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SUBCLINICAL HYPOTHYROIDISM

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SUMMARY – The term 'subclinical hypothyroidism' describes the state of slightly elevated serum TSH and normal serum free T4 and T3 levels, usually without any other clinical findings characteristic of hypothyroidism. The state is quite common in the elderly, especially in women. Subclinical hypothyroidism is most commonly an early stage of overt hypothyroidism. Progression to overt hypothyroidism ranges from 5 to 20 percent *per* year in patients with slightly elevated serum TSH and high thyroid antibody levels. Patients with subclinical hypothyroidism may have increased levels of are total and HDL cholesterol, which are less pronounced than in overt disease but predispose these patients to the development of severe cardiac disease. For this reason, it is necessary to consider levothyroxine therapy in some of these patients, in order to improve their quality of life and to prevent development of full-blown disease with all its sequels. Because subclinical hypothyroidism is common in the elderly (4% - 8% of people older than 60), it is necessary to establish a screening policy based on serum TSH level measurement.

Key words: *Hypothyroidism; Hypothyroidism, diagnosis; Thyroid function tests, methods; Screening, methods; Thyroid hormones, analysis*

Introduction

Subclinical hypothyroidism is a state associated with slightly elevated serum thyrotropin (TSH) concentration (5 to 25 mU/L) and normal serum free thyroxine (FT4) and free triiodothyronine (FT3) concentrations[1]. Some authors, especially those studying the neuropsychiatric aspects of hypothyroidism, also include patients who have basal serum TSH concentration in the upper normal range and supranormal serum TSH response to thyrotropin-releasing hormone (TRH)[2].

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Subclinical hypothyroidism is usually an asymptomatic state. However, some of the patients may have clinical symptoms. Each individual has his/her own setpoint for optimal concentration of free T4. TSH secretion increases when serum free T4 falls below this optimal level. Although the normal range for serum free T4 is wide (10 to 36 pmol/L), values below the optimal level but still within the normal range can be low for this particular individual. This could explain the occurrence of symptoms in some patients. However, the symptoms are usually nonspecific and unreliable to confirm the diagnosis[3]. These patients may have mild abnormalities of serum lipoproteins[4,5], significantly higher mean total cholesterol concentrations[6,7], and abnormalities of cardiac function[8,9]. The recent Rotterdam study has revealed that subclinical hypothyroidism is an independent risk factor for the development of atherosclerosis and myocardial infarction in elderly women[10].

Laboratory Testing

Laboratory confirmation of hypothyroidism consists of measuring serum TSH and FT4 concentrations. Primary hypothyroidism is characterized by high serum TSH concentration and low serum FT4 concentration. Patients with slightly elevated serum TSH concentration and normal FT4 concentration have subclinical hypothyroidism. Secondary hypothyroidism is characterized by low serum FT4 concentration and serum TSH concentration that does not show proportional elevation. Additional tests should be performed to differentiate pituitary and hypothalamic disorders.

Primary hypothyroidism accounts for more than 95 percent of cases. Therefore, serum TSH measurement is an excellent screening test for hypothyroidism in ambulatory patients being evaluated for nonspecific symptoms such as fatigue, depression, or menstrual irregularity[11].

Differential Diagnosis

Besides primary hypothyroidism, there are several conditions that are associated with increased serum TSH levels: recovery from nonthyroidal disease[11-13], TSH-producing pituitary adenoma, adrenal insufficiency[14], generalized thyroid hormone resistance, and some drugs (dopamine antagonists, amiodarone, and sodium ipodate → oral cholecystogram dye). Elevated serum TSH concentration may rarely be due to resistance to TSH caused by alterations in TSH receptor or failure of the cell to express the receptor on its surface. All patients with elevated serum TSH concentrations associated with these conditions are either hyperthyroid or euthyroid.

Once an elevated serum TSH value has been detected, the test should be repeated and serum FT4 measured, as it may be due to laboratory error or an episode of silent thyroiditis with a hypothyroid stage. In these cases, TSH will probably be normal if measured again several months later.

