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'Low – T3 syndrome' among patients with acute myocardial infarction

Review Article

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Abstract: Background: Recent clinical studies have found that cardiovascular incidents are sufficient triggers to affect HPA hypothalamic-pituitary-thyroid axis and cause a decrease in the serum levels of triiodothyronine (T3). This phenomenon is so called 'Low – triiodothyronine (T3) syndrome' and is related to changes in heart remodeling. However, the pathophysiology of Low–T3 syndrome remains unclear. The present systemic literature review was designed to organize the latest scientific papers and is seeking to draw evidence-based conclusions regarding clinical aspects of the topic. Methods: Accessible scientific databases were analyzed using key words to obtain scientific papers regarding the field of interest. Research findings were assessed and compared between studies in order to find out clinical impact of thyroid hormone and heart function following acute myocardial injury. Results: Different studies indicate that the presence of Low-T3 syndrome after myocardial infarction is a strong predicting factor of patient morbidity and mortality. Some researchers believe that the decrease in T3 concentrations might be a compensatory reaction of the body in order to suppress cellular metabolism during tissue damage. On the other hand, a limited number of recent experimental and clinical investigations have shown positive response to treatment with thyroid hormone. Conclusion: Deeper analysis is needed to understand the pathophysiology of Low-T3 syndrome and possibilities of its use for treatment.

Keywords: *Low – T3 syndrome • Triiodothyronine • Myocardial infarction • Heart remodeling*

1. Introduction

Acute myocardial infarction (AMI) results in cardiac dysfunction due to myocardial loss and series of changes in the non-ischemic myocardium, which include alteration in the chamber size and shape as well as interstitial structure. This process is known as cardiac remodeling and involves several cellular and molecular mechanisms, including other factors still under investigation, which begins only a few hours after AMI and persists for weeks or months following an initial incident [1,2]. The early stage of ventricular remodeling is defined as acute dilatation and thinning of the infarction area. Infarct expansion may lead to development of aneurysm and rupture of the myocardium [3,4]. The late stage of ventricular remodeling involves progressive ventricular chamber dilation and eccentric hypertrophy of non-infarcted area, as a compensatory response. Long-term dilation increases diastolic and systolic wall stress and stimulates further ventricular enlargement [5]. Left ventricle (LV) remodeling may occur in about 49% of ST-elevation acute myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (P-PCI) [6]. The changes taking place during remodeling comprise heart becoming less elliptical and more spherical [7]. Changes in ventricular mass, composition and volume are also present [8]. LV volume is a powerful functional predictor of survival in patients with coronary heart disease (CHD) [9].

LV remodeling is associated with unfavorable hemodynamic performance and adverse outcomes at long–term follow-up, including symptomatic heart failure, death due to pump failure, and sudden cardiac death [10].

The thyroid and cardiovascular system are closely related. Experimental and clinical analyses have shown,

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that thyroid hormone (TH) has a fundamental role in cardiovascular homeostasis, influencing cardiac contractility, heart rate, diastolic function and systemic vascular resistance [11]. Abnormal metabolism of TH may lead to various heart diseases, like accelerated coronary atherosclerosis [12]. Coceani et al. have demonstrated that free triiodothyronine (T3) levels are inversely correlated with the presence of coronary artery disease (CAD), whereas Low – triiodothyronine (T3) syndrome causes an adverse prognosis for CAD [13]. Few studies have shown possible beneficial effects of thyroid hormone replacement in patients with ischemic heart disease [14].

2. Thyroid hormone and its mechanisms of action

Secretion of thyroid hormone is controlled by pituitary gland and its secretion of thyroid-stimulating-hormone (TSH), which is stimulated by hypothalamic thyrotropin-releasing hormone (TRH) [15]. Thyroid gland secretes several hormones, including thyroxine (T4), triiodothyronine (T3), and reverse triiodothyronine (rT3). The main product of thyroid gland is T4, which is converted into T3 that can bind to TH receptors and further modulates hormone dependent cellular actions [14]. Conversion of T4 toT3 is catalyzed by selenoenzymes called iodothyronine deiodinases, which exist in several forms. Type I deiodinase (D1) is located in the liver and kidneys and is responsible for production of as much as 80% of T3. Type II deiodinase (D2) is located in the brain and muscles including the heart muscle in humans, and contributes to the total tissue T3 concentration. Type III deiodinase (D3) converts T4 into inactive rT3 and degrades T3. T3 is able to pass through the cell membranes and is responsible for genomic and non-genomic effects of TH [16].

A typical pattern of altered TH metabolism is characterized by the low circulating levels of T3 and has already been described in patients with AMI [17]. This phenomenon is known as Low triiodothyronine (T3) syndrome and involves decreased serum levels of T3, increased levels of rT3 but unchanged TSH or T4 levels [14]. Although the mechanisms underlying low serum T3 are not yet understood, some investigators have elucidated that low hepatic D1 activity could result from an increased serum interleukins level (particularly interleukin-6), which occurs after the AMI [14,15].

It is revealed that following pathological ventricular remodeling, many cardiac genes that are involved in contractile dysfunction are transcriptionally regulated by the TH and TH receptors (TRs). Cell culture studies have identified a number of factors, which can stimulate D3 activity through the transcriptional activation of DIO3 gene, directly or in combination with other factors [18]. These factors include: - transforming growth factor (TGFβ), mitogen-activated protein kinase (MAPK) system, p38 MAPK, as well as the extracellular responsive kinase (ERK) and hypoxia-inducible factor 1 (HIF-1). The present contributors result in synergistic stimulation of transcription of DIO3 gene. Increased D3 activity converts T3 to inactive metabolite rT3, resulting in reduced T3 level, which in turn effects contractile activity and energy metabolism [19].

