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Original Article

Internal Medicine Section

Effect of Low T3 Syndrome on Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome: A Cross-sectional Study

BASAVARAJ DEVENDRAPPA BALIGAR[1], SATEESHKUMAR BAPUGOUDA PATIL[2], ISHWAR SIDDAPPA HASABI[3], ANAND KOPPAD[4]

ABSTRACT

Introduction: Low Triiodothyronine (T3) syndrome is a hormonal imbalance that significantly influences cardiovascular haemodynamics by altering the vascular endothelial function through the Nitric Oxide (NO) pathway. In Acute Coronary Syndrome (ACS), inflammation disrupts plaque, which stimulates thrombosis, coagulation, activation of the sympathetic system, and release of cytokines, mainly Interleukin 6 (IL-6), a pleotropic and pro-inflammatory cytokine that exerts inhibitory effects on thyroid axis function.

Aim: To study the association of low T3 syndrome and severity of Coronary Artery Disease (CAD) in ACS.

Materials and Methods: This cross-sectional study was conducted in the Intensive Critical Care Unit (ICCU) under the Department of Cardiology at Karnataka Institute of Medical Sciences, Hubli, Karnataka, India, from July 2021 to August 2022. A total of 120 consecutive ACS patients who underwent Coronary Angiography (CAG) were included in the study. The severity of CAD was assessed using the Gensini risk scoring, system, and the patients were divided based on their thyroid function status. Low T3 syndrome was defined as <0.846 ng/mL with normal values of Thyroxine (T4) and Thyroid Stimulating Hormone (TSH). Receiver operating characteristic curves were generated to correlate low T3 syndrome and angiographic severity of CAD. Multinomial logistic regression analysis demonstrated that LT3S is an independent risk factor for CAD. The Chi-square test was used for ordered categorical data with the severity of coronary artery lesions.

Results: The severity of coronary artery lesions in the low T3 syndrome group (n=29, 24.16%) and hypothyroidism (n=20, 16.6%) group was significantly greater than that of the euthyroid group (n=71, 59.1%), with all groups showing statistical significance (p-value=0.047). Multinomial logistic regression analysis demonstrated that low T3 syndrome was an independent risk factor for moderate (Odds ratio=2.34, 95% CI: 0.47-11.39, p<0.02) and severe (Odds ratio=8.56, 95% CI: 1.52-47.9, p<0.015) lesions.

Conclusion: The results of this study suggest that patients with low T3 syndrome are associated with more severe and diffuse CAD and low T3 syndrome is an independent risk factor for ACS.

Keywords: Interleukin 6, Nitric oxide, Pro-inflammatory cytokine, Triiodothyronine

INTRODUCTION

Thyroid hormones affect almost every cell and organ in the body. T3 is the biologically active hormone, and T4 acts as a prohormone that needs deiodination to become an active hormone in the bloodstream [1]. T3 plays an essential physiological role in the cardiovascular system, including proangiogenic, vascular resistance, cardiac contractility, cardiac output, and electrophysiological effects [2].

The cellular and molecular mechanisms proposed for the effect of T3 include genomic (nuclear) and non-genomic (extranuclear) actions. The genomic effects are more rapid. T3 enters the nucleus and binds with a specific nuclear receptor (TRα or TRβ). The T3 receptor complex then binds to Thyroid Hormone-Response elements (TREs) in the promoter regions of specific target genes and modifies their expression. Non-genomic effects include the regulation of membrane ion channels and pumps with activation of Protein Kinase C (PKC) and Mitogen-Activated Protein Kinases (MAPKs) [3]. Low T3 levels are associated with the occurrence and severity of CAD [4]. This is because low T3 syndrome is correlated with risk factors such as vascular endothelial dysfunction, abnormal lipid metabolism, hyperglycaemia, and decreased left ventricular ejection fraction. It has been recognised that reduced thyroid hormone activity may produce cardiovascular disorders.

Appropriate levels of T3 stimulate cell growth, neo-angiogenesis, prevent cardiac myocyte death, and reduce interstitial fibrosis. Low T3 directly changes blood vessel endothelial function, blood pressure, lipids, insulin sensitivity, homocysteine, C-reactive protein, and procoagulant state by influencing the production of NO [5,6] and lead to impaired vasodilation and arterial stiffness. Although the mechanism underlying low T3 syndrome is not yet completely understood, some studies suggest that low hepatic D1 (deiodinase type 1), which is required for the conversion of T3 from T4 in the bloodstream, could result from increased serum Interleukin level 6 (IL-6) [7,8].

In ACS, inflammation of the coronary artery endothelium leading to plaque rupture and thrombosis also leads to the release of cytokines, mainly IL-6, which is primarily produced by macrophages and T cells. It has been noted as a key driver of atherogenesis and plaque destabilisation, acting as a pleotropic, pro-inflammatory cytokine and exerting an inhibitory effect on thyroid axis function [9].

With this background, the study was conducted to evaluate the association of low T3 syndrome and the severity of CAD in ACS. The secondary aim was to see whether low T3 syndrome is an independent risk factor for CAD.

MATERIALS AND METHODS

The cross-sectional study was conducted in the ICCU under the Department of Cardiology, Karnataka institute of Medical Sciences, Hubli, Karnataka, India, from July 2021 to August 2022. All the

patients had signed consent forms and Institutional review board approval was sought prior to the initiation of the present study. (IEC No: KIMS: ETHCS COMM: 412:2020-21, Reg No: ECR/486/Inst/KA/2013/RR-16).

Inclusion criteria: A total of 120 consecutive patients with CAD in ACS who were admitted in the ICCU were included. CAD was defined as the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaque in the arteries of the heart. A 50% stenosis was taken as "significant" or "clinically important," and patient enrollment was restricted to those with a stenosis of that caliber or greater in at least one major vessel [10,11]. ACS describes a group of conditions resulting from acute myocardial ischemia (insufficient blood flow to heart muscle) and ranging from unstable angina (increasing, unpredictable chest pain) to myocardial infarction (heart attack) [12].

Exclusion criteria: Subclinical hypothyroidism and hyperthyroidism, clinical hyperthyroidism, known hypothyroidism, known CAD, patients on amiodarone, chronic kidney disease, clinical signs of sepsis.

Study Procedure

Coronary Angiography (CAG) and the severity: CAG was done, and each study was reviewed by two interventional cardiologists who were blinded to the study. CHD was defined in present study as a greater than 50% stenosis by visual assessment in at least one major vessel [11]. Gensini Score (GS) was used to evaluate the severity of coronary artery lesions [13]. The Gensini score divided into mild lesion (GS 0-24), moderate lesion (GS 24-54) and severe lesions (GS >54). The ultravist solution was used as a contrast media.

Thyroid hormone determination: Fasting venous blood samples were performed before the CAG to measure the levels of Triglycerides (TG), Total Cholesterol (TC), Low Density Lipoprotein-Cholesterol (LDL-C), High-Density Lipoprotein-Cholesterol (HDL-C), along with thyroid profile (T3, T4, TSH). The reference intervals of the laboratory are as follows: T3 (0.846-2.02 ng/mL), T4 (66-181 nmol/L), TSH (0.270-4.20 ulU/mL). The patients were divided into three groups based on thyroid hormone profile: euthyroid group (patients with normal values of T3, T4 and TSH), low T3 syndrome group [14]. (Patients with T3 <0.846 ng/mL, normal T4 and TSH), hypothyroid group (patients with TSH >4.20 ulU/mL, T3 <0.846 ng/mL, T4 <66 nmol/L).

STATISTICAL ANALYSIS

Continuous data were expressed as Mean±SD, and the differences were analysed with one-way Analysis of Variance (ANOVA, normal distribution) or Mann-Whitney U test (abnormal distribution or unequal variances, and the differences were tested using the Chi-square test. The Chi-square test was used for ordered categorical data with the severity of coronary artery lesions, and the risk factors of the severity of coronary artery lesions were estimated by multinominal logistic regression analysis. Cumulative event rates were evaluated using Kaplan-Meier estimates and compared using a logrank test.

RESULTS

One hundred twenty patients were divided into three groups based on thyroid hormone profile-euthyroid group (n=71, 59.16%), low T3 syndrome group (n=29, 24.16%), and hypothyroid group (n=20, 16.66%). As compared to euthyroid patients low T3 syndrome and hypothyroid group has significantly higher prevalence of CAD. Age, alcohol, LDL-C levels, Haemoglobin (Hb) and platelets which were statistically significant (all p<0.05) [Table/Fig-1].

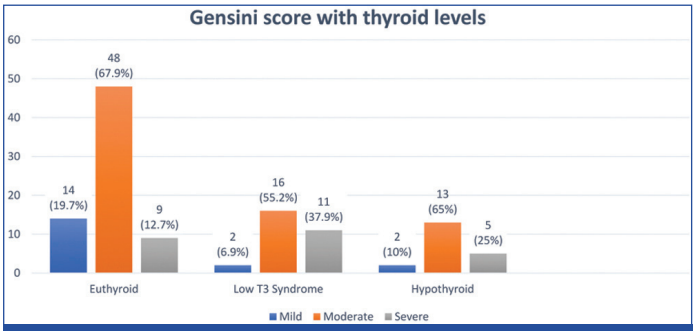
As compared to euthyroid group, patients with low T3 syndrome and hypothyroid patients, severity of lesion were significantly greater. CAG showed that low T3 syndrome among 29, In mild lesion (GS <24) is 2 (6.9%), moderate lesion (GS 24-54)- 16 (55.2%), severe lesion (GS >54)- 11 (37.9%). The severity of coronary artery lesions (Gensini score) in low T3 syndrome group and hypothyroidism group were significantly greater than euthyroid group all (p<0.047) [Table/Fig-2,3]. [Table/Fig-4] represents the multinominal logistic regression analysis about the severity of coronary artery lesions. Odds ratio and 95% Confidence Interval (CI) has been depicted in moderate low T3 syndrome and severe category patients in respect to alcohol, LDL-C and hypothyroid.

Variables	Euthyroid n=71 (59.1%)	Low T3 syndrome n=29 (24.16%)	Hypothyroid n=20 (16.6%)	p-value
Age (years) Mean±SD	55.21 (9.8)	59.1 (10.8)	59.3 (7.3)	0.08
Male	43 (60.6)	20 (69.0)	15 (75.0)	0.42
HTN	41 (57.7)	19 (65.5)	12 (60.0)	0.77
DM	35 (49.3)	15 (51.7)	8 (40.0)	0.69
Smoking	29 (40.8)	14 (48.3)	9 (45.0)	0.78
Alcohol	22 (31.0)	9 (31.0)	11 (55.0)	0.02*
Tobacco	22 (31.0)	14 (48.3)	5 (25.0)	0.16
Family history of CAD	5 (7.0)	2 (6.9)	0 (0)	0.47
DVD	39 (54.9)	19 (65.5)	11 (55.0)	0.62
TC (mg/dL) mean±SD	160.49 (33.1)	155.5 (29.5)	160.5 (33.6)	0.77
TG (mg/dL) mean±SD	180.97 (64.04)	205.76 (70.58)	201.1 (69.4)	0.17
LDL (mg/dL) mean±SD	103.97 (39.1)	115.27 (39.1)	128.0 (43.1)	0.02#
HDL (mg/dL) mean±SD	42.66 (9.27)	39.89 (7.75)	40.4 (7.73)	0.28
TLC (ulU/mL) mean±SD	7606.5 (2271.1)	7544.13 (2007.1)	7675.1 (2066.3)	0.97
Hb (g/dL) mean±SD	11.54 (1.46)	11.44 (1.39)	12.47 (1.86)	0.03#
Platelet (ulU/mL) mean±SD	278380.2 (67423.4)	317206.8 (98322.2)	313450 (99203.2)	0.05#
Creatinine (mg/dL) mean±SD	0.99 (0.23)	1.02 (0.24)	0.915 (0.26)	0.28

[Table/Fig-1]: Clinical characteristics of study population.
*HTN: Hypertesion; DM: Diabetes mellitus; DVD: Degenerative valve disease; *-<0.05 p-value statistically significant, Chi-square test; #-<0.05 p-value statistically significant, ANOVA test

Gensini score	Euthyroid	Low T3 syndrome	Hypothyroid	p-value
Mild	14 (19.7)	2 (6.9)	2 (10)	0.047*
Moderate	48 (67.9)	16 (55.2)	13 (65.0)	
Severe	9 (12.7)	11 (37.9)	5 (25.0)	
Total	71 (100.0)	29 (100.0)	20 (100.0)	

[Table/Fig-2]: The analysis of severity of coronary artery lesions.
*p-value <0.05 statistically significant, Chi-square test



[Table/Fig-3]: Bar graph of severity of coronary artery lesions in low T3 syndrome and hypothyroid group compared with euthyroid group.

Parameters	OR	OR 95% CI	p-value
Moderate			
Alcohol	2.71	0.718-10.158	0.05*
LDL-C	1.12	1.01-1.3	0.04*
Hypothyroid	1.89	0.38-8.21	0.21
Low T3 syndrome	2.34	0.47-11.39	0.02*
Severe			
Alcohol	4.615	1.064-20.14	0.04*
LDL-C	1.34	1.1-1.5	0.001*
Hypothyroid	3.8	0.61-24.1	0.01*
Low T3 syndrome	**8.56**	1.52-47.9	0.015*

[Table/Fig-4]: Multinominal logistic regression-severity of coronary artery lesions with Gensini score.
*p-value <0.05 statistically significant
Coronary artery mild lesion was regarded as reference category
OR: Odds ratio; LDL-C: Low density lipoprotein cholesterol

DISCUSSION

The present study enrolled 120 patients with ACS who underwent CAG. The study looked at thyroid dysfunction as a risk factor, along with traditional risk factors like age, diabetes, hypertension, dyslipidemia, smoking, alcohol, tobacco and family history. It mainly emphasised on existence of association between biologically active T3 levels and presence and severity of CAD in ACS patients and showed that there is an inverse relationship between T3 levels and severity of CAD patients, who underwent CAG.

Many studies reported varied relation between thyroid function and severity of CAD. A study done by Daswani R et al., enrolled 100 euthyroid patients with stable angina, who underwent CAG [15]. It was concluded that in the absence of primary thyroid disease, there is occurrence and severity of CAD is associated with lower levels of Free Triiodothyronine (FT3). Coceani M et al., enrolled 1047 euthyroid patients and found that serum FT3 levels inversely correlated with the presence of CAD and low T3 syndrome conferred an adverse prognosis even after adjusting traditional risk factors [16]. Mani S et al., analysed a total of 300 patients who underwent CAG and showed that free T4 was more strongly associated with CAD and the severity of atherosclerosis [17]. However, the index study did not find an association between Free Thyroxine (FT4) and CAD. In a study done Ertas F et al., enrolled 119 patients and found that free T3 levels inversely correlated to the CAD severity [18]. Moreover, lower FT3 concentrations correlated with the Gensini score and independently predicted the presence and severity of CAD, which is concordance with the present study.

The present study lends support to the Daswani R et al., Coceani M et al., and Ertas F et al., as isolated T3 reduction constitute important and independent risk factor of presence and severity of CAD [15,16,18]. Since low T3 directly changes vascular endothelial function, blood pressure, lipid metabolism, insulin sensitivity, homocysteine, C-reactive protein and procoagulant state by influencing production of NO led to impaired vasodilation and arterial stiffness [5,6]. However, in present study looked at traditional risk factors for CAD, but did not rule out their potential influence on the present study findings.

In the present study, multinominal logistical regression analysis demonstrated that low T3 levels correlated with Gensini risk score for severity of CAD and predicted as independent risk factor in addition to hypothyroid LDL-C and alcohol, which is in concordance with the study done by Daswani R et al., and Ertas F et al., [15,18].

Limitation(s)

The study was single-centered, with a limited number of study subjects. The study being cross-sectional study, lacked a prospective arm.

CONCLUSION(S)

Serum T3 levels were found to be inversely correlated with the severity of Coronary Artery Disease (CAD) in patients with Acute Coronary Syndrome (ACS). Low T3 syndrome and hypothyroidism were also found to correlate with the Gensini score and independently predict the severity of CAD. Recognition of the severity of lesions in ACS patients can be aided by thyroid function tests, specifically T3 levels, which act as a biological risk factor for CAD. This simple and inexpensive laboratory investigation can help with early recognition of severity and referral to tertiary care for early intervention, aiding in the prevention of complications and increasing the survival rate.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Cardiology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India.
2. Postgraduate Student, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India.
3. Professor and Head, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India.
4. Associate Professor, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Sateeshkumar Bapugouda Patil,
Dhavalagi, Tq: Muddebihal Dist: Vijayapur-586116, Karnataka, India.
E-mail: docsatishpatil1743@gmail.com

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