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STUDY OF THE CLINICAL COURSE OF CORONARY HEART DISEASE IN PATIENTS WITH THYROID DYSFUNCTION

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Abstract
Every year, coronary heart disease (CHD) - the leading cause of death and disability in the world - becomes the cause of 9.4 million deaths. To date, extensive and substantial evidence of the connection between heart pathology and thyroid hypofunction has been accumulated. Subclinical hypothyroidism occurs in 15.8% of women and 6.7% of men with coronary heart disease. The thyroid gland is responsible for metabolism, as well as heart function and the peripheral vascular system. Thyroid dysfunction is associated with an increased risk of cardiovascular diseases, including heart failure and coronary heart disease, atrial fibrillation, due to impaired heart contractility, stroke volume, heart rate, peripheral vascular resistance, and electrical activity. Thyroid dysfunctions also alter several risk factors for cardiovascular diseases such as atherosclerosis, hypertension, and dyslipidemia, as well as cause stroke associated with atrial fibrillation. In the myocardium, these hormones stimulate both the diastolic relaxation of the myocardium and the systolic contraction of the myocardium, have a proangiogenic effect, and play an important role in maintaining the extracellular matrix. Thyroid hormones regulate the function of the heart mitochondria. Thyroid axis dysfunction worsens the bioenergetic status of the myocardium. Both clear and subclinical hypothyroidism are associated with a higher frequency of coronary events and an increased risk of heart failure progression.

Keywords: Thyroid hormones, hypothyroidism, coronary heart disease, hyperlipidemia, thrombogenesis.

Introduction

Physiology of thyroid function

Thyroid hormones (TH) play a fundamental role in cardiovascular homeostasis. In cardiovascular diseases, especially in coronary heart disease, deviations in thyroid hormone levels are common and are an important factor to consider. In fact, low levels of thyroid hormones should be

