Meanwhile, the colloid gets depleted and follicular atrophy, or simply gets smaller. In other words, as the disease progresses, the thyroid gland contains more immune cells and connective tissue, and less functioning thyroid cells.



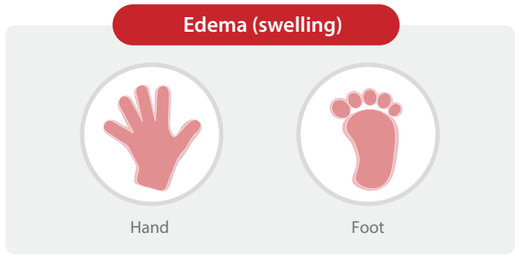
Symptoms of Hashimoto's Disease [20]

Symptoms of Hashimoto's thyroiditis usually start in the hypothyroid phase and are directly related to the low T3 and T4 levels. Individuals often have a goiter, meaning that their thyroid is enlarged and sometimes has nodules, or lumps, which can sometimes press on the trachea, causing voice hoarseness, or on the esophagus, causing difficulty swallowing. The decreased metabolic rate could cause individuals to get tired easily, feel weak and cold, have constipation, and experience rapid weight gain even without any change in diet or exercise. Typically the heart rate and respiratory rate slow down as well.



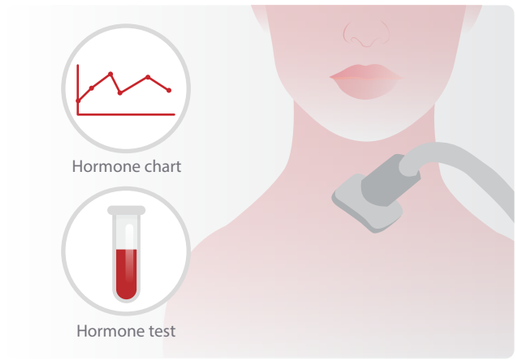
Symptoms of Hashimoto's Disease

The skin can become dry and rough due to decreased sweat secretion, and the hair and nails can become brittle and sometimes fall off. Elevated prolactin levels from the increased thyrotropin-releasing hormone could also cause problems like menstrual abnormalities, galactorrhea, which is a milky nipple discharge, and infertility. In severe cases, myxedema develops, meaning that there is increased deposition of various proteins and mucopolysaccharides in the upper skin layers, leading to edema or swelling, in particular around the eyes, hands and feet.



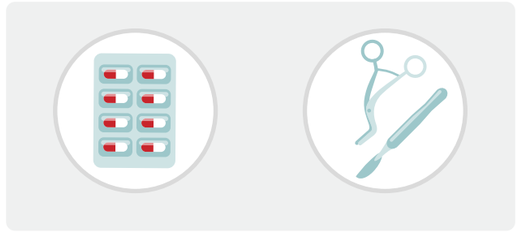
Diagnosis of Hashimoto's Disease[21-23]

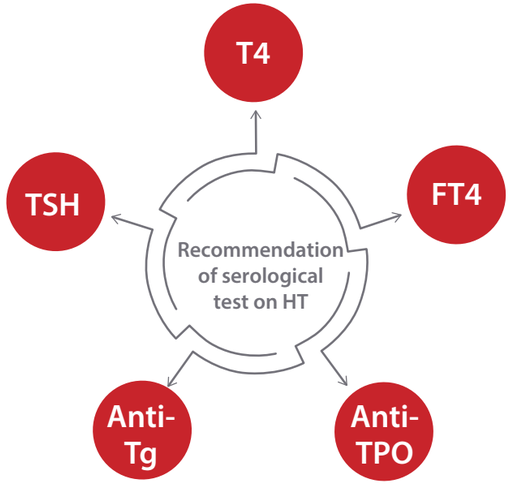
Diagnosis of Hashimoto's thyroiditis is usually based on a combination of low serum levels of free thyroid hormones and increased TSH levels with high levels of the associated autoantibodies, mainly anti-thyroid peroxidase and antithyroglobulin antibodies. Fine- needle aspiration should be used to get a biopsy, when thyroid lymphoma is suspected.



Treatment of Hashimoto's Disease[24]

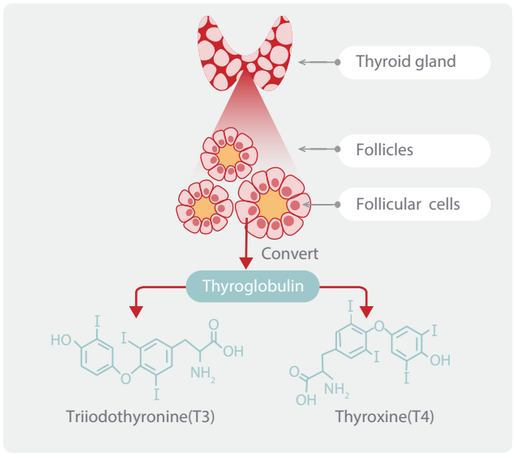
Treatment of Hashimoto's thyroiditis typically requires lifelong thyroid hormone replacement, mainly with levothyroxine. If there is a very large goiter compressing the airways or the esophagus, or if there is suspicion of a lymphoma, then surgical removal may be needed.



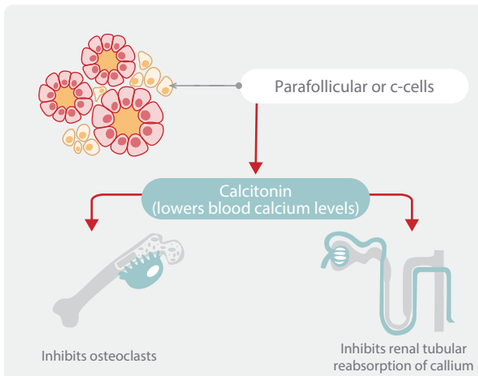


Thyroid cancers and their CLIA tests

Structure and physiology of the thyroid



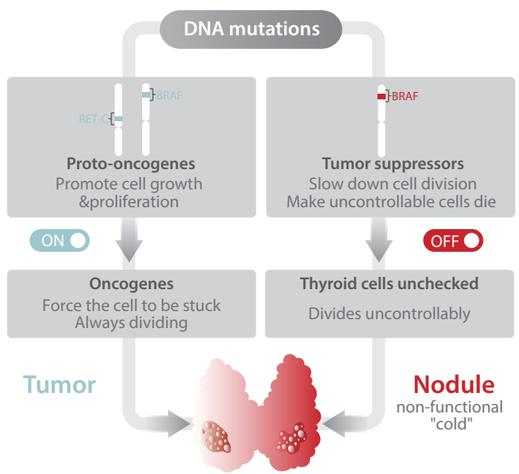
The thyroid gland is an endocrine gland in the neck that produces thyroid hormones. If the cells of the thyroid gland start to divide uncontrollably, then that is considered a thyroid cancer. If we zoom into the thyroid gland, we will find thousands of follicles, which are small hollow spheres whose walls are lined with follicular cells, and are separated by a small amount of connective tissue. Follicular cells convert thyroglobulin, a protein found in follicles, into two iodine-containing hormones, triiodothyronine or T3, and thyroxine or T4[25].



The thyroid is also made up of parafollicular or C cells, which are near the follicles. These cells produce calcitonin, a hormone that lowers blood calcium levels by inhibiting osteoclasts. Osteoclasts are bone cells that break down bone tissue which frees up the calcium to enter the bloodstream. Calcitonin also inhibits renal tubular cell reabsorption of calcium, allowing the calcium to be excreted in the urine. DNA mutations can cause thyroid cells to become cancerous[25].

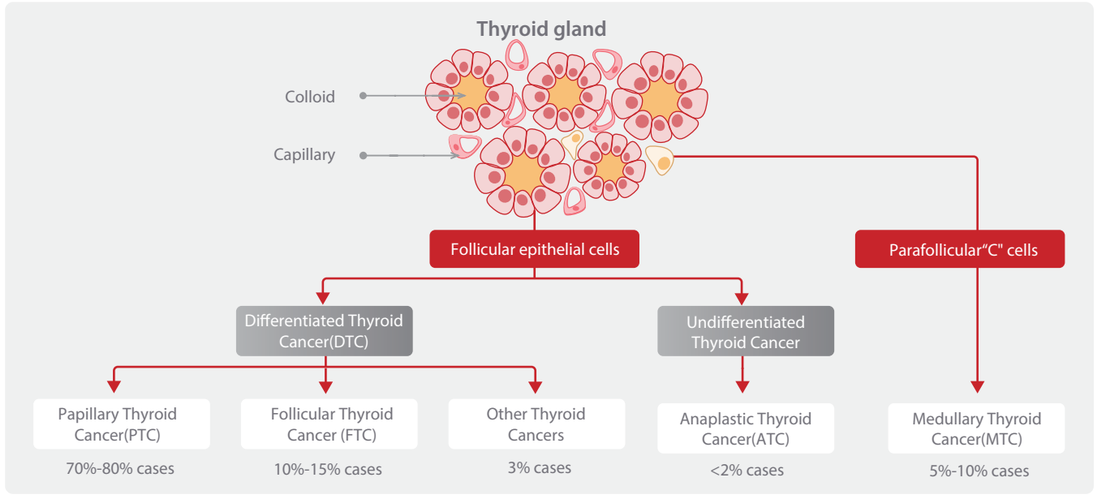
Etiology of thyroid cancer and nodule

DNA mutations can cause thyroid cells to become cancerous. For example, a mutation might change proto-oncogenes like RET and BRAF, which are genes that code for proteins that promote cell growth and proliferation, into oncogenes. That would mean that the proteins force the cell to be stuck in the "on" position, always dividing, and that causes the thyroid cell to turn into a tumor. There are other genes, called tumor suppressors, such as PTEN and that slow down cell division or make cells die if they divide uncontrollably. DNA mutations might also turn off tumor suppressor genes, which allows thyroid cells that try to divide uncontrollably to go unchecked. Over time, a thyroid cell that divides uncontrollably, will lead to a lump of cells within the thyroid, called a nodule. Most often, nodules are non-functional, so they do not produce thyroid hormones, and these are called "cold" nodules[25].

