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CARDIOVASCULAR RISK IN SUBCLINICAL HYPOTHYROIDISM

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Summary
Subclinical hypothyroidism (HSC) is a relatively common thyroid dysfunction, characterized by the increase of the thyroid stimulating hormone (TSH) in the presence of normal free thyroxine values. Thyroid hormones are known for the cardiovascular effects, and the consequences of HSC on the cardiovascular system have become the focus of many studies lately. There are clear indications of the relationship between HSC and cardiovascular risk factors such as hypertension, dyslipidemia and atherosclerosis; also, HSC is associated with metabolic syndrome, BMI increase and cardiac insufficiency. Therefore, many clinical trials investigate the benefits and risks of HSC treatment with L-thyroxine.
Key words*: subclinical hypothyroidism, cardiovascular risk factors, L-thyroxine substitution therapy.*

Rezumat
Hipotiroidismul subclinic (HSC) este o disfuncţie tiroidiană relativ frecventă, caracterizată prin creşterea hormonului de stimulare tiroidiană (TSH), în prezenţa valorilor normale ale tiroxinei libere. Hormonii tiroidieni sunt cunoscuţi pentru efectele cardiovasculare, iar consecinţele HSC asupra sistemului cardiovascular au devenit ţinta a numeroase studii în ultima perioadă. Sunt date evidente care indică relaţia dintre HSC şi factorii de risc cardiovascular precum hipertensiunea arterială, dislipidemia şi ateroscleroza; de asemenea, HSC se asociază cu sindromul metabolic, creşterea indicelui de masa corporală şi insuficienţa cardiacă. De aceea, numeroase studii clinice investighează beneficiile şi riscurile tratamentului HSC cu L-thyroxină.
Cuvinte cheie*: hipotiroidism subclinic, factori de risc cardiovascular, terapie de substituţie cu L-thyroxină.*

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General Reviews

The impact of HSC on the cardiovascular system is the target of numerous studies lately, given that thyroid hormones have multiple actions on the heart and the vascular system.

There are obvious data supporting the relationship between HSC and cardiovascular risk factors such as dyslipidemia, hypertension and sclerosis; there is also conclusive data indicating the association of HSC with metabolic syndrome and heart failure. Therefore, it is very important to identify patients with HSC and increased cardiovascular risk. The risk of progression toward hypothyroidism manifestations is related to a number of factors, such as baseline of serum TSH, auto antibodies, family history, age, sex, race, BMI, dietary iodine intake, presence of goiter. On the other hand, benefits and risks of HSC treatment with L-thyroxine are studied.

Definition

Subclinical hypothyroidism, the early form of thyroid insufficiency, is characterized by mild deficiency of thyroid hormones and its identification is possible due to the increase in the current performance of thyroid functional tests[2]. Most authors define HSC by the isolated increase in serum TSH (thyroid stimulating hormone) > 4-6 mIU/L in the presence of normal levels of FT4 (free thyroxine) and T3 (triiodothyronine)[2, 3, 4, 5]. However, the exact definition and clinical significance of HSC is confronted with controversy over the correct upper limit of the baseline of serum TSH. A classification of HSC in mild and severe form is also attempted, depending on the serum TSH elevation:

- medium form - TSH 4.5-9 mU/l
- severe form - TSH ≥ 10 mU/l.

Etiology

The most common cause of HSC (60-80%) is chronic autoimmune thyroiditis associated with the presence of anti-thyroid antibodies (anti-thyroid peroxidase antibodies - ATPO), which are characteristics of chronic lymphocytic Hashimoto thyroiditis[3]. This is more common in women, but the incidence increases with age for both sexes[1]. Increased titre of thyroid auto antibodies and / or serum TSH >6 ml/L are solid arguments for the diagnosis of the disease and indicate possible progression to manifest hypothyroidism.

Other causes of HSC can be[1]:

- inappropriate substitution treatment for manifest thyroid insufficiency;
- low compliance with treatment;
- inappropriate monitoring of treatment;
- drug interaction

Prevalence

Prevalence of ischemic hypothiothyroidism varies according to the type of population, age, gender, race, geographical area and method of TSH measurement, and it is necessary to standardize the normal reference level for TSH at each specialized laboratory[1]. The HSH prevalence is relatively high, in 4-15% of the general population, with older, elderly and deficient iodine[5, 6, 8, 9] being higher, up to 20%. The average form can be found in approximately 75% of HSC patients.

Diagnosis

Diagnosis of hypothyroidism is biochemical and is based on TSH, FT4 dosing and the exclusion of other causes of TSH elevation. Although HSC has high prevalence, there is currently no consensus on screening for this type of dysfunction and the benefits of treatment, and the establishment of a consensus requires long-term clinical studies.