3. Clinical implications

High levels of D3 activity in the infarcted LV are associated with an apparent heart failure. Olivares et al. conducted a 12-week analysis of LV remodeling, using a rat model of myocardial infarction (MI). They observed a chronic heart failure, with reduced ejection fraction and increased LV end-diastolic diameters and D3 activity was observed in the infarcted LV at 1-week post MI [20]. This activity was identical to that of increased D3 measured in another study by Wassen et al. in the RV following AMI [21]. The authors suggested that increased D3 activity is responsible for the transient decrease in plasma T3 levels, within first 3 weeks following AMI. Pol et al. analyzed post – AMI LV remodeling and D3 expression in mouse model. The induction of D3 was found in hypertrophic, noninfarcted area of LV at first week after the incident. At the same time the LV function was severely reduced from week 1 after MI onwards., with increased LV end–diastolic and end–systolic diameters and reduced fractional shortening. Moreover, D3 activity remained high at 4-8 week following AMI [22].

Changes in plasma T3 levels are closely correlated with the early and late recovery of cardiac function post AMI. Lymvaios et al. observed a significant correlation between left ventricular ejection fraction (LVEF, %) and T3 plasma levels (P=0,0004; P=10^{-6}). The changes in T3 plasma levels were observed early after AMI (48 h) and at 6 month after AMI. There was not a significant correlation between LVEF % and T4 or TSH [23]. In a cohort study of 1047 patients who underwent coronary angiography, FT3 plasma levels were linked with the presence of CAD (p<0,001). After 31 months follow-up, cardiac mortality was greater among patients with Low-T3 syndrome [13]. From unselected sample of 573 patients with cardiac disease, cumulative and cardiovascular mortalities were significantly higher in patients with low T3, compared with those without it (14,4 vs 3%, and 7,5 vs 1,5%) [24]. In a group of 281 patients with post-ischemic and non-ischemic dilated cardiomyopathy,

T3 levels and LVEF% were the only independent predictors of cardiovascular and total mortality. Patients with combination of reduced LVEF% and T3 showed significantly higher mortality in comparison with patients who showed similar LVEF% but normal T3 [25]. Forty-seven euthyroid patients with AMI were studied prospectively during the first 5 days and again 6 and 12 weeks later. It was noticed that thyroid hormone system is down-regulated after AMI. The changes in hormone levels were rapid during the first 24 - 37 hours after onset of ischemic symptoms. The mean level of T3 decreased by 19%, the inactive metabolite rT3 levels increased by 22%, whereas thyrotropin levels have declined by 51%. Patients who died within the first year of AMI had lower mean levels of T3 and higher levels of rT3 during the hospital period [26].

AMI results in the loss of cardiac function due to tissue necrosis, reperfusion injury and cardiac remodeling, causing significant morbidity and mortality (with a high risk 30-75%) [26,27].

Researches have revealed previously undetected actions of TH on the heart. The beneficial effects of TH administration at early or late stage of myocardial infarction have documented the role of this hormone in the process of cardiac remodeling post MI. TH can control contractile function via regulation of contractile proteins, calcium handling, and ion channels [29]. It is possibly implicated in post-ischemic functional recovery. Treatment with T3 improves post-ischemic recovery of cardiac function while limiting apoptosis in experimental models of ischemia-reperfusion injury [30]. In addition, TH administration after the MI changes the LV geometry. TH is able to normalize stress of the cardiac wall by increasing cardiac mass. It is noticed, that at later stages, TH induces changes in cardiac geometry by preventing the spherical shape of LV chamber. This effect is modulated by TH reshaping LV chamber toward a more ellipsoidal shape. The above mentioned responses seem to involve distinct signaling pathways, comprising: low TH levels, increased D3 activity, increased expression of thyroid receptor protein α1 (TRα1) and decreased TR β1 protein expression in the myocardium [31,32].

To recapitulate, there exist strong evidences that plasma levels of T3 correlate with the outcomes of AMI. However, the causes of Low-T3 syndrome remain unclear. Some researchers believe that TH is detrimental to ischemic myocardium due to the acceleration of heart rhythm. Thus, low T3 stage has a protective role and doesn't need treatment. These beliefs are now being challenged by recent experimental or clinical investigations [33].

4. Conclusion

Myocardial infarction inevitably leads to a heart failure, which further involves cardiac remodeling. This process is closely related to pituitary-thyroid neuroendocrine axis and its components. Occurrence of Low-T3 syndrome following cardiovascular incident is clearly related to further negative prognosis and poor outcomes. Experiments with animals have recently indicated positive effects of T3 administration after acute myocardial injury on cardiac remodeling and ventricular function. Apart from this, in a randomized, placebo-controlled study Pingitore A. et al. concluded that short-term administration of replacement dose of synthetic T3 to patients with chronic heart failure and Low-T3 syndrome improves both neuroendocrine profile and left ventricle stroke volume. On the other hand, the study had many limitations relating to small number of patients, lack of assessment of diastolic function and other systems. Furthermore, reliable conclusions about substitute T3 therapy for patients with acute heart failure leading to myocardial infarction with the Low-T3 syndrome, are impossible to be drawn due to lack of clinical data. To sum up, deeper analysis is needed to understand the pathophysiology of Low-T3 syndrome as well as possibilities and necessity of its treatment for patients with acute myocardial infarction.

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