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"Hypothyroidism: how to recognize and treat?"

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Annotation: Hypothyroidism is a common thyroid hormone deficiency condition that is easily diagnosed and treatable, but in severe cases can be fatal if left untreated. The definition of hypothyroidism is based on statistical reference ranges of relevant biochemical parameters and is increasingly a subject of debate. The clinical manifestations of hypothyroidism range from life-threatening to no signs or symptoms. The most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, voice change, and dry skin, but clinical manifestations may vary with age and gender, as well as other factors. The standard treatment is thyroid hormone replacement therapy with levothyroxine. However, a significant proportion of patients who achieve biochemical treatment targets have persistent complaints. In this seminar, we will discuss the epidemiology, causes, and symptoms of hypothyroidism; We summarize the evidence on diagnosis, long-term risk, treatment, and management; and highlight future research directions.

Keywords:hypothyroidism, hormones, thyroid gland

Definition of hypothyroidism. Hypothyroidism refers to a common pathological condition associated with thyroid hormone deficiency. If untreated, it can lead to serious adverse health consequences and ultimately death. Because of the wide variety of clinical manifestations and the general lack of specificity of symptoms, the definition of hypothyroidism is predominantly biochemical. Overt or clinical primary hypothyroidism is defined as thyroid stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. Mild or subclinical hypothyroidism, which is usually considered a sign of early thyroid failure, is defined as TSH concentrations above the reference range and free thyroxine concentrations within the normal range. Whether existing TSH and free thyroxine reference ranges should be used to define thyroid dysfunction is a matter of debate. This issue is of clinical importance because reference ranges are commonly used as cutoff values for treatment. Thyroid hormone replacement with levothyroxine is the standard treatment for patients with hypothyroidism. However, a significant proportion of patients treated with levothyroxine have persistent complaints despite achieving biochemical therapy targets, raising the question of whether levothyroxine treatment is sufficient for all patients or whether alternative treatments (e.g., combination with levothyroxine preparations) can be used.

Epidemiology

Prevalence and risk factorsThe prevalence of overt hypothyroidism in the general population ranges from 0–3% to 3–7% in the United States and from 0–2% to 5–3% in Europe, 4–8 depending on the

