Therapeutic strategies of subclinical hypothyroidism, including statin therapy

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Abstract

Background: Thyroid disorders are an actual problem of contemporary medicine. Hypothyroidism represents the insufficiency of thyroid to secrete thyroid hormones in necessary quantities for human body. Primary hypothyroidism is the most common endocrine disease. Although the diagnosis and treatment of hypothyroidism is often considered simple, there are large numbers of people with this condition who are suboptimally treated. We are very concerned that some patients with and without thyroid disease are being inappropriately diagnosed and managed, using levothyroxine and other thyroid hormones, in ways which compromise patient safety. Subclinical hypothyroidism has multiple etiologies and manifestations. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions. Clinical symptoms of hypothyroidism are nonspecific and may be subtle, especially in older persons. Diagnosis and treatment of hypothyroidism is often considered simple and is mostly carried out in a primary care setting. The dangers of statin use in hypothyroid patients have been illustrated and the necessity for appropriate biochemical monitoring has been emphasized. Statin therapy is safe and effective when patients are appropriately diagnosed, educated, and followed up. Statins can be cautiously reinitiated once a euthyroid state has been established in patients who developed statin-induced myopathy while hypothyroid.

Conclusions: Despite the fact that nowadays problems persist in the management of subclinical hypothyroidism, administration of statins in secondary dyslipidemia will prevent cardiovascular diseases especially atherosclerosis thus enhancing the quality of life of patients with hypothyroidism.

Key words: subclinical hypothyroidism, thyroid, statin therapy.

Introduction

Hypothyroidism is the complex syndrome, caused by the lack of action of thyroid hormones of different metabolisms, devices and systems. Hypothyroidism is one of the most common thyroid disorders, predominantly in females. According to world literature data from 3 to 5% of the population suffer from hypothyroidism [3,4].

According to some epidemiological studies, the prevalence of subclinical hypothyroidism reaches 10-12%. Subclinical hypothyroidism, in most cases, does not have clinical manifestations, which would allow it to be suspected. Very often, hypothyroidism occurs being "disguised" along with numerous somatic diseases, gynecological and other endocrine diseases. Under many prospective studies, subclinical hypothyroidism has quite serious consequences [5.13].

A study conducted on a group of patients in Rotterdam (with subclinical hypothyroidism) revealed that the risk of atherosclerosis was 1.7 times greater, and that of acute myocardial infarction 2.3 times higher than in the general population [4].

With the emergence of highly sensitive methods for determining the hormones, subclinical thyroid dysfunction concept was formed. The term "subclinical" means that the level of thyroid stimulating hormone (TSH) is increased, while all the other thyroid functional parameters remain within the normal limits. The absence of clear symptoms of subclinical hypothyroidism arose the question whether subclinical hypothyroidism is a pathology or a laboratory phenomenon, that does not require hormone therapy and normalization of TSH. Subclinical hypothyroidism is the subject of several studies, which analysis showed that in subclinical hypothyroidism changes in various organs and systems occur, and thyroid hormone replacement therapy improves patient's well-being and normalizes many functional parameters [2].

Subclinical hypothyroidism frequency in the general population ranges from 1.3 up to 17.5%, depending on age and sex. Subclinical hypothyroidism prevalence is higher in women than in men and increases with age, reaching the peak of 21% of women and 16% men after 74 years. According to Framingham study, conducted for 10 years by monitoring elderly patients, showed that in studied 2139 patients over 60 years , subclinical hypothyroidism was detected in 126 patients (5.9 %) and among women almost 2 times more frequently [7]. Whickham study showed the risk of developing clinical hypothyroidism: 4.3% per year, if they show increased serum TSH and thyroid antibodies are present from the start, only 2.6% per year if serum TSH is increased, 2.1 % per year if only thyroid antibodies are present, and after 20 years the three examined groups have developed hypothyroidism in 55%, 33 %, 27 % and 4% of those without TSH increased serum and thyroid antibodies. The likelihood of developing hypothyroidism increases with TSH serum rise [24].