Causes of Subclinical Hypothyroidism

The causes of subclinical hypothyroidism are the same as those of overt hypothyroidism. The most common cause is chronic autoimmune thyroiditis (Hashimoto's disease). The disease is usually associated with increased titers of antithyroid antibodies such as antithyroid microsomal antibodies (antithyroid peroxidase) and antithyroglobulin antibodies. In a study conducted in the USA, 54% of patients with subclinical hypothyroidism had chronic autoimmune thyroiditis[15]. In an English study, 67% of women and 40% of men with subclinical hypothyroidism had increased antibody titers[16]. Another cause of subclinical hypothyroidism is the treatment of Graves' disease, mostly after radioiodine ablative therapy, which accounted for 39% of cases in the Michigan study[15]. About half of clinically euthyroid patients who received radioiodine for Graves' hyperthyroidism and up to two thirds of those treated surgically had elevated serum TSH concentrations[17-19]. Antithyroid drugs may also cause subclinical hypothyroidism[20]. Inadequate replacement therapy for overt hypothyroidism is another important cause, especially in the elderly, found in 37 percent of patients[21]. It is usually caused by poor patient compliance or by inappropriate therapy monitoring. In some patients, inappropriate therapy may be intentional because of the coexistent heart disease. A less common cause of subclinical hypothyroidism is the use of medications such as lithium, iodine and amiodarone. Finally, external radiotherapy of the neck and thyroid surgery for some indication other than hyperthyroidism are rare causes of subclinical hypothyroidism.

The Prevalence of Subclinical Hypothyroidism

Subclinical hypothyroidism is quite common in the elderly. Studies from the United Kingdom and United States report on the rates of 4% to 8% in the elderly[16,22,23]. The prevalence is higher in women than in men[24], however, higher prevalence has also been reported. In the Framigham study (USA), subclinical hypothyroidism was recorded in about 16% of women over age 60 and 8% of elderly men[25]. In women older than 80, the prevalence of subclinical hypothyroidism is lower (6%)[23]. Studies from Japan report on the rates of 5.5% and 3.2% in women and men over the age of 40, respectively[26]. In a study from South Africa, elevated TSH was found in 6.2% of old-people home residents from Cape Town[27].

Subclinical hypothyroidism is more prevalent in areas of iodine sufficiency. In European studies (Hungary), its prevalence ranged from 4.2% in iodine deficient areas to 23.9% in those characterized by increased iodine intake, despite a similar prevalence of patients with high serum antibody levels in these areas[28].

Clinical Course

Subclinical hypothyroidism is usually an early stage of overt hypothyroidism. Progression to overt hypothyroidism occurs in patients with both slightly elevated TSH and high thyroid antibody levels. The rate of progression ranges from 5% to 20% *per* year in different studies. In a study from the United Kingdom, patients were followed up after 20 years. The women with slightly elevated serum TSH and high thyroid antibody levels developed overt hypothyroidism with a 4.3% rate of progression *per* year[29]. In a study including elderly patients, the rate of progression was 20% *per* year[30]. Besides autoimmune thyroid disease, another important cause of progression to overt hypothyroidism is radioiodine ablative therapy or high-dose external radiotherapy[31].

The state of slightly elevated TSH may remain unchanged. It is more likely in patients who have undergone thyroid surgery for indications other than hyperthyroidism[31]. The third possibility, in some cases, is returning to normal TSH level.

Clinical Features

Some patients with subclinical hypothyroidism may have nonspecific clinical symptoms such as fatigue, dry skin, and cold intolerance. These symptoms improved after treatment with levothyroxine[32]. Some patients may have goiter. Many studies investigated the effect of slightly elevated serum TSH level on serum lipid and apoprotein levels. The reports were different and contradictory. In the largest study to date, which included 25 862 participants in total, patients with mild TSH elevation (5-10 mU/L) had significantly higher mean total cholesterol concentrations than those with euthyroidism[6]. Other studies reported on increased levels of lipoprotein a[4,5]. However, many studies failed to confirm these findings, and the levels of serum cholesterol and lipoproteins were similar in patients with slightly elevated TSH and those with euthyroidism. A recent Rotterdam study has revealed that subclinical hypothyroidism and thyroid autoimmunity are associated with an increased risk of atherosclerosis and myocardial infarction in elderly women[10]. Patients with subclinical hypothyroidism may have abnormalities of cardiac function[8,9].

