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## DIAGNOSIS OF HYPOTHYROIDISM

### *Definition and classification*

Hypothyroidism is a condition of hypometabolism with insufficient production or inadequate effect of thyroid hormones.

Hypothyroidism may be classified on the basis of the time of development (congenital or acquired), site of occurrence (primary, secondary, tertiary and quaternary) and the severity of clinical picture and manifestation (manifest /clinical/ or mild /subclinical/). In addition, hypothyroidism may be transient, when it is manifested as a phase during some inflammatory conditions of thyroid gland.

### *Etiology*

#### **Congenital hypothyroidism**

Transient hypothyroidism of a newborn may develop due to transplacental transfer of mother's inhibitory antithyrotropin receptor antibodies. The most common cause worldwide of congenital hypothyroidism is endemic deficit of iodine. In regions with normal supply of iodine, the incidence of congenital hypothyroidism is about 1/4000 of live births; the proportion is as twice as frequent in female children (1). In most cases, hypothyroidism is the result of thyroid agenesis or dysgenesis or impaired synthesis of hormones due to dyshormonogenesis. Numerous congenital defects cause termination of synthesis or synthesis of inefficient thyrotropin including the mutation of gene controlling the differentiation of hypophyseal, receptor of thyrotropin-releasing factor, thyrotropin beta chain and thyrotropin receptor. Thyroid dysgenesis has been found to be associated with *PAX8* gene mutations and

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thyroid transcriptional factors 1 and 2 (*TITF1* and *FOXE1*). (2) Deficit of thyroid hormones biosynthesis may be also associated with mutated genes coding the thyroid peroxidase, sodium iodide symporter, pendrin, thyroid oxidase 2 and thyroglobulin (3). Rare causes of hypothyroidism in newborns and small children are hemangiomas with so high activity of deiodinase 3 that thyroxine catabolism overpasses the production capacity of thyroid gland (4). Syndrome of congenital resistance to thyroid hormones, attributed to mutation of gene for beta receptor of triiodothyronine, interferes with action of thyroid hormones in the majority of tissues (5,6). More details on congenital hypothyroidism were presented in a separate chapter dealing with this problem.

### ***Acquired primary hypothyroidism***

#### **Autoimmune thyroiditis**

Presently, the most frequent cause of acquired hypothyroidism is chronic autoimmune thyroiditis. The disease is seven times more frequent in women than in men with the incidence rate rising with age. The disease is hereditary whose nature has not been elucidated yet. Polygenic basis of autoimmune thyroiditis relies on finding of the connection of disease with several loci of the affected person (7). It is assumed that the role of autoimmunity in development of such thyroiditis is based on histological picture of diffuse lymphocyte infiltration of thyroid gland, properties of thyrocytes of the affected person to express atypically the II class MHC antigens necessary for CD4 presentation by T lymphocytes specific for thyroid antigens, then on findings of thyroid autoantibodies in circulation as well as animal models of diseases mediated by thyroid antigen immunization. It is believed that iodine induces thyroiditis by action on thyroglobulin molecule although the exact mechanisms of action of the external factors have only to be identified (8).

Characteristical physical finding in patients with autoimmune thyroiditis is diffusely enlarged thyroid gland with uneven but usually solid consistency, pseudolobular, with regular contours or extremely asymmetric, therefore, misinterpreted as nodously modified. In latter phase of disease, thyroid gland may be impalpable. Sometimes it may be sensitive or pretty painful. The patients with autoimmune thyroiditis are euthyroid for a long period of time, sometimes with transient episodes of thyrotoxicosis (not hyperthyroidism), but in advanced stage, they are, more or less, hypothyroid (9). Finding of antibodies against thyroid peroxidase, may, to a large extent, be supportive to diagnosis of autoimmune thyroiditis in people with characteristic clinical findings: hard, elastic, lobular goitre and hypothyroidism.