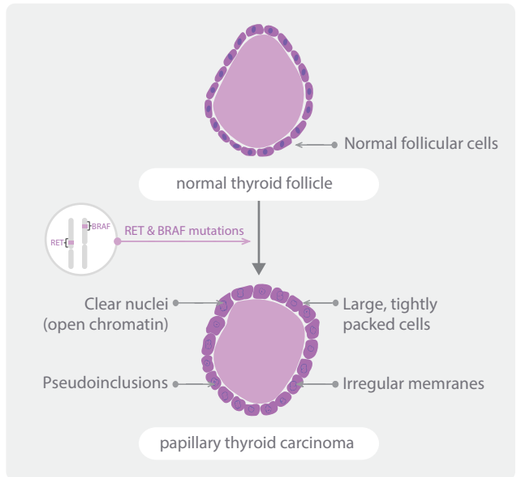


Types of thyroid cancer

Now, there are three main types of thyroid cancer: differentiated, medullary, and anaplastic. A differentiated thyroid cancer (DTC) arises from follicular cells, and it is known as differentiated because the cancer cells look and act like normal thyroid cells. Within DTCs there are three groups: papillary, follicular, and other thyroid cancers, like Hurthle cell carcinoma[25].

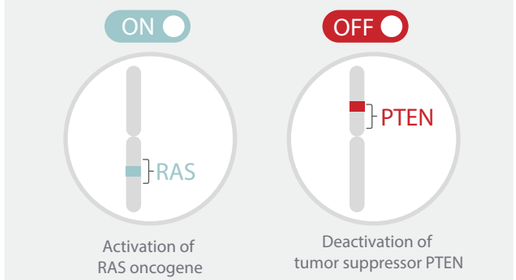


Papillary Thyroid Cancer (PTC)



The first group, papillary carcinomas, represents the most common form of thyroid cancer and is associated with RET and BRAF gene mutations as well as exposure to ionizing radiation during childhood. The name "papillary" refers to the fact that these tumors have finger-like prolongations of follicle cells known as papillae that tend to grow slowly towards nearby lymphatic vessels and invade nearby lymph nodes in the neck. Most people with this type of cancer can be cured if they are diagnosed early. It is the most common type of thyroid cancer, and 70% to 80% of thyroid cancers are PTC. Although it can occur at any age, most occur between the ages of 30 and 60. The disease is three times more common in women than men, and is usually more aggressive for older patients[26].

Follicular Thyroid Cancer (FTC)



The second type, follicular carcinomas, also known as follicular adenocarcinomas, represent the second most common form of thyroid cancer. This type of thyroid cancer is more frequently associated with countries where people have low dietary iodine, but is also with the activation of RAS oncogene or the deactivation of the tumor suppressor gene PTEN. From there, follicular carcinomas can invade into nearby blood vessels and spread to other parts of the body like the lungs, liver, bone, and brain, but interestingly they do not typically invade nearby lymph nodes. Follicular thyroid cancer accounts for less than 15% of all thyroid cancers. Hurthle cells are variants of FTC. Hurthle cells are also seen in disorders like Hashimoto's thyroiditis where the thyroid is also inflamed. This type of thyroid cancer occurs mostly in adults between the ages of 40 and 60. Women get it more often than men. Cancer cells can invade blood vessels and travel to tissues such as bones or lungs[27].

PTC and FTC, as well as the less common Hürthle cell carcinoma, are classified as differentiated thyroid carcinoma (DTC), which originate from follicular epithelial thyroid cells. Both PTC and FTC are slow to progress and usually have a good prognosis, especially if diagnosed early[28].

Medullary Thyroid Cancer (MTC)

So moving beyond DTCs, there are the medullary thyroid carcinomas which arise from C-cells. There is a higher concentration of C-cells in the upper of the thyroid medulla which is where these tumors usually arise. It accounts for about 3% of all thyroid cancers . It is developed by C-cells or parafollicular cells that produce calcitonin (which regulates calcium and phosphate levels in the blood and promotes bone growth) , and elevated levels of calcitonin indicate cancer. It is usually diagnosed between the ages of 40 and 50, and women and men are equally affected. Compared to other types of thyroid cancer, it is more likely to run in the family (familial medullary thyroid carcinoma, FMTC)[29-30].

Anaplastic Thyroid Cancer (ATC)

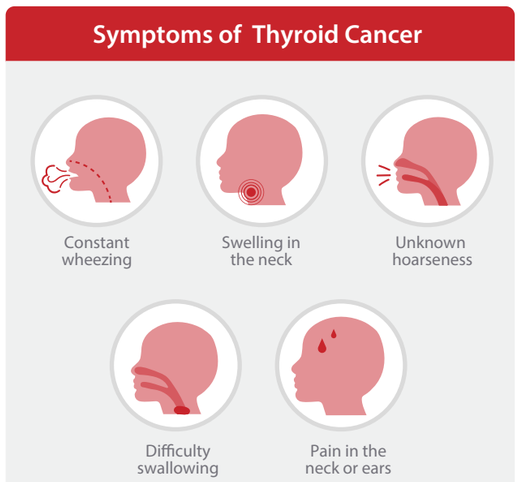
Finally, there are the anaplastic thyroid carcinomas. These are a rare form of thyroid cancer, named for having altered cells that do not look anything like normal thyroid cells. It accounts for less than 2% of all thyroid cancers (77% in women). Unlike other thyroid tumors, it is aggressive and grows and spreads rapidly. Therefore, ATC is the most invasive type of thyroid cancer among all thyroid cancers. It often grows beyond the fibrous capsule of the thyroid gland and invade nearby structures. It usually occurs in patients over the age of 65, and women are slightly more affected than men. Its prognosis is the worst among all thyroid cancers, with a 5-year survival rate of 5%[31-32].

Symptoms of Thyroid Cancer

In the early stages, thyroid cancer usually shows no signs or symptoms.

As a thyroid tumor grows, it may produce the following symptoms [33]:

- Neck mass or node: This is the most common symptom of thyroid cancer. A hard, fixed mass with an uneven surface is found in the thyroid gland. The glands are less mobile up and down during swallowing.
- Persistent hoarseness or changes in voice, and frequent coughs unrelated to a cold may occur.
- Difficulty swallowing or breathing.
- Swollen lymph nodes in the neck.
- Pain in ears, occiput, shoulders, and other parts. may occur in the late stage.



Risk Factors for Thyroid Cancer

Risk factors for thyroid cancer include ionizing radiation, family history, gender, obesity, alcohol consumption, and smoking. Recent studies have also demonstrated the relationship between exposure to flame retardants and PTC[34].

1. Gender and Race

Thyroid cancer is more common in women than men. White or Asian people are more likely to develop thyroid cancer.

2. Age

Most thyroid cancer patients are between 20 and 55 years old.

3. Radiation Exposure

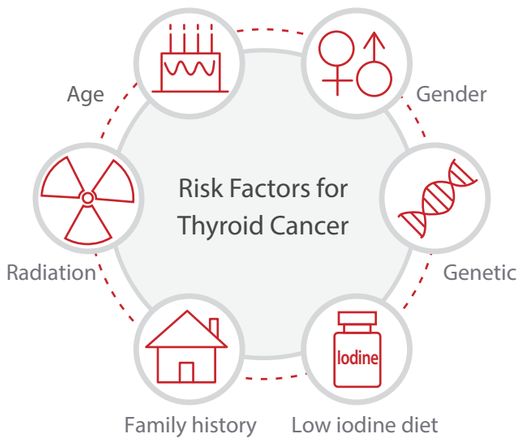
Exposure to high levels of radiation may increase the risk of thyroid cancer.

4. Genetic Factors

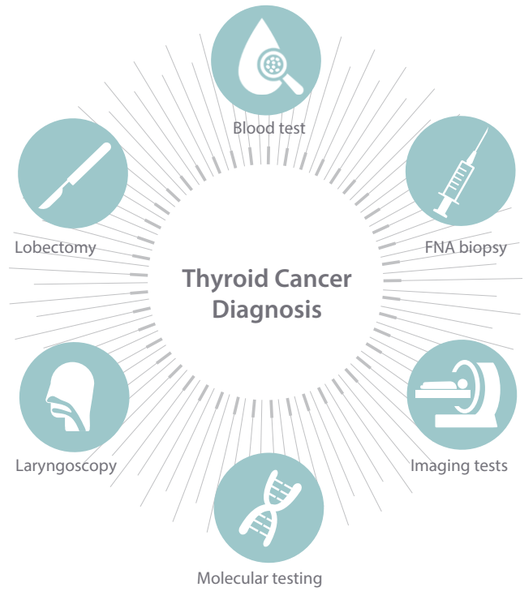
Most thyroid cancer cases are sporadic, only 5% of DTC is characterized as familial (mainly PTC), and about 25% of MTC is inherited as an autosomal trait.

