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SICK EUTHYROID SYNDROME IN ACUTE MYOCARDIAL INFARCTION AND ITS CORRELATION WITH LEFT VENTRICULAR FUNCTION

Shilpa Deoke[1] , Ujwala Walvi[2]

1. *Associate Professor, Department of Medicine, NKPSIMS, Nagpur, India*
2. *Junior Resident, Department of Medicine, NKPSIMS, Nagpur, India*

Abstract

Introduction: Sick Euthyroid Syndrome (SES), an alteration in thyroid function due to non-thyroidal diseases is seen in Acute myocardial infarction (AMI), besides other conditions like starvation, sepsis, surgery (post Coronary Artery Bypass Grafting) and Bone marrow transplant. The present study was undertaken to study SES in AMI and its correlation with left ventricular function as assessed by Echocardiography.

Material and Methods: 72 consecutive cases of AMI were included in the study. The thyroid profile was done on day 1 (24 -36 hours after onset of chest pain) and on day 7. Left Ventricular function was assessed by Echocardiography in all patients.

Results: On comparing the mean values on day-1 and day-7, no significant difference in serum T3, T4 or TSH was observed. There was no correlation between the location of AMI and T3 levels ($p<0.05$).100% (n=4) patients with LVEF <30% had suppressed serum T3 whereas none of the patients with LVEF >60% had suppressed T3 ($Chi2 = 33.54$, $p<0.001$). Considering a cut-off of 40% significantly more patients with LVEF < 40% had suppressed T3 ($p<0.001$). 100% (n=4) patients with cardiogenic shock had low T3 levels

Conclusions: There was a statistically significant correlation between T3 and left ventricular function as well as presence of cardiogenic shock. Thus SES in AMI was associated with poor LV dysfunction during short term follow- up.

Key words: Sick Euthyroid Syndrome, Acute Myocardial infarction, LVEF.

Author for correspondence: *Dr. Shilpa Deoke, Associate Professor, Department of Medicine, NKPSIMS, Nagpur, India* *E-mail:dr.shilpa_deoke@rediffmail.com*

Introduction:

Many cardiovascular diseases (acute myocardial infarction, heart failure, Coronary artery bypass, stress cardiomyopathy) and systemic illness like starvation [1], sepsis [2], surgery[3] and bone marrow transplantation[4] cause thyroid dysfunction. Such an alteration in thyroid function due to non-thyroid illness is described as 'Sick Euthyroid Syndrome' (SES). It is characterized by low T3 and/or free T3, increased reverse T3 (rT3) and normal TSH, T4 and free T4 levels [5]. Impaired peripheral de-iodination of tetra-iodothyronine (T4), decreased Thyroid Releasing Hormone \(TRH) metabolism and reduced thyroid receptor expression are the suggested pathophysiological mechanisms [6, 7, 8]. Studies have shown that the degree of thyroid dysfunction is associated with the severity of these

diseases and low levels of biologically active T3 predicts poorer prognosis [9].

Though SES in the setting of acute myocardial infarction (AMI) has traditionally been viewed as an adaptive phenomenon to reduce the work-load of the diseased heart by reducing energy consumption [10]; there is evidence that it has an effect on the prognosis, both short term as well as long term. Its presence predicts more frequent complications, poorer left ventricular function and increased mortality [11- 14]. Hence the present study was carried out to study the rate of occurrence of SES in AMI and its correlation with the left ventricular function.

Materials & Method:

It was a hospital based longitudinal study carried out over a 2 year period from November 2009 to November 2011. The study was initiated after prior permission of the Institutional Ethics Committee. With 19% expected reduction in serum T3, precision of 10%, desired C.I. of 95%, the minimum sample size calculated was 60 [11]. Patients with first episode of acute myocardial infarction irrespective of age, sex and clinical severity admitted in the ICCU were included in the study.

Patients using drugs like Amiodarone, corticosteroid, thyroid disease drugs; patients who have received any iodinated contrast agents within previous 2 weeks or patients with established diseases such as malignancy, chronic obstructive pulmonary disease, chronic renal failure, and cirrhosis of liver, active infection or uncontrolled diabetes mellitus (DM) were excluded.

Detailed clinical history and a thorough physical examination of all subjects were carried out. Besides routine investigations, serial ECGs and 2 D Echocardiography were done in all patients. 2D Echocardiography of the patients was done by Toshiba Nemio XG SSA-580A machine with a 3MHz cardiac probe. The left ventricular ejection fraction (LVEF) as a measure of left ventricular function was assessed echocardiographically by using modified Simpson Biplane Method.

