Indian Heart Journal 73 (2021) 143–148

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

Prognostic implications of thyroid hormone alterations in acute coronary syndrome—A systematic review

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ARTICLE INFO

Article history:
Received 27 April 2020
Accepted 20 November 2020
Available online 23 November 2020

Keywords:
Cardiovascular
Thyroid hormone
STEMI
NSTEMI
Hypothyroidism

ABSTRACT

There is considerable association of thyroid function and the cardiovascular system during various acute systemic illnesses. It is well established that the normal thyroid homeostasis is known to alter in disease states including the acute coronary syndromes (ACS). Abnormal thyroid hormonal status has been shown to be related to worse outcomes and prognosis. This review focuses on the relationship of alterations in thyroid function and its influence on the pathophysiological mechanisms and cardiovascular hemodynamics in ACS and based upon the literature, summarises all the existing evidence to this date on this subject. The data largely points out that low levels of triiodothyronine (T3) levels seen in ACS might be useful in prognosticating the outcomes of ACS.

1. Introduction

Cardiovascular diseases have been recognized as a serious public health problem. The abnormalities of the thyroid function both hyper and hypothyroidism by way of affecting the cardiovascular system directly or through indirect means can have a major impact in health and disease. A typical pattern of altered thyroid hormone metabolism is characterized by low T3 circulating levels and has been described on patients with acute myocardial infarction and heart failure in adults. The cardiovascular system is one of the most important targets on which thyroid hormones act.[1] In spite of advances in pharmacotherapy and myocardial reperfusion procedures, short-and long term -haul mortality of patients suffering an acute coronary syndrome (ACS) continues to remains significant. It has been perceived since a long time that alteration in plasma concentration of thyroid hormones (THs) is related with acute illness. The expression “low T3 disorder” refers to alterations of THs plasma concentrations, mainly diminished triiodothyronine (T3) or potentially free T3 (fT3) amid different acute and chronic ailments in patients with no known intrinsic thyroid disease. It has been found to be an indicator for early and late mortality,[2,3] Patients showing ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) have similar risk factor but their long-term prognosis may or may not be the same and is debatable.[4] Considering the important role of THs on the cardiovascular system, there is enough evidence that suggests towards a potential prognostic role of THs alterations in patients with ACS.[4,5]

The aim of the current review is to describe the role of TH alteration during ACS, Comprehensive information was searched on PubMed, KoreaMed, EuroPMC, EMBASE, and Web of Science electronic databases regarding THs alteration during ACS.

2. Thyroid hormones and their influence on cardiovascular system

Thyroid hormone is an essential regulator for cardiac function and cardiovascular hemodynamics. Thyroid-stimulating hormone (TSH) activates the synthesis of thyroxine (T4) and T3 in the thyroid gland.[6] Almost 85% of T4 is secreted by the thyroid gland and then converted in the liver, kidneys, and skeletal muscles to T3 by the enzyme 5′-monodeiodinase.[6] Reverse T3 (rT3) is a biologically inactive alternate product of T4 deiodination. It is a small fraction of the THs which is unbound and biologically active, because most of the circulating THs are bound to transport proteins.[6]

The thyroid hormone nuclear receptor (TRs) binds with the thyroid hormone response elements (TREs) as heterodimers and

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https://doi.org/10.1016/j.ihj.2020.11.147

starts transcription in the promoter region, Triiodothyronine is a physiologically active form of thyroid hormone which binds to nuclear receptor proteins and activates the expression of several cardiac genes which induces the transcription of positively regulated genes like alpha-myosin heavy chain (MHC) and the sarcoplasmic reticulum calcium.[7] It is the only TH transported into the myocyte. In the presence of T3 numerous key structural cardiac genes, such as α-myosin heavy chain, sarcoplasmatic reticulum Ca2+-adenosine triphosphatase (SERCA 2), and Na+/K+-adenosine triphosphatase, are positively regulated.[8] and negatively regulated genes which include beta-MHC and phospholamban are down regulated in the presence of normal serum levels of thyroid hormone.[7] On a vascular level, T3 helps in maintenance and upkeep of endothelial integrity, peripheral arterial resistance and diastolic blood pressure.[9] The advancement in the cellular biology has now enabled to explore and present a clear mechanistic insight in the role played by the THs on the cardiac cells.