Certain genetic syndromes increase the risk of thyroid cancer. These include familial myeloid thyroid cancers and multiple endocrine neoplasms (type 2A and type 2B).

Mutations in certain genes are also important causes of thyroid cancer. Mutations in BRAF and RAS family also occur frequently in thyroid cancer. Chromosomal translocations also occur in thyroid cancer, such as peroxisome proliferation-activated receptor (PPAR gamma) translocations in about 30% of follicular thyroid cancer cases[35-36].



Diagnosis of Thyroid Cancer [37]



Comprehensive and thorough diagnosis of thyroid cancer involves a number of procedures and tests that your healthcare provider may use to diagnose thyroid cancer and rule out other thyroid conditions. Usually, the process of evaluating for thyroid cancer starts with finding a lump or nodule in your gland.

Some of the main methods for diagnosing thyroid cancer are:

Blood tests: Blood tests cannot diagnose thyroid cancer itself or detect a cancerous thyroid nodule, but they can rule out other conditions and determine if your thyroid is working the way it should. Blood tests your healthcare provider may use include thyroid stimulating hormone(TSH), T3, T4, calcium and thyroglobulin.

1. TSH: Your healthcare provider may check the TSH level in your blood to evaluate your thyroid's activity and test for hypothyroidism (underactive thyroid) or hyperthyroidism (overactive thyroid). The result of this test can help your healthcare provider determine which imaging tests to do to

visualize your nodule. That said, with thyroid cancer, your TSH level is typically normal.

2. T3 and T4: These are the main hormones that your thyroid makes. Your healthcare provider may test your levels to check how your thyroid is functioning. Like TSH, these hormone levels are usually normal when you have thyroid cancer.

3. Calcium: When medullary thyroid cancer is suspected, your healthcare provider will typically test for high levels of calcium, as this can be an indicator of the disease.

4. Thyroglobulin: The thyroid makes a protein called thyroglobulin that is then converted into T3 and T4. If you have already been treated for thyroid cancer and you have had a thyroidectomy, your healthcare provider may check to make sure your cancer is gone or to see if it has come back by looking at your thyroglobulin level. Though this test cannot diagnose cancer, it can be a marker for it. Since you no longer have a thyroid to make thyroglobulin, if there is more than a very low level in your blood, or if it rises after having been low, this may indicate cancer. In this case, your healthcare provider will likely do some other tests to verify and treat you accordingly.

Ultrasound Guided Fine Needle Aspiration (FNA) Biopsy

Fine needle aspiration (FNA) is a diagnostic method for thyroid cancer. Cancer cells usually look different from normal cells, so the type of thyroid cancer is determined by microscopic examination of thyroid cells found in nodules (neck masses) or growth.

Lobectomy

In the case of indeterminate samples, the biopsy is usually repeated and/or genetic or molecular testing may be done. If it is indeterminate a second time, your healthcare provider may consider a surgical biopsy or surgery to remove half of your thyroid gland, called a lobectomy.

Molecular (Genetic) Testing

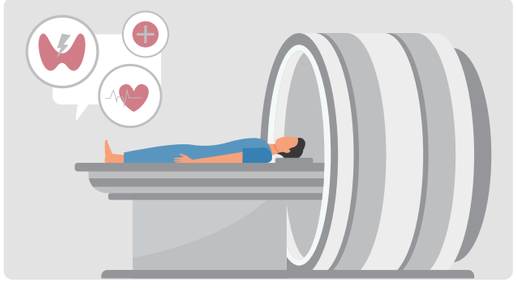
Many genetic changes are thought to play an important role in thyroid tumor formation. The frequent occurrence of RAS mutations in follicular adenoma suggests that the activated RAS may play a role in the early stage of tumorigenesis. Molecular tests (classification of gene expression) can be used to help make a diagnosis when the result of an FNA biopsy is uncertain.

Laryngoscopy

Less commonly, if a thyroid nodule is close to your larynx, a laryngoscopy may be performed to make sure it is not interfering with your vocal chords. You may also have a laryngoscopy if you are going to have surgery to remove part or all of your thyroid to see if your vocal chords are moving the way they should.

Imaging

A variety of imaging tests and scans are used to help find suspicious areas that could be cancer and to see how far it might have spread. These include ultrasound, radioiodine scan, computed tomography (CT) scan and magnetic resonance imaging (MRI) scan.



Treatment of Thyroid Cancer [38-40]

1. Surgical Treatment

Surgery is the basic method for treating various types of thyroid cancer except for ATC. Other auxiliary treatment methods such as nuclide, thyroid hormone and external radiation are usually used.

Surgical treatment of thyroid cancer includes partial thyroidectomy or lobectomy and total thyroidectomy.

2. Endocrine Therapy

TSH can stimulate the proliferation of thyroid cancer cells through its receptor. Therefore, thyroid hormone therapy such as TSH inhibitors is used after surgery. This method can significantly reduce recurrence and cancer-related mortality in patients with different types of thyroid cancer. Meanwhile, patients should take enough thyroxine supplements.

3. Radionuclide Therapy

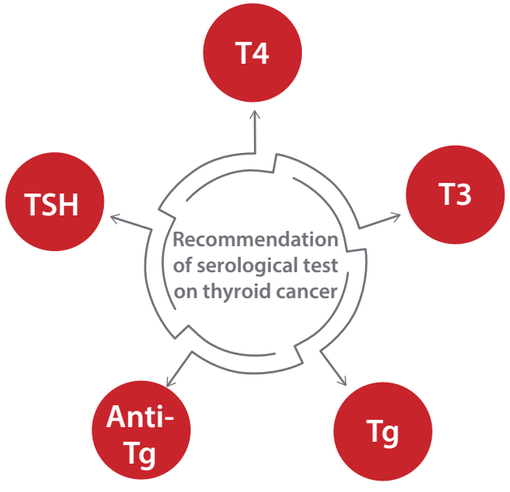
Some patients with papillary or follicular carcinoma may require systemic radioactive iodine (RAI) after thyroidectomy. When radioactive iodine enters the bloodstream, it selectively destroys the remaining thyroid tissue and cancer cells without affecting any other cells. The adjuvant therapy is applicable to patients over 45 years old, multiple cancerous foci, locally invasive tumors, and distant metastases.

4. Chemotherapy

Chemotherapy is rarely used to treat thyroid cancer, except for malignant tumors such as undifferentiated thyroid cancer.

5. External Radiation Therapy

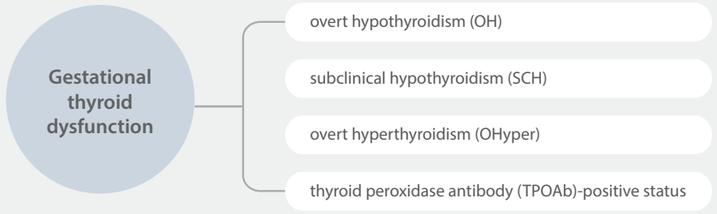
This method is mainly used to treat ATC.



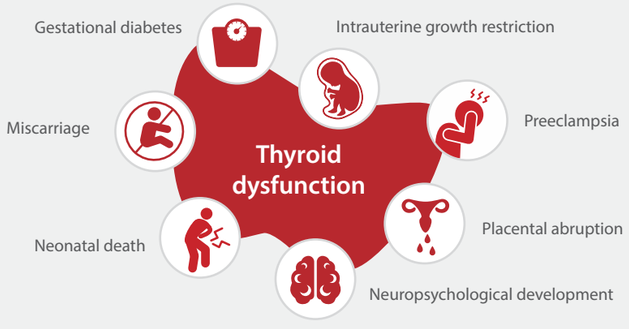
Different types of groups for thyroid function evaluation and special reference interval range

During pregnancy, proper maternal thyroid function is important for both the mother and child [41], especially for the first trimester, in which the developing fetus is completely dependent on its mother for thyroid hormones that are critical for brain and nervous system development[42].

Gestational thyroid dysfunction is a common endocrine disease, with a prevalence of 2%-4%[43], and typical types of gestational thyroid dysfunction include overt hypothyroidism (OH), subclinical hypothyroidism (SCH), overt hyperthyroidism (OHyper), and thyroid peroxidase antibody (TPOAb)-positive status.



Thyroid dysfunction has been shown to be associated with pregnancy complications and adverse perinatal outcomes, including placental abruption[44], preeclampsia[45], miscarriage[46,47], gestational diabetes[48], neonatal death[49], intrauterine growth restriction[50] and neuropsychological development[51].



Several studies revealed that a high proportion of pregnant women suffer from thyroid disorders, especially subclinical hypothyroidism and overt hypothyroidism, in their first trimester[52]. Hyperthyroid disorders are rare in pregnant women. Routine antenatal thyroid screening should be performed in all pregnant women. However, pregnant women with thyroid disorders do not always develop symptoms, and when they do, these symptoms can sometimes be attributed to the pregnancy itself[53].

Pregnancy
Thyroid disorders
Fatigue
Nausea
Weight gain
Changes in skin, hair, nails
Insomnia
Constipation
Dizziness
Mood swings
Headache

Given these facts, it is critical to accurately assess maternal thyroid function in the laboratory and to determine reference intervals for normal thyroid function during pregnancy. The guidelines of the Endocrine Society, American Thyroid Association (ATA), and European Thyroid Association (ETA) recommend that trimester-specific reference intervals be calculated for each center[54-56].