In Colorado population studies, which included 25862 people aged 18-91 years, manifested hypothyroid frequency increase and subclinical hypothyroidism with age were also observed. As a result of long-term monitoring of patients with subclinical hypothyroidism during 4-8 years, it was proved, that subclinical hypothyroidism in 20-50% passes into manifested hypothyroidism. In the presence of thyroid antibodies in patients aged over 65, the risk of developing manifested hypothyroidism in the next four years is 80% [5].

In subclinical hypothyroidism and in the presence of thyroid antibodies the risk of developing hypothyroidism manifested in the general population is 5% per year. In epidemiological studies subclinical hypothyroidism is more common, but in clinical practice is less diagnosed [13].

The etiology of subclinical hypothyroidism is the same as in manifested hypothyroidism. Subclinical hypothyroidism is most often caused by autoimmune thyroiditis. Other proces-

ses, underlying subclinical hypothyroidism development are destroying thyroid tissue with a reduction in its functional activity, impaired thyroid hormone synthesis in endemic, sporadic goiter in toxic effects on the thyroid gland.

The modern laboratory diagnosis of subclinical hypothyroidism is based on TSH and FT4 level determination. The manifested hypothyroidism is characterized through TSH increased level and FT4 low level and in subclinical hypothyroidism TSH level is increased and FT4 levels within the norm. Hormonal changes characteristic for primary hypothyroidism are based on the principle of negative feedback between the thyroid gland and the pituitary gland, in accordance with the reduction in T4 and T3 leading to increased synthesis of TSH.

The priority testing in diagnosis of primary hypothyroidism is assessing TSH.

It should be noted that subclinical hypothyroidism may be transient and it is not always possible to avoid technical errors in determining hormones. Therefore, for subclinical hypothyroidism diagnosis TSH levels and FT4 should be repeated within 3-6 months and if TSH increase is confirmed, a decision on replacement therapy will be taken.

The data from the specialty literature show that in patients with hypothyroidism various disorders of the cardiovascular system can develop, first of all the changes generated by the increase of cholesterol, of lipids with a low density and triglycerides. Protein metabolism is disturbed by the basic structures impairment of myocardial contractile proteins, as well as, by changes in the cardiovascular system and contribute to the composition of the fluid from the pericardial effusion, and fibrinolysis system disorders [2, 4].

In patients with subclinical hypothyroidism endothelial dysfunction is determined (early marker of atherosclerosis), which can be reversible on the background therapy with levothyroxine. Subclinical hypothyroidism is 2-3 times more often detected in patients with hypercholesterolemia. In individuals with subclinical hypothyroidism elevated levels of triglycerides, low density lipoproteins (LDL), apolipoprotein B and lipoprotein A are identified. The atherogenic changes of lipid profile diminish on levothyroxine replacement therapy background [6.14].

In patients with subclinical hypothyroidism, as in manifested hypothyroidism the myocardial hypertrophy, hypertrophy of interventricular septum, the maximum increase rate of atria blood flow, are determined reducing the average value of the acceleration of blood flow in the aorta, to extend the relaxation isovolumic period, inferior variation of systolic index.

Thyroid hormones exert different effects on the cardiovascular system and its hemodynamics. Cardiac activity indicators such as heart rate, cardiac output, blood flow, blood pressure, total peripheral vascular resistance, cardiac contractile function, are directly linked to thyroid function status. Changes of cardiovascular system in insufficiency of thyroid hormones are: coronary atherosclerosis, ischemic heart disease, arrhythmias and management disturbances, arterial hypertension.

