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THYROID FUNCTION TEST IN PATIENTS OF ACUTE CORONARY SYNDROME

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Conflicts of Interest: Nil

ABSTRACT:

Objectives: The purpose of this study was to evaluate regulation of most important metabolic hormones free T3, free T4 and TSH in patients with acute coronary syndrome (ACS) having unstable angina and/or non-ST-segment elevation acute myocardial infarction (UA/NSTEMI); ST-segment elevation acute myocardial infarction (STEMI).

Methods: We conducted a analysis of 100 patient of acute coronary syndrome admitted in Intensive Cardiac Care Unit between 40-70 yr of age in tertiary level hospital with age ,sex matched control group. Blood samples were collected on 6hr, 24-36 hr, 72hr and 7 day following admission. Clinical evaluation and electrocardiograms were performed during hospitalization.

Results: serum FT3 fell in the both subgroups (STEMI and NSTEMI/UA) as comparable to the levels in control during 24-36 hr and then Serum FT3 levels increased gradually with in subsequent days. The FT3 level returns to the normal in 78% of patients by the 7th day but not to the initial values. The serum concentration of FT4 and TSH remain in normal range without significant change in both subgroups ($p > 0.05$ NS).

Conclusion: **T**hyroid hormone system is rapidly down regulated mainly FT3 in patient of acute coronary syndrome, The degree of free T3 decrease is proportional to the severity of cardiac damage and may have a possible prognostic value. Thus, freeT3 serum levels may contribute to the elaboration of an ACS severity index.

Keyword: Acute Coronary Syndrome., T3, T4, TSH, STEMI ST segment elevation myocardial infarction. NSTEMI Non ST Segment Elevation Myocardial Infarction.

Introduction

Acute coronary syndrome may induce profound change in number of neuro-endocrine systems. The changes within the hypothalamic-pituitary-thyroid (HPT) axis also occur in illness and typically associated low levels of total tri-iodothyronine (T3), and this gives rise to term as **"low T3 syndrome" or "Euthyroid sick syndrome"** was widely used in past. **"Non-thyroidal illness syndrome" (NTIS)** is now more commonly use to describe the typical changes in thyroid related hormone concentrations which can arise in the serum following any acute or chronic illness, that is not caused by an intrinsic abnormality in thyroid function. [1] In recent decades it has become increasingly apparent that acute and chronic cardiovascular diseases may alter thyroid hormone metabolism and contributes to cardiovascular impairment. This syndrome has been found in acute myocardial infarction (AMI) and as a rapidly emerging phenomenon during open heart surgery. The more profound change in thyroid hormone pattern, the poorer is the prognosis. [2] The aim of this study was to investigate what kind of potential changes occur in thyroid hormone homeostasis in patient presenting to intensive cardiac care unit with acute coronary syndrome and also to compare the changes in thyroid hormone function between two subgroups based on therapeutic implications and distinct prognosis, that is Non-ST-segment elevation acute myocardial infarction/unstable

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angina (UA/NSTEMI) and ST-segment elevation acute myocardial infarction (STEMI).

Material and method:

It is case control study conducted in department of biochemistry over Hundred patients with first episode of acute coronary syndrome, who were admitted in the intensive cardiac care unit 1to 6 hours after onset of pain between the age group of 45 to 75 years were included in study. Exclusion criteria included patients with Past H/O of acute coronary syndrome, TFT abnormalities or thyroid disorder, medication that could alter TFT (thyroxin , antithyroid drugs amiodarone & phenytoin excluding β-blokers, heparin & dopamine),any acute and chronic illness other than AMI ,co-morbid conditions (malignancy, hepatic or renal failure) All details about the study were explained to the subject and informed consent was taken. Patients enrolled in the study underwent clinical evaluation, consisting of medical history, physical examination, and electrocardiogram. After informed consent was obtained, blood sample were collected in plain bulb at the time of admission within 6hr and at 24-36 hr, 72hr and 7 days after onset of symptoms for the serial estimation of Free tri-iodothyronine (FT3), Free thyroxin (FT4), Thyroid stimulating hormone (TSH). .Thyroid hormones TSH, free T3 and free T4 were measured by) chemiluminescent method kit provided by MONOBIND, INC. Lake forest, (USA).. Measured hormones and their respective reference values were: TSH (0.39 to 6.16 mU/mL), free T3 (1.4 to 4.2 pg/mL), free T4 (0.8 to 2.0 µg/dL). Subsequently, plasma thyroid hormone levels were compared in the UA/NSTEMI and STEMI groups on days 6hr and at 24-36 hr, 72hr and 7 days. All result was expressed as mean ± SD and Statistical analysis was done by persons correlation and "t" test. A two-tailed p-value < 0,05 was considered statistically significant (significance level = 5%). A database was created using Epi info. This study was approved by the institutional Research Ethics Committee of the government medical college Aurangabad

Result:

The study included a total number of hundred (100) apparently healthy normal individuals as controls. They were compared with hundred (100) patients with acute coronary syndrome admitted in the intensive cardiac care unit Group I includes 62 patient with ST segment elevation MI (STEMI) and group II includes 38 patients with Non ST segment elevation MI or Unstable angina (NSTEMI/UA). The characteristics of the control and cases are shown in table 1 and characteristics between subgroups are shown in table 2.

Table 1: Age and sex distribution

Variable	**Control N=100**	**Case N=100**
Male	69	70
Female	31	30
Age	57.62 ± 7.21	56.99 ± 7.33

Table 2: Subgroup STEMI and NSTEMI

Cases	Male n=70	Female n=30	Total n=100
STEMI	42	20	62
NSTEMI/UA	28	10	38

Table 3: FT3, FT4, TSH of Cases and Control Subjects

