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DISORDERS OF CARDIOVASCULAR FUNCTION AND ECHOCARDIOGRAPHIC PARAMETERS OF THE HEART IN OVERT AND SUBCLINICAL HYPOTHYROIDISM

Summary: Decreased thyroid function leads to changes in cardiovascular hemodynamics, changes in myocardial contractility and accelerated atherosclerosis. Peripheral circulation in hypothyroidism is characterized by increased vascular resistance and prolonged circulatory duration. Endothelial dysfunction that occurs in hypothyroid patients predisposes to the development of atherosclerosis, and increases arterial stiffness. The influence of subclinical hypothyroidism on the cardiovascular system is manifested through systolic and diastolic cardiac function, myocardial anatomy and effort endurance. Subclinical hypothyroidism in acute myocardial infarction increases cardiac mortality 3.6-fold and 2.3-fold overall mortality. Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL cholesterol and apolipoprotein B. Subclinical hypothyroidism is associated with a small increase in LDL cholesterol, a decrease in HDL cholesterol, increasing the risk of developing atherosclerosis and coronary artery disease. Isovolumic relaxation time (IVRT) is significantly prolonged in hypothyroid patients, which indicates impaired passive relaxation of the left ventricle. Global right ventricular strain and right ventricular free wall strain are reduced in hypothyroid patients compared to healthy subjects. These changes are completely reversible after the application of thyroid replacement therapy and mostly after 6 months of L-thyroxine administration.

Keywords: hypothyroidism, L-thyroxine, subclinical hypothyroidism, hypercholesterolemia, atherosclerosis, diastolic dysfunction.

Thyroid hormones have effects on the heart and peripheral vascular system by reducing systemic vascular resistance (SVR), increasing resting heart rate (positive

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chronotropic effect), increasing left ventricular contractility (positive inotropic effect) and increasing blood volume. (1)

The action of thyroid hormones on blood vessels reduces peripheral arteriole resistance through direct effects on vascular smooth muscle and reduces mean arterial pressure, which leads to activation of the renin-angiotensin-aldosterone system (RAAS) in the kidneys and increased renal sodium absorption. Triiodothyronine also increases the synthesis of erythropoietin, which leads to an increase in the mass of erythrocytes. These changes combined lead to an increase in blood volume and preload. In hyperthyroidism these effects lead to an increase of cardiac output by 50-300%, and in hypothyroidism to a decrease of cardiac output by 30-50%. (2)

Thyroid hormones affect lipid metabolism through several mechanisms. Triiodothyronine induces increased LDL degradation mediated by an increase in the number of LDL receptors, with no change in LDL affinity for its receptor. (3) Several key liver enzymes involved in lipid metabolism are directly influenced by triiodothyronine, which exhibits transcription effects through thyroid receptors (TRs) by binding to the T3 element (TREs) as a thyroid receptor (TR) binding site to triiodothyronine (T3). TREs represent a promoter of the hepatic lipase region and the apolipoprotein A1 gene. The sterol-regulatory-element of binding protein 2 is under the regulatory role of thyroid hormones that induce an increase in LDL receptor expression. Triiodothyronine (T3) is important in the hepatic degradation of cholesterol to bile acids by increasing the transcription of the enzyme cholesterol-7alpha-hydroxylase which is involved in this process. (4)

HYPOTHYROIDISM AND CARDIOVASCULAR FUNCTION

Decreased thyroid function leads to changes in cardiovascular hemodynamics, changes in myocardial contractility and accelerated atherosclerosis. In severe hypothyroidism, cardiac output is reduced as a result of a decrease in stroke volume and heart rate. (5)

Preload depends on the total volume of blood and venous filling, as well as of the contractile activity of the atria and the possibility of filling the ventricles. In hypothyroid patients, preload is reduced, which is correlated with a decrease in blood volume in hypothyroidism. (2)