According to the results of the Rotterdam study (a. 2000), subclinical hypothyroidism was detected in 10.8% of women aged 69 ± 7.5 years, which often have been associated with signs of aortic atherosclerosis and myocardial infarction. In subclinical hypothyroidism the level of LDL and total cholesterol in contrast with the total cholesterol is positively correlated with the level of TSH and negatively with FT4 level. Meanwhile, the level of high-density lipoprotein (HDL) decreases, and the ratio between total cholesterol / HDL increases. However, data on subclinical hypothyroidism lipid disorders are contradictory. In some studies there were neither increased cholesterol levels nor lipid metabolism dynamic parameters during treatment with levothyroxine [4].

In a study conducted in 2004, researchers examined and pursued the association between subclinical hypothyroidism and cardiovascular disease in a group of 212 men and women aged between 20 and 69 years without a known thyroid pathology, untreated with drugs that interfere with thyroid function or with TSH analysis. There have studied the clinical signs of cardiovascular disease based on the indices of lipid metabolism, atherosclerotic risk markers, C-reactive protein and TSH. It was found high incidence of subclinical hypothyroidism 19.7% in the investigated group. Subclinical hypothyroid was associated with higher concentrations of triglycerides and C-reactive protein. Cardiovascular disease was more common in men under the age of 50 years with subclinical hypothyroidism compared to the euthyroid ones. The probability report for cardiovascular disease was 3.4 (confidence interval (1.6 to 6.8) compared to euthyroid men of the same age. In the NHANES III study, where people Caucasian, African-American and Hispanic races were investigated the prevalence of hypothyroidism was 5.1%, 1.7% and 4.1% and the category the most susceptible included the woman in the "post-partum" and also subjects with a family history of autoimmune thyroid disorders [25 26].

Subclinical hypothyroidism in pregnant women has certain features. During pregnancy, a number of factors that have an impact on its functional activity are seen. These factors include: the excess synthesis of human chorionic gonadotropin (hCG), estrogens, which induce an increased synthesis of transport proteins, which cause a decrease in the free fraction of the thyroid hormones, the increase of renal iodine clearance and the change of the metabolism of thyroid hormones in correlation with active functioning of the fetus placental complex. These factors contribute to the increased synthesis of thyroid hormones during pregnancy by 30-50%. In first trimester of pregnancy placenta actively produces hCG. Increased hCG level leads to stimulation of the thyroid gland, increased levels of FT4, which after negative feedback mechanism reduces the level of TSH. In the second trimester of pregnancy the production of hCG reduces and TSH returns back to normal. So now, thanks to the variety of factors that act on the thyroid gland during pregnancy, altering thyroid function, in different trimesters of pregnancy, has its own characteristics. In the first trimester, due to overproduction of hCG, gestational transient thyrotoxicosis can develop, which should be distinguished from true thyrotoxicosis. The reduction of FT4 in the first trimester instead of the expected growth should alert the clinician for an increased risk of hypothyroidism. The presence

of both subclinical and manifested hypothyroidism can have irreversible consequences for the fetus development, primarily for the central nervous system. It is known that during the first 16 weeks of pregnancy, the thyroid gland of the fetus is in the process of formation and the fetal development is realized only formed under the action of thyroid hormones of the mother. If during pregnancy the lack of thyroid hormone is not adjusted, in women with hypothyroidism, the child may have malformations and decreased intelligence. Numerous studies have shown that children born from mothers who have not been treated for subclinical hypothyroidism have a low coefficient of intellect, of survival, Apgar score is worse compared with the children whose mothers had received appropriate dose of levothyroxine.

It is necessary to conduct immediately a screening for hypothyroidism, including the subclinical stage for all pregnant or planning a pregnancy women for a thyroid hormone replacement therapy.