Autoimmune thyroiditis may develop in conjunction with other conditions of endocrine insufficiency, most often with hypoparathyroidism, adrenal insufficiency

Table 1. Causes of hypothyroidism

Autoimmune lymphocytic thyroiditis <ul style="list-style-type: none"> <li>• Atrophic thyroiditis</li> <li>• Hashimoto thyroiditis (struma lymphomatosa)</li> </ul>	Associated with iodine supply <ul style="list-style-type: none"> <li>• Iodine deficit</li> <li>• Iodide-induced</li> </ul>
Following the ablative therapy <ul style="list-style-type: none"> <li>• Radioiodine (RAI) therapy</li> <li>• Thyroidectomy</li> </ul>	Infiltrative <ul style="list-style-type: none"> <li>• Reidel's thyroiditis</li> <li>• Scleroderma</li> <li>• Amyloidosis</li> <li>• Hemochromatosis</li> </ul>
Transient <ul style="list-style-type: none"> <li>• Subacute thyroiditis</li> <li>• Postpartum thyroiditis</li> <li>• Early postablative (RAI, subtotal thyroidectomy)</li> <li>• Drug-induced</li> <li>• Thioamides</li> <li>• Lithium</li> <li>• Amiodarone</li> <li>• Interferon</li> <li>• Drug and substances interfering with thyroxin in treated patients (iron salts, cholestyramine, sucralfate..)</li> </ul>	Neonatal/congenital <ul style="list-style-type: none"> <li>• Thyroid agenesis/ectopy</li> <li>• Genetic disorders of TSH, TSH receptors, thyroid peroxidase, thyroglobulin, pendrin</li> <li>• Transplacental passage of blocking TSH-receptor antibodies</li> </ul> Central <ul style="list-style-type: none"> <li>• Hypophyseal or hypothalamic diseases</li> </ul> Others <ul style="list-style-type: none"> <li>• Resistance to thyroid hormones</li> </ul>

and chronic mucocutaneous candidiasis or together with type 1 diabetes mellitus and praemature ovarian insufficiency. The patients with autoimmune thyroiditis are prone to some other organ-specific disease, such as vitiligo, atrophic gastritis, pernicious anemia, systemic sclerosis and Sjögren's syndrome (10).

### ***Other causes of acquired primary hypothyroidism***

In developed world regions, the most frequent cause of the acquired primary hypothyroidism is surgical or radiotherapeutic extirpation or considerable reduction of thyroid tissue volume. Acquired primary hypothyroidism may also develop due to action of other aspects of radiation (external head or neck radiation for malignant conditions), accidental exposure to radiation as well as utilization of labeled globulins for treatment of malignancy. Perchlorate pollutants may cause transient hypothyroidism if they reach the water supplies (11). Toxic

Table 2. Risk factors of hypothyroidism

Autoimmune conditions	Drugs and medical interventions	Hypothalamic and hypophyseal disorders
<ul style="list-style-type: none"> <li>- Earlier Grave's disease, de Quervain's thyroiditis, painless thyroiditis</li> <li>- Postpartum thyroiditis</li> <li>- Family history of autoimmune thyroid disease</li> <li>- Down's syndrome</li> <li>- Turner's syndrome</li> <li>- Personal or family history of other autoimmune diseases (vitiligo, pernicious anemia, adrenal insufficiency, type 1 diabetes mellitus, premature ovarian insufficiency, celiac disease, Sjögren's syndrome)</li> <li>- Primary pulmonary hypertension</li> <li>- Multiple sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>- Surgery of thyroid gland or other cervical organs</li> <li>- Application of radioactive iodine</li> <li>- External radiotherapy</li> <li>- Lithium</li> <li>- Amiodarone</li> <li>- Aminoglutethimide</li> <li>- Interferon <math>\alpha</math></li> <li>- Thalidomide</li> <li>- Stavudine</li> <li>- Perchlorate</li> <li>- Exposure to polyhalogenated biphenyls and resorcin</li> </ul>	<ul style="list-style-type: none"> <li>- Hypothalamic or suprasellar tumor</li> <li>- History of radiation or hypothalamic surgery</li> <li>- Disorders causing hypothalamic dysfunction – sarcoidosis, hemochromatosis, histiocytosis</li> <li>- Hypophyseal tumors</li> <li>- Signs of other hypophyseal deficits</li> <li>- Signs of sellar mass (headache, bitemporal hemianopsia or diplopia)</li> <li>- History of hypophyseal surgery or radiotherapy</li> <li>- History of head trauma</li> <li>- History of vascular injury of hypophysis</li> <li>- History of other diseases causing hypopituitarism – cancer metastasis, lymphocytic hypophysitis.</li> </ul>

\damage of thyroid gland may result from use of polyhalogenated biphenyls (polybromide and polychloride). Gallic acid contained in water-flows, washing out the coal deposits, may interfere with iodides and give rise to hypothyroidism with goitre (12). Iron infiltration of thyroid gland may rarely cause hypothyroidism in hemochromatosis.