Thyroid hormones particularly T3, can modify ion channels for calcium, sodium and potassium and influence a variety of intracellular pathways in cardiac and vascular smooth-muscle cells[10] which results in an increase of cardiac output, the heart rate can essentially be influenced by even modest changes in the thyroid status. The arrhythmogenic impacts of THs alters the electrophysiological characteristics of atrial myocytes by enhancing their automaticity. It also triggers shortening the action potential duration. It is important to note that there is an increased cardiac output as THs cause a decrease in systemic vascular resistance by rapid relaxation of vascular smooth muscle cells. Various clinical and experimental studies suggest potential proarrhythmic effects of the THs and a direct effect on electrogenesis in myocardial cells.[10,11]

3. Clinical impact of alterations in thyroid function

Altered function of thyroid leading to hyper or hypothyroidism affects molecular pathways in the heart and vasculature leading to derangements in the cardiovascular system.[12] It is well established that overt hyperthyroidism initiates hyperdynamic cardiovascular state[12] like increased systolic blood pressure, pulmonary hypertension, and atrioventricular valve regurgitation,[4] whereas overt hypothyroidism is correlated with diastolic hypertension, dyslipidemia, atherosclerotic plaque progression and instability, including endothelial dysfunction.[6,7,13]

The presenting symptoms of chest pain and ECG abnormalities can be manifestations of overt hyperthyroidism or thyrotoxicosis. The increase in oxygen demands in response to enhanced cardiac contractility and workload results in these symptoms.[6] It has also been reported that patients with hyperthyroidism often with underlying asymptomatic heart disease can present with signs and symptoms of heart failure because of enhanced cardiac output and contractility.

Subclinical hypothyroidism is a common clinical problem, especially in our country, There is a growing evidence that subclinical hypothyroidism is associated with increased cardiovascular risk,[12] subclinical hypothyroidism increases isovolumetric relaxation time, decreases endothelial relaxation and decrease cardiac contractility.[14] These consequences are very important for the onset of ACS where parts of myocardium functionality is impaired due to ischaemia related injury.[15] Since all cardiovascular abnormalities are reversed restoration of euthyroidism ("subclinical hypothyroidism") should be the goal. The clinical features of hyperthyroidism can be blunted by using beta adrenergic or drugs like neo mercazole. On the other hand L-thyroxine (L-T4) dose tailoring is the treatment for subclinical hypothyroidism, It is recognized by abnormally high serum TSH value with normal fT4 and fT3 concentration. Subclinical hypothyroidism is linked with lipid metabolism abnormalities and neuropsychiatric disorders and timely treatment is required to avoid adverse cardiovascular effects.[14,16]

4. Abnormal thyroid hormone status during critical illness

Change in the serum thyroid hormone profile level has been depicted in various non-thyroidal illness,[17–19] Abnormal thyroid status increases the risk of coronary artery disease and cardiovascular mortality,[20] alterations in TH plasma concentrations during a variety of acute and chronic illnesses in patients with no known intrinsic thyroid disease are described by various terms in literature, such as "euthyroid sick syndrome", "nonthyroidal illness syndrome," and "low T3 syndrome",[4,2] It is known that changes in thyroid hormone develop within hours in case of acute non-thyroidal diseases.[20] It is most frequently characterized by low T3 or fT3, elevated rT3, normal T4 and TSH.[21–25] Low level of fT3 is also associated with greater LV diameters and LV end-diastolic volume, and decreased systolic LV function.[26] It was found that high-normal level of TSH is an independent predictor for mortality during 6 months hospitalization in euthyroid sick syndrome.[27]

5. Impact of altered thyroid hormonal status on coronary artery disease

Coronary atherosclerosis is a condition caused by the build-up of the plaque inside the arterial wall which limits the flow of blood entering the myocardium especially during increased demand and leads to angina. On the other hand, acute myocardial ischemia is the situation when the blood flow to the heart is abruptly markedly reduced or stopped and leads to necrosis of the cardiac muscle resulting in ACS. Thrombus formation is an integral part of the pathophysiology of ACS which triggers an immediate inflammatory cascade.[28]

The literature has considerable evidence documenting a fall in total T3 and/or fT3 concentration and rise in rT3 concentration after an acute coronary event. Therefore, normal thyroid homeostasis seems to get altered in a subgroup of patients with ACS.[29,30] There is a wide variability in the population studies on ACS patients for the association of the altered THs and its implications on the ACS. There is a wide range in prevalence from (5%–35%) on low T3 syndrome among patients suffering from ACS.[4,5,29,31] It is noteworthy that low T3 syndrome seems to occur more often in STEMI patients as compared to NSTEMI patients, The occlusive thrombus results in larger area of myocardial damage and poorer prognosis.[29,32]

In a study done by Pavlou et al (2002) regarding the THs it was found out that mean fT3, fT4, T4 and TSH stay unaltered in all patients with ACS during the initial 5 days after confirmation of the diagnosis, whereas low levels of T3 and maximum rT3 occur on day 3 and day 4[33].