In hypothyroidism associated with pregnancy, the determination of serum TSH in pregnant women should be done at the first visit, which is one of the most useful investigations, giving the high specificity of TSH, which can diagnose subclinical forms. The level of TSH> 4.0 mU / L, requires the determination of fT4, which also has a high sensitivity. The dosage of antithyroperoxydase - ATPO antibody is indicated, to exclude an autoimmune process because ATPO positive women with hypothyroidism have a higher risk of miscarriage or premature birth and to develop a portpartum thyroiditis. For hypothyroid screening dosage of T3 and T4 free levels will be done. Monitoring of pregnancies with hypothyroidism should be complex - clinical, biochemical and ultrasound, but thyroid parameters monitoring will be done dynamically. Thyroid insufficiency during pregnancy requires maintainance of TSH in the first trimester is less than 2.5 mIU / l, while the second and third trimesters is less than 3 mIU / l. The discovery of hypothyroidism during pregnancy requires the administration of an early treatment, since starting the follow up of a pregnant woman, ideally from 4-8 weeks of gestation to prevent maternal-fetal complications. The dose of the thyroid hormones should be adjusted to maintain TSH serum under 2.5 M / l, which requires control of TSH repeatedly at every 4-8 weeks of gestation. In pregnant women with hypothyroidism pre-existing to pregnancy it's recommended to increase the dose of L-thyroxine on an average by 50% compared with preconception dose. The collaboration between obstetrician and endocrinologist is particularly important for preventing complications associated with maternal-fetal hypothyroidism in pregnancy [1,13].

In women with subclinical hypothyroidism vaginal bleeding, infertility, failure during in vitro fertilization, preterm delivery, placental abruption, high blood pressure are more common, cesarean need arises. Pregnancy in hypothyroidism is accompanied by an increased incidence of anemia, preeclampsia, eclampsia and uteroplacental apoplexy, there is a tendency to swelling and weight gain due to fluid retention.

Subclinical hypothyroidism is often transient, which can develop as a result of destructive forms of thyroiditis (subacute, induced by amiodarone) and can be determined as options of autoimmune thyroiditis (postpartum), especially in women with personal or family history of autoimmune thyroiditis. Postpartum thyroiditis occurs in 3-6 months after birth and is manifested by hypothyroidism or hyperthyroidism. Hyperthyroidism lasts 1-3 months, after which most women return to normal thyroid function, or may have hypothyroidism. Thyroid dysfunction is due to a destructive thyroiditis associated with thyroid microsomal autoantibodies. Postpartum thyroiditis often tends to recur in subsequent pregnancies, which ultimately develop subclinical or manifested hypothyroidism.

Subclinical hypothyroidism can develop after surgery, antithyroid drug administration, potassium perchlorate, lithium preparations. TSH research is recommended in 3-6 months and if it is necessary, the replacement therapy with levothyroxine administration and TSH level will be repeated after 3 months [10,11,12].

Treatment

Until the mid-twentieth century hypothyroidism treatment was performed using animal thyroid extract. The emergence of synthetic thyroid hormone treatment has fundamentally changed the treatment of thyroid pathology. Levothyroxine therapy in hypothyroidism is considered the "gold standard" [13], there are several reasons for this statement:

- easy diagnosis of hypothyroidism (in most cases only by determining the level of TSH);
- the single vital function of the thyroid gland is to produce thyroid hormones;
- the circadian rhythm of secretion of thyroid hormone is almost absent and, therefore, the daily intake of levothyroxine, in the same dose is sufficient;
- high bioavailability for peroral administration of levothyroxine;
- breaking time of levothyroxine in plasma (approximately 7 days);
- availability of the exact test (TSH level), which fully reflects the quality of compensation of hypothyroidism;
- relatively low price of levothyroxine;
- Patients that administer sufficient doses of levothyroxine are recommended to determine TSH levels once in 6-12 months.
- The quality of life in patients with hypothyroidism, who permanently administer levothyroxine and are compensated, is no different from that of patients without hypothyroidism.

