Sick Euthyroid Syndrome in Acute Myocardial Infarction - Is it really benign?

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ABSTRACT

Introduction : Sick Euthyroid syndrome, characterized by altered thyroid function, is seen in many non- thyroidal illnesses including acute myocardial infarction. Though traditionally considered 'benign', it has been shown to be associated with increased morbidity and mortality. Hence the study was carried out to profile the thyroid function in AMI and its association with short term outcome of AMI.

Methods : 72 Consecutive patients of AMI admitted at a tertiary care centre were included. Besides detail clinical examination, serial ECGs, 2 D Echo (for left ventricular function) and CPK-MB on admission was done. Total T3, T4 and TSH were done 24-36 hours after onset of chest pain (day 1) and again on day 7.

Results : The mean age was 56.51 ± 5.87 years in males and 61.13 ± 9.80 years in females. The male : female ratio was 2.1:1. There was no significant difference in the mean values of T3, T4 and TSH on days 1 and 7. Statistically significant association ($p<0.05$) was observed between the day 1 serum T3 and CK-MB, Killip class, cardiogenic shock, acute complications and reduced LVEF. All non-survivors had reduced T3 levels.

Conclusion : Altered thyroid function in AMI is associated with poor prognosis and may predict poorer LV function and increased mortality.

Key-words : Sick euthyroid syndrome, AMI

Introduction :

Though the thyroid hormones are integral to the functioning of almost all the systems in the body, the cardiovascular system seems to bear the maximum brunt of thyroid dysfunction. The biologically active hormone tri-iodothyronine (T3) plays a major role in modulating the heart rate and cardiac contractility as well as peripheral arterial resistance.[1,2] Actions of thyroid hormone, T3, are carried out by binding with specific nuclear receptors that regulate responsive genes encoding for structural and functional cardiac proteins; direct, extranuclear, non-transcriptional effects have also been described.[3-5] Thus thyroid dysfunction may directly or indirectly affect the cardiovascular system.

Paradoxically, cardiovascular diseases (acute myocardial infarction, heart failure, CABG, stress cardiomyopathy) as well as other non thyroid illnesses like starvation, sepsis, surgery and bone marrow transplantation cause thyroid dysfunction.[6-10] Such a state of altered thyroid function due to non thyroid illness is described as "sick euthyroid syndrome" (SES) and it is usually characterized by low total T3 and/ or free T3, increased reverse T3, and normal TSH, T4 and free T4 level.

Though SES in acute myocardial infarction (AMI) may be regarded as a protective phenomenon, as the consequent reduction in BMR may decrease the work-load on the "sick" heart, studies have shown its association with poorer outcomes of AMI. SES in AMI portends poorer prognosis, being associated with more complications and increased short term and long term morbidity and mortality.[11-14] Thus this study was carried out to study the thyroid hormone profile in AMI and its association with the complications of AMI (arrhythmias, cardiogenic shock, left ventricular dysfunction) and short term mortality during hospital stay.

Methods :

This hospital based longitudinal study was carried

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out in the department of medicine at a tertiary care hospital. Prior approval of the Institutional Ethics Committee was taken. With 19% expected reduction in serum T3, precision of 10%, desired C.I. of 95%, the minimum sample size calculated was 60. Consecutive patients with acute myocardial infarction were included in the study. Patients were excluded if they were using drugs like Amiodarone, corticosteroids, thyroid disease drugs, had received any iodinated contrast agents within previous 2 weeks or had pre-existing established diseases such as hypo/hyperthyroidism, malignancy, chronic obstructive pulmonary disease, chronic renal failure, cirrhosis of liver, active infection or uncontrolled diabetes mellitus (DM). Patients not willing to participate were also excluded.

Patients diagnosed with acute myocardial infarction on the basis of history, clinical examination, ECG changes and biochemical markers and admitted in ICCU were included in the study. All the patients were subjected to detail clinical examination. The clinical course of patients was noted till the time of discharge/death. Complications like arrhythmias, heart failure, cardiogenic shock, ventricular aneurysm were noted.