Peripheral circulation in hypothyroidism is characterized by increased vascular resistance and prolonged circulatory duration. This results in redistribution circulating fluids and decreased renal flow. Plasma renin activity and aldosterone levels are reduced in hypothyroidism, suggesting that the renin-angiotensin-aldosterone system (RAAS) plays a minor role in the development of hypothyroidism-induced hypertension. Since plasma volume is reduced in hypothyroidism, the greatest contribution to the development of hypertension is increased peripheral vascular resistance. Increased afterload

can further reduce cardiac output which contributes to prolonged circulation duration. The myocardium in hypothyroidism is characterized by an increase in afterload, which is energy inefficient despite the low level of total oxygen consumption. Afterload is increased as a result of increased systemic vascular resistance and arterial stiffness and it is one of the important determining factors of myocardial oxygen consumption. (6)

An increase in diastolic blood pressure is often in hypothyroidism which is normalized reaching the euthyroid state. In severe hypothyroidism, systemic arterial hypertension is present in about 30% of patients, mean arterial pressure is elevated, and about 20% of patients have diastolic hypertension. (7)

Endothelial dysfunction that occurs in hypothyroid patients predisposes to the development of atherosclerosis and increases arterial stiffness. Increased central arterial stiffness may further contribute to the development of hypertension in hypothyroidism. Aortic stiffness and systemic vascular resistance are increased in all patients with hypothyroidism, whether or not they have hypertension; the effects of these two conditions are additive. (8) Aortic stiffness and systemic vascular resistance are reduced during L-thyroxine therapy in hypothyroid patients with normal blood pressure and in patients with persistent hypertension. However, patients with higher basal aortic stiffness are less likely to normalize systolic blood pressure, which correlates with a decrease in aortic stiffness. Impairment of the elastic properties of the aorta may be the cause of incomplete normalization of blood pressure after replacement therapy in 50% of patients with hypothyroidism and hypertension, which requires the need for additional antihypertensive therapy. (9)

The influence of subclinical hypothyroidism on the cardiovascular system is manifested through systolic and diastolic cardiac function, myocardial anatomy and effort endurance. Numerous observational studies have shown that people with thyroid dysfunction have a worse cardiovascular outcome, including increased mortality. Even small changes in the concentration of thyroid hormones can have a negative effect on the cardiovascular system. Subclinical hypothyroidism is a strong independent risk factor for coronary artery disease. Prospective observational studies have shown that subclinical hypothyroidism in acute myocardial infarction (AIM) is associated with poorer cardiovascular outcome. Subclinical hypothyroidism in acute myocardial infarction increases cardiac mortality 3.6-fold and overall mortality 2.3-fold. (10)

Subclinical hypothyroidism in the time around acute myocardial infarction (AIM) is a condition that favors heart failure. AIM leads to lower serum levels of thyroid hormones as well as to downstream regulation of thyroid receptors in the myocardium, leading to tissue hypothyroidism. Prospective study by Friberg et al. has shown that thyroid hormone levels decline rapidly one week after AIM. (11) Second study by Friberg et al. showed that in-hospital mortality and post-hospital mortality were higher in patients who had lower serum thyroid hormone levels after AIM, suggesting that hypothyroidism was associated with a poorer prognosis. (12)

Compared with other organs, the heart is much more vulnerable in the hypothyroid state, because cardiomyocytes do not have the ability to convert T4 precursors to T3, as is the case in other organs. This may explain why even mild thyroid dysfunction has more pronounced effects on the heart than other organs. (3)

RISK FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN PATIENTS WITH HYPOTHYROIDISM

Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL cholesterol, and apolipoprotein B. Due to the reduced fractional clearance of LDL cholesterol as a consequence of the reduced number of LDL receptors in the liver, the catabolism of LDL cholesterol is reduced and thus its half-life in circulation is prolonged. The application of L-thyroxine significantly improves the catabolism of LDL particles in the liver by activating LDL receptor mRNA. Observational studies have shown that hypothyroidism causes qualitative changes in circulating lipoproteins by increasing their atherogenicity. LDL cholesterol is more sensitive to oxidation in patients with hypothyroidism with normalization of oxidation by achieving a euthyroid state. (4) Hypothyroidism is associated with a reversible reduction in the activity of cholesterol-ester transfer protein, hepatic endothelial lipase, 7-alpha hydroxylase and hepatic LDL receptor. Lipoprotein(a) levels are elevated in hypothyroid patients, but the response to thyroid replacement therapy is unclear, although several studies have shown a decrease in lipoprotein(a) levels to L-thyroxine therapy. Triiodothyronine and HDL cholesterol are inversely correlated with the development of coronary heart disease. Hypothyroidism is associated with lower HDL cholesterol levels. Observational studies have shown a significant increase in HDL cholesterol with L-thyroxine (L-T4) therapy and normalization of serum TSH levels. (13)