Clinical symptoms are usually absent or unspecific. The reduction in thyroid hormone levels, even minor, is recognized promptly by the anterior pituitary gland; it is extremely sensitive to small changes in thyroid hormone serum levels and secretes an additional amount of TSH through the feedback mechanism. It is also possible for tissues other than the anterior pituitary gland to recognize the suboptimal level of thyroid hormones[2]. Prospective studies have shown that TSH level 1-1.9 mIU/l indicates the lowest thyroid dysfunction score and TSH increase >2mIU/l is associated with an increase in hypothyroidism[3]. HSD may persist for years or may develop into myxoedema, especially in persons with autoimmune thyroidism and high titre of thyroid autoantibodies[4] The risk of progression to manifest hypothyroidism (3-8% per year) is related to multiple factors such as TSH >6 mIU/l, the presence of autoantibodies and their high titre, family history, age, sex, race, BMI, iodine intake, and presence of goiter[1,2].

Cardiovascular risk factors in subclinical hypothyroidism

Numerous studies indicate the relationship between HSC and the unfavorable lipid profile and the beneficial effects of L-thyroxine treatment on the lipid profile. At the same time, there are indications that treatment can improve other markers associated with cardiovascular disease, such as endothelial function. However, there is no unanimous opinion on the interaction between HSC and cardiovascular risk.

- HSC as manifest form is associated with dyslipidemia. It correlates positively with serum TSH and has an atherogenic intense profile: total serum cholesterol, LDL-cholesterol and triglycerides are elevated and HDL-cholesterol is low. Cholesterol elevation is mainly due to the increase in LDL concentration due to decreased LDL receptor count and activity in the liver and therefore LDL catabolism, and thyroid failure also favors the oxidation of LDL particles, thereby increasing their atherogenic effect. Increase in triglycerides is induced by the promotion of esterification of fatty acids in the liver. In addition, lipoprotein lipase activity is reduced in thyroid insufficiency resulting in a decrease in triglyceride-rich clearance of ureilipoproteins, hypertri-glyceridemia, VLDL elevation and sometimes postprandial growth of chylomicrons. At

the same time, low levels of HDL are found in HSC, a decrease in the plasma clearance rate of HDL in the liver cell[7]. Through all these mechanisms, HSC may be one of the causes of secondary hyperlipidemia and is a risk factor independent of atherosclerosis along with many other factors including obesity, hypertension, diabetes. Therefore, there is interest in using thyroid hormone therapy to treat HSC-associated dyslipidemia, but also in familial hypercholesterolemia and obesity.

- Subclinical hypothyroidism is associated with increased inflammatory markers, which together with dyslipidemia promotes increased cardiovascular risk and clinical manifestations associated with it. Reactive C protein (CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNFα) were studied, and their level increased as progression of hormone deficiency and lack of substitution treatment.
- The action of thyroid hormones on insulin sensitivity is of great interest, but the current results are still contradictory. Hypothyroidism is associated with disorder of glucose and insulin metabolism manifested by alteration of insulin secretion during glucose loading, hyperinsulinemia, glycemic disorders and insulin resistance (IR). IR indicates the presence of a low peripheral tissue response to endogenous insulin secretion and promotes elevated hepatic cholesterol production, VLDL and increased HDL cholesterol clearance. Therefore, the association of serum TSH increased by IR increases the risk of dyslipidemia and contributes to increased cardiovascular risk in hypothyroidism. The predisposition of patients with HSC to IR is demonstrated by numerous studies. The mechanism of this association is unclear, but generic studies have described some gene polymorphisms in these patients[16,17,18].
- Endothelial dysfunction, one of the early signs of sclerosis, has been observed in HSC[19, 20, 21]. Numerous multicenter studies have indicated an increased risk of atherosclerosis in people with HSC. Multiple lipid plaques in the large artery wall have been identified in patients with HSC, comparable to those seen in the elderly with other risk factors such as hypercholesterolemia, hypertension, smoking and diabetes. Also, the incidence of myocardial infarction or congestive heart failure has been increased in the elderly with TSH > 7mU/l[22, 23, 24, 25]. In manifest or subclinical hypothyroidism, endothelial nitric oxide (NO) activity - the major biological marker of endothelial dysfunction - is reduced and is associated with decreased vasodilatation induced by various stimuli and accelerated atherogenesis. Endothelial function is

accelerated in HSC by the interaction of multiple mechanisms:

- hyperlipidemia, especially post-prandial, favors serum LDL growth, subintimal lipid deposits, which may disrupt NO synthesis in endothelial cells, with worsening of endothelial dysfunction;
- chronic inflammation;
- oxidative stress that is favored by chronic inflammation; there are also observations that demonstrate the direct effect of TSH to promote oxidative stress[26]; it has profoundly unfavorable effects on NO synthesis in endothelial cells with endothelial dysfunction;
- Insulin resistance (IR) frequently accompanies dyslipidemia, chronic inflammation and oxidative stress, especially in the context known as metabolic syndrome; IR favors endothelial dysfunction either indirectly through the other components of the metabolic syndrome or directly by disrupting the production of NO and endothelin-1 at the endothelium level[27].
- The action of TSH on extratiroidal TSH receptors identified in: liver (promotes cholesterol synthesis), adipocytes (induces synthesis of interleukin-6 - IL-6), bone marrow (induces secretion of tumor necrosis factor α - TNFα), endothelial cells (these recently identified endothelial cell receptors could be a direct mechanism of endothelial dysfunction).

Cardiovascular disease in subclinical hypothyroidism

Thyroid deficiency is associated with HTA, atherosclerosis / coronary artery disease, heart failure and increased cardiovascular mortality[22, 23, 24, 25]. The elevated level of TSH plays an important role in the mechanisms that induce atherosclerosis and its progression[28]:

- hyperlipaemia, oxidative stress, chronic inflammation, insulin resistance;
- endothelial dysfunction;
- proliferation of vascular smooth muscle cells.

However, there is no unanimous acceptance of these actions, and chronic atherosclerosis, being a chronic disease, long-term studies are needed to track histopathological changes related thereto. Recent studies highlight the positive correlation between serum TSH levels and the presence of coronary calcifications assessed by calcium arterial coronary score (CACS)[29, 30, 31, 32]. Maintenance of TSH within normal limits balances plasma lipid balance and delays progression of sclerosis[33, 34]. L-thyroxine correction treatment in early stages of HSC with decreased TSH has favorable effects on endothelial function, lipid balance, and haemodynamic changes.

Numerous studies suggest that HSC induces profound effects on cardiac structure and function with decreased myocardial contractility and relaxation, altered left ventricle diastolic function, cardiac output, and heart rate. Cardiac insufficiency is a possible manifestation in HSC by reducing systolic function and diastolic dysfunction of the left ventricle due to decreased left ventricle relaxation with critical impairment of ventricular filling during exercise. The risk of heart failure increases with elevated TSH, and this is more common in the elderly with high cardiovascular risk; in these cases, L-thyroxine substitution treatment has favorable effects, and recent studies of spectroscopic RM have shown that HSC's bio-

energetic deficit is reversible under T4 treatment[35,36,37].

Relationship between serum TSH and HTA

The prevalence of HTA in HSC is significantly higher than in the elderly, and the HTA risk was significantly higher after correction of age, sex, smoking, the HOMA-IR (homeostatis modem assessment of insulin resistance) index and BMI (body mass index). The increase in TA in hypothyroidism is explained by multiple mechanisms[38,39]:

- increased systemic vascular resistance attributed in part to decreased T3 (T3 produces vasodilatation by direct action on smooth muscle cells); it has also been shown that increased TSH favors the proliferation of vascular smooth muscle cells and endothelial dysfunction[40,41];
- abnormalities in sodium metabolism;
- increased levels of catecholamines and SN Simpatic activity;
- decrease in glomerular filtration rate and increase in total water and salt content;
- TA sensitivity to salt-mediated, in part, by vascular action of T3.
- increased risk of atherosclerosis due to associated anomalies: hypercoagulability, increased blood viscosity, lipid abnormalities; in this way, hypothyroidism also influences TA[42,43].

Pericarditis may be common in hypothyroidism in general and rarely in HSC, and therefore thyroid insufficiency should be considered as a possible etiology in the detection of pericardial fluid. The incidence of pericarditis is correlated with the severity and duration of thyroid insufficiency: in severe hypothyroidism, pericarditis is frequently reported with a variable incidence of 30 to 80% and in HSC the incidence is 3 to 25% of cases. In the HSC, small / medium quantities of pericardial fluid may be detected, unlike myxedema, where medium or large amounts of liquid may develop, reaching up to cardiac tamponade. The onset and fluid evolution is insidious and asymptomatic in general, and the diagnosis is echocardiographic. The fluid is exudated and biochemically rich in mucopolysaccharides and cholesterol. The occurrence of pericardial fluid in hypothyroidism is linked to multiple mechanisms:

- hygroscopic extravasation of albumin and mucopolysaccharides in the pericardial cavity;
- increased capillary permeability;
- decrease of lymphatic drainage;
- increased water and salt retention.