definition used. A meta-analysis of studies in nine European countries found that the prevalence of undiagnosed hypothyroidism, including both overt and mild cases, was about 5%. Differences in iodine status influence the prevalence of hypothyroidism, which is more common both in populations with relatively high iodine intake and in populations with severe iodine deficiency. Hypothyroidism is more common in women, in older people (over 65 years), and in whites, although data on ethnic differences are sparse. Hypothyroidism is more common in patients with autoimmune diseases such as type 1 diabetes, autoimmune gastric atrophy, and celiac disease, and may occur as part of multiple autoimmune endocrinopathies. People with Downs syndrome or Turners syndrome have an increased risk of developing hypothyroidism. In contrast, tobacco smoking and moderate alcohol consumption are associated with a decreased risk of developing hypothyroidism. Causes Hypothyroidism can be classified as primary (due to thyroid hormone deficiency), secondary (due to TSH deficiency), tertiary (due to thyrotropin-releasing hormone deficiency), and peripheral (extrathyroid; panel). Central hypothyroidism (including both secondary and tertiary) and peripheral hypothyroidism are rare, accounting for less than 1% of cases. Primary hypothyroidism In areas with sufficient iodine, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (also known as Hashimoto's disease). High levels of antithyroid antibodies (primarily thyroid peroxidase antibodies and thyroglobulin antibodies) are present in most patients with autoimmune thyroiditis. Elevated thyroid peroxidase antibody levels are also found in approximately 11% of the general population. In patients with subclinical hypothyroidism, measurement of thyroid peroxidase antibodies helps predict progression to overt disease. The exact mechanisms underlying autoimmune thyroiditis are unknown, but both genetic and environmental factors have been implicated. A higher genetic risk score calculated using five thyroid peroxidase antibody genetic variants identified in genome-wide association studies showed a graded association with higher TSH concentrations and clinical hypothyroidism. Smokers have lower levels of thyroid peroxidase antibodies than nonsmokers, and the incidence of autoimmune thyroiditis increases after smoking cessation. Other environmental factors that influence autoimmune thyroiditis include vitamin D and selenium deficiency, and moderate alcohol consumption. Hypothyroidism often develops after radioactive iodine treatment, after hemithyroidectomy,and after radiation to the neck or surgery for cancer. In the long term, approximately 80% of patients with Graves' disease treated with radioactive iodine will develop hypothyroidism, even when low doses are used. Hypothyroidism has been reported to occur in 55% of patients treated for toxic nodular goiter40 and in approximately 8% of patients treated for solitary toxic nodules. In a meta-analysis43 of 32 studies, 20% of patients developed hypothyroidism after hemithyroidectomy. Other causes of primary hypothyroidism include transient thyroiditis and infiltrative disease. Central hypothyroidism Central hypothyroidism is rare and affects both sexes equally. It is more often associated with abnormalities of the pituitary gland than the hypothalamus, but often involves both. Biochemically, central hypothyroidism is defined by low or near-normal TSH levels and disproportionately low free thyroxine levels. Occasionally, TSH levels are slightly elevated, probably because of decreased biological activity. More than half of cases of central hypothyroidism are caused by pituitary adenomas. Other causes of central hypothyroidism include pituitary or hypothalamic dysfunction due to head trauma, pituitary apoplexy, Sheehan syndrome, surgery, radiation therapy, genetic disorders, and infiltrative diseases. Several drugs are known to affect the hypothalamic-pituitary-thyroid axis. Peripheral hypothyroidism. Consumptive hypothyroidism is caused by abnormal expression of the enzyme deiodinase-3 (which inactivates thyroid hormone) in tumor tissues. Although such overexpression is very rare, it can cause

severe hypothyroidism. Elevated deiodinase 3 levels were first described in a neonate with infantile hemangiomatosis of the liver, but may also be seen in patients with vascular and fibrous tumors and gastrointestinal stromal tumors. Patients with rare genetic syndromes resulting in decreased sensitivity to thyroid hormones (panel) usually have normal TSH levels but may also have tissue-specific hypothyroidism. Clinical presentation and sequelae Myxedema, coma, and severe hypothyroidism The clinical manifestations of hypothyroidism range from life-threatening, in the case of myxedema coma, to the absence of any signs or symptoms. Myxedema coma, which was first described in the late 1900s as a result of prolonged, untreated, and severe hypothyroidism, has become a rare disorder. However, since the disease course is dramatic and the mortality rate is 40% despite treatment, early recognition is vital. Myxedema coma results in altered mental status, hypothermia, progressive lethargy and bradycardia and can ultimately lead to multiple organ dysfunction syndrome and death.Therefore, early initiation of thyroid hormone therapy and other supportive measures is essential. Although very rare, severe primary hypothyroidism may result in pituitary hyperplasia with associated pituitary pathology (eg, secondary adrenal insufficiency) and symptoms (eg, amenorrhea).

Signs and symptomsThe most common symptoms of hypothyroidism in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, voice change, and dry skin, but the clinical picture may include a wide range of symptoms that vary with age, sex, and time between presentation and diagnosis. Symptoms for diagnosing hypothyroidism are nonspecific, particularly in older patients, who have fewer classic signs and symptoms than younger adults. An increase in symptom severity may suggest hypothyroidism, since a change in seven or more symptoms over the past year increases the likelihood of developing hypothyroidism. However, in a case-control study, none of the 34 symptoms associated with hypothyroidism could be used to identify patients with hypothyroidism. Furthermore, 15% of patients with autoimmune hypothyroidism are asymptomatic or report only one hypothyroidism-related symptom, whereas 70% of euthyroid controls have one or more thyroid-related complaints.