6. Impact and association of cytokines

Cytokines are multifunctional molecules with various biological impacts on target cells, which can apply autocrine (on similar cells that discharge them), paracrine (on adjacent cells) and endocrine (on distant cells) activities.[34] In general, cytokines bind to specific cell-surface receptors that are also demonstrated in the thyrocytes. Cytokines participate in the pathogenesis of thyroid auto-immune disease by contributing to the development and differentiation of B and T cells, by initiating the expression of HLA class II antigens and adhesion molecules.[35] Interleukin-6 (IL-6) and other cytokines are useful markers of thyroid-destructive processes.[36] The acute effects of cytokines are well explored for the causal relationship and

play a key role in the pathogenesis of the low T3 syndrome. Interferon-α when administrated in healthy volunteers can cause disturbances in TH metabolism.[37] During critical illness, various pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor-α, and interferon-γ can directly affect the pituitary gland and impair TSH release.[22] THs alterations are supposed to develop through the inflammatory response activation. Increase in IL-6, a pleiotropic, pro-inflammatory cytokine; soluble IL-6 receptor (sIL-6R); and CRP levels may exert an inhibitory effect on thyroid axis function.[5,23,38–40]

It is pertinent to note that during ACS decreased levels of THs have been reported. This has been evident in various clinical studies with specific clinical and biochemical parameters. Worsening angina pectoris preceding the AMI, chronic heart failure or previous MI and DM are known to be associated with lower T3 levels during the acute coronary event,[5,41,42] There are no exact evidence for the development of low T3 syndrome among patients with ACS. But, certainly, there are specific factors that include older age, lower body mass index, DM, high plasma levels of N-terminal pro-brain natriuretic peptide and CRP correlates for the development of low T3 syndrome in patients with ACS.[4,23,30,41–43]

7. The prognostic value of thyroid dysfunction in ACS

Patients with severe nonthyroidal illness often experience concomitant disorders in thyroid function. In severe illness of nonthyroidal origin including Existing proof has supported the assumption of a prognostic role for the low T3 syndrome in patients with ACS. Several clinical studies have been done to investigate the prognostic value of THs alterations in patients suffering from ACS, It has been found that there is a correlation between increased rT3 levels in patients with MI and higher 1-year mortality, independently of other risk factors.[42] In STEMI patients undergoing PCI it was observed that low fT3 was an independent marker for MACE.[44] A small sample study has demonstrated an association of abnormal THs alterations with worse prognosis.[4] Short term and long-term mortality have been related with the low T3 syndrome in patients undergoing primary percutaneous coronary angioplasty for STEMI,[30,45] Even in patients recovering after ACS and undergoing a cardiac rehabilitation program have reported an association of lower fT3 levels with mortality.[46]

A study done by Iltumur et al (2005) compared function of patients with resuscitated cardiac arrest due to ACS in patients with uncomplicated AMI, the study highlighted that the latter group was characterized by a milder form of the low T3 syndrome[38] whereas another study done by Pimentel et al (2006) reported alterations in THs to be more evident in the STEMI group compared to the NSTEMI group.[4] THs alterations can manifest in patients with unstable angina and also be linked to adverse prognosis. Lower T3 and higher rT3 levels have been significantly more pronounced in patients with complicated infarctions compared to uncomplicated infarctions or unstable angina.[33] Limited studies were done on patients with AMI and have demonstrated a correlation between THs and extent of myocardial injury. Lower fT3 levels have been correlated with heart failure, serum biomarkers (troponin T and N-terminal pro-brain natriuretic peptide) as indicators for myocardial injury as well as lower left ventricular ejection fraction.[43,47] It was found out that heart failure, length of hospital stay and higher mortality was found in patients with abnormal thyroid function in ACS group.[17]

A study done by de Matos Soeiro et al (2017) with 505patients found out that the ACS patients having TSH >4 mlU/L at admission had worse prognosis in terms of higher incidence of in-hospital combined events, cardiogenic shock and bleeding.[48] There is a strong connection of low T3 with impaired ventricular function among AMI patients which concludes that T3 levels may represent as a predictor for ventricular functional recovery,[49] Also, it has been reported that the extent of trans mural involvement in patients with STEMI assessed by cardiac magnetic resonance imaging 40 days after the event is strongly associated with T3 levels.[50] The association of the low T3 syndrome relates to worse prognosis and mortality among patients suffering from AMI and may also be an independent marker not necessarily associated only with the degree of myocardial necrosis.