Patients were investigated by - serial ECGs, CPK-MB (on admission), fasting lipid profile and 2D-echocardiography. 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. Blood sample for thyroid profile (total T3, T4, TSH) was collected 24 - 36 hrs. after onset of chest pain (day-1) and again after 7 days (day-7). Thyroid hormone levels (total T3, T4 and TSH) were measured by using chemilluminescent immunoassay 10 MAX 410 monobind IMNA.

The data was collected and analyzed at the end of the study using Statistical software STATA version 10.0.

Results :

75 consecutive patients of acute myocardial infarction were studied. However 2 patients were excluded as their day 7 thyroid profile could not be done and another patient developed hospital acquired pneumonia during her hospital stay. Thus the final study group comprised of 72 patients.

Table 1 : **Age & gender distribution of patients**

Age (years)	Male (n=49)	Female (n=23)	Total (n=72)
20-30	1 (2.1%)	0 (0%)	1 (1.3%)
31-40	5 (6.9%)	1 (4.3%)	6 (8.3%)
41-50	11 (15.2%)	2 (8.6%)	13 (18.1%)
51-60	15 (20.8%)	11 (47.8%)	26 (36.2%)
61-70	12 (16.6%)	5 (21.8%)	17 (23.7%)
>71	5 (6.9%)	4 (17.3%)	9 (12.5%)
Total	49 (100%)	23 (100%)	72 (100%)
Mean Age	56.51±12.32 (30-85)	61.13±9.80 (40-80)	57.98±11.71 (30-85)

The mean age was 56.51 ± 5.87 years in males and 61.13 ± 9.80 years in females. The male : female ratio was 2.1:1 ***(Table 1).*** In an attempt to estimate the recovery of thyroid function the mean T3, T4, TSH levels on days 1 and 7 were compared. However there was no statistically significant ($p>0.05$) difference ***(Table 2).*** The mean T3, T4 and TSH levels on days 1 and 7 were within normal range.

Table 2 : **Serial T3, T4 and TSH levels on day 1 and day 7**

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

Further correlation of various parameters (clinical and biochemical) was done with the day 1 serum T3 levels. For analysis, a random cut-off of 150 IU/L was considered for CPK-MB and 40% was taken for LVEF, as it indicates poor systolic LV function. Patients with Killip class I and II were compared as a group with classes III and IV. Statistically significant association was observed for CK-MB levels (P=0.001), Killip class (0.0019), LVEF<40%

Table 3 : **Distribution of study subjects according to various parameters and Day1 Serum T3 levels**

Parameters		Day 1 Serum T3 (ng/ml)			P value
		<0.52	0.52-1.9	>1.9	
CPK-MB (IU/L)	< 150 (n=61)	6 (9.9%)	54 (88.5%)	1 (1.6%)	Chi2=13.4674 P=0.001
	>150 (n=11)	6(54.5%)	5(45.5%)	0(0%)	
Killip class	I+II (n=63)	3(4.8%)	59(98.4%)	1(1.6%)	p=0.0019
	III+IV (n=9)	9 (100%)	0(0%)	0(0%)	
Cardiogenic shock	Present (n=4)	4(100%)	0(0%)	0(0%)	Chi 2=21.1765 p=0.000
	Absent (n=68)	8(11.7%)	59(86.8%)	1(1.5%)	
LVEF	=40 (n=25)	10(40%)	15(60%)	0(0%)	Chi2=15.2932 P=0.000
	>40 (n=57)	2(4.2%)	44(93.7%)	1(2.1%)	
Complications	Present(n=20)	12(60%)	8(40%)	0(0%)	Chi2=37.62 P=0.000
	Absent (n=52)	0(0%)	51(98.1%)	1(1.9%)	
Mortality	Non- survivors (n=4)	4(100%)	0(0%)	0(0%)	Chi 2=21.1765 p=0.000
	Survivors (n=68)	8(11.7%)	59(86.8%)	1(1.5%)	

(p=0.000), cardiogenic shock (p=0.000), complications (p=0.000) and mortality (p=0.000) ***(Table 3).***

Table 4 : **Multivariate analysis showing association of serum T3 (day-1) with CPK-MB, LVEF and Killip class**

