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QALQONSIMON BEZ DISFUNKSIYASI BO'LGAN BEMORLARDA YURAK ISHEMIK KASALLIGINING KLINIK KECHISHINI PRAGNOZ QILISH

Annotatsiya: Qalqonsimon bez metabolizm, shuningdek, yurak faoliyati va periferik qon tomir tizimi uchun javobgardir. Qalqonsimon bezning disfunktsiyasi yurak qisqarishi, insult xavfi, yurak tezligi, periferik qon tomirlarining qarshiligi va elektr faolligini buzish orqali yurak-qon tomir kasalliklari, shu jumladan yurak yetishmovchiligi va koronar yurak kasalligi va aritmiyalar xavfining oshishi bilan bog'liq. Qalqonsimon bezning disfunktsiyalari ateroskleroz, gipertenziya va dislipidemiya kabi bir qator yurak-qon tomir xavf omillarining ham sababchidir, shuningdek, atriyal fibrilatsiya bilan bog'liq bo'lgan aritmiyani keltirib chiqaradi. Qalqonsimon bez gormonlari miokardning diastolik bo'shashishini va sistolik miokard qisqarishini ta'monlaydi. Qon tomirlarga ham ta'sir ko'rsatadi va hujayradan tashqari matritsani saqlashda muhim rol o'ynaydi. Qalqonsimon bez gormonlari yurak mitoxondrial funktsiyasini modulyatsiya qiladi. Qalqonsimon bezning disfunktsiyasi miyokardning bioenergetik holatini buzadi. Ochiq va subklinik gipotiroidizm koronar hodisalarning yuqori chastotasi va yurak etishmovchiligining rivojlanish xavfining oshishi bilan bog'liq.

Kalit so'zlar: qalqonsimon bez garmonlari, gipotiroidizm, gipertiriodizm, yurak ishemik kasalligi, giperlipidemiya, trombogenez, mitoxondrial regulyator, qon bosimi.

ПРОГНОЗ КЛИНИЧЕСКОГО ТЕЧЕНИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ С НАРУШЕНИЕМ ФУНКЦИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

Аннотация: Щитовидная железа отвечает за метаболизм, а также за сердечную функцию и периферическую сосудистую систему. Дисфункции щитовидной железы связаны с увеличением риска сердечно-сосудистых заболеваний, включая сердечную недостаточность и ишемическую болезнь сердца, мерцательную аритмию, за счет нарушения сократимости сердца, ударного объема, частоты сердечных сокращений, периферического сосудистого сопротивления и электрической активности. Дисфункции щитовидной железы также изменяют несколько факторов риска сердечно-сосудистых заболеваний, таких как атеросклероз, гипертония и дислипидемия, а также вызывают инсульт, который связан с мерцательной аритмией. В миокарде эти гормоны стимулируют как диастолическое расслабление миокарда, так и систолическое сокращение миокарда, оказывают проангиогенный эффект и играют важную роль в поддержании внеклеточного матрикса. Гормоны щитовидной железы модулируют функцию митохондрий сердца. Дисфункция тиреоидной оси ухудшает биоэнергетический статус миокарда. Как явный, так и субклинический гипотиреоз связаны с более высокой частотой коронарных событий и повышенным риском прогрессирования сердечной недостаточности.

Ключевые слова: гормоны щитовидной железы, гипотиреоз, гипертиреоз, ишемическая болезнь сердца, гиперлипидемия, тромбогенез, митохондриальный регулятор,артериальное давление.