ATA guidelines have recommended universal thyroid function screening for the entire gestational population than screening only for high-risk pregnancies[57]. Mindray, has specified the reference intervals for normal thyroid function for pregnant women in three trimesters (see the table below). This solution allows laboratories to assess maternal thyroid function accurately and avoid misdiagnosis and missed diagnosis of subclinical thyroid disease. This in turn helps to reduce adverse pregnancy outcomes, such as miscarriage, premature delivery, stillbirth, and reduced fetal intelligence.

Items	Trimester	Mindray Specific Reference Ranges
TSH μIU/mL	First	0.09-4.87
	Second	0.47-4.79
	Third	0.50-5.40
FT4 pmol/l	First	10.63-19.82
	Second	7.21-17.04
	Third	6.95-13.45
FT3 pmol/l	First	3.25-4.93
	Second	2.94-4.81
	Third	2.89-4.23
T3 nmol/l	First	1.09-2.46
	Second	1.3-3.0
	Third	1.1-2.84
T4 nmol/l	First	90-211
	Second	99-226
	Third	85-218

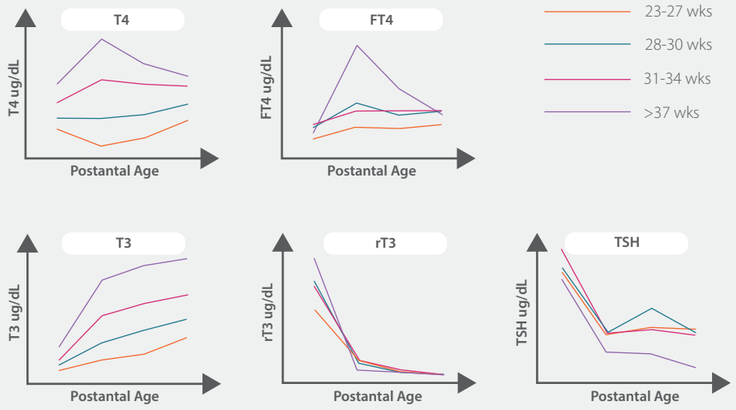
Thyroid hormones have a large impact on children's growth, nervous system myelination, metabolism and organ functions. Thyroid disorder is one of the most common endocrinopathies in childhood, and it may cause a series of diseases include congenital hypothyroidism, acquired hypothyroidism, Graves' disease, and thyroid nodules. Considering the foundational function of thyroid hormones, children with thyroid disorder may develop sequelae such as agenesis and impaired lung maturation that last over their remaining lifetime. To prevent sequelae, infant and adolescent patients should be diagnosed and treated as early as possible[58].

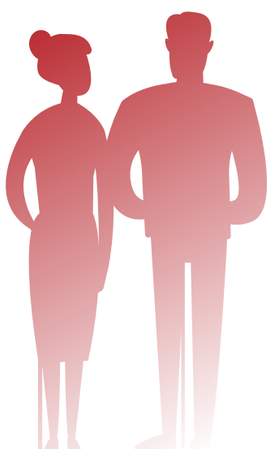
Infant and adolescent patients show different clinical symptoms and etiology from adult patients. Due to their immaturity and growth, infant and adolescent patients do not have absolutely consistent serum level of thyroid hormones with adult patients.

Therefore, the reference intervals for thyroid hormones of adults are not suitable for directly application to infant and adolescent patients[58,59].

The thyroid hormone level of infant patients matches the following dynamics basically. After birth, a surge in pituitary TSH secretion is followed by an increase in circulating T3 and T4 concentrations, reaching hyperthyroid levels when compared with those later in childhood and adolescence. Subsequently, TSH decreases during the first week after birth due to feedback inhibition by the elevated serum T4 at both the hypothalamic and the pituitary level. These perinatal changes in thyroid hormone secretion must be considered when thyroid function tests are performed in preterm and full-term neonates. Some specific reference intervals have been established for iodothyronines. Taking into account the significant effects of age and sex, these reference intervals provide an essential clinical tool for assessing thyroid function accurately in children and adolescents[59].

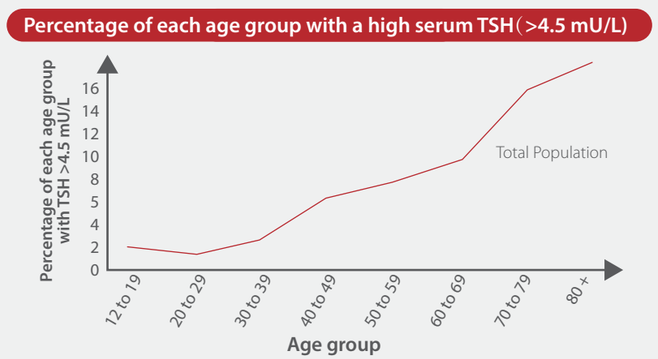
Mindray is dedicated to offering better healthcare for all patients. We have worked with renowned hospitals in China to establish sex- and age-specific reference intervals for infants and adolescents. The related reference intervals can be applied in the CL-series platform to offer a powerful tool for clinicians and doctors to make accurate diagnosis. This study has been published on scientific journals[60].





The thyroid gland, similar to other endocrine organs, experiences important functional changes during aging. Physiological changes of the hypothalamic-pituitary-thyroid axis, confusion between thyroid disease symptoms and aging manifestations, comorbidities or coexistence with geriatric syndromes, and multiple organ dysfunction all increase the complexity of the diagnosis and treatment of thyroid diseases in the elderly[61].

Thyroid hormone change with aging



With the change of the thyroid gland, thyroid hormones also change with aging. Compared with young adults, the upper limit of the TSH reference range for the elderly increases by 0.3 mU/L for every 10-year increase in age over 40 years[62]. (The number may vary slightly among different studies). The percentage with high level serum TSH (4.5 mU/L) increases with aging. Besides, the TT3 level and FT3 level decreases slightly, the FT4 level increases slightly or remains unchanged, and the FT3/FT4 ratio decreases slightly. According to American Cardiovascular Health Survey (CHS), after 13 years of follow-up on subjects with an average age of 72, the TSH level increased by 13% (0.34 mU/L), the FT4 level increased by 1.7% (0.2 ng/L), and the TT3 level decreased by 13% (-149 ng/L). The survey showed no big difference between the subjects and the disease-free reference population[63]. The change of the HPT axis with aging may be a protective mechanism for the elderly to slow down their own catabolism. Specifically, as the elderly's metabolism slows down, the conversion of T4 to T3 decreases, and the feedback inhibition of TSH is weakened, which causes the TSH level to increase.

Change of thyroid hormone level during disease screening and diagnosis

Current thyroid hormone reference ranges are mainly intended for young adults, so they may lead to misdiagnosis of subclinical disease.

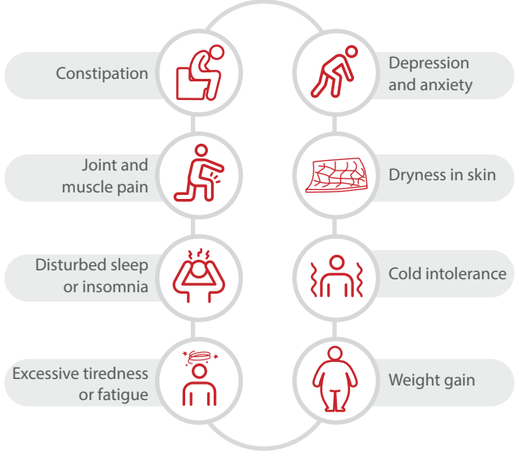
Take subclinical hypothyroidism for example which is characterized by normal FT4 and increased TSH level. If a common thyroid hormone reference range is used, subclinical hypothyroidism may be diagnosed at an increasing rate with increasing age. In particular, the prevalence of subclinical hypothyroidism ranges from 3% to 16% in individuals aged 60 years and older[64]. In contrast to overt hypothyroidism, subclinical hypothyroidism in elderly subjects is not associated with the impairment of physical and cognitive function, depression, metabolic disturbances or poor quality of life[65].

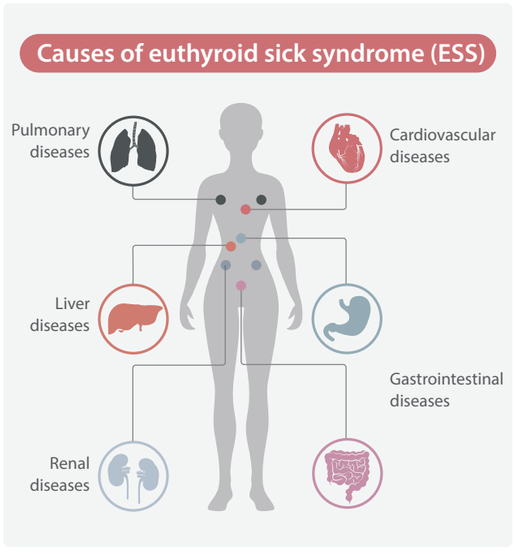
As a result, it is advised to fully evaluate thyroid status in the elderly by using Comprehensive Geriatric Assessment (CGA), which assesses daily living activities, mental and emotional status, nutrition, etc. However, TSH is always recognized as the best marker for thyroid disease screening.