Several medicaments may cause hypothyroidism interfering with synthesis of thyroid hormones or inducing thyroiditis. Lithium carbonate interferes with release of hormone from the gland and leads to rise of serum thyrotropin; about 10% of these persons develop hypothyroidism, in particular if they have autoimmune thyroiditis as well (13). Pharmacological quantities of iodide as found in amiodarone or expectorants may interfere with production of thyroid hormones, especially when thyroiditis has been induced, leading to hypothyroidism (14). Interferon alpha may trigger the autoimmune process of thyroid gland which may be manifested by hypothyroidism or transient thyrotoxicosis that usually subside with discontinuation of drug. Aminoglutethimide inhibits the synthesis of thyroid hormones and may cause hypothyroidism with struma.

Transient primary hypothyroidism may be developed in subacute (de Quervain's) thyroiditis and in lymphocytic thyroiditis occurring after delivery (that is why it is often called postpartum thyroiditis). In both condition, hypothyroidism lasts several weeks to several months, and is usually developed after transient phase of thyrotoxicosis which is the sequela of mechanical damage of follicles and not the hyperfunction of thyroid gland (hyperthyroidism). Damaged follicles, uncontrolled discharge of deposited hormones and impaired hormonogenesis are followed by secondary, hypothyroid phase. Subacute thyroiditis is most probably viral inflammation of thyroid gland with usually very painful struma of uneven consistency with systemic signs of viral infection. Today, postpartum thyroiditis is relatively often condition manifesting in the first year of delivery in 5% to 20% of women; it is rare in men or in women not connected with pregnancy (15). Thyroid gland is mildly to moderately enlarged, rather discreetly firm than hard and with uneven consistency, but not sensitive (16). The majority of patients go well without consequences – in over 85% of patients with subacute thyroiditis and over 75% with painless, lymphocytic thyroiditis.

There is a significant probability of recurring postpartum thyroiditis in each of the following pregnancies with metabolic disorder more profound than in the previous one. This is the reason for indispensable examination of every pregnant woman with the history of earlier postpartum thyroiditis, because accelerated metabolism of thyroxine in gestation may lead to increased requirement for substitution during pregnancy (17).

### ***Central (secondary and tertiary) hypothyroidism***

Central hypothyroidism may develop due to hypothalamic disorder of synthesis of releasing hormone for TSH (TRH), TRH transport to hypophysis or the sequela of impaired synthesis of thyrotropin in hypophysis because of disorder or damage of hypophyseal thyrotrophs. In some cases, the hypophysis synthesizes and secretes the inactive isoforms of thyrotropin which are different by degree of molecule glycosylation, on what account their biological activity is being altered (18). Lymphocytic hypophysitis, infection, metastasis, infarction and retinoid X receptor selective ligands may affect the function of thyrotrophs and alter the secretion of thyrotropin (19). The most frequent causes of the central hypothyroidism are hypophyseal adenomas, i.e. adenomas of the hypophysis treated by surgery or radiotherapy (20). Head trauma causing the injury of hypophyseal stem may interfere with TRH distribution (21). Central hypothyroidism may develop due to tumors penetrating from the surrounding into the space of Turkish saddle (meningiomas, gliomas, germinomas) or hypophyseal stem as well as suprasellar space (craniopharyngiomas, chordomas). Sarcoidosis, hemochromatosis and histiocytosis may affect the production of TRH in hypothalamus (22).

### ***Resistance to thyroid hormones***

The majority of classical effects of thyroid hormones is being effectuated by genomic action after bonding of triiodothyronine to one of three receptor isoforms (TR $\alpha$ 1, TR $\beta$ 1 and TR $\beta$ 2) which all belong to superfamily of nuclear receptors. The receptors are bound to DNA on the loci with specific orientation of paired elements having specific hexanucleotide sequences typically located on 5' regulatory gene segments responsive to thyroid hormones (23)

