

## Hypothyroidism is a Problem of Modern Endocrinology

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**Abstract:** Among diseases of the endocrine system, hypothyroidism is the second most common after diabetes [1]. The difficulty of diagnosing hypothyroidism lies in the diversity and nonspecificity of symptoms. This is due to the fact that thyroid hormones have an effect on almost all organs and systems. At the same time, the severity of manifestations of thyroid insufficiency can be different and does not always correlate with the severity of laboratory changes [2,4]. In the clinical picture, a patient with hypothyroidism may have multiple symptoms, which makes diagnosis difficult, especially in elderly and multimorbid patients. Patients often experience a predominance of symptoms from one system, and therefore there is a concept of diseases - "masks" of hypothyroidism, the clinical manifestations of which are discussed in this review [3,5,6]. Under the "mask" of hypothyroidism, diastolic hypertension, dyslipidemia, and hydropericardium can occur; chronic constipation, cholelithiasis, polyarthritis, alopecia, onycholysis, depression, dysfunctional uterine bleeding, infertility, anemia, etc. Due to the variety of clinical manifestations, a patient with hypothyroidism may be seen by a doctor of almost any specialty or simultaneously observed by several different specialists. The doctor must remember the likelihood of hypothyroidism in the patient, know the features of damage to organs and systems when thyroid function decreases. It is necessary to ask the patient in detail about concomitant diseases, which will allow one to suspect the presence of hypothyroidism as the cause of a combination of various nosologies[7,8]. hydropericardium; chronic constipation, cholelithiasis, polyarthritis, alopecia, onycholysis, depression, dysfunctional uterine bleeding, infertility, anemia, etc. Due to the variety of clinical manifestations, a patient with hypothyroidism may be seen by a doctor of almost any specialty or simultaneously observed by several different specialists. The doctor must remember the likelihood of hypothyroidism in the patient, know the features of damage to organs and systems when thyroid function decreases. It is necessary to ask the patient in detail about concomitant diseases, which will allow one to suspect the presence of hypothyroidism as the cause of a combination of various nosologies[7,8]. hydropericardium; chronic constipation, cholelithiasis, polyarthritis, alopecia, onycholysis, depression, dysfunctional uterine bleeding, infertility, anemia, etc. Due to the variety of clinical manifestations, a patient with hypothyroidism may be seen by a doctor of almost any specialty or simultaneously observed by several different specialists. The doctor must remember the likelihood of hypothyroidism in the patient, know the features of damage to organs and systems when thyroid function decreases. It is necessary to ask the patient in detail about concomitant diseases, which will allow one to suspect the presence of hypothyroidism as the cause of a combination of various nosologies[7,8]. Due to the variety of clinical manifestations, a patient with hypothyroidism may be seen by a doctor in almost any specialty or simultaneously observed by several different specialists. The doctor must remember the likelihood of hypothyroidism in the patient, know the features of damage to organs and systems when thyroid

function decreases. It is necessary to ask the patient in detail about concomitant diseases, which will allow one to suspect the presence of hypothyroidism as the cause of a combination of various nosologies[7,8]. Due to the variety of clinical manifestations, a patient with hypothyroidism may be seen by a doctor in almost any specialty or simultaneously observed by several different specialists. The doctor must remember the likelihood of hypothyroidism in the patient, know the features of damage to organs and systems when thyroid function decreases. It is necessary to ask the patient in detail about concomitant diseases, which will allow one to suspect the presence of hypothyroidism as the cause of a combination of various nosologies[7,8].

**Keywords:** Autoimmune thyroiditis, hypothyroidism, subclinical hypothyroidism, euthyroidism, dyslipidemia, cardiovascular diseases, arterial hypertension.

**Relevance.** Among diseases of the endocrine system, hypothyroidism is the second most common after diabetes mellitus. Moreover, the vast majority of cases of hypothyroidism are primary, the causes of which are most often: surgical removal of part or all of the thyroid gland (TG), treatment with radioactive iodine or autoimmune thyroiditis (AIT). The incidence of primary hypothyroidism is about 4.6%. The majority of this is due to subclinical hypothyroidism (SH) - 4.3%, and 0.3% - to manifest hypothyroidism. Women tend to get sick more often than men. The incidence of new cases of hypothyroidism among women is 3.5 cases per 1000 people per year [9].