	All participants(n=657)			Disease-free reference population(n=533)		
	Baseline	Δ over time	% Δ	Baseline	Δ over time	% Δ
TSH (mU/L)	2.6 (3.6)	0.34 (2.3)[α]	+13%	2.3(1.4)	0.28(1.4)[α]	+12%
FT4 (ng/dl)	1.2 (0.2)	0.02 (0.18)[α]	+1.7%	1.2(0.2)	0.03(0.17)[α]	+2.5%
T3 (ng/dl)	116.9 (19.5)	-14.9 (20.8)[α]	-13%	116.9(19.5)	-14.9(19.5)[α]	-13%

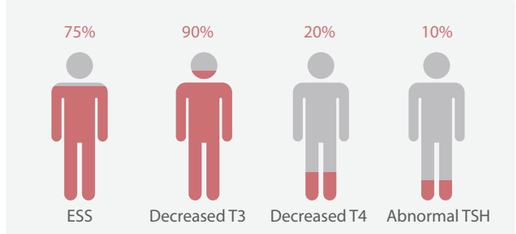
The diagnostic value of rT3 in euthyroid sick syndrome (ESS)

Euthyroid sick syndrome (ESS) is also known as nonthyroidal illness syndrome and refers to changes in thyroid function tests that are administered in the inpatient or intensive care setting during critical illness. It is not a true syndrome, and transient alterations in the hypothalamic-pituitary-thyroid axis are present in about 75% of hospitalized patients. This condition is often seen in patients with severe critical illness, deprivation of calories, and after major surgeries. The causes of ESS vary, including critical illness, pneumonia, starvation, anorexia nervosa, sepsis, stress, history of trauma, cardiopulmonary bypass, myocardial infarction, malignancies, congestive cardiac failure, hypothermia, inflammatory bowel disease, cirrhosis, major surgeries, renal failure, and diabetic ketoacidosis.





Prevalence of Euthyroid Sick Syndrome[66]



Prevalence of hospitalized patients

- Up to 75%
- Decreased serum T3 syndrome in ~50%, even 90% of patients
- Decreased serum T4 syndrome in 15%~20% of patients
- Abnormal TSH in ~10% of patients

Symptoms of Euthyroid Sick Syndrome

ESS very often mimics hypothyroidism. It is a condition in which the patient generally exhibits signs and symptoms of hypothyroidism such as:

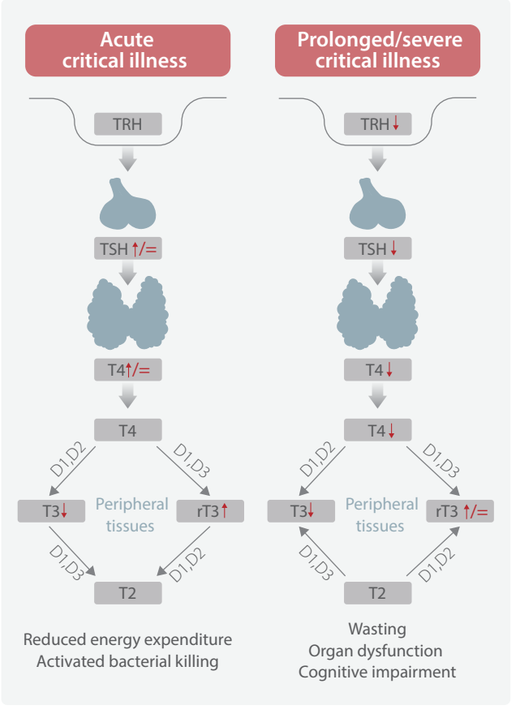
Who is at high risk of ESS?

ESS is seen in 40% of patients presenting with any major illness. Other conditions that may put the patients at an increased risk of ESS include:

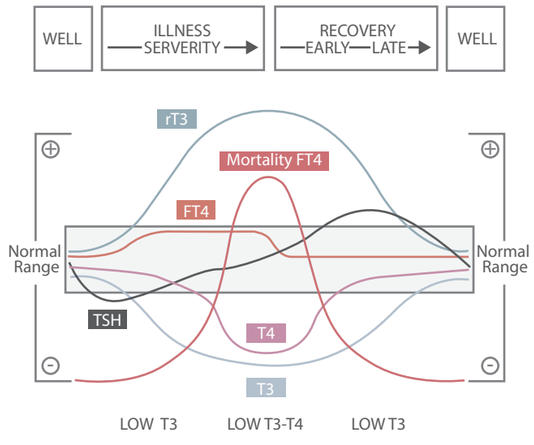
- Congenital hypothyroidism
- Surgical removal of part or all of the thyroid gland
- Radiation therapy of the thyroid
- Some medications, such as amiodarone, propylthiouracil, methimazole and Lithium.
- Age over 50 years
- Female

Pathophysiology of Euthyroid Sick Syndrome

The actual pathogenesis of ESS is still unknown and a lot of research is going on. The most accepted theory claims that ESS is caused by decreased peripheral conversion of T4 to T3. There is decreased clearance of reverse T3 (rT3) that has been generated by T4 and also decreased binding of thyroid hormones to TBG (thyroxine-binding globulin). Studies have proven that cytokines such as tumor necrosis factor –alpha, IL-1 play a vital role in development of ESS.

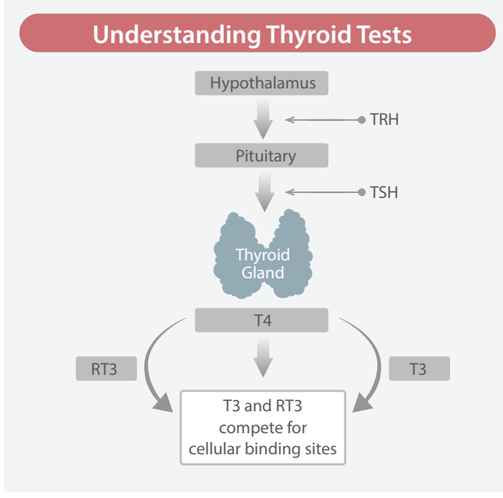


Changes in thyroid tests during the course of Euthyroid Sick Syndrome[67]

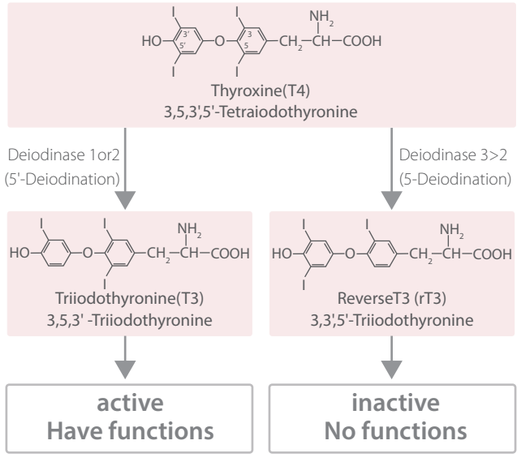


An overview of reverse T3

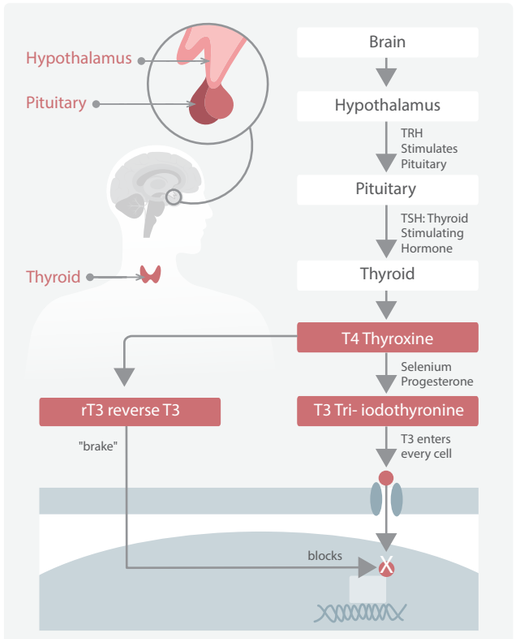
Thyroid Releasing Hormone is made by the hypothalamus and it stimulates the pituitary gland in the brain to make TSH (Thyroid Stimulating Hormone). TSH stimulates the thyroid gland to produce Free T4 as the final product. Free T4 undergoes two forms of conversion: into an ACTIVE Free T3 or INACTIVE ReverseT3 (rT3)[68].



Circulatory rT3 is mainly synthesized by peripheral deiodination of T4. rT3 differs from T3 in that the missing deiodinated iodine is from the inner ring of the thyroxine molecule compared with outer ring on T3. rT3 is an inactive form of T3 that is produced in the body particularly during periods of stress.



The role of rT3 in thyroid function



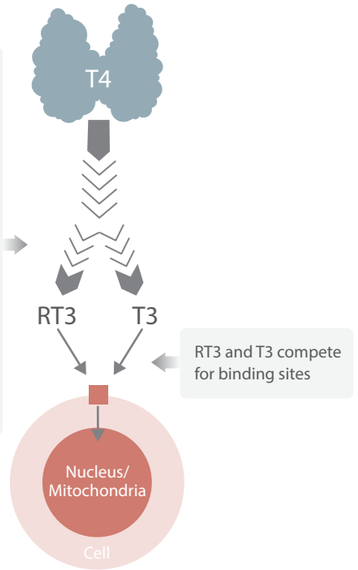
Reverse T3 is like a break on thyroid function and metabolism. High Reverse T3 slows down the metabolism by attaching to the cell receptor sites for the Free T3, so Free T3 cannot get into the cell and optimize its function. So, your levels on the paper could be great (including optimal Free T4 and Free T3, as well as TSH), but you are still struggling with the weight gain, hair loss, constipation, cold hands, etc. Reverse T3 acts like a key in the keyhole (receptors) of the cell. It is impossible to put a Free T3 key into a keyhole that already has a different key in it (rT3). With the wrong key, the door will not open, the car will not start, and similarly, the cell will not get the required Free T3 to function properly.