Hyperhomocysteinemia is an independent risk factor for occlusive vascular disease, including coronary atherosclerosis, and predisposes to the development of atherosclerosis by stimulating LDL cholesterol oxidation, endothelial dysfunction and vascular damage of endothelial cells. Hyperhomocysteinemia occurs in patients with hypothyroidism due to reduced glomerular filtration of homocysteine (decreased clearance of homocysteine), and lack of thyroid hormones affects the activity of enzymes involved in folate metabolism, which leads to increased creatinine levels and reduced folate and vitamin B12. After achieving adequate thyrosubstitution, homocysteine levels in the blood return to normal. Reduction of homocysteine in the blood by 2-5 micromol/L, which is achieved by using L-thyroxine and achieving optimal TSH levels, significantly reduces cardiovascular risk. In contrast to overt hypothyroidism, subclinical hypothyroidism is not associated with hyperhomocysteinemia and no significant reduction in blood homocysteine has been observed in clinical studies after treatment of subclinical hypothyroidism with L-T4. (14)

Elevated levels of C-reactive protein (CRP), endothelial dysfunction, and coagulation abnormalities are additional risk factors for atherosclerosis in hypothyroid patients. (5)

The degree of hypothyroidism determines the effects of coagulation parameters. One study compared women with moderate hypothyroidism (TSH 10-50mU/L) and severe hypothyroidism (TSH> 50 mU/L) compared to euthyreoid women and measured blood hemostatic parameters. Women with moderate hypothyroidism had decreased fibrinolytic activity, with decreased D-dimer levels, elevated alpha2-antiplasmin activity, and elevated levels of tissue plasminogen antigen activator and plasminogen activator antigen inhibitor. In contrast, women with severe hypothyroidism had high levels of D-dimer, decreased alpha2-antiplasmin activity, and decreased levels of tissue plasminogen antigen activator and plasminogen activator antigen inhibitor. These results suggested an increased risk of thrombosis that may precipitate myocardial and cerebral infarction in moderate hypothyroidism and an increased tendency for bleeding in patients with severe hypothyroidism. (15)

Many studies have shown that insulin resistance and metabolic syndrome are independent risk factors for cardiovascular disease, even in people without diabetes disease. Although, hypothyroidism has no direct effect on the development of insulin resistance, decreased levels of thyroid hormones in the blood may amplify the increased cardiovascular risk associated with insulin resistance by acting to increase total and LDL cholesterol levels. (4)

Subclinical hypothyroidism is associated with a small increase in LDL cholesterol, a decrease in HDL cholesterol, increasing the risk of developing atherosclerosis and coronary artery disease. These changes are based on the significant influence of thyroid hormones on lipid metabolism. (16) Subclinical hypothyroidism with a mild degree of thyroid dysfunction can induce the development of atherosclerosis in various ways - through endothelial dysfunction and impaired coagulation parameters. Additional risk factors that contribute to the increased prevalence of myocardial infarction in subclinical hypothyroidism are known risk factors for the development of coronary artery disease: hypercholesterolemia, hypertension, smoking and diabetes mellitus. Patients with subclinical hypothyroidism, who also had lower total cholesterol values compared to the control group, had manifest atherosclerotic vascular disease, suggesting that other factors contribute to an increased risk of developing atherosclerosis. Elevated serum LDL cholesterol, increased LDL oxidation, elevated serum triglycerides, and lipoprotein(a) are thought to explain the association of subclinical hypothyroidism and cardiovascular disease. (17)