PROGNOSIS OF THE CLINICAL COURSE OF ISCHEMIC HEART DISEASE IN PATIENTS WITH THYROID DYSFUNCTION

Abstract: The thyroid gland is responsible for metabolism, as well as cardiac function and the peripheral vascular system. Thyroid dysfunctions are associated with an increase in the risk of cardiovascular diseases, including heart failure and coronary heart disease atrial fibrillation, by impairing heart contractility, stroke volume, heart rate, peripheral vascular resistance, and electrical activity. Thyroid dysfunctions also alter several cardiovascular risk factors, such as atherosclerosis, hypertension, and dyslipidemia, as well as causing stroke, which is associated with atrial fibrillation. In myocardium, these hormones stimulate both diastolic myocardial relaxation and systolic myocardial contraction, have a pro-angiogenic effect and an important role in extracellular matrix maintenance. Thyroid hormones modulate cardiac mitochondrial function. Dysfunction of thyroid axis impairs myocardial bioenergetic status. Both overt and subclinical hypothyroidism are associated with a higher incidence of coronary events and an increased risk of heart failure progression.

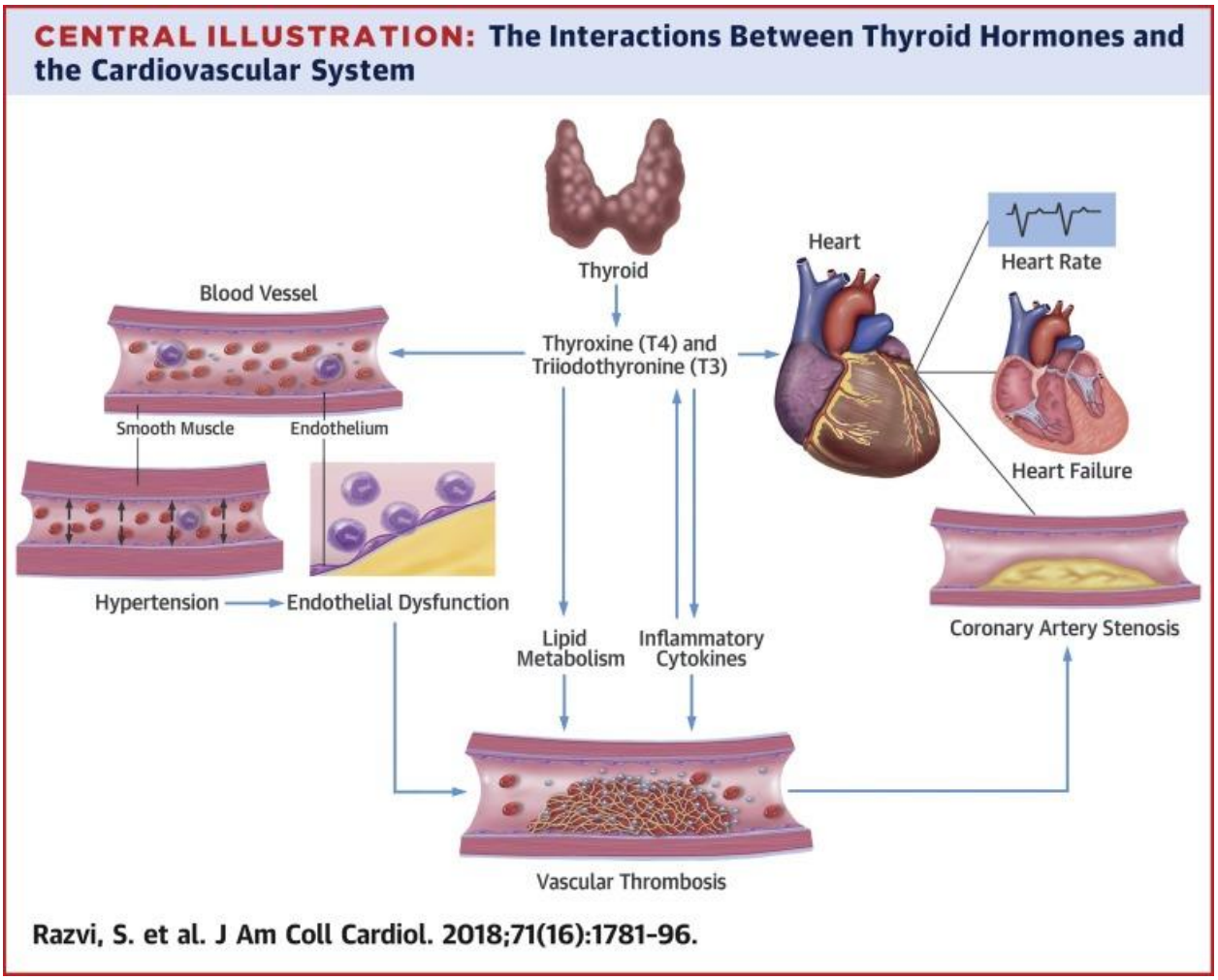
Key words: thyroid hormones, hypothyroidism, hyperthyroidism, ischemic heart disease, hyperlipidemia, trombogenesis, mitochondrial regulator, blood pressure.