The causes of high rT3

So, what are the causes of high rT3?

Factors that increase conversion of T4 to RT3:

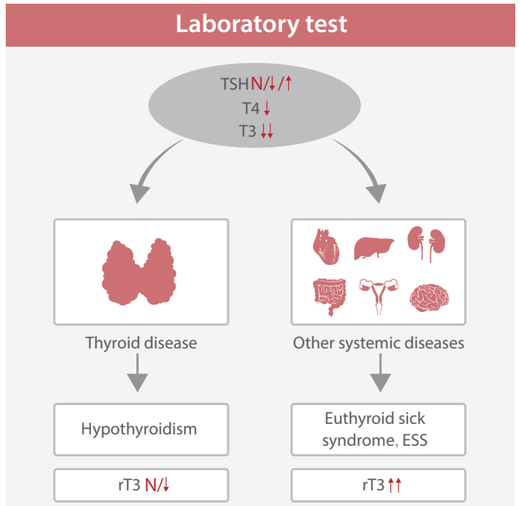
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, otc.)
- Toxins
- Infections
- Liver/kidney
- Dysfunction
- Certain medications



Clinical applications of rT3 assay

Clinical application 1: Differential diagnosis of ESS and hypothyroidism

rT3 plays a very important role in the differential diagnosis of ESS and hypothyroidism!



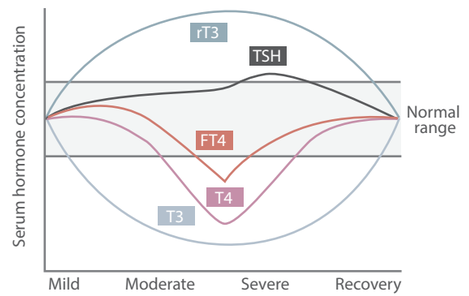
Testing Result

	ESS	Primary Hypothyroidism
TSH	N/↓/↑	↑-↑↑
T3	↓↓	↓↓
T4	N/↓	↓
rT3	↑↑	↓

Clinical Syndrome

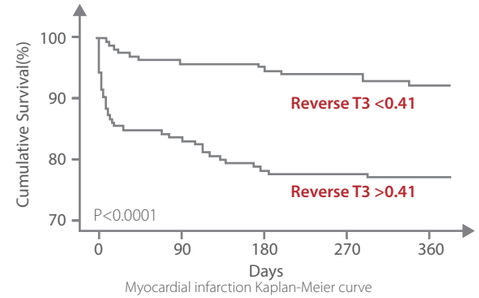
	ESS	Primary Hypothyroidism
Hypothyroidism Medical History	×	√
Hypothyroidism Syndrome	×	√

Clinical application 2: Prediction of prognosis of ESS[69-70]

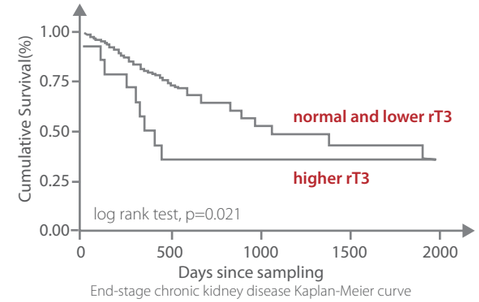


Relationship between serum thyroid hormone concentrations and severity of nonthyroidal illness

Critically ill patients with ESS have a poor state of health. Higher rT3 values are associated with severe illness.

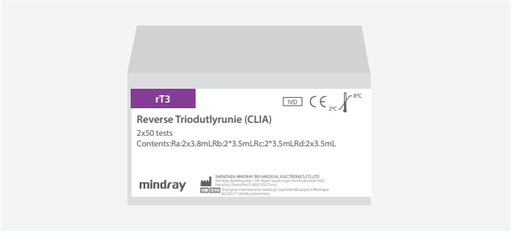


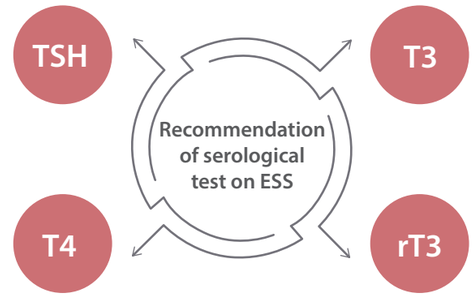
Myocardial infarction Kaplan-Meier curve



End-stage chronic kidney disease Kaplan-Meier curve

Ultimately, if you're experiencing unexplained symptoms of hypothyroidism, or symptoms that don't fit the picture as told on your blood tests, it's worth investigating these further and a conversation with your GP or naturopath may be all it takes to get the ball rolling! If you would like to book an appointment to investigate or assess your rT3 level, you can do so with Mindray assay.





Summary and presentation of thyroid-related publications

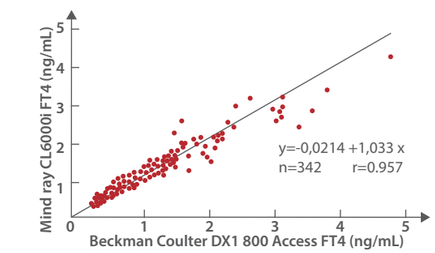
The method comparison and the verification of precision of Mindray CL-6000i thyroid function tests(TFTs)[71]

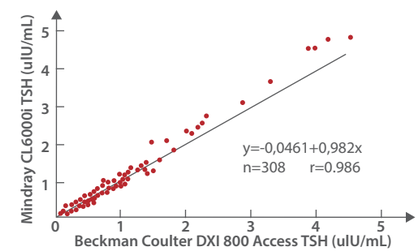
Mindray CL-6000i FT3, FT4, TSH, Anti-Tg and Anti-TPO methods have good analytical performance and good precision in all tests

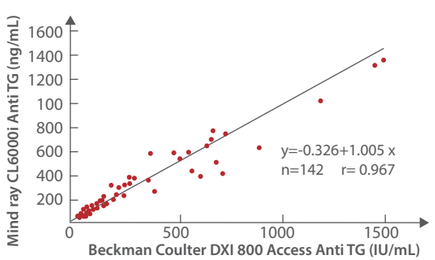
Table 1: Results of precision study on use of BioRad QC by Mindray CL- 6000 for measurement according to CLSI EP 15-A3.

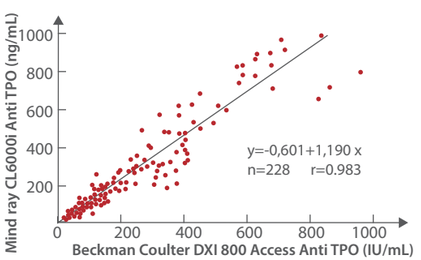
		Our study			Manufacturer's claims		
Measurands	Level	Mean	Repeatability (CV %)	WL imprecision (CV %)	Mean	Repeatability (CV %)	WL imprecision (CV %)
FT3 (pg/ml)	1	2.27	2.36	2.57	4.60	4.20	8.54
	2	6.04	1.85	2.85	14.78	3.54	7.47
	3	10.23	1.86	2.43	*	*	*
FT4 (ng/dL)	1	0.98	1.66	4.61	1.28	4.47	9.07
	2	2.22	1.45	3.79	2.61	3.56	7.29
	3	3.99	0.91	3.93	*	*	*
TSH (ulU/mL)	1	0.28	2.38	2.59	0.58	3.53	8.14
	2	3.64	1.89	2.10	62.54	3.32	7.61
	3	24.34	1.36	2.14	*	*	*
Anti-TG Ab (IU/mL)	1	40.98	3.48	3.78	8.29	4.65	8.99
	2	80.01	3.08	3.09	261.32	4.70	8.94
Anti-TPO Ab (IU/mL)	1	30.13	3.30	3.35	10.14	4.72	8.77
	2	83.89	3.31	3.60	100.48	3.93	6.82

For FT4, TSH, Anti-Tg and Anti-TPO, Mindray assay was satisfactorily comparable with the Beckman Coulter-DXI 800 assay