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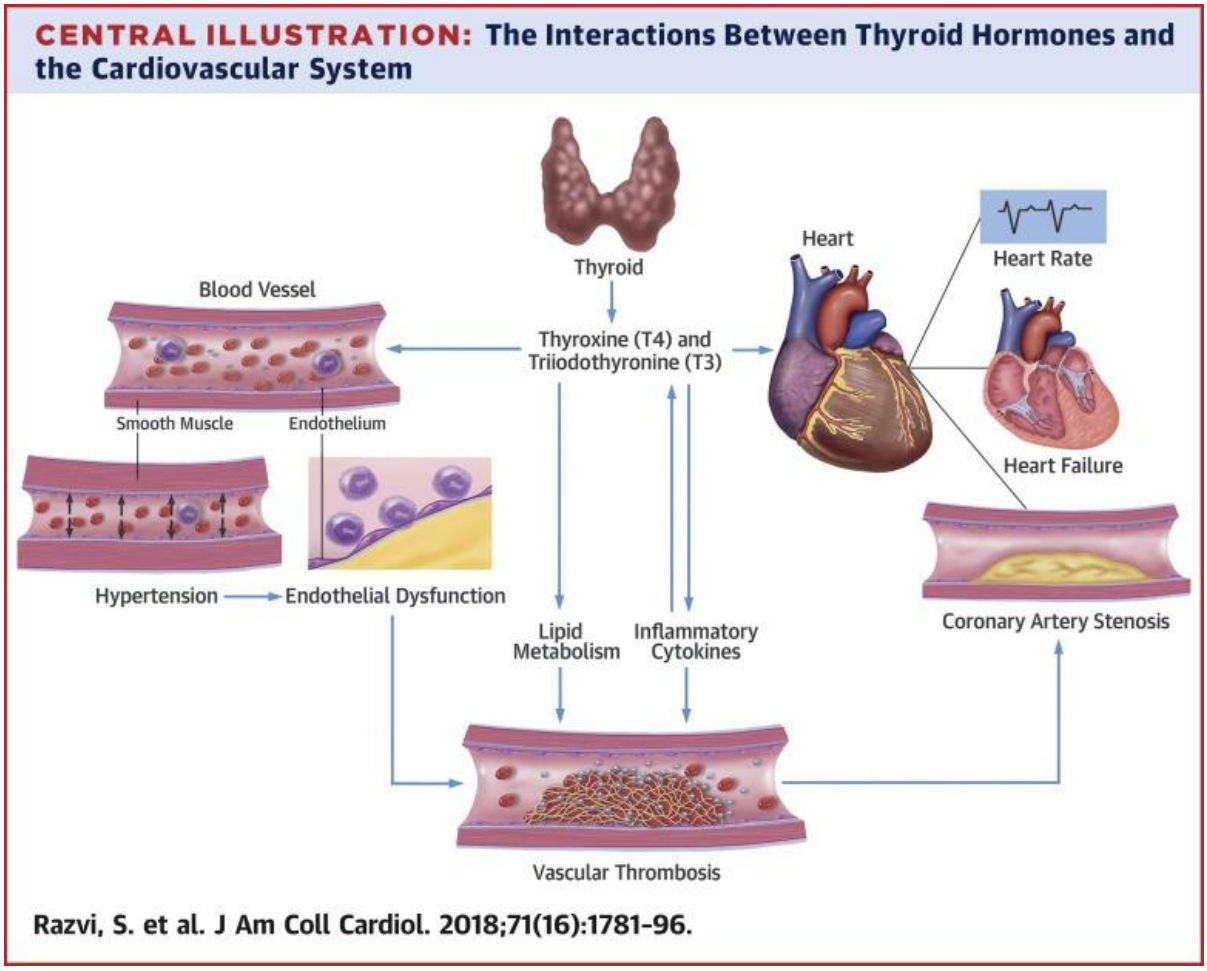
interpreted as a risk factor for the cardiovascular system. Regarding coronary heart disease, in the late post-infarction period, thyroid hormones regulate the structure, function, and geometry of the left ventricle. Almost all organs have receptors for thyroid hormones and are regulated to some extent by the thyroid axis (hypothalamus-pituitary-thyroid axis). TSH is produced by the thyroid gland, which is mainly regulated by thyroid-stimulating hormone (TSH). TSH is secreted by the pituitary gland and regulated by the thyroid-stimulating hormone (TSH) [1]. Ninety percent of the secreted TG is thyroxine (T4), and the remaining 10% - triiodothyronine (T3). T3 is 20 times more active than T4, making T3 a biologically active hormone of the thyroid axis (2). Most T3 is formed peripherally from the transformation of T4 with the help of deodinases. These enzymes are also responsible for converting TG into inactive isomers such as reversible T3 (pT3) and 3,3-diiodothyronine (T2). There are three deodinases with different functions: type 1 deodinases (D1) are localized in the plasma membrane and are expressed in the liver, thyroid gland, and kidneys; this enzyme is primarily responsible for the peripheral conversion of T4 to T3; type 2 deodinases (D2) appear to be more effective than D1; the main role of this enzyme is to regulate intracellular T3 concentration, converting T4 to T3, especially in the brain, pituitary gland, and skeletal muscles; and type 3 deodinases (D3) irreversibly inactivate TG, forming T2 or pT3; thus, by reducing the levels of these hormones, D3 is considered an important regulator of the thyroid axis [2].



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Thyroid diseases and cardiovascular disease risk factors

TH and hyperlipidemia

Hyperthyroidism reduces cholesterol levels, which are restored in euthyroidism. Hypothyroidism is associated with a slight, but significant increase in lipid parameters, in particular, with an increase in low-density lipoprotein levels. Hypothyroidism is associated with increased LDL oxidation, which contributes to atherogenicity and is reversible during treatment. Lipoprotein (a), a more potent atherogenicity marker, also increases with pronounced hypothyroidism and decreases with TH replacement therapy. The effect of subclinical hypothyroidism (SHT) on hyperlipidemia is less pronounced. Hyperlipidemia in hypothyroidism is caused by a decrease in LDL receptors (LDL receptor), which leads to a decrease in cholesterol excretion from the liver and a decrease in the activity of cholesterol 7α-hydroxylase, which is activated by TG, in the breakdown of cholesterol[9]. A Cochrane 6RKI review showed that thyroxine during SHT treatment did not have a general effect on decreasing total cholesterol, but suggested a trend towards a decrease in LDL cholesterol levels of >155 mg/dL in the subgroup analysis[10]. Two subsequent trials showed that LDL-C decrease was approximately 0.3 mmol/l (11.6 mg/dl) [3]. Thus, the connection, if present, is likely to be weak, contributing to a slight increase in serum LDL-C in the range of 3 to 15 mg/dl (0.1 to 0.4 mmol/l) [4].