Clear evidence of an increased prevalence of atherosclerotic cardiovascular disease in subclinical hypothyroidism was shown in a large randomized study involving 1,149 women living in Rotterdam over the age of 55 (Rotterdam study). This study showed that middle-aged women with subclinical hypothyroidism are more likely to

develop myocardial infarction and aortic wall calcification. Women with TSH greater than 4 mU/L (and normal FT4 values) had a higher prevalence of coronary artery disease compared to a control subjects with TSH less than 4 mU/L. A Rotterdam study found that women with elevated levels of antiperoxidase antibodies and normal thyroid function had a similar prevalence of atherosclerosis and myocardial infarction as euthyroid women without elevated levels of antibodies to thyroid peroxidase, suggesting that the development of atherosclerotic is mediated by a relative deficiency of thyroid hormones, rather than by immune dysfunction. (18)

EFFECTS OF THYROID REPLACEMENT THERAPY ON CARDIOVASCULAR SYSTEM

In most patients, the goal of thyroid replacement therapy is the TSH values between 0.5 and 2.5 mU/L, thus avoiding the effect of inadequate thyro-substitution. Optimal thyroid replacement therapy must take into account the patient's lifespan as well as the cause of hypothyroidism. The full dose of L-thyroxine therapy can be given with certainty to younger patients with overt hypothyroidism who do not have cardiovascular disease. In elderly patients with known or suspected coronary heart disease or in patients with manifest heart disease, thyroid replacement therapy should be initiated in small doses and gradually increased with monitoring of the patient's health. (19)

In large retrospective studies, new-onset angina pectoris and myocardial infarction occur relatively rarely after thyroid hormone administration. The beneficial effects of thyrosubstitution are much more common in reducing anginal symptoms (38%) compared to worsening angina (16%). One-year cardiovascular mortality in these patients diagnosed with angina and treated hypothyroidism was 3%, which is less than the one-year cardiovascular mortality of 9-15% observed in patients with angina during the same observation period. Administration of thyroid hormones leads to improved myocardial contractility and diastolic function and reduces afterload, which is the main determinant of oxygen consumption. This may explain how thyroid hormone therapy improves myocardial efficacy and leads to regression of anginal symptoms in hypothyroid patients. Worsening of angina, myocardial infarction and death may occur when L-thyroxine therapy is initiated at full doses in elderly patients with ischemic myocardial disease. Conversely, ventricular arrhythmias may improve or resolve completely after L-thyroxine therapy. (20)

The latest consensus formulated for guidelines for the treatment of patients with subclinical hypothyroidism recommends initiating L-thyroxine therapy in patients with subclinical hypothyroidism with TSH values above 10 mU /L in order to prevent progression to overt hypothyroidism. Thyroid replacement therapy improves the lipid profile and reduces cardiovascular risk in patients enrolled in multiple selected studies

who had a TSH greater than 10 mU/L, which supported the view that patients with subclinical hypothyroidism should be treated. (21)

CHANGES OF ECHOCARDIOGRAPHIC PARAMETERS IN OVERT AND SUBCLINICAL HYPOTHYROIDISM

During the development of thyroid dysfunction, there are changes in the structure and function of the myocardium, which can be manifested by: 1. structural and functional remodeling of the left ventricle, which can lead to impaired systolic, diastolic and global function of the left ventricle; 2. impaired left ventricular mechanics; 3. impaired structure, diastolic and global function of the right ventricle; 4. impaired right ventricular mechanics. (17)