Physiology of thyroid function

Thyroid hormones (THs) play fundamental roles in cardiovascular homeostasis. In heart disease, particularly in ischemic heart disease, abnormalities in thyroid hormone levels are common and are an important factor to be considered. In fact, low thyroid hormone levels should be interpreted as a cardiovascular risk factor. Regarding ischemic heart disease, during the late post-myocardial infarction period, thyroid hormones modulate left ventricular structure, function and geometry. Nearly all organs have thyroid receptors and are in some way regulated by the thyroid axis. THs are produced by the thyroid gland, which is mainly regulated by thyroid-stimulating hormone (TSH). TSH is secreted by the pituitary gland and is regulated by thyrotropin-releasing hormone (TRH) secreted by the hypothalamus [1]. Ninety percent of the TH secreted is thyroxine (T4) and the remaining 10% is triiodothyronine (T3). T3 is 20 times more potent than T4, making T3 the biologically active hormone of the thyroid axis (2). Most T3 is generated peripherally from T4 conversion by deiodinases [2]. These enzymes are also responsible for converting THs into inactive isomers such as reverse T3 (rT3) and 3,3-diiodothyronine (T2). There are three deiodinases with different functions: type 1 deiodinase (D1) is localized in the plasma membrane and is expressed in the liver, thyroid and kidney; this enzyme is mainly responsible for the peripheral conversion of T4 into T3; type 2 deiodinase (D2) seems to be more efficient than D1; the major role of this enzyme is to regulate the intracellular concentration of T3, converting T4 into T3, especially in the brain, pituitary gland and skeletal muscle; and type 3 deiodinase (D3) irreversibly inactivates THs generating T2 or rT3; thus, by lowering the levels of these hormones, D3 is considered an important regulator of the thyroid axis [3]. Furthermore, THs are mainly active when not bound to transport proteins. Therefore, variations on binding protein levels can change the peripheral activity of THs [4]. In order to perform their roles, THs must bind to thyroid hormone receptors. These receptors are intracellular DNA-binding proteins that bind as hormone-receptor complexes to thyroid hormone response elements (TREs) in the regulatory regions of target genes [5]. Consequently, THs modulate essential functions in the growth, development and metabolism of a variety of tissues. There are different subtypes of receptors – TRα1, TRα2, TRβ1 and TRβ2 – which have different functions. TRα1 is the subtype most expressed in the myocardium, regulating important genes related to cell growth, contractile function and electrical activity. Although TRβ1 is also expressed in the myocardium, it is expressed at a lower level [6].