Thyroid function tests were done twice; first sample was withdrawn 24-36 hrs after the onset of chest pain (day- 1) as maximal changes in thyroid status are seen at this time as reported in previous studies and the second sample was withdrawn after 7 days (day-7). Thyroid hormone levels (total T3, T4 and TSH) were measured by using chemilluminescent immunoassay 10 MAX 410 monobind IMNA.

Statistical Analysis: Continuous variables like age, serum T3, T4 and TSH were presented as mean ± S.D. Relation coefficient was computed for the correlation of serum T3 level with LVEF. $p<0.05$ was considered as statistically significant. Statistical software STATA version 10.0 was used for data analysis.

The P values represent probability values for testing the simultaneous equality of the means and P values below 0.05 were considered to be statistically significant. The values of all the parameters were presented as geometric means.

Statistical software namely SPPS10.0 and Systat 8.0 were used for the analysis of the data. Microsoft word and Excel have been used to generate graphs, tables, etc.

Results:

The study group comprised of 75 consecutive patients of acute myocardial infarction admitted at the tertiary care centre over a period of 2 years, out of which 2 were excluded because they expired before 7 days (before the day-7 sample for thyroid profile could be collected); one patient developed hospital acquired pneumonia during her hospital stay. Thus the final group included 72 patients of acute myocardial infarction who were further evaluated.

There were 49 (68%) males and 23(32%) females. Male: female ratio was 2.1:1. The mean age was 56.51± 5.87 years in males and 61.13±9.80 years in females.

On comparing mean T3 values on day-1 and day-7, no significant difference in recovery of serum T3 value was observed (p=0.2586) (Table 1). Similarly, there was no statistically significant difference between mean T4 values on day 1 and day 7 (p=0.767) and TSH values on day 1 and day 7(p=0.363) (Table 1).

Maximum number of patients had inferior (40.2%) followed by extensive anterior wall

myocardial infarction (33.3%). Though more patients with extensive anterior MI had suppressed T3 (n=7, 29.2%), followed by Inferior MI (n=4, 15%), no statistically significant correlation between the reductions in serum T3 level with the type of myocardial infarction was observed (p=0.110 for inferior and p=0.403 for anterior wall MI) (table 2).

Left ventricular ejection fraction (LVEF) as a measure of cardiac function was correlated with serum T3 level observed on day 1. It was observed that 100% (n=4) patients with LVEF <30% had suppressed serum T3 whereas none of the patients with LVEF >60% had suppressed T3. Decreased LVEF was associated with suppressed T3 (p<0.001) (Table 3, Figure 1).

A cut-off of 40% for LVEF was correlated with serum T3 level observed on day 1. Patients were divided into two groups depending upon the ejection fraction (Group 1 LVEF<40% and Group 2 LVEF≥ 40%). Significantly more patients with LVEF <40% had suppressed serum T3 level (Table 4).

Four patients presented with cardiogenic shock. All had suppressed serum T3 values. Thus serum T3 strongly correlated with cardiogenic shock (r=-0.359, p<0.001) (Table 5).

Discussion:

In the present study, the male: female ratio was 2.1:1. Thus males were more frequently affected. Similarly Leif Friberg et al 11 in their study of patients with acute myocardial infarction noted male: female ratio of 2.4:1. In another study by Friberg et al [15], the male: female ratio was 1.9:1. Similarly, studies by Lymvaios et al [16] and Pimentel et al [17] observed male preponderance (male: female ratios of 1.6:1 and 1.5:1 respectively).

Gender is an important non-modifiable risk factor for AMI, males being affected earlier and more frequently. In the present and earlier studies males are affected almost twice as frequently as females. Part of this protection is due to higher HDL levels in pre-menopausal women; after menopause the levels fall down and protective effect is lost.

The mean age of presentation of acute myocardial infarction in the present study was 57.98±11.71 years. The mean age in male and female patients was 56.51±12.32 years and 61.13±9.80 years respectively. The mean age of presentation is significantly lower than that observed in western studies like those carried by Friberg et al [11] (mean age for males and females 66± 13 years and 74±9 years respectively), Friberg et al [15] (mean age for males and females - 66±2 and 77±2 respectively), and Lymvaios et al [16] (mean age of presentation was 62.3±10.2 years).

Sharma et al [18] observed that heart diseases were rising in Asian Indians 5–10 years earlier than in other populations around the world. The mean age for first presentation of acute myocardial infarction in Indians was 53 years.

The present study did not reveal significant changes in the T3, T4 and TSH levels on the first and seventh days (Table 1). Friberg et al[11] in their study noted that the thyroid hormone system was rapidly down-regulated with maximal changes occurring 24 to 36 hours after onset of symptoms [mean level of the total T3 decreased by 19% (p=.02), the inactive metabolite reverse T3 (rT3) levels increased by 22% (p =.01), and TSH levels declined by 51% (P< .001)].