Clinical hypothyroidism indicates the absence of the effect of thyroid hormones either because of absolute deficit of hormones or impaired tissue thyroid hormone receptors. If hypothyroidism appears in intrauterine or early postpartum period, then the development and maturation of the central nervous system are particularly impaired. Impaired thermogenesis and oxidative metabolism are manifested in the adults. Thyroxine, exclusively produced in thyroid gland, is converted to triiodothyronine by action of monodeiodinases in cytoplasm and nucleus of target tissues. Based on this model, some manifestations of hypothyroidism may be comprehended at molecular level. Incapacity of stimulation of gene which controls the growth hormone induces the retardation of growth and small height in prepuberty child (24). Deficit of the expression of hepatic LDL receptor gene due to defect of thyroid hormone regulated SREBP2 (sterol regulatory element binding transcription factor 2) diminishes the LDL-cholesterol clearance, what results in hypercholesterolemia, and lower expression of myocardiac sarcoplasmatic reticulum ATPase and beta myosin heavy chains may damage both systolic and diastolic ventricular functions (25).

Many other effects of thyroid hormones have not been explained by genome action. Other than nuclear effects, triiodothyronine stimulates the entry of amino acids and glucose into the cells, enhances the calcium ATPase activity in cardiomyocytes and changes the mitochondrial production of ATP by non-genomic mechanisms. Thyroid hormones react with G protein-bound membrane receptors and activate the mitogen-activated protein kinase (MAPK), and deficit of non-genomic effect may account for some of additional consequences of hypothyroidism (26).

### ***Clinical manifestation***

Systemic manifestations of hypothyroidism vary considerably, depending on the cause, duration, and severity of the hypothyroid state. Gradual and imperceptible onset and sometimes diminished capacity to recognize the changes due to hypothyroidism itself have impact on inconclusive clinical diagnosis of hypothyroidism. New symptomatology or combined manifestations are more valuable in diagnostics (27).

Skin changes are prevalent among hypothyroid patients. The skin is dry, pale, thick, and rough with scales, and it feels cold. Dryness is related to decreased function of sebaceous and sweat glands. Pallor is related to decreased skin blood flow and anemia. Yellowish discoloration of the skin can be present, especially on the palms and soles, because of the deposition of carotene (28). The thick rough skin with scales is caused by mucinous swelling of the dermis and hyperkeratosis of the stratum corneum in the epidermis (29).

Changes in cardiovascular dynamics in hypothyroidism include an increase (of 50% to 60%) in peripheral vascular resistance and a decrease (of 30% to 50%) in cardiac output. Aortic stiffness is increased. As a result, mean blood pressure is largely unaltered, although systolic pressure may decrease, and diastolic pressure may increase (30). Triiodothyronine acts as a vasodilator, and thyroid hormone deficiency increases vascular smooth muscle tone, possibly by interference with ion fluxes (31). The decrease in cardiac output is due to a decrease in stroke volume and heart rate. The pre-ejection time and isovolumetric contraction time are prolonged, and the ventricular relaxation rate during diastole is slower (32). Blood volume is decreased. Edema may develop by albumin extravasation as a result of increased capillary permeability; it may give rise to pericardial, pleural, or peritoneal effusions (33).

Thyroid hormone deficiency causes slowing of a wide variety of metabolic processes, which results in decreased resting energy expenditure, oxygen consumption, and use of substrates. Reduced thermogenesis is related to the characteristic cold intolerance of hypothyroid patients. The decline in metabolic rate and substrate use contributes to decreased appetite and food intake. Body weight increases on average by 10% because of an increase in body fat and retention of water and salt. Hypothyroidism delays glucose absorption from the intestine. Insulin secretion in response to oral glucose is appropriate for the slightly flattened oral glucose tolerance curve. Hepatic gluconeogenesis and glucose use usually remain normal, and blood glucose levels are maintained within normal limits.

The increase in plasma cholesterol is largely accounted for by an increase in low-density lipoprotein (LDL) cholesterol (associated with an increase in apolipoprotein B) because of decreased expression of the  $T_3$ -responsive LDL receptor gene in the liver, which is involved in LDL clearance. The ratios of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol decrease with treatment of hypothyroidism. Taken together, the changes in plasma lipids in hypothyroidism result in an atherogenic lipid profile (34-38).

Muscle symptoms are prevalent in hypothyroid patients and include myalgia, weakness, stiffness, cramps, and easy fatigability (39). Carpal tunnel syndrome is common in hypothyroidism.