Thyroid Hormones and Cardiovascular Function and Diseases

TH effects on the vasculature include genomic and nongenomic mechanisms that occur at both the vascular smooth muscle and endothelial cell levels. Nongenomic, indirect effects of TH include ion channel activation (Na^+, K^+, Ca^{2+}) and regulation of specific signal transduction pathways. Activation of phosphatidylinositol 3-kinase and serine/threonine protein kinase pathways cause the production of endothelial nitric oxide, leading to a reduction in systemic vascular resistance through its effects on vascular smooth muscle cells [7]. Several studies have shown that TH regulates endothelial nitric oxide production and vascular tone, and that patients with hypothyroidism (both overt and subclinical) exhibit impaired endothelial function, which improves with TH replacement therapy [8]. In addition, T_3 can produce a vasodilatory effect within hours after administration to patients undergoing coronary artery bypass grafting [9]. Similar effects are observed when patients with chronic HF are treated with intravenous T_3 [10]. Thus, T_3 has the unique pharmacological properties of an inodilator acting primarily on diastolic dysfunction. The pulmonary vasculature is not as responsive to the vasodilatory effects TH as is the systemic vasculature [11]. Pulmonary artery hypertension that resolves after return to the euthyroid state has been reported in patients with thyrotoxicosis mainly due to a fall in cardiac output. The therapeutic targets of cardioprotection should not be limited to cardiomyocytes, but should also include other cells such as fibroblasts and endothelial cells that play important roles in preserving myocardial function. THs can modulate metalloproteinases (MMP), increasing MMP 1 and 2 as well as collagen gene expression; consequently, they may have an important impact on the extracellular matrix of the heart . Tissue inhibitors of MMP are downregulated by THs [12]. The antifibrotic effect of T3 is suggested by evidence that early T3 replacement after ischemia/reperfusion in rats is associated with a reduction in scar size. Moreover, hypothyroid status is marked by an increased susceptibility to collagen deposition and cardiac fibrosis [13].



Thyroid Disease and CV Risk Factors

TH and hyperlipidemia

Hyperthyroidism reduces cholesterol levels, which are reversed when euthyroidism is achieved. Hypothyroidism is associated with a small but significant increase in lipid parameters [14], in particular, an elevation of low-density lipoproteins (LDLs) [15]. Hypothyroidism is associated with increased oxidation of LDL, which promotes atherogenesis and reverses with treatment [16]. Lipoprotein(a), a more potent marker of atherogenesis, also increases in overt hypothyroidism and decreases with TH replacement [17] The effect of subclinical hypothyroidism (SCH) on hyperlipidemia is less clear [18]. Hyperlipidemia in hypothyroidism is due to a decrease in LDL receptors, resulting in reduced cholesterol clearance from the liver and decreased activity of cholesterol 7α-hydroxylase, which is activated by TH, in breaking down cholesterol [19]. A Cochrane review of 6 RCTs concluded that levothyroxine treatment of SCH had no overall effect in reducing total cholesterol, but suggested a trend toward reducing LDL cholesterol (LDL-C) levels >155 mg/dl in a subgroup analysis [20]. Two subsequent trials suggested that the reduction of LDL-C was approximately 0.3 mmol/l (11.6 mg/dl) [21]. Thus, an association, if present, is likely to be weak, with SCH contributing to a small increase in serum LDL-C, ranging between 3 and 15 mg/dl (0.1 to 0.4 mmol/l) [22].

TH and thrombogenesis

Overt and SHyper have been associated with increased markers of thrombogenesis (fibrinogen and factor X levels) [23]. Hyperthyroid patients may also have higher von Willebrand antigen levels compared with euthyroid patients, leading to enhanced platelet plug formation, which decreases after treatment [24]. The relevance of these findings is uncertain, although a review of published case reports in hyperthyroidism suggests a tendency toward increased overall thrombosis [25]. The increased cerebral thrombosis and cerebrovascular events in overt hyperthyroidism warrant further scrutiny to investigate if such events are due to increased thrombosis, related to alterations in the vascular tree (increased carotid intima-media thickness), or due to a higher risk of atrial fibrillation (AF) . Studies investigating coagulation in overt hypothyroidism have yielded conflicting results, with 2 studies showing hypercoagulability and 1 study showing increased fibrinolysis [26]. Interestingly, a study comparing moderate and severely hypothyroid patients with euthyroid controls found that patients with moderate hypothyroidism had decreased fibrinolytic activity and were more susceptible to clot formation, whereas patients with severe hypothyroidism had increased fibrinolysis and lower tissue plasminogen activator antigen [27]. In SCH, factor VII activity and the factor VII activity–to–factor VII antigen ratio were significantly increased in women with SCH compared with controls [28]. Another study showed decreased antithrombin III activity and increased levels of fibrinogen, factor VII, and plasminogen activator inhibitor antigen in SCH patients to explain a potential hypercoagulable state [29]. This is further supported by a study that found lower global fibrinolytic activity, such as tissue plasminogen activator, in SCH patients than in euthyroid controls [30]. The effects of TH on platelet function are unclear. A study using the Badimon chamber, a surrogate ex vivo model of plaque rupture in a moderately stenosed coronary artery, showed increased thrombus in patients with SCH 7 to 10 days post–non-ST-segment elevation myocardial infarction compared with euthyroid patients, despite dual antiplatelet therapy [31].