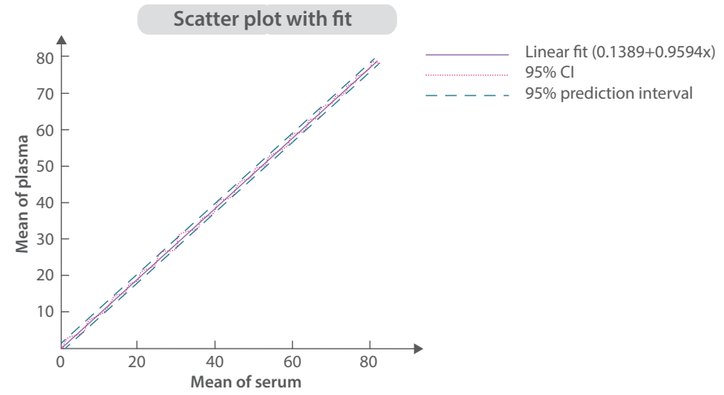




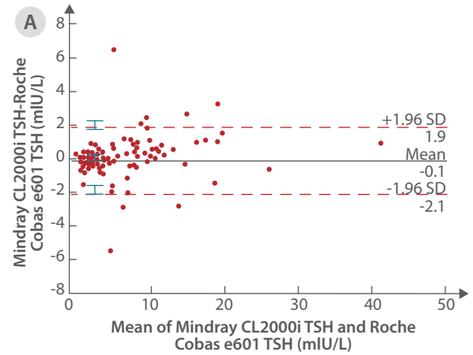


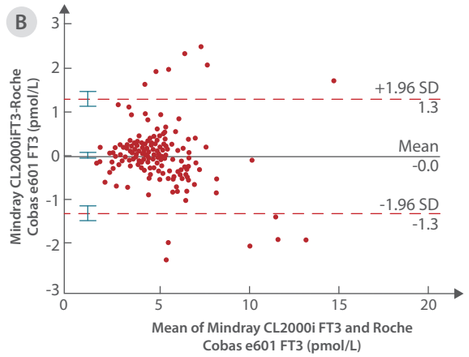
Evaluation of the analytical performances of six measurands for thyroid functions of Mindray CL-2000i system[72]

Plasma and serum samples have good agreement and interchangeability (Matrix effect was negligible for TSH)

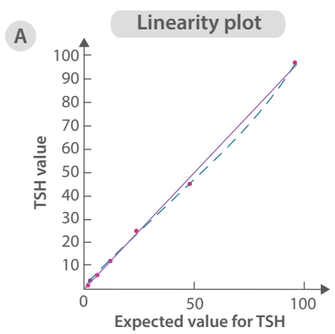


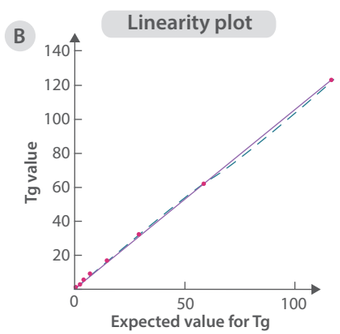
TSH and FT3 showed a good comparability between the Mindray CL-2000i and the Roche Cobas 6000 e601



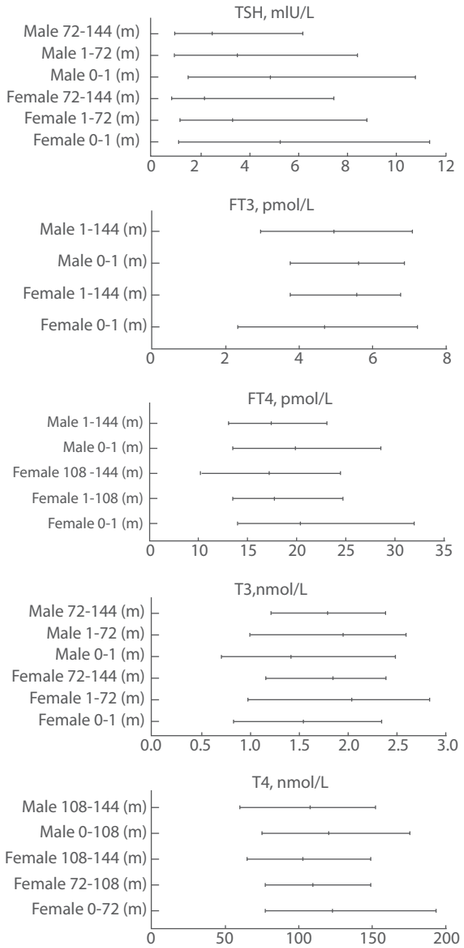


Linearity assays demonstrated a good linearity for TSH and Tg





Age-and sex-specific reference intervals for thyroid hormones in a Chinese pediatrics: a prospective observational study of 1,279 healthy children[73]

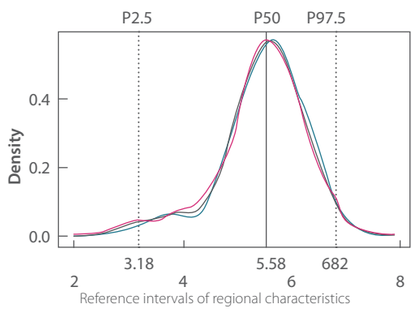


Thyrold hormones	Groups	Age group (m)	RI, P50 [P2.5, P97.5]
TSH(mIU/L)	Female	0-1	5.23 [1.08, 11.35]
		1-72	3.24 [1.14, 8.83]
		72-144	2.14 [0.83, 7.42]
	Male	0-1	4.91 [1.46, 10.78]
		1-72	3.40 [0.95, 8.38]
FT3(pmol/L)	Female	72-144	2.48 [0.96, 6.21]
		0-1	4.67 [2.35, 7.27]
		1-144	5.58 [3.77, 6.80]
	Male	0-1	4.95 [2.96, 7.08]
		1-144	5.64 [3.81, 6.86]
FT4(pmo/L)	Female	0-1	20.08 [13.82, 31.83]
		1-108	17.63 [13.26, 24.80]
		108-144	17.12 [10.16, 24.34]
	Male	0-1	19.89 [13.34, 28.65]
		1-144	17.43 [12.90, 23.04]
T3(nmol/L)	Female	0-1	1.40 [0.72, 2.46]
		1-12	1.94 [0.99, 2.58]
		12-144	1.78 [1.22, 2.38]
	Male	0-1	1.54 [0.83, 2.33]
		1-12	2.02 [0.98, 2.83]
		12-144	1.83 [1.15,2.39]
T4 (nmol/L)	Female	0-72	120.48 [75.28, 192.48]
		72-108	107.87 [77.03, 146.91]
		108-144	100.92 [63.29, 146.94]
	Male	0-108	118.36 [73.63, 173.85]
		108-144	105.68 [59.31, 150.72]

Sex- and age-specific pediatric reference intervals for TSH, FT3, FT4, T3, and T4

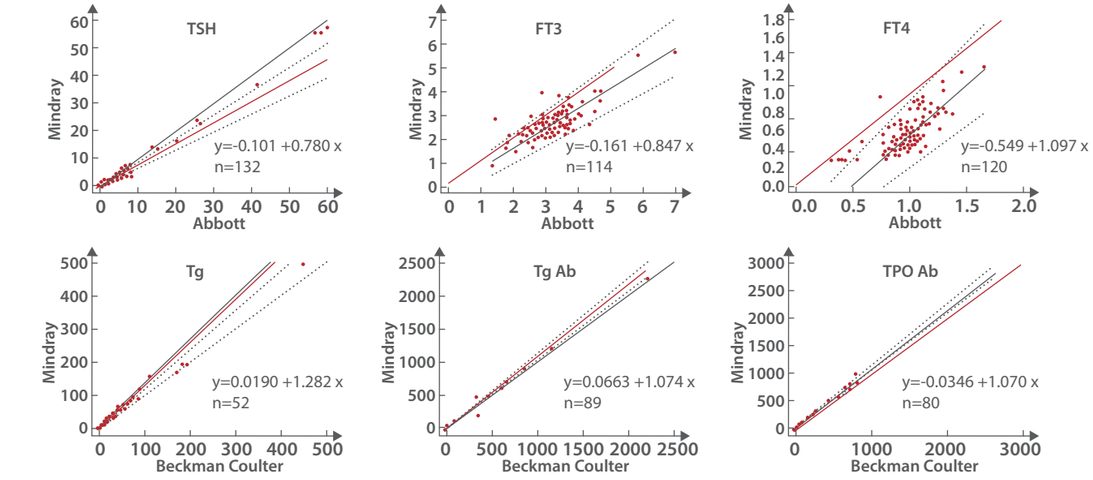
Regional pediatric hospital

Famous pediatrician



Performance evaluation of the new Chemiluminescence Immunoassay CL-1200i Thyroid Panel[74]

Mindray CL-1200i has good correlation with Abbott for TSH, FT3, FT4, and Beckman Coulter for Tg, TgAb and TPOAb

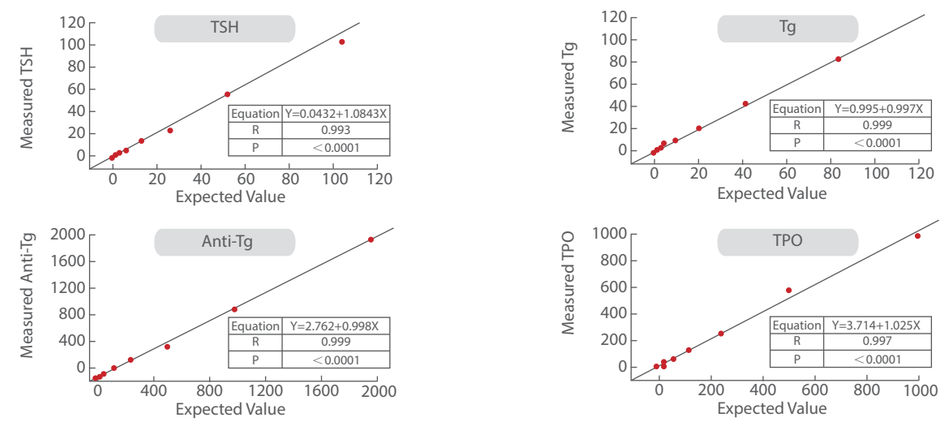


Similar precision with Abbott Architect Plus or Beckman Coulter UniCel Dxl 800

Table. Sensitivity indicated as Lower Level of Quantitation (LLoQ) for each analyte/platform.