Regression of pericardial fluid in hypothyroidism is slow (weeks or months), in parallel with L-thyroxine replacement therapy, and the pericardium is usually thickened due to prolonged fluid persistence or recurrence. However, the evolution towards constriction is extremely rare

because the fibrous pericardium is not infiltrated or inflamed. For all these characteristic elements, HSC should be considered when detecting small / medium quantities of pericardial fluid, sometimes persistent or recurrent. Metabolic syndrome is characterized by abdominal obesity, insulin resistance / glucose intolerance, dyslipidemia, hypertension and is associated with increased cardiovascular risk and mortality. Numerous population studies have observed the association of metabolic syndrome with HSC[44, 45]. The imbalance between the hypothalamus, pituitary, thyroid, and adipose tissue is responsible for the pathophysiological mechanisms of HSC association with obesity in metabolic syndrome[46]. The association of subclinical hypothyroidism with the increase of BMI and obesity is demonstrated by many studies, but the causal relationship between TSH and BMI is not clear, with other factors such as age, gender, smoking, drug use, non-thyroid disorders being involved. This relationship is supported by numerous arguments about the association between thyroid function, body weight and adipose tissue. In general, hypothyroidism is associated with a reduction in metabolic rate and lipid and carbohydrate metabolism disorders. On the other hand, obesity is associated with thyroid dysfunction and dyslipidemia. Body mass was shown to be a major determinant of thyroxine demand, and increased body mass may require increased TSH thyroid gland stimulation to maintain normal serum thyroxine levels[47]. The intimate mechanism of altering thyroid function in obesity was linked to the adaptation to increased energy consumption of obesity, and the increase in TSH was explained by multiple mechanisms[48]:

- HSC produced by iodine deficiency;
- autoimmune thyroiditis;
- mutations of the TSH gene and the presence of TSH receptors for thyroid hormones in the adipose tissue;
- increased leptin-mediated production of prothytrophin;
- resistance to thyroid hormones;
- mitochondrial dysfunction;
- insulin resistance - an essential mechanism in thyroid dysfunction, metabolic syndrome and type 2 diabetes;
- the involvement of thyroid hormones in lipogenesis and lipolysis mediated by the local level of noradrenaline and / or by the post-receptor adrenergic signal pathways;
- the influence of adipose tissue and caloric intake on TSH synthesis and thyroid hormones: for example, weight loss has been shown to be associated with TSH reduction. The mechanism of this relationship seems to be related to the leptin secretion by adipose tissue; leptin stimulates TSH biosynthesis in vitro and synchronization of leptin secretion and TSH[49,50,51] has been demonstrated.

Treatment with L-thyroxine - benefits and risks

L-thyroxine substitution therapy in HSC increases the FT4 and FT3 levels and reduces pituitary secretion of TSH through the negative feedback mechanism. The beneficial effects of substitution therapy concern the decrease in vascular resistance and markers of progression of atherosclerosis, improve TA and dyslipidemia. Numerous studies report the decrease in total cholesterol, LDL-cholesterol, and improvement in endothelial function with decreased progression of atherosclerosis. However, there is currently no consensus on the benefit of substitution therapy in HSC, especially in older people at high cardiovascular risk. Hormone therapy itself

may have adverse effects, especially atrial fibrillation and osteopenia, especially in the elderly[53, 54, 55]. Substitution treatment is indicated in symptomatic or at risk of progression to manifest hypothyroidism, pregnancy, infertility. Recent guidelines on the management of patients with TSH <10mIU/l suggest that the therapeutic decision should be based on patient age, associated risk factors and co-morbidity. Moreover, many authors consider that L-thyroxine substitution treatment is warranted only at people with TSH >10 mIU/l, the authors say that the treatment recommendation should be correlated with the benefits of L-tyrosine substitution and associated risks.

Conclusion

In conclusion, serum TSH elevation is an early marker of tissue hypothyroidism when T3 and T4 are within normal limits. The favorable effect of diagnosis and treatment of HSC is related to two consequences with an impact on the state of health:

- preventing progression toward manifested hypothyroidism;
- reducing the risk of cardiovascular morbidity and mortality.

It is currently known that HSC may be one of the causes of secondary hyperlipidemia, and TSH levels correlate positively with inflammatory markers and dyslipidemia and thus contribute to an increased risk of developing cardiovascular disease. Thus, HSC can be considered as an independent risk factor for atherosclerosis along with obesity, hypertension, diabetes. Therefore, knowing the prevalence and risk factors for HSC could influence risk factors and prevent cardiovascular disease. On the other hand, the relationship between HSC and cardiovascular risk factors correlates with increased interest in the use of thyroid hormones in many pathological conditions such as HSC-associated dyslipidemia, obesity and familial hypercholesterolemia. However, the overall significance of HSC remains controversial, and its influence on potential cardiovascular risk factors still requires extensive clinical trials.

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