Thyroid hormone as a cardiac mitochondrial regulator

THs modulate cardiac mitochondrial function by increasing mitochondrial mass, respiration, oxidative phosphorylation, enzyme activity and mitochondrial protein synthesis such as that of cytochrome as well as phospholipid and mtDNA content [32]. Changes in the levels of circulating THs may impair myocardial bioenergetic status with consequences on cardiac function [33]. Mitochondrial dysfunction plays a central role in cardiac dysfunction and in the occurrence and progression of heart failure [34] The regulation of mitochondrial function and biogenesis by THs is an emerging mechanism in the therapeutics of cardioprotection. THs promote the upregulation of proteins that are functionally relevant to the rescue of mitochondrial function. Consequently, these hormones may reduce cardiomyocyte loss in the peri-infarct zone. Reversal of the post-ischemic decline of TH levels has been shown to downregulate tumor suppressor protein (p53) possibly via the upregulation of miRNA 30a [35]. Additionally, premature activation of the c-Jun N-terminal kinase (JNK) cascade occurs minutes after myocardial infarction. JNK protein expression is associated with apoptosis in the infarction border zone, cardiac dilatation and pathological remodeling [36]. Given that p53 can regulate the JNK pathway through a positive feedback loop, THs might reduce JNK levels through a p53-dependent mechanism [35]. T3 treatment (14 ng/g body weight, dose given daily) for 3 days after acute myocardial infarction in rats reduced myocyte apoptosis in the border area, possibly via Akt signaling [37].T3 administration in rats significantly increases the expression of transcription factors implicated in mitochondrial biogenesis, including nuclear regulatory factors – NRF-1 and NRF-2 which mediate the expression of HIF-1α, mitochondrial transcription factor A (mt-TFA) and peroxisome proliferator-activated receptor coactivator-1α (PPARc-1α), particularly in the peri-infarct zone

TH, vasculature, and blood pressure Hyperthyroidism causes a hyperdynamic circulation, characterized by increased cardiac contractility and heart rate, increased preload, and decreased systemic vascular resistance (SVR), resulting in significantly increased cardiac output. Although hyperthyroidism can increase systolic blood pressure, the net effect is dependent on the balance between increased cardiac output and decreased SVR [39]. The relationship between subclinical hyperthyroidism (SHyper) and blood pressure is less clear, with most published studies showing no association [40]. Furthermore, some studies have shown SHyper patients to have increased carotid intima-media thickness and carotid artery plaques [41] , although this was not confirmed in a recent large, population-based study [42]. Overt and SCH are associated with diastolic hypertension, impaired vascular function, and increased carotid intima hyperplasia [43]. Endothelial-dependent vasodilation is lower in overtly hypothyroid and SCH patients [44], and improves with levothyroxine treatment as does pulse wave velocity, a surrogate measure of arterial stiffness [45] Several factors could likely contribute to arterial stiffness and endothelial dysfunction in SCH and hypothyroidism, including hyperlipidemia and a proinflammatory state . Thus, in the Rotterdam Study, aortic calcification and the prevalence of myocardial infarction was higher in patients with SCH who were positive for thyroid autoantibodies than in those with SCH alone [46]. Both hyperlipidemia and thyroid antibodies are thought to reduce expression of endothelial nitric oxide synthase, thereby impairing vasodilation . In addition, increased arterial stiffness and a low renin state are contributory factors leading to blood pressure and vascular dysregulation due to the lack of the normal vasodilatory effects of T_3.