Diagnosis of hypothyroidism includes determining the concentration of thyroid-stimulating hormone (TSH), thyroxine (T4sw), triiodothyronine (T3sw). To confirm the autoimmune nature of the disease, the titer of antibodies to thyroid peroxidase (AT-TPO) is determined. Assessing the prevalence of AIT in the population is difficult, since in the euthyroid phase it does not have precise diagnostic criteria. There is carriage of AT-TPO, which occurs in 10% of women [34]. Manifest hypothyroidism is characterized by an increase in TSH levels and a decrease in T4freeze. Separately, SG is distinguished, in which TSH is elevated, and T4F remains within the reference values. About 2.5% of cases of HS progress within a year to a clinically obvious decrease in thyroid function. More rapid progression is observed in patients with an increased titer of AT-TPO and a higher (above 10 mIU/l) TSH level. In approximately 40% of cases, thyroid function in HS can spontaneously return to normal [13,14]. Therefore, if FH is detected in the absence of clinical manifestations, repeated hormone testing is required after 3–6 months[35,36].

However, timely detection of hypothyroidism is not an easy task. The difficulty of diagnosis lies in the diversity and nonspecificity of the symptoms of this disease. This is due to the fact that thyroid hormones have an effect on almost all organs and systems. At the same time, the severity of manifestations of thyroid insufficiency can be different and does not always correlate with the severity of laboratory changes, which will be shown below [36].

In the clinical picture, a patient with hypothyroidism may present a variety of symptoms from various organs and systems, which makes diagnosis difficult, especially in elderly and multimorbid patients. Also, patients often experience a predominance of symptoms from one system, and therefore there is a concept of diseases - “masks” of hypothyroidism. There are cardiological “masks” (diastolic hypertension, dyslipidemia, hydropericardium), gastroenterological (constipation, cholelithiasis, hepatitis), rheumatological (polyarthritis, polysynovitis, osteoarthritis), dermatological (alopecia, hyperkeratosis, onycholysis), psychiatric (dementia and depression) , gynecological (infertility, menstrual irregularities), hematological (anemia) [37].

### **“Masks” of hypothyroidism**

#### **Cardiac “masks”**

The cardiovascular system is primarily affected by hypothyroidism. Thyroid hormone deficiency leads to a decrease in heart rate and cardiac output, as well as a decrease in stroke volume and

myocardial contractility [15]. Hypothyroidism, including subclinical, with TSH values greater than 10 mIU/l increases the risk of coronary heart disease, heart failure, cerebrovascular diseases and the risk of mortality [4,6]. In addition, the risk of hospitalization increases among people with cardiovascular pathology [33].

Thyroid insufficiency contributes to dystrophic changes in the myocardium due to insufficiency of coronary blood flow and metabolic disorders. Clinically, this is manifested by patient complaints of pain in the heart, rhythm disturbances and shortness of breath. The examination reveals bradycardia, dullness of heart sounds, decreased or, conversely, increased blood pressure (BP), often diastolic. Heart rate variability in patients with hypothyroidism is characterized by a sharp decrease in the overall power of the spectrum with a predominance of the activity of the sympathetic part of the autonomic nervous system [10]. The size of the heart can be increased due to dilatation of the ventricles and increased myocardial volume as a result of edema. A third of patients with hypothyroidism have pericardial effusion, which is characterized by increased protein and cholesterol content. Effusion can also be in the abdominal and pleural cavities. Already with subclinical thyroid insufficiency, a violation of the diastolic function of the heart is observed [11, 12].

Arterial hypertension is a common companion to hypothyroidism. Its features in this disease are a more pronounced increase in diastolic pressure, as well as increased variability of blood pressure during the day and its insufficient decrease at night due to autonomic imbalance [8,10]. Uncompensated hypothyroidism, including FH, can lead to insufficient control of hypertension. Decreased thyroid function is a risk factor for the ineffectiveness of antihypertensive therapy. Achieving euthyroidism helps to reduce blood pressure levels and normalize its daily profile [14,15].

The prognosis for heart failure in patients with hypothyroidism worsens. According to [11], in patients with FH and concomitant CHF, a TSH level of more than 7 mIU/L and an isolated low T3 level were associated with a poor prognosis (more severe CHF).

Timely initiation of treatment for hypothyroidism is important to reduce the risk of developing cardiovascular disease. Thus, cardiovascular risk increased in untreated patients compared to patients receiving replacement therapy. Moreover, the increase in risk is influenced not only by insufficient compensation, but also, conversely, by too high a dose of levothyroxine. Therefore, it is necessary to control hormone levels during treatment and maintain biochemical euthyroidism in this category of patients to reduce cardiovascular risk and the risk of death [11,13].