Progression to overt hypothyroidism is usually slow. The symptoms and signs of hypothyroidism are less pronounced in elderly patients and may be attributed to aging. Elderly patients generally suffer from some other diseases with similar or at least partially overlapping clinical symptoms. Results of Lloyd and Goldberg showed that clinical examination led to definite diagnosis in only 10% of patients with verified hypothyroidism[33].

Treatment

There are no clear attitudes concerning the treatment of these patients, however, there are recommendations proposed by many authors and editorials[34-36]. Many authors currently recommend treatment for most patients with subclinical hypothyroidism. Individual approach probably is most important for decision whether or not to treat (patients with arrhythmias, coronary heart disease, etc.). However, follow-up of TSH level is required in patients with slightly elevated serum TSH.

It seems reasonable to treat patients with TSH level greater than 10 mU/L and high serum thyroid antibody level. Treatment will prevent progression to overt hypothyroidism. In patients with TSH level between 5 and 10 mU/L, treatment will improve the symptoms such as fatigue, constipation, or depression[32] and prevent the growth of goiter[37]. An important therapeutic benefit is improvement and correction of serum lipid concentrations[8] and myocardial contractility[32,38]. Considering data from the Rotterdam study[10], treatment will prevent development of atherosclerosis and myocardial infarction. Levothyroxine is a basis for the treatment of hypothyroidism. Patients with subclinical hypothyroidism can be controlled with 25 to 50 mg daily. The initial dose usually is 25 mg daily, rising by 25 mg every four to six weeks after equilibration has been reached. The final dosage is the lowest dose required to reduce serum TSH within the normal range without causing any clinical sequels. Age and lean mass are the main determinants of dosage requirements. Older patients require lower dosage and therapy should be slowly instituted, because T4 half-life increases with age.

Screening Policy

Recommendations for thyroid screening are inconsistent and have not been globally accepted. The cost could be quite high if applied at the large-scale, population level. Some authors recommend screening in women older than 40 and in geriatric patients[39]. One group of researchers

have shown that TSH screening every five years, starting from age 35, was cost-effective because progression to overt hypothyroidism was prevented, serum cholesterol levels were reduced, and the patient quality of life was improved[40].

It seems reasonable to determine TSH level in patients with nonspecific complaints, positive family or personal history of thyroid disease, presence of thyroid antibodies, radiotherapy to the head, neck or chest, other autoimmune diseases, therapy with lithium, amiodarone or iodine, and in the elderly[36].

The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of serum TSH concentration, beginning at age 35 and every five years thereafter. The indication for screening is particularly compelling in women, but it may also be justified in men[41].

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Sažetak

SUPKLINIČKA HIPOTIREOZA

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Pojam 'supklinička hipotireoza' opisuje stanje blago povišene razine TSH uz uredne referentne vrijednosti FT4 i FT3 u serumu, obično bez drugih kliničkih nalaza znakovitih za hipotireozu. Ovo je stanje često u starijoj životnoj dobi, osobito kod žena. Supklinička hipotireoza je najčešće rani stadij manifestne hipotireoze. Oko 5% do 20% bolesnika s blago povišenim TSH i visokom koncentracijom tiroidnih protutijela prijeđe u hipotireozu kroz godinu dana. Bolesnici sa supkliničkom hipotireozom mogu imati povišene vrijednosti ukupnog i HDL kolesterola, koje su manje izražene nego u manifestnoj hipotireozi, ali povećavaju rizik za nastanak teške bolesti srca. Zbog navedenih činjenica neophodno je neke od ovih bolesnika liječiti tiroksinom radi poboljšanja kvalitete života i sprječavanja razvoja uznapredovale bolesti sa svim mogućim posljedicama. Zbog visoke supkliničke hipotireoze u starijoj životnoj dobi (4% – 8% osoba starijih od 60 godina) neophodno je uvesti metodu probiranja koja se temelji na mjerenju serumske vrijednosti TSH.

Ključne riječi: *Hipotiroidizam; Hipotiroidizam, dijagnostika; Funkcionalne pretrage štitnjače, metode; Probiranje, metode; Hormoni štitnjače, analiza*