The impact of thyroid hormone dysfunction on myocardial ischemia Myocardial ischemia is a major cause of mortality and morbidity worldwide [47]. An understanding of the mechanisms of interaction between THs and their receptors is crucial to assess their impact in myocardial ischemia. TRα1 plays a key role during post-ischemic adaptation as it appears to present dual action and may be able to convert pathologic to physiologic growth depending on its ligand availability . In fact, TRα1 overexpression in the nucleus of cardiomyocytes in the absence of adequate THs as ligands may induce pathological hypertrophy and fetal phenotype, with predominant β-MHC expression. In contrast, higher levels of THs stimulate an α-MHC growth pattern, enhancing more physiological growth [48]. The precise prevalence of NTIS among patients with acute coronary syndrome has not been defined, but a prevalence of 5–35% has been reported in the literature. Several studies demonstrated a decrease in T3 and an increase in rT3 concentration in patients after an acute coronary event [49]. Some factors may predict a more pronounced decline in T3 levels, such as worsening angina pectoris preceding acute myocardial infarction, known chronic heart failure or previous myocardial infarction and diabetes mellitus. Low T3 levels also induce oxidative stress and increase apoptotic rate, which may worsen ventricular dysfunction [50]. Therefore, THs levels are an important factor modulating left ventricular structure, function and geometry during the late post-myocardial infarction period. Patients with ST-elevation myocardial infarction (STEMI) and alterations in thyroid function have almost a 3.5-fold increased risk of major adverse cardiac events, including cardiogenic shock and death, compared with patients with STEMI and no thyroid disorder [51]. In fact, alterations in thyroid function seem to occur more frequently in STEMI than in NSTEMI (non-ST-elevation myocardial infarction), possibly because of poorer short-term prognosis and features of the occlusive coronary thrombus typical of STEMI [51]. Recent evidence indicates that circulating T3 levels are an independent determinant of the recovery of left ventricular ejection fraction 6 months after acute myocardial infarction in humans [52]. Friberg *et al.* found a positive correlation between rT3 levels and 1-year mortality in patients with myocardial infarction, independent of other risk factors [53]. In line with these results, a recent study with patients attending a cardiac rehabilitation program after an acute coronary syndrome also reported an association between lower T3 levels and all-cause mortality [54]. In patients with myocardial injury, lower T3 levels have been correlated with increased serum levels of cardiac biomarkers such as troponin T and N-terminal pro-brain natriuretic peptide and with lower left ventricular ejection fraction. T3 levels may represent a predictor of the potential recovery of ventricular function [52]. One of the priorities in the treatment of myocardial ischemia is the reestablishment of coronary circulation. Early reperfusion has a great impact on short-term mortality after a myocardial ischemic event [55]. Coronary revascularization by either coronary bypass surgery (CABG) or percutaneous coronary intervention (PCI) constitutes the primary option in the treatment of coronary artery disease. Despite its indisputable benefits, reperfusion after a myocardial ischemic event may contribute to adverse cardiac remodeling with possible evolution to heart failure. The pathophysiology of IRI is complex; however, recent evidence suggests that mitochondrial dysfunction may be one of the major mechanisms of IRI [56]. The incidence of post-ischemic heart failure remains critical, increasing the risk of both cardiac and all-cause deaths [55]. After reperfusion, extracellular washout of accumulated H^+ ions creates a large gradient that increases the influx of sodium via the Na^+/H^+ exchanger. This stimulates the reverse action of the Na^+/Ca^{2+} exchanger pump, increasing oxidative stress [55]. THs improve the balance of proapoptotic and pro-survival signaling pathways which may limit IRI [57]. T3 enhances the expression of HIF-1α, limiting the mitochondrial opening of permeability transition pores and thereby protecting the cardiomyocyte from reperfusion injury . Serum THs levels after CABG are often decreased [58]. In fact, NTIS is reported in 50–75% of patients after cardiac surgery and some authors consider this as a poor prognostic factor and a predictor of mortality [58]. Pantos *et al.* were the first to observe that pretreatment with THs confers protection against IRI in isolated rat hearts in a pattern similar to ischemic preconditioning . The interest in the role of THs in cardioprotection is increasing. In fact, THs pretreatment may confer protection against