Thyroid hormone as a regulator of heart mitochondria

THs modulate the function of cardiac mitochondria by increasing mitochondrial mass, respiration, oxidative phosphorylation, enzyme activity, and the synthesis of mitochondrial proteins such as cytochrome, as well as the content of phospholipids and mtDNA [5]. Changes in circulating TH levels can disrupt the bioenergetic status of the myocardium with consequences for heart function [6]. Mitochondrial dysfunction plays a central role in heart dysfunction and in the occurrence and progression of heart failure [7]. Regulation of TH mitochondrial function and biogenesis is a new mechanism in cardioprotective therapy. THs contribute to increased protein regulation, which is functionally important for the restoration of mitochondrial function. Consequently, these hormones can reduce the loss of cardiomyocytes in the peri-infarction zone. It has been shown that reversing the post-ischemic decrease in TG levels reduces tumor suppressor protein (p53), possibly through an increase in miRNA 30a levels. Considering that p53 can regulate the JNK pathway (c-Jun N-terminal kinases) through positive feedback, THs can lower the JNK level through a p53-dependent mechanism [8]. Treatment of T3 (14 ng/g body weight, dose administered daily) for 3 days after acute myocardial infarction in rats reduced apoptosis of myocytes in the border zone [9].

Effects of thyroid hormone dysfunction on myocardial ischemia

Myocardial ischemia is one of the main causes of mortality and morbidity worldwide [10]. Understanding the mechanisms of interaction between THs and their receptors is crucial for assessing their impact on myocardial ischemia. TRα1 plays a key role during post-ischemic adaptation, as it appears to have a dual effect and can transform pathological growth into physiological growth depending on the availability of its ligand. In fact, increased expression of TRα1 in the cardiomyocyte nucleus, with the absence of adequate THs as ligands, can cause

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pathological hypertrophy and fetal phenotype with predominant β-MHC expression. Conversely, higher TH levels stimulate the α-MHC growth model, enhancing more physiological growth [11]. Several studies have demonstrated a decrease in T3 and an increase in rT3 concentration in patients after an acute coronary event. Some factors can predict a more pronounced decrease in T3 levels, such as angina pectoris worsening before an acute myocardial infarction, known chronic heart failure, or previous myocardial infarction and diabetes mellitus. Low T3 levels also cause oxidative stress and increase the rate of apoptosis, which can worsen ventricular dysfunction [12]. Thus, TG levels are an important factor in modulating the structure, function, and geometry of the left ventricle in the late period after myocardial infarction. Patients with STEMI and thyroid functional changes have almost 3.5 times higher risk of serious adverse cardiac events, including cardiogenic shock and death, compared to patients with STEMI and without thyroid diseases [13]. In fact, changes in thyroid function appear to occur more frequently in STEMI than in NSTEMI (myocardial infarction without ST elevation), possibly due to a worse short-term prognosis and the characteristics of occlusive coronary thrombus typical for STEMI [14]. Recent data indicate that circulating levels of T3 are an independent factor determining the restoration of left ventricular ejection fraction 6 months after acute myocardial infarction in humans [15]. Scientists found a positive correlation between rT3 levels and mortality within 1 year in patients with myocardial infarction, regardless of other risk factors. According to these findings, a recent study involving patients attending a cardiac rehabilitation program after acute coronary syndrome also reported a link between lower T3 levels and any cause of death [16]. In patients with myocardial damage, lower T3 levels correlate with elevated levels of heart serum biomarkers such as troponin T and N-terminal pro-cerebral natriuretic peptide, as well as lower left ventricular ejection fraction. T3 levels can be a predictor of potential restoration of ventricular function. One of the priorities in treating myocardial ischemia is the restoration of coronary blood flow. Early reperfusion has a significant impact on short-term mortality after a myocardial ischemic event [17]. Coronary revascularization through aortocoronary bypass grafting (ACG) or transcutaneous coronary intervention (TCG) is the primary treatment option for coronary heart disease. Despite its undisputed advantages, reperfusion after a myocardial ischemic event can contribute to unfavorable cardiac remodeling, potentially leading to heart failure. The pathophysiology of IRP is complex; However, recent data indicate that mitochondrial dysfunction can be one of the main mechanisms of IRP [18]. The frequency of post-ischemic heart failure remains critical, increasing the risk of both cardiac and general death. After reperfusion, the extracellular washing out of accumulated H+ ions creates a large gradient that increases sodium inflow through the Na+/H+ exchanger. This stimulates the reverse action of the Na+/Ca2+ exchanger pump, increasing oxidative stress. THs improve the balance of pro-apoptotic and survival signaling pathways, which can limit IRP [19]. T3 enhances the expression of HIF-1α, limiting the mitochondrial opening of transition pores and thereby protecting cardiomyocytes from reperfusion damage. TH levels in the blood serum often decrease after CABG [20]. In fact, NTIS is registered in 50-75% of patients after heart surgery, and some authors consider this a poor prognostic factor and predictor of mortality.