Hypothyroidism has clinical consequences involving nearly every major organ system, but the cardiovascular system has been most thoroughly studied. Hypothyroidism results in increased vascular resistance, decreased cardiac output, decreased left ventricular function, and changes in several other markers of cardiovascular contractility. Myocardial injury and pericardial effusion are more common in hypothyroid patients than in euthyroid controls. In addition, patients with hypothyroidism have a higher prevalence of cardiovascular risk factors and often have features of the metabolic syndrome, including hypertension, increased waist circumference, and dyslipidemia. Hypothyroidism also increases total cholesterol, low-density lipoprotein, and homocysteine levels. Patients with acute hypothyroidism in the context of thyroid cancer treatment experience decreased mood and quality of life. Hypothyroidism has been implicated as a cause of reversible dementia; however, how often it occurs and in what proportion of patients the dementia is truly reversible is unclear. Other manifestations include neurosensory, musculoskeletal, and gastrointestinal signs and symptoms. Because of the pleiotropic effects of thyroid hormones, hypothyroidism may also influence the course of other diseases. For example, statin intolerance is more common in individuals with hypothyroidism than in nonhypothyroid controls. Hypothyroidism has also been associated with nonalcoholic fatty liver disease, cancer mortality, arthritis, renal dysfunction, and diabetes; however, in most cases, a causal relationship is suspected but not proven. Diagnosis Primary hypothyroidism is defined by a TSH concentration above the reference range (most commonly 0-4-4-0

mIU/L) and a free thyroxine concentration below the reference range, depending on the type of assay used and the population studied. In addition, patients may recognize the previous symptoms only after starting levothyroxine treatment.

Diagnosis and treatment of primary hypothyroidismTSH = thyroid-stimulating hormone. TSH has a circadian pattern, with higher concentrations in the late afternoon. Patients with severe hypothyroidism have abnormal TSH secretion. Seasonal variations have also been described, with TSH concentrations being higher in winter and spring than in fall and summer. There is no indication for routine measurement of total triiodothyronine, total thyroxine, or free triiodothyronine. Measurement of thyroid peroxidase antibodies is not strictly necessary for the diagnosis of hypothyroidism, but is useful to confirm the diagnosis of autoimmune primary hypothyroidism. Hypothyroidism is often characterized by a hypoechoic pattern on thyroid ultrasound, even in the absence of elevated thyroid peroxidase antibody concentrations. However, ultrasound is not required in the absence of additional clinical indications, such as abnormal thyroid palpation.

Conditions that interfere with diagnosis: Several conditions can interfere with laboratory measurements of thyroid analytes. Interference should be suspected when thyroid function test results are inconsistent with the clinical picture. Human anti-animal antibodies in the patient's serum can cause falsely elevated TSH concentrations and can interfere with free thyroxine steady-state dialysis platform assays. Heparin, including low-molecular-weight heparin, can cause falsely elevated free thyroxine concentrations. High intake of biotin, a popular over-the-counter supplement, can interfere with biotin-based hormone assays, leading to false thyroid function test results.

TreatmentSolid levothyroxine monotherapy administered on an empty stomach is the treatment of choice. The presence of clinical features of hypothyroidism with biochemical confirmation of overt hypothyroidism is an indication for initiating treatment. There is no reason not to prescribe generic preparations, but switching between levothyroxine preparations in stable patients is not recommended. The optimal daily dose in overt hypothyroidism is 1 5–1 8 μg/kg body weight. In patients with ischemic heart disease, the initial dose is usually 12 5–25 0 μg/day and should be gradually increased depending on symptoms and TSH concentration. This regimen is often preferred in the elderly, especially in those with many comorbidities. Younger patients without comorbidities can usually be given the full dose from the start with appropriate monitoring to avoid overtreatment. After initiation of therapy, TSH levels should be measured again after 4 to 12 weeks, then every 6 months, and once stable, annually. Adjustments should be made based on laboratory test results, bearing in mind that in some patients (e.g., low body weight or elderly patients) small dose changes may have a significant effect on serum TSH levels. The clinical significance of low triiodothyronine levels in some patients despite achievement of normal TSH levels is unknown. Routine measurement of triiodothyronine levels should not be used to assess the effectiveness of treatment.