Another risk factor for cardiac pathology in hypothyroidism is atherogenic dyslipidemia and, as a consequence, atherosclerosis. Patients with hypothyroidism experience an earlier onset and more rapid progression. Changes in lipid metabolism in hypothyroidism include increased levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides [11,14]. Similar changes are already present in HS. From 1% to 11% of patients with lipid profile disorders have FH [15]. A more pronounced effect of TSH on the concentration of total cholesterol and LDL was found in patients aged 40–49 and 60–69 years compared to younger individuals. It is possible that subclinical thyroid insufficiency exacerbates the effect of age on lipid metabolism [16]. Also, the increase in LDL levels is facilitated by a significant increase in the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9), which is involved in lipid homeostasis, in FH with higher TSH levels compared to euthyroid individuals [19]. Prescription of levothyroxine replacement therapy is accompanied by correction of lipid metabolism disorders after 4–6 weeks. [20], although in some patients they persist even against the background of euthyroidism. Dyslipidemia is one of the risk factors for increasing the thickness of the intima-media complex (IMT) of the carotid artery. Data from two meta-analyses demonstrated a decrease in IMT thickness after 6 months. replacement therapy with levothyroxine. The authors believe that this effect depended on various factors, Among other things, an important role was played by the improvement of lipid metabolism and the effect of therapy on the course of hypertension.

Among patients whose TSH was initially above 10 mIU/L, the decrease in IMT thickness was more pronounced compared with patients whose initial TSH level was below 10 mIU/L [21]. However, a number of researchers have not established a reliable connection between FH and IMT thickness [23] and have not identified differences in the IMT value in patients with mild FH when prescribed levothyroxine [24].

The treatment of FH and its impact on cardiovascular risk is currently a controversial issue, especially in the elderly. This is due to the fact that only a small proportion of patients with FH have clinical manifestations, and often the disease is practically asymptomatic. The main goal of treating patients in the older age group is to improve the quality of life. However, research evidence on this issue is mixed. Thus, subclinical thyroid insufficiency in patients under 65 years of age is associated with an increased risk of cardiovascular pathology. However, it is not clear whether levothyroxine therapy can reduce these risks, although a retrospective observational study using a UK database showed a reduction in the risk of CAD when levothyroxine replacement therapy was given to patients under 70 years of age [18]. Thus, The decision to prescribe therapy for HS is made individually, taking into account the patient's age and clinical manifestations. Since thyroid function may recover over time in HS, careful monitoring of hormonal status is recommended [16].

Thus, when examining cardiac patients, it is advisable to study thyroid function in the presence of poorly controlled hypertension, lipid metabolism disorders, heart failure, hydropericardium to exclude hypothyroidism and timely prescription of replacement therapy, especially in patients with manifest hypothyroidism, as well as HS with a TSH level above 10 mIU/l.

#### **Gastroenterological “masks”**

Symptoms from the gastrointestinal tract (GIT) with hypothyroidism occur with a frequency of up to 68.5% [18]. In most cases, patients complain of decreased appetite, nausea, constipation, heaviness and discomfort in the epigastric region, and flatulence. Gastrointestinal motility slows down: there is a slower emptying of the stomach and slower passage of food through the intestines. Due to impaired motility, biliary dyskinesia occurs, which contributes to the formation of gallstones and the formation of cholelithiasis during a long course of the disease. AIT can be combined with autoimmune gastritis, which is caused by the presence of antibodies to parietal cells and intrinsic Castle factor. These antibodies are detected in 32–40% of patients with hypothyroidism due to AIT [17]. Swelling and atrophy of the gastric mucosa, hypo- or achlorhydria are possible.

#### **Rheumatological “masks”**

Rheumatological symptoms and syndromes (polysynovitis, polyarthritis, osteoarthritis) in some cases may precede other manifestations of hypothyroidism. This is, for example, Raynaud's syndrome, which occurs in 6% of patients with thyroid hypofunction [19]. One of the common rheumatological manifestations of thyroid insufficiency is arthropathy. This symptom is observed in 20–25% of patients. Joint damage is most often symmetrical. The knee joints, metacarpophalangeal joints, proximal interphalangeal joints of the hands, and metatarsophalangeal joints may be involved [20,21]. The main manifestations of arthritis in thyroid insufficiency are swelling and pain in the joints, limited range of motion, stiffness, and instability of the ligamentous apparatus. Thickening of the synovial membrane and non-inflammatory effusion into the articular cavities occurs. However, radiography often does not reveal pathological changes. In this regard, there may be an erroneous diagnosis of rheumatic joint disease. However, treatment with nonsteroidal anti-inflammatory drugs, as a rule, does not bring the expected effect in such patients [22]. Prescription of levothyroxine therapy promotes regression of clinical manifestations, reduction and complete disappearance of stiffness, swelling, pain and limitations of movement.

Myopathies in patients with hypothyroidism occur in 25–60% of cases and can be of varying severity [20]. The literature describes a case of hypothyroid rhabdomyopathy, which was

clinically manifested by muscle weakness, myalgia, increased levels of creatine phosphokinase, myoglobin and transaminases [24].