According to population surveys conducted by K. Peterson [8], which lasted for 12 years (1968-1969 up to 1980-1981), and that included 1462 middle-aged women, in 29 women aged up to 28 years levothyroxine replacement therapy was administered with the diagnosis of primary hypothyroidism. As a result, it was shown that the duration and the quality of life and the risk of major diseases, did not differ in patients with hypothyroidism treated with levothyroxine, and in the control group (n = 968). The treatment of hypothyroidism, regardless of its clinical form, is substituted by administering

thyroid hormones. The effectiveness of therapy is judged by clinical status, normalization of hormonal status. The treatment lasts a lifetime, and for the hypothyroidism replacement therapy levothyroxine is indicated.

In adults levothyroxine dose of 1.6 mcg / kg of body weight per day is indicated. The need for levothyroxine is significantly higher in children and can be from 2 micrograms / kg to 5 mcg / kg per day.

The need for levothyroxine decreases with age. Some elderly can manage no more than 1 mcg / kg per day of levothyroxine for hypothyroidism compensation. The need for levothyroxine increases during pregnancy. Evaluation of thyroid function in pregnant women with TSH and free T4 is recommended every trimester of pregnancy.

The starting dose of the drug is determined individually depending on the age, body weight, and the presence of concomitant cardiovascular diseases.

Subclinical hypothyroidism treatment is solved individually. Taking into consideration the high frequency of dyslipidemy and atherosclerosis and increased risk of heart attack justifies the prescription of levothyroxine for subclinical hypothyroidism. The indications for replacement therapy with levothyroxine TSH levels are ≥ 10 IU / L or TSH level between 5 and 10 mU / l and concomitant dyslipidemia. Typically, the starting dose is selected based on the age of the patient and the presence of concomitant heart pathology. The aim of replacement therapy is to maintain subclinical hypothyroidism TSH values in the range of 0.5-2.0 mIU / l [6,13].

TSH level varies slowly after a change in dose of levothyroxine. TSH level will be examined sooner than 6-8 weeks after changing the dose.

The treatment should be slowly progressive, with a gradual dose increase, especially in the elderly ones and in case of severe hypothyroidism. It begins with daily doses of 25 mcg levothyroxine and gradually rising every 7-14 days, at doses of 50, 75, 100, 125 mcg etc. until euthyroid state is achieved. For older people, 1 mcg/kg of levothyroxine per day is enough for compensation of hypothyroidism.

The treatment of subclinical hypothyroidism in patients with concomitant cardiac disease, particularly coronary artery disease and cardiac arrhythmias should begin with minimal doses of levothyroxine - from 12.5 to 25.0 mcg, by gradually increasing the dose with 12.5 to 25.0 mcg every 1-2 months to reduce TSH levels to normal levels. Replacement therapy is performed under ECG supervision or Holter ECG monitoring, avoiding decompensation of cardiac abnormalities or arrhythmias. After values normalization it is recommended to repeat TSH after 3-6 months [2.14].

In elderly and coronary subjects is recommended the concomitant use of β- blockers coronary dilators, calcium channel blockers.

The effectiveness of therapy is judged by clinical status, normalization of hormonal status and of parameters, indicating the action of thyroid hormone at the level of tissue receptor.

Ideally, levothyroxine is administered on an empty stomach, 30 minutes before a meal.

It will be taken into account the possible medicaments interactions: thyroid hormones intensify K antivitaminic actions, which are important in the blood clotting process, reduce the permeability of capillaries, promote tissue regeneration, enhance the action of tricyclic antidepressants, reduce hypoglycaemic action. Their action is reduced by cholestyramine.

Often, levothyroxine hormone replacement finally normalizes the lipid metabolism, nervous system and psycho-emotional sphere disorders.

If the hormone replacement therapy does not lead to normalization of plasma lipids, the patients with hypothyroidism are indicated a lipid-lowering therapy [15].

The most perspective drugs for the correction of lipid metabolism are in present inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes an early step in the biosynthesis of cholesterol.