Decreased diastolic function is detectable in the early stages of hypothyroidism. Isovolumic relaxation time (IVRT) is significantly prolonged in hypothyroid patients, which indicates impaired passive relaxation of the left ventricle, which leads to reduced early filling in diastole. Early/late (E/A) ratio of diastolic transmitral flow registered by Doppler echocardiography is already reduced in the early stages of hypothyroidism. These conditions are completely reversible after 3-6 months of adequate thyroid replacement therapy. Diastolic dysfunction can lead to increased morbidity, decreased exercise endurance and diastolic heart failure. Some studies have indicated a reduction in aortic root diameter after the application of L-thyroxine therapy, which is reflected in an improvement in aortic compliance and may be associated with an improvement in diastolic function. In hypothyroidism, asymmetric septal hypertrophy can be detected, which is reversible upon reaching the euthyroid state. This condition can be seen as one of the causes of left ventricular diastolic dysfunction, but also as an adaptive response to increased afterload, especially in the elderly. (22) Monzani et al. are showed an increase in left ventricular mass index in subclinical hypothyroidism relative to control, and the application of L-thyroxine therapy leads to a reduction in left ventricular mass and wall thickness. The mechanism leading to left ventricular hypertrophy in thyroid dysfunction is an increase in systemic vascular resistance and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) which play a significant role in left ventricular hemodynamics and structural changes. (23) Reduction of left ventricular mass after L-thyroxine administration has positive effects on the improvement of diastolic dysfunction. Pulsed tissue Doppler can detect prolonged myocardial precontraction time and myocardial relaxation time at the level of the posterior septum and mitral annulus, which indicates impaired systolic and diastolic function in hypothyroidism. (24)

The influence of overt and subclinical hypothyroidism on systolic function is controversial. Sensitive echocardiographic methods, especially during physical stress, showed changes in systolic function in patients with thyroid dysfunction in relation

to control subjects. Impaired systolic function of the left ventricle at rest, defined by an increase in the ratio of preejection period (PEP) / left ventricular ejection time (LVET) and prolongation of left ventricular preejection period (PEP) has been shown in several studies involving patients with subclinical hypothyroidism . These changes are completely reversible after the application of thyroid replacement therapy and mostly after 6 months of L-thyroxine administration. (25)

Some studies also indicate depression of the global longitudinal stain of the left ventricle and the strain of the lateral wall and the interventricular septum of the left ventricle in patients with subclinical hypothyroidism. Changes in the mechanics of the left ventricle are mostly reduced after the application of L-thyroxine therapy. These results indicate that left ventricular hypertrophy is not the only mechanism responsible for left ventricular dysfunction in subclinical hypothyroidism. Hemodynamic changes in subclinical hypothyroidism lead to an increase in systemic vascular resistance, which plays a very important role in the relationship between thyroid hormones and left ventricular mechanics. In subclinical hypothyroidism, impaired left ventricular function and cardiorespiratory adaptation to exertion become manifest during exercise. These changes are reversible after the restitution of the euthyroid state. (26)

The right ventricle has been less studied echocardiographically, mainly due to the more complicated anatomy and the lack of reliable and accessible imaging techniques. There are conflicting studies on the effect of thyroid dysfunction on the thickness of the right ventricular wall. Several studies have shown that thyroid dysfunction did not lead to changes in right ventricular wall thickness. In contrast, several controlled studies showed that there was an increase in right ventricular wall thickness, impaired global and diastolic right ventricular function in patients with subclinical hypothyroidism compared to controls healthy subjects. There were no reduction in right ventricular wall thickness after thyroid replacement therapy in these studies, in contrast to improvements in global and diastolic right ventricular function after L-thyroxine administration. It has been shown that the mechanics of the right ventricle using “speckle tracking imaging” are significantly impaired in subclinical hypothyroidism. Global right ventricular strain and right ventricular free wall strain are reduced in hypothyroid patients compared to healthy subjects. The interaction between the right and left ventricles is one of the most important causes of impaired right ventricular function resulting from an increase in left ventricular filling pressure and a consequent increase in pulmonary flow and right ventricular pressure. The mechanism that leads to the remodeling of the right ventricle is the increased filling pressure, which is reflected in the increased E/e· ratio. Other possible mechanisms of right ventricular hypertrophy in hypothyroidism are endothelial dysfunction of the pulmonary circulation, increased sympathetic and RAAS activity, as well as inadequate calcium uptake, leading to increased pulmonary vascular resistance. A large number

of studies have shown that disturbed mechanics of the right ventricle are completely repaired after adequate thyrosubstitution. (25,26)

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