Treatment goals. The goals of treatment include normalising TSH concentrations and relieving physical and mental complaints, while avoiding under- or over-treatment.101 However, it is estimated that 35–60% of patients receiving levothyroxine do not achieve target TSH levels (either through over- or under-treatment). Results of a retrospective cohort study in the UK109 showed that after 5 years of levothyroxine therapy, almost 6% of patients had TSH concentrations below 0–1 mIU/L and more than

10% had TSH concentrations above 10–0 mIU/L. Over-treatment (eg, iatrogenic subclinical or overt hyperthyroidism) can have detrimental health consequences such as atrial fibrillation and osteoporosis and should always be avoided, particularly in the elderly and postmenopausal women. Undertreatment (ie, persistent thyroid hormone deficiency) may result in an increased risk of cardiovascular disease and persistent signs and symptoms. The treatment goals for central hypothyroidism differ from those for primary hypothyroidism because clinicians cannot rely on the so-called TSH reflex strategy. Conclusion Despite significant advances in identifying the causes, understanding the clinical consequences, diagnosing, and treating hypothyroidism, several unanswered questions remain, particularly regarding diagnosis and treatment. Many risk factors for abnormal TSH, free thyroxine, and thyroid disease have been identified, but only a small proportion of the variability has been explained. It is therefore important to identify risk factors. Increasing evidence suggests that endocrine disrupting chemicals may be incidental factors in the development of endocrine diseases. Exposure to thyroid disrupting chemicals can occur from a variety of sources, ranging from the environment (eg, flame retardants) to foods (eg, food packaging material). To address these questions in a collaborative effort, a transatlantic call to action has been made. The diagnosis of hypothyroidism is currently based on statistically determined reference values for TSH and free thyroxine, which do not take into account whether patients are at risk for developing the disease. Because of the arbitrary nature of the cutoff values defining mild and overt hypothyroidism, an alternative scoring system based on thyroid function tests has been proposed. The arbitrary nature of these cutoffs has also been noted by the US Preventive Services Task Force 83 as an important factor hindering decisions about screening for thyroid dysfunction in asymptomatic patients. These limitations also impact treatment decisions for asymptomatic patients with hypothyroidism. More research is needed to determine what adverse health events occur following long-term thyroid dysfunction. In addition, it is necessary to establishwhat TSH and free thyroxine concentrations are associated with an increased risk of disease. Levothyroxine monotherapy is the standard treatment for hypothyroidism. However, there are several unanswered questions regarding patients who are well biochemically controlled but are dissatisfied with their treatment results. Future research should examine whether alternative treatment regimens may provide a solution for at least some patients with residual symptoms. Areas of research most urgently needed include: identifying the causes of persistent symptoms in patients with well-controlled biochemical parameters, assessing whether a more adequate dose (e.g., adapted to the patient's serum triiodothyronine or to the patient's own specific TSH value) results in more satisfactory results, investigating whether new formulations provide more satisfactory results. (eg, extended-release liothyronine) or increasing the frequency of dosing of levothyroxine-liothyronine combination therapy (eg, liothyronine three times daily) may improve a patient's symptoms and may also identify subgroups of patients who may benefit from therapy other than levothyroxine monotherapy (eg, by identifying additional genetic polymorphisms that could provide information about the patient's individual thyroid setting). Genome-wide association studies that include large numbers of individuals with detailed genotyping could provide such information.which could provide information about the individual patient's condition). thyroid gland setting). Such information could be provided by genome-wide association studies involving large numbers of individuals with detailed genotyping.which could provide information about the individual patient's condition). thyroid gland setting). Such information could be provided by genome-wide association studies involving large numbers of individuals with detailed genotyping.

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