LLoQ	CL-1200i (Mindray)	Architect Plus (Abbott)	UniCel Dxl 800 (Beckman Coulter)
TSH	≤0.02 μlU/ml	≤0.01ulU/ml	——
FT3	≤0.88 pg/ml	≤1.0pg/ml	——
FT4	≤0.3 ng/dl	≤0.4 ng/dl	——
Tg	≤0.1 ng/ml	——	≤ 0.1 ng/ml
Anti-Tg	≤0.9 IU/ml	——	≤ 0.9 IU/ml
Anti-TPo	≤0.25 IU/ml	——	≤ 0.25 IU/ml

Excellent linear correlation coefficients have been found for TSH, Tg, Anti-Tg and TPO



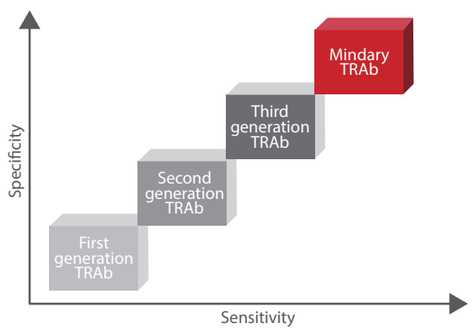
TRAb - A new member of mindray's product family

Graves' disease is the most common cause of hyperthyroidism. Since TRAb (thyrotropin receptor antibody) is the pathogenic antibody of Graves' disease, TRAb is considered to be one of the most important serum biomarkers for diagnosis, differential diagnosis, treatment monitoring and prognosis of Graves' disease[75]. To provide a total thyroid solution for end-users, Mindray spent five years on patented antibody authorization, reagent performance optimization and clinical validation, and ultimately launched TRAb.

Preferred raw materials for reagents

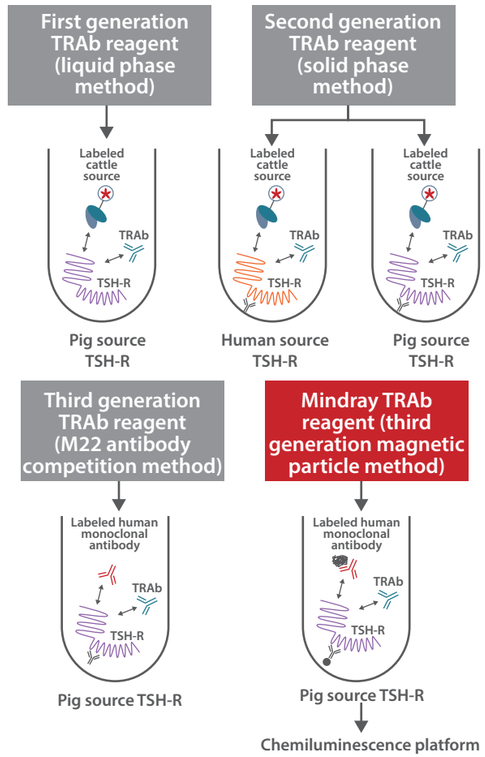
Mindray's TRAb reagent is produced by a specific antibody – human monoclonal antibody M22, so as to improve the specificity and sensitivity of tests. The chemiluminescence platform allows the detection to be performed automatically with much improved efficiency.

Characteristics of Third generation TRAb assay



In 1956, the presence of "thyroid stimulating factor" in the serum of hyperthyroidism patients was demonstrated for the first time. In 1974, the first-generation TRAb detection reagent was made available. After decades of evolution and optimization, human monoclonal antibody M22 has emerged, which represents from liquid phase to solid phase detection and from animal derived antibody to humanized antibody, to bring revolutionary improvement to the detection of TRAb[76]. Mindray TRAb adopts the third-generation TRAb detection reagent, which is upgraded and optimized on this basis. Its detection sensitivity, specificity and repeatability take the lead in the industry, providing accurate evidence for the diagnosis and treatment of Graves' disease.

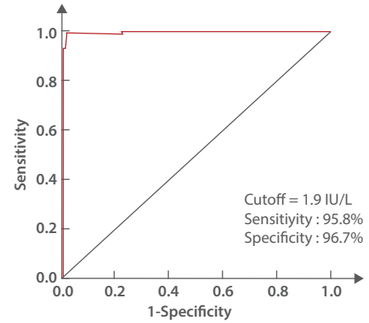
Methodology of third generation TRAb detection reagent



Reliable clinical performance

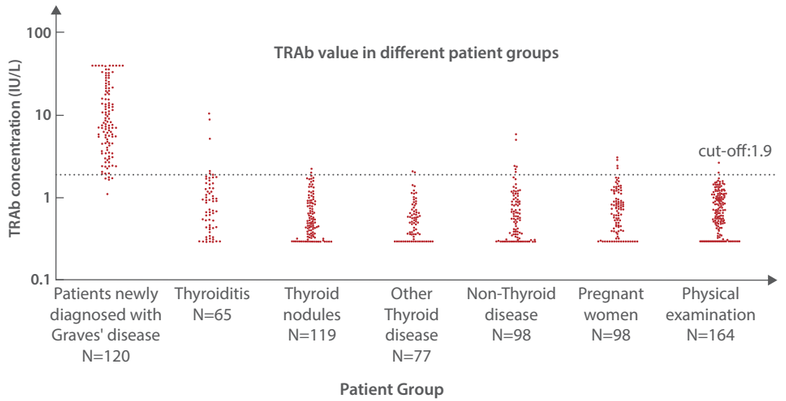
To ensure TRAb assay can meet all clinical requirements, we thoroughly evaluated the clinical coincidence rate of TRAb assay before it was launched. Excellent results were achieved, showing Mindray TRAb assay has good sensitivity and specificity and is suitable for the diagnosis and differential diagnosis of Graves' disease.

ROC curve represents the results when cutoff value is 1.9 IU/L. The sensitivity of Graves' disease diagnosis is 95.8% and the specificity is 96.7%.

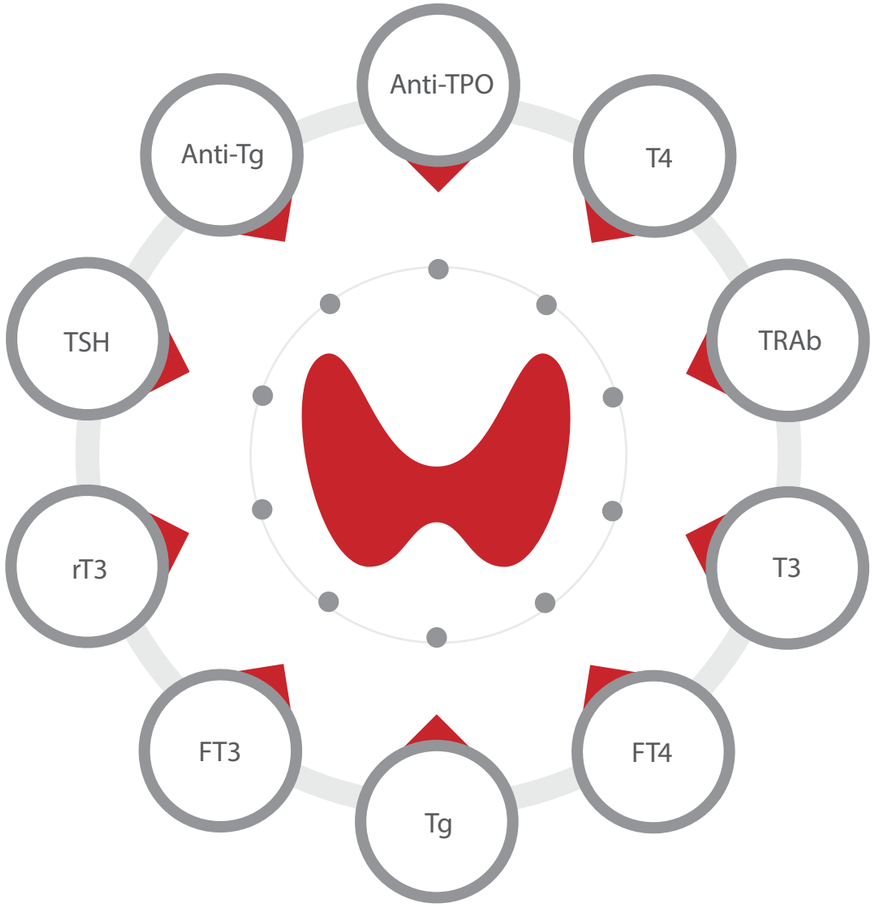


A total of 545 samples were tested, including 120 samples from patients newly diagnosed with Graves' disease, 261 samples with other thyroid diseases, and 164 physical examination samples.

According to the concentration distribution of TRAb in different diseases, the concentration of serum TRAb is significantly higher in patients newly diagnosed with Graves' disease than that in other patient groups, which means Mindray TRAb is suitable for the diagnosis and differential diagnosis of Graves' disease.



Thyroid Panel



CL-6000iM2

960T/h

CL-900i

180T/h

CL-1000i

CL-8000iM2

1000T/h

CL-2000i

240T/h

SAL 6000

800T/h
+240T/h

CL-6000i

480T/h

SAL 9000

2000T/h
+480T/h

CL-8000i

500T/h

mindray

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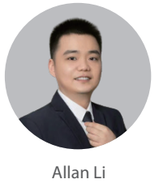
Miki He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