The statins along with the lipid-lowering effect have a number of pleiotropic effects: anti-inflammatory, antioxidant, anti-thrombotic properties. Statins are the most effective cholesterol lowering drugs acting selectively on HMG-CoA reductase, the key enzyme in cholesterol synthesis; they decrease LDL-C by 20-40% triglycerides - by 10-20% and increase LDH-C by 5-10% [23]. Statins are the most successful cardiovascular drugs that have the ability to prolong life and to improve its quality. These data confirm the overriding importance and need for hypolipimiant treatment in hypothyroidism.

Complication of statin therapy is the myopathy induced by these drugs [15,16], which is manifested through spontaneous muscle pains, cramps and weakness that are typical clinical features, regardless of other factors. The risk of myopathy increases by the concomitant use of fibrates, inhibitors of hepatic cytochrome P-450, major trauma and surgery. The most servere complication is rhabdomyolysis [19] having a lethal potential [17,18]. Data from clinical trials show that the rate of statin-induced myopathy in the general population is 0.1% to 0.2%. Knowing this negative effect of statins is very important, the risk being possibility of myopathy appearance due to hypothyroidism. Hypothyroid myopathy was first of all described by Johann Hoffmann in 1887. In patients with primary hypothyroidism this syndrome may occur with a frequency of 25% - 60%. Hypothyroid myopathy manifests with muscle fatigue, myalgia, slowness in movements, muscle stiffness [18]. Sometimes muscle weakness, "rigidity" of muscles are accompanied by severe myalgia and a significant increase in the serum of creatine phosphokinase (CK). A number of publications report the association of myopathy with rhabdomyolysis complicated by acute muscle necrosis, due to the lack of diagnosis of hypothyroidism in time [17,18].

Although the biochemical mechanism both of myopathy in hypothyroidism and that induced by statins remains unclear, but hypothyroidism increases the risk of statin-induced myopathy [15,16]. However, some authors believe that for the mechanism of myopathy hypothyroid are responsible glycogenolysis defects or impairment of mitochondrial oxidation [17]. Presumably, these mechanisms are synergistic when statins are prescribed to patients

with hypothyroidism. Myopathy is more likely to occur after administering high doses of statins to patients with acute coronary syndrome who undergo coronary angioplasty [21]. Therefore the use of statins in patients with hypothyroidism should be carefully indicated. Biochemical testing is essential for patients with symptoms that can be attributed to myopathy on the background of statin therapy.

ATP III (Adult Panel III) guide of the National Cholesterol Education Program 13 and American College of Cardiology ACC / AHA 11 recommend that the determination of creatine phosphokinase (CK) is determined before initiating statin therapy and that will be re-evaluated in comparison with the initial if patients report any muscle symptoms. More frequent determinations of CK and transaminase are indicated to patients, that got maximum statin doses and those who receive a combination therapy, usually with fibrates [21,22]. Finally, statins are not absolutely contraindicated to patients who developed myopathy induced by statins [20,22]. Statin therapy should be performed with caution, with re-initiation of statins therapy in this context, and the patients should always be instructed that if muscle pains or cold-like symptoms develop, statins should be discontinued immediately and they should contact the doctor.

Conclusions

Hypothyroidism is a well-known cause of secondary dyslipidemia and the link with atherosclerosis has been known for 125 years. Elevated circulating levels of a very low density lipoprotein (VLDL) and low density lipoproteins (LDL) cholesterol are major lipid abnormalities observed in patients with hypothyroidism.

The reduction in circulating levels of atherogenic lipoproteins (VLDL and LDL) is the main goal of treatment with statins. In addition, the statins possess pleiotropic properties: improve endothelial dysfunction, have anti-inflammatory, antioxidant, antiplatelet, antiproliferative effect; stabilize and slow the progression of atherosclerotic plaque.

Thus the administration of statins in secondary dyslipidemy will help to prevent cardiovascular diseases, especially atherosclerosis, which will enhance the quality of life of patients with hypothyroidism.

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