Parameter	r/l value	p value
CPK-MB	-0.3131	0.0074
LVEF	0.2769	0.0185
Killip class	-0.3591	0.19

On multi-variate analysis, CPK-MB (p=0.0074) and Killip class (p=0.0019) showed significant negative correlation while LVEF (p=0.0185) showed significant positive correlation with day 1 serum T3 values ***(Table 4).***

Discussion :

The present study was carried out to study the thyroid function in AMI. The mean T3, T4 and TSH levels on day 1 were normal and did not show any significant difference on serial estimation. As reported earlier[11,12,15,16] rapid down-regulation of thyroid function occurs in AMI, usually in the form of reduced T3 / free T3 and normal T4 and TSH. However this dysfunction may be transient and recovery predicts better prognosis. Further, the recovery depends on the extent of myocardial injury and dysfunction. Free T3 and reverse T3 are better biochemical markers of SES. These were not done in the present study and this could be the probable reason why no changes from the baseline levels were observed.

CPK-MB, as a marker of extent of cardiac injury was correlated with T3 (day 1) in the present study. A random cut-off of 150 IU/L was taken and showed significant positive correlation with the T3 level. Similar observations have been made by Rajappa et al[11] and Friberg et al[13]. However Lymvaios et al[12] did not observe any such correlation. One of the proposed pathogenetic mechanisms of SES is production of inflammatory cytokines. Inflammatory cytokines like Interleukin-6 (IL-6), produced by the cardiac myocytes in the border zone of re-perfused viable myocardium, monocytes and macrophages, appear to inhibit the hepatic mono-iodinase activity thereby affecting the peripheral conversion of T4 to T3. The increase in cytokines is directly related to the extent of myocardial damage and necrosis which in turn is also reflected by the CK-MB levels.

Since its original description[17], Killip classification has served as an useful surrogate marker of left ventricular (LV) function in AMI and has been shown to correlate with Echocardiographically

determined LVEF[18].Used for categorizing subjects according to advancing heart failure, increasing Killip class suggests worsening systolic function; class IV indicates cardiogenic shock. Present study revealed significant inverse correlation of worsening Killip class and cardiogenic shock with reduced T3 in the study population. Adawiyah et al[14] and Kang et al[19] made similar observations.

The present study reveals significant positive association of LVEF with day 1 serum T3. Low LVEF in turn is an adverse prognostic factor in AMI. Similar findings have been noted by Rajappa et al[11] Lymvaios et al[12], Friberg et al[13], Iervasi et al[20] and Pantose et al[21]. Since thyroid hormones regulate the quantity of calcium in the sarcoplasmic reticulum available for systolic contraction, a reduction in thyroid hormones probably affects the systolic function. The increased peripheral vascular resistance may further add to the increased LV workload resulting in LV dysfunction.

In the present study, low day 1 serum T3 correlated positively with the morbidity (acute complications) as well as mortalityin AMI. Friberg et al[13], Pimentel et al[16], Lazzeri et al[22], Molinaro et al[23] and Ozcan KS et al[24] have similarly noted higher short term as well as long term major adverse cardiac events (MACE) and mortality in AMI patients with SES.

Thus SES in AMI may not be a 'benign' adaptive response as it is associated with poor outcome. However the treatment of this entity in AMI remains debatable and further large scale studies to study thyroid replacement as a therapeutic modality need to be carried out before recommending it.

Conclusion :

This study was done to study the thyroid function in AMI and its association with short term morbidity and mortality during hospital stay. Though the mean thyroid hormone levels were within normal range, significant association was observed between day 1 serum T3 and LV systolic function. Patients with cardiogenic shock and acute complications like arrhythmias, heart failure were more likely to have reduced day 1 serum T3. There was also significant positive association with the extent of myocardial injury as assessed by CPK-MB and mortality. Thus SES in AMI may be regarded as a predictor of poor prognosis.

Limitations :

This was a hospital based study and the smaller sample size is undoubtedly a major limitation. Estimation of free T3 and free T4 as well as reverse T3 has not been done. Finally, the patients who were included in this study were urgently admitted to the hospital so that thyroid hormone disorders were excluded on the basis of the medical history and treatment and thus, silent thyroid dysfunction cannot be excluded.

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