### **Dermatological “masks”**

Manifestations from the skin and its appendages are also quite common with hypothyroidism. As a rule, patients complain of dry skin, hyperkeratosis, which often occurs on the feet, as well as brittle hair and hair loss. The cause of these symptoms is a decrease in skin perfusion, which, in turn, occurs due to compensatory vasoconstriction in response to a decrease in body temperature and a slowdown in thermogenesis. Also, with hypothyroidism, the secretion of sweat and sebaceous glands decreases, which contributes to dry skin. Hair loss and slower growth also occurs on the face and in areas of secondary hair growth. Loss of eyelashes and the outer third of the eyebrows may occur (Hertog's sign). The growth of the nail plates slows down, the nails become brittle, and their longitudinal and transverse striations appear.

### **Neurological and psychiatric “masks”**

The prevalence of neurological disorders in hypothyroidism varies. Thus, the frequency of polyneuropathy ranges from 3.2% to 90% of cases, and myopathy – from 4.4% to 80% [23]. Although in a number of patients these manifestations are one of the first symptoms of hypothyroidism. With this disease, polyneuropathies, myopathies and tunnel syndromes occur mainly [32]. Patients experience paresthesia and muscle pain; neurological examination reveals impaired vibration and muscle-articular sensitivity, decreased tendon reflexes, and weakness of the proximal muscles of the pelvic girdle. There may be a myotonic phenomenon, which is manifested by delayed muscle relaxation [34].

Among mental disorders and cognitive changes, it is primarily necessary to highlight a decrease in memory and attention, and in more than half of the patients, varying degrees of depression and anxiety disorders can be identified [34]. In this case, it is worth paying attention to elderly patients, whose cognitive impairment, especially with manifest hypothyroidism, is often attributed to age-related changes. Opinions about the neurological manifestations of HS are controversial. According to [26], FH is associated with depression only in patients under 60 years of age, and no similar connection was observed in older people. There were also no significant differences in the severity of depression when prescribing levothyroxine therapy compared with the placebo group.

### **Gynecological “masks”**

Among reproductive disorders in women, various menstrual cycle disorders and infertility should be highlighted. Screening for hypothyroidism with determination of TSH and T4F levels is necessary for women with infertility; patients with a history of previous pregnancies that ended in miscarriage or premature birth; patients who are carriers of AT-TPO; women who became pregnant using assisted reproductive technologies. Hypothyroidism during pregnancy can cause miscarriage and also increases the risk of premature birth. Prescribing levothyroxine to pregnant women with hypothyroidism reduces the incidence of these complications [27]. In case of FH during pregnancy, levothyroxine therapy can be recommended for women with carriage of thyroid autoantibodies and TSH >2.5 and <4 mU/L and for women in the absence of autoantibodies, but with TSH >4, 0 and <10 mU/l [18, 19]. Menstrual irregularities such as a- or polymenorrhea with hypothyroidism occur in 33–80% of women [28] and are therefore also an indication for examination to identify hypothyroidism.

Women with hypothyroidism may experience hyper-androgenism, manifested by mild or moderate hirsutism and caused by a decrease in aromatase activity, inhibition of the synthesis of estradiol from testosterone and, as a consequence, an increase in its level [21].

### **Endocrinological “masks”**

In 40% of patients with hypothyroidism, hyperprolactinemia occurs [29], and an increase in prolactin levels can occur in both women and men. This is due to excessive secretion of

thyrotropin-releasing hormone by the hypothalamus, which stimulates the production of both TSH and prolactin in the adenohypophysis.

A study of thyroid function should be carried out in male patients if there are complaints of decreased potency and libido, or with male infertility. Hypogonadism in hypothyroidism can be caused by both hyperprolactinemia and direct dysfunction of the gonads. This is due to the fact that thyroid hormones affect the male reproductive system and the level of sex hormones [36]. The incidence of androgen deficiency and its clinical symptoms in hypothyroidism is 5 times higher than in euthyroid men [30].

### **Hematological “masks”**

Some hematological disorders may also be a manifestation of decreased thyroid function. As a rule, various types of anemia are detected in such patients, which is probably associated with iron deficiency. The most common types of anemia are normochromic normocytic and hypochromic iron deficiency anemia. B12 deficiency (pernicious) anemia occurs in only 10% of patients with hypothyroidism [35]. Anemia is diagnosed already in FH. In this case, mild anemia, micro- or normocytic, is detected, but it is persistent and worsens without replacement therapy, leading to more severe iron deficiency. Prescribing levothyroxine replacement therapy already in patients with HS helps to improve iron metabolism, especially in patients with initially more pronounced microcytosis [37].

### **Conclusion**

Thyroid hormones affect the functioning of all human organs and systems. Therefore, thyroid insufficiency is manifested by a wide variety of nonspecific symptoms. A thorough, detailed history will help identify combinations of various diseases, which will help to suspect hypothyroidism as the cause of multimorbidity and examine the patient to confirm this preliminary diagnosis.

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