Anemia occurs in about 30% and is usually mild and normocytic normochromic (40). Microcytic hypochromic anemia is mostly due to iron deficiency caused by

excessive menstrual bleeding or by reduced iron absorption in the case of hypochlorhydria; both conditions are common in hypothyroid women (41). Macrocytic hyperchromic anemia indicates vitamin B<sub>12</sub> or folic acid deficiency and is caused by either the hypothyroid state itself or pernicious anemia associated with chronic autoimmune thyroiditis.

Hypothyroid patients may have bleeding symptoms, such as easy bruising, menorrhagia, or prolonged bleeding after tooth extraction. The most frequent defects in hemostasis are a prolonged bleeding time, decreased platelet adhesiveness, and low plasma concentrations of factor VIII and von Willebrand factor (42)

Table 3. Clinical symptoms and signs of hypothyroidism

Fatigue
Intolerability of coldness
Constipation
Impaired memory
Slow mental processes
Depression
Syndromes of nerve herniation
Ataxia
Muscle weakness
Muscle cramps
Impaired menstrual cycle
Infertility
Bradycardia
Diastolic hypertension
Hoarseness
Struma
Periorbital edemas
Dry, cold and scaly skin
Hypercarotenemia
Gaining of weight
Galactorrhea

Psychiatric changes include mood disturbance, depression and psychosis to complete loss of conscious and finally coma. Hypothyroidism is characterized by severe neurocognitive disorders, especially memory functions. Such condition is traditional in differential diagnosis of reversible dementia although thyroid hormone substitution rarely results in abatement of dementia in all persons.



### ***Diagnosis of hypothyroidism***

The clinical diagnosis of hypothyroidism can be easy but also difficult because of the nonspecific nature of the symptoms and signs and the marked diversity of findings. At first, it should be ascertained whether a thyroid hormone deficiency exists (syndromal diagnosis). Thereafter, the cause of the demonstrated thyroid hormone deficiency should be looked for (nosologic diagnosis). Diagnosis of the hypothyroid syndrome starts with the history and physical examination and ends in the case of sufficient clinical suspicion with an assay of TSH, FT<sub>4</sub> and thyroid peroxidase autoantibodies in serum. One of the rationales for clinical examination is to increase the pretest likelihood of hypothyroidism so that fewer patients need hormone tests (43).

### ***Laboratory analyses***

The ideal diagnostic test for hypothyroidism would be one that accurately measures the effect of thyroid hormone deficiency in target tissues. Peripheral tissue function tests, such as serum cholesterol and creatine kinase, lack sufficient sensitivity and specificity to be of much use.

### ***Measurement of serum thyrotropin***

Serum TSH is the best assay for detection of hypothyroidism (44). The test is used both in single cases and in large population. Higher serum thyrotropin identifies the patients with primary hypothyroidism regardless of the cause as well as those whose disorder is so mild that thyroid hormone values remain within reference values for population (45). Normal thyrotropin level in persons without any observable disorder usually ranges from 0.4mU/L to 4.0mU/L, logarithmically distributed in the way that geometric mean value in the lower half of limits is about 1.5 mU/L (46). Based on such finding, even subtle changes, i.e. TSH value close to the upper normal limit (over 3.0mU/L) may suggest very mild thyroid dysfunction with greater hazard of progress towards hypothyroidism, especially in case of positive peroxidase antibodies results.

### ***Limitations of thyrotropin testing***

Serum thyrotropin testing may have limitations in some circumstances (47). There is no increase of thyrotropin in persons with the central hypothyroidism (TSH is low, inadequately normal or only slightly elevated) because of impossibility to be secreted

from hypophyseal thyrotrophs or the isoforms of TSH molecules are being secreted. The central hypothyroidism is possible when there are clinical manifestations and there is no laboratory evidence of TSH level increase; in addition, if there are signs of deficit of other hypophyseal hormones, finding of sellar mass or if patient has such conditions signaling the probability of hypothyroidism – sarcoidosis, head trauma or radiotherapy, and malignancy with potential metastases. In these events, other than thyrotropin, free thyroxin in serum should be measured. If low concentration of free thyroxin was found, regardless of TSH value, further testing and visualization of saddle region were required as well as tests for evaluation of hypophyseal capacity of thyrotropin and other hormones secretion. In case of serious suspicion, even if free thyroxin is in lower third of normal values, one should be very careful and repeat test in regular intervals (48).