It has been postulated that down-regulation of the thyroid hormone system in patients suffering from myocardial ischemia, even prior to AMI manifestation might be beneficial in reduce myocardial oxygen demands. However, a persisting down-regulated thyroid system after AMI might become maladaptive because of the loss of the positive effects of T3 on the cardiovascular system. The low T3 syndrome might represent a hormonal homeostatic escape response, meaning a beneficial and physiologically adaptive mechanism during the early stress phase of an acute ischemic event, by minimizing myocardial metabolic demands and protecting against arrhythmias.[21,23] The low T3 syndrome is evident in a small group of ACS patients that seem to have the worse outcome. It is still unclear whether the low T3 syndrome is directly linked to the worse prognosis or it constitutes a marker for the severity of illness including ACS which is the underlying factor for increased mortality, however the syndrome should not be underestimated as disturbances in the T3, fT3, and rT3 levels seem to carry out an additive prognostic value in ACS independently of the traditional risk factors. The routine determination of plasma levels of THs among patients suffering from ACS might reveal a silent prognostic marker despite of the fact that the exact timing of THs alterations is still not clearly defined. Although there are several studies (Table 1) on this subject but most of them are underpowered for giving an answer

Table 1
Thyroid Hormone Alterations in ACS and their prognostic significance.

Study	Year	Design	Condition	Sample Size	Time of TSH Measurement	Follow-up	Result/Conclusion
Cikrikcioglu et al.[18]	2010	Prospective	ACS	135	At admission	6 months	Complications were seen more frequently in low T3 in ACS patients.
Friberg et al.[39]	2001	Prospective	AMI	331	At admission	1 year	High rT3 levels are associated with an increased risk of 1-year mortality.
Ertugrul et al.[12]	2011	Retrospective	AMI	604	Between 2004 and 2009	NR	Mild subclinical hypothyroidism (TSH 4.5–9.9mU/l) was present in 54 (8.94%) participants and severe subclinical hypothyroidism (TSH 10.0–19.9mU/l) in 11 (1.82%).

(continued on next page)

Table 1 (*continued*)

Study	Year	Design	Condition	Sample Size	Time of TSH Measurement	Follow-up	Result/Conclusion
Pavlou et al.[30]	2002	Prospective	ACS	114	During the first 5 days after admission and at 1 month	1 month	ESS can manifest both in AMI and UA; the rT3 increase and T3 decrease were significantly greater in complicated MIs compared with uncomplicated MIs and UA; low T3 levels may have prognostic value.
Khalil et al.[1]	2015	Prospective	ACS	196	At admission	6 months	The prevalence of thyroid dysfunction in a cohort of ACS patients was 23%. Thyroid dysfunction in acute coronary syndrome increase relative risk of death by 5.49 fold than euthyroid patients.
Iltumur et al.[35]	2005	Prospective	Cardiac arrest due to ACS	121	At 72 h and 2 months	2 months	THs are significantly altered in cardiac arrest induced by ACS; T3 and fT3 levels were lower in non-survivors compared with survivors up to 2 months
Jankauskiene et al.[24]	2015	Prospective	AMI	140	At admission	6 months	Low fT3 levels are significantly associated with worse LV mechanics during the late post-myocardial infarction period.
Pimentel et al.[4]	2006	Prospective	STEMI and NSTEMI/ UA	70	Days 1, 4 and 7 after admission	7 days	Greater THs alterations were found in STEMI compared with NSTEMI/ UA Patients.
Qari AF[23]	2015	Prospective	STEMI and NSTEMI/ UA	400	From day 1–4 after admission	2 years	The mortality rate was 9.8%; all death patients had low triiodothyronine (T3) syndrome and were associated with statistically significant low free triiodothyronine (fT3)
Adawiyah et al.[38]	2010	Prospective	STEMI and NSTEMI/ UA	85	Days 1, 5, and 42	6 months	ESS can manifest in patients with STEMI, NSTEMI, and UA and is related with mortality.
Helmy et al.[15]	2016	Prospective	ACS	300	At admission	1 year	Prevalence of subclinical hypothyroidism is 5% in ACS patients.
Lymvaios et al.[44]	2011	Prospective	AMI	47	At 24 h, 48 h, 5 days and 6 months	6 months	Lower T3 levels are associated with poor early and late myocardial functional recovery
Xue et al.[22]	2017	Prospective	ACS Patient treated with drug-eluting stent	528	From 24 h to 48 h after admission	1 year	A low fT3 level is a predictor of worse HRQOL improvement in ACS patients treated with DES.
Zhang et al.[43]	2012	Retrospective	AMI	501	After admission	10 ± 2 months	Decreased fT3 levels are correlated with worse short- and long-term prognosis.
Sah et al.[16]	2017	Cross sectional	ACS	100	At 24 h after admission	NR	The overall prevalence of abnormal thyroid hormone profile was statistically significant in the STEMI group
Kim et al.[45]	2014	Retrospective	STEMI treated with PCI	40	At admission	1–2 months	Lower T3 levels are associated with larger myocardial area at risk and increased salvage index in STEMI patients.
Seo et al.[13]	2018	Retrospective	AMI	1977	At admission	3.5 years	TSH elevation was a predictor of all-cause mortality in patients with AMI. Thyroid function in patients with AMI is associated with prognosis.
Ozcan et al.[41]	2014	Prospective	STEMI treated with PCI	457	Within 12 h after admission	14.4 ± 5.4 months	ESS is related to higher in-hospital and long-term mortality.
Yazıcı et al.[28]	2016	Prospective	NSTEMI/UA	274	Before angiography	1 month and 1 year	Low T3 and fT3 levels are related to increased early and late mortality

Abbreviations: ACS: Acute Coronary Syndrome; T3: Triiodothyronine; AMI: Acute Myocardial Infarction; rT3: Reverse Triiodothyronine; TSH: Thyroid Stimulating Hormone; ESS: Euthyroid Sick Syndrome; UA: Unstable Angina; MI: Myocardial Infarction; fT3: Free Triiodothyronine; LV: Left Ventricular; NR: Not Reported; NSTEMI: Non–ST-Segment Elevation Myocardial Infarction; STEMI: ST-Segment Elevation Myocardial Infarction; THs: Thyroid Hormones; HRQOL: Health-Related Quality of Life; DES: Drug-Eluting Stent; PCI: Percutaneous Coronary Intervention.

whether the alterations in TSH have a causal relationship or just a nonspecific response to the stress of illness. Coupled with this is the issue of timing of TH alterations and different definitions used. These gaps need to be addressed to by a multicentric study with specific objectives before one can label low T3 and other TH abnormalities as a prognostic marker in a wide spectrum of patients with ACS.

8. Thyroid replacement therapy for low T3 syndrome in ACS

Animal experimental studies have shown the benefits of administering THS in situations of AMI by improving the cardiac hemodynamics, remodeling and ventricular function. There is promising data of supplementing THS in clinical situations following coronary artery bypass surgery or in patients of congestive heart failure. The benefit or lack of it, by TSH supplementation in patients with ACS and low T3 syndrome is not available at present. This will also be compounded by issue of which hormone (T3 or T4) and at what stage of ACS and for how long? Presumably some of these issues will get more clarity by a few ongoing studies.[39,52]

9. Conclusion

Alterations in thyroid function tests are common in patients with ACS, especially in STEMI patients. The low T3 syndrome represents a hormonal imbalance that may significantly influence pathophysiological mechanisms and cardiovascular hemodynamics, Considering the significant effects of THs on the cardiovascular system, mounting evidence suggests a potential prognostic role of THs alteration in patients suffering from ACS.[52] Further high-quality studies and additional research is required to clarify the variable interpretations of thyroid dysfunctions in ACS, These would also clarify when and how this potentially powerful prognostic marker could be operationalized in the clinical setting. Although low TH plasma concentrations have been linked to adverse prognosis but, it has also been proposed that this transient low T3 status during an AMI may be cardio protective, by reducing energy expenditure, heart rate, and oxygen consumption during the ischemic stress. Thus, it may not be needing any replacement therapy.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This review article didn't receive any kind of funding.

Conflict of interest

Miss Priyadarshini Arambam declares that she has no conflict of interest with any authors listed in the paper, Dr. Upendra Kaul declares that he has no conflict of interest with any authors listed in the paper, Dr. Priya Ranjan declares that he has no conflict of interest with any authors listed in the paper and Dr. Rajiv Janardhanan declares that he has no conflict of interest with any authors listed in the paper.

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