subsequent IRI by inducing pharmacological preconditioning in cardiomyocytes, mainly by enhancing heat-shock protein 27 (HSP27) and heat-shock protein 70 (HSP70) and decreasing the activation of proapoptotic p38MAPK [58]. Recent studies using TH replacement therapy in animal models with regional or global myocardial ischemia followed by revascularization and/or reperfusion showed improved reversal of myocardial dysfunction compared with the absence of TH replacement therap Low T_3 syndrome (an isolated reduction of serum T_3 levels with normal T_4 and TSH concentrations) after AMI is observed in up to 1 in 5 patients [59], whereas SCH is observed in almost 12% [60]. T_3 down-regulation is consistent with experimental data showing that changes in circulating TH parameters after AMI are a result of increased D3 activity and reduced D1 and D2 activity. Convincing data show that TH metabolism abnormalities occurring during early stage of AMI are associated with increased incidence of cardiac events. The degree of TH down-regulation is associated with higher impairment of cardiac function and higher inflammatory response [59]. The increase in rT_3, the inactive TH metabolite, is a predictor of both short- and long-term mortality independent of other traditional parameters [62]. Similarly, in 501 patients with AMI (of whom 34% had low T_3 syndrome), the rate of major cardiac events at follow-up was higher in those with low free triiodothyronine (FT_3) levels than in those with preserved FT_3 circulating levels, and, importantly, FT_3 was the most important predictor of subsequent cardiac events [63]. In another study of 457 AMI patients, thyroid dysfunction including SCH, SHyper, and low T_3 syndrome was associated with higher incidence of major cardiac events . Furthermore, in patients with AMI and early reperfusion therapy, T_3 circulating levels correlated with LV ejection fraction both at the early, in-hospital phase and at the 6-month follow-up visit. Interestingly, T_3 at 6 months was an independent predictor of LV ejection fraction changes between the early and follow-up periods [64]. However, pathophysiological and therapeutic relevance of the thyroid dysregulation after AMI are far from elucidated. No interventional studies of TH replacement in AMI patients have been published to date, therefore making a causal relationship between thyroid dysfunction and outcomes difficult to ascertain. Overall, the experimental and observational findings mentioned previously are in contrast to the common interpretation that TH down-regulation after AMI is an adaptive, favorable process that helps in reducing catabolism and energy expenditure [65], and suggests the potential critical role of the thyroid system in cardioprotection in AMI. Future research to better understand the interaction between acute TH changes and cardiac ischemia, particularly ischemia-reperfusion injury, and whether normalizing thyroid function parameters may have a role, is required.

Conclusions

The CV system is a major target of TH action, and even subtle changes in thyroid function can lead to cardiac dysfunction. A number of experimental studies and observational clinical data in both hypo- and hyperthyroidism suggest that modulation of TH may be beneficial in reducing CV disease. However, high-quality evidence is required before this can be translated into clinical practice. Similarly, there is increasing evidence that changes in TH levels in otherwise euthyroid patients with CV disease (such as AMI or HF) may be a marker of poor prognosis, and clinical trials are required to see if TH therapy may be efficacious and safe. Experimental and clinical evidence suggests a close link between low TH levels and poor prognosis in ischemic heart disease. This condition should therefore be regarded as a cardiovascular risk factor. Accordingly, TH replacement therapy may yield improvements in lipid profiles, potentially reversing myocardial dysfunction and preventing the progression to heart failure. TH replacement treatment exhibits anti-ischemic and cardioprotective effects, acting as a promising target for ischemic heart disease. Moreover, subclinical hypothyroidism treatment and nonthyroidal illness syndrome constitute topics garnering increased interest; recent studies suggest that therapy with physiological doses of T3 are safe and provide beneficial effects on ischemic heart disease. Large clinical trials involving TH replacement treatment are necessary to evaluate the potential

benefits on morbidity and mortality in patients with ischemic heart disease, as well as any potential long-term consequences.

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