Vice versa, there are conditions where the increase of thyrotropin may not mean hypothyroidism, including the euthyroid patients with adrenal insufficiency, renal failure, persons exposed to low temperature or extreme physical exercise. Circulating antibodies against thyrotropin or murine immunoglobulins used in TSH tests may mislead to false higher values of thyrotropin. Two rare forms of hypothyroidism induced by TSH, hypophyseal tumor secreting the TSH and syndrome of resistance to thyroid hormones, may be manifested as clinical and biochemical hypothyroidism with inadequately high serum TSH, but increased values of thyroxin or triiodothyronine (or both) indicate the diagnosis (49).

### ***The influence of non-thyroid diseases and drugs***

The greatest challenge in diagnosis of hypothyroidism is the changes of thyroid hormones and results of thyroid function test that may be seen in some severe non-thyroid diseases and conditions. In some systemic diseases, the suppression of thyrotropin secretion may mask mild but not severe hypothyroidism. Three medicaments used frequently in severe cases, glucocorticoids, dopamine and dobutamine, may suppress TSH secretion even in patients with manifest primary hypothyroidism. Conversely, patients recovering from very severe non-thyroid disease may have transient increase of TSH concentration. For this reason, thyroid function test in very severe and critical patients should be performed only if there were significant clinical evidence, otherwise, altered results may have been false positive. Diagnostic problem may also emerge in patients receiving the antiepileptics such as phenytoin or carbamazepine, which induce reduction of thyroxine and TSH concentrations in blood, what all may mislead to diagnosis of the central hypothyroidism.

### ***Determination of free thyroid hormones***

As higher TSH value has been obtained by measurement, it is advisable to determine one of free fractions of thyroid hormones, free triiodothyronine or free thyroxine; it is not necessary to measure both hormones. If obtained value of free thyroid hormones is normal along with (usually slightly) elevated TSH, it is the question of subclinical form of hypothyroidism. In this form of hypothyroidism, TSH rarely exceeds 10mU/L. When free fractions of thyroid hormones are lower, TSH is usually considerably increased, as a rule over 10mU/L, and then it is about clinically manifested hypothyroidism (50). Although TSH is adopted procedure in diagnosis of hypothyroidism, in introduction of therapy or changes of levothyroxine dose during therapy, the measurement of free thyroid hormone fractions is recommended test because the concentrations of thyroid hormones are more flexible and appropriate for monitoring of therapy effects. When the dose is leveled off, only determination of serum TSH may be required in further follow-up (51).

If slightly elevated TSH values are accompanied with lower values of thyroid hormones, the option of secondary or tertiary (central) has to be sought.

Peripheral resistance to thyroid hormones and hypophyseal tumor excreting the TSH are very rare conditions. Besides clinical picture of hypothyroidism, which is usually slightly manifested, laboratory analyses reveal elevated values of TSH and thyroid hormones. Since tissue distribution of resistance to thyroid hormones is typically uneven, the extent of hypothyroidism in different organs is unequally manifested.

### ***Antithyroid antibodies***

Laboratory tests are rarely adequate to define the underlying process of primary hypothyroidism, and medical history is usually insufficient and it identifies the factors such as earlier neck radiotherapy, surgical interventions or isotope application, postpartum condition or usage of drugs that may induce the thyroid dysfunction. In persons without any of these factors and with permanent hypothyroidism, an autoimmune thyroiditis must be considered. Although not necessary, it is useful to confirm diagnosis by determination of thyroid autoantibodies (52) Another reason for measuring these autoantibodies is anticipation of manifest hypothyroidism progress in persons with mild disease, pregnant and nursing women, and in differential diagnosis of struma.

Antiperoxidase antibodies may be found in 95% to 100% patients with chronic autoimmune thyroiditis, while thyroglobulin antibodies are unspecific and present up to 60% of patients. Peroxidase antibody test is the most sensitive test for laboratory verification of chronic thyroiditis (53). Peroxidase antibody titer is in far much better correlation with TSH increase than thyroglobulin antibody titer.

***Recommended diagnostic algorithm of primary hypothyroidism***

Clinically suspected hypothyroidism		
Serum TSH		
Normal TSH	Higher TSH	Higher TSH
No substitution therapy is applied		
No signs of insufficiency of other endocrine glands antibodies	Determine FT3 or FT4	Determine FT3 or FT4 and antiperoxidase
No hypothyroidism	Normal thyroid hormones	Reduced thyroid hormones
No further tests	Subclinical hypothyroidism	Primary hypothyroidism

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