In another study of 457 patients with MI, thyroid dysfunction, including subclinical hypothyroidism and hyperthyroidism and low T3 syndrome, was associated with a higher

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frequency of major cardiac events. In addition, in patients with AMI and early reperfusion therapy, circulating levels of T3 correlated with LV ejection fraction both in the early, hospital phase and at 6 months of subsequent visits. Interestingly, T3 after 6 months was an independent predictor of changes in LV ejection fraction between early and subsequent periods [21]. However, the pathophysiological and therapeutic significance of thyroid regulation disorders after MI remains unclear. To date, no interventional studies on TH replacement in patients with AMI have been published, therefore, it is difficult to establish a causal relationship between thyroid dysfunction and the results. Overall, the previously mentioned experimental and observational results contradict the generally accepted interpretation that decreased TH regulation after MI is an adaptive, favorable process that helps reduce catabolism and energy expenditure, and suggests the potential critical role of the thyroid system in cardioprotection in MI. Future research is needed to better understand the interaction between acute TH changes and cardiac ischemia, particularly ischemic-reperfusion damage, and whether the normalization of thyroid function parameters can play a role.

Conclusions

The CC system is the primary target of TH action, and even minor changes in thyroid function can lead to cardiac dysfunction. A number of experimental studies and observational clinical data for both hypo- and hyperthyroidism show that TH modulation can be beneficial for reducing cardiovascular diseases. However, high-quality evidence is needed before it can be implemented in clinical practice. Similarly, there is increasing evidence that changes in TH levels in other euthyroid patients with cardiovascular diseases (such as MI) can be a marker of a poor prognosis, and clinical trials are necessary to see if TH therapy can be effective and safe. Experimental and clinical data indicate a close relationship between a low TH level and a poor prognosis in coronary heart disease. Therefore, this condition should be considered a cardiovascular risk factor. Accordingly, replacement therapy for TH can lead to improved lipid profile, potentially reversing myocardial dysfunction and preventing the progression of heart failure. TH replacement therapy demonstrates anti-ischemic and cardioprotective effects, acting as a promising target for coronary heart disease. Moreover, the treatment of subclinical hypothyroidism and the syndrome of a non-thyroid disease are topics of increased interest; recent studies have shown that physiological dose therapy of T3 is safe and has a beneficial effect on coronary heart disease. Large clinical trials using TS replacement therapy are needed to assess potential benefits regarding morbidity and mortality in patients with coronary heart disease, as well as any potential long-term consequences.

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