Similarly Rajappa [19] studied thyroid profile serially upto 7 days after onset of symptoms in acute myocardial infarction and observed gradual increase in T3 with normalisation on 7th day. Pimental et al[17] prospectively studied mean T3, T4, TSH on days 1, 4 and 7 and observed that greatest hormonal changes occurred on day 4. Mean reverse T3 was highest on day 4 whereas serum TSH, T4, and free T4 remained normal. Lymvaios et al [16] that T3 level were progressively normalised after 6 months in subjects with change in LVEF <50% whereas they remained unchanged from baseline value in subjects with change in LVEF >50%.

The pattern of recovery in SES depends upon the extent of myocardial dysfunction. Changes in reverse T3 are more prominently seen. Further, serial estimation of thyroid hormone is more informative. In the present study, neither reverse T3 nor daily thyroid hormone estimation was done.

Hence statistically significant difference between day-1 and day-7 values was probably not observed.

There was no significant correlation of T3 levels with the type of AMI in the present study. We have not come across any study correlating SES with the type of AMI, though there are studies which show correlation of SES with the extent and 'severity' of AMI as assessed by CK-MB [11, 19].

The probable reason for more subjects with suppressed T3 in extensive anterior wall MI is that extensive anterior wall MI indicates more severe and extensive myocardial damage (due to a possible proximal left anterior descending artery lesion) and consequently results in profound down-regulation of the thyroid hormone system. However, the smaller sample size of the present study probably did not yield statistically significant correlation.

In the present study, with decreased LVEF significantly more patients had reduction of serum T3 ($p<0.001$). Considering a cut- off of 40%, serum T3 was significantly lower in patients with LVEF <40% as compared to patients with LVEF >40% ($p<0.001$). In a similar study done by Lymvaios et al [16] total T3 levels in plasma at 48h significantly correlated with LVEF at 48h ($r=0.50$, $p=0.0004$). On further follow-up, persistently low T3 levels at 6 months was associated with poor and non-significant recovery of LVEF thus correlating with late functional recovery.

Rajappa et al [19] observed significantly lower T3 in subjects with LVEF < 50% than in subjects with LVEF > 50% ($p <0.001$). Friberg et al [15] concluded that patients with Atrio ventricular plane displacement less than 8 mm, corresponding to a left ventricular ejection fraction of approximately 35%, had a significantly ($p=0.03$) lower mean concentration of T3 as compared to other patients. Iervasi et al [12] observed that patients with low fT3 had slightly, but significantly, lower left ventricular ejection fraction as compared to the with normal fT3 ($p=0.025$).

Pantose et al [20] found significant correlation between total T3 and EF% ($r=0.56$, $p=0.0004$). Adawiyah et al (2010)[21] noted significant difference in killips classification on day-1 between SES and non SES group ($p=0.030$). In their study, more patients admitted with killips class III and IV (cardiogenic shock) developed SES. Thyroid hormones are important for the systolic as well as diastolic function of the heart. When the thyroid hormone system is down-regulated in AMI, intracellular calcium handling is affected in a way that may contribute to myocardial stunning and reperfusion injury due to calcium overload. Furthermore, there is increased systemic vascular resistance leading to increased cardiac workload due to this down-regulation. If the heart is unable to cope with this, cardiac output and consequently LVEF is reduced.

The proposed sequence of events occurring in the thyroid hormone metabolism during myocardial infarction is as follows. (1) Inhibition of the 5‟-deiodination of T4, resulting in increased inactive metabolite, plasma rT3 and decreased plasma T3 value. (2) Increased secretion of TSH resulting in increased secretion of T4 and T3 which is then switched off by the negative feedback of thyroid hormone on the pituitary[4].

Other possible mechanisms are reduced thyroxin secretion (with reduced T3 and T4); Thyroxin binding globulin, albumin and the affinity of both for the thyroid hormone may be reduced, impairing 5-monoiodeiodinase action, T4 uptake as well as post receptor action.

All the above mechanisms may be directly affected by the catecholamine levels14, 22, 23. Unchanged or minimally changed serum TSH is likely to be explained by (i) failure of hypothalamo-pituitary axis response to serum T3 concentration and /or (ii) suppressed TSH secretion due to normal or slightly elevated serum T4 [3, 4].

Conclusion:

There was no significant difference between the mean levels of T3, T4 and TSH on day 1 and day 7. There was a statistically significant correlation between T3 and left ventricular dysfunction, reduced T3 was associated with poor LVEF. Patients with cardiogenic shock had significantly reduced T3 levels. Thus it can be concluded that SES in AMI is associated with poor LV function during short term follow- up.

Table 1: Distribution of subjects according to serum T3, T4 and TSH levels

Mean Thyroid hormone level	Day 1 Mean ± S.D.	Day 7 Mean ± S.D.	p value
Serum T3 (ng/ml)	0.86±0.34	0.92±0.31	0.2586
Serum T4 level (mcg/dl)	7.01±2.07	6.96±2.05	0.8815
Serum TSH level (mcIU/ml)	2.12±1.55	2.08±1.46	0.8741

Table 2: Correlation of serum T3 (day-1) with types of myocardial infarction

Location Of MI	Serum T3 level (ng/ml)			'p' value
	<0.52 (n=12)	0.52-1.9 (n=59)	>1.9 (n=1)	<0.52 (n=12)
Extensive anterior MI (n=24)	7(29.2%)	17(70.8%)	0(0%)	p=0.110
Anteroseptal MI (n=6)	0(0%)	6(100%)	0(0%)	p=0.486
Anterolateral MI (n=8)	0(0%)	8(100%)	0(0%)	p=0.371
Inferior MI (n=26)	4(15.4%)	21(80.8%)	1(3.8%)	p=0.403
Inferolateral MI (n=3)	0(0%)	3(100%)	0(0%)	p=0.708
Posterior MI (n=3)	3(100%)	0(0%)	0(0%)	p=0.708
Lateral MI (n=1)	0(0%)	1(100%)	0(0%)	p=0.894

Table 3: Correlation of Day 1 serum T3 with LV Ejection Fraction

LVEF	Day-1 Serum T3 level (ng/ml)			P value
	<0.52	0.52-1.9	>1.9	
<30 (n=4)	4(100%)	0(0%)	0(0%)	Chi^2=33.5419 P<0.001, HS
30-40 (n=21)	6(28.6%)	15(71.4%)	0(0%)	
40.1-50 (n=35)	2(5.7%)	33(94.3%)	0(0%)	
50.1-60 (n=10)	0(0%)	9(90%)	1(10%)	
>60 (n=2)	0(0%)	2(100%)	0(0%)	

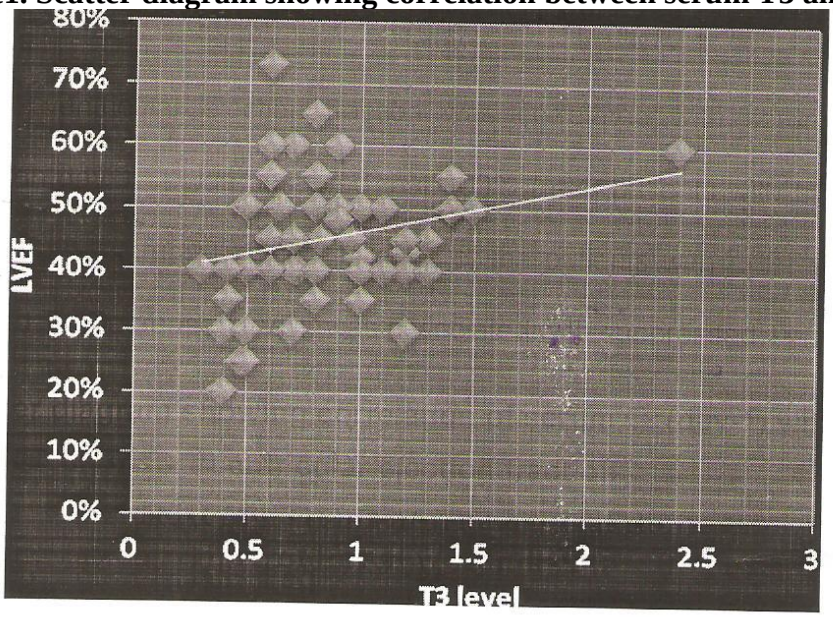
Table 4: Correlation of Day 1 Serum T3 with the two groups according to LVEF

LVEF (%)	Day-1 Serum T3 level (ng/ml)			P value
	<0.52	0.52-1.9	>1.9	
< 40 (n= 25)	10 (40%)	15 (60%)	0 (%)	Chi^2= 15.932, p<0.001
≥ 40 (n= 47)	2 (4.2%)	44 (93.7%)	1 (2.1%)	

Table 5: Correlation of serum T3 (day-1) with cardiogenic shock

Serum T3 day- 1 (ng/ml)	Cardiogenic shock		p value
	Absent (n=68)	Present (n=4)	
<0.52	8(11.7%)	4(100%)	<0.52
0.52-1.9	59(86.8%)	0(0%)	0.52-1.9
>1.9	1(1.5%)	0(0%)	>1.9
Total(n=72)	68(100%)	4(100%)	Total(n=72)

Figure1. Scatter diagram showing correlation between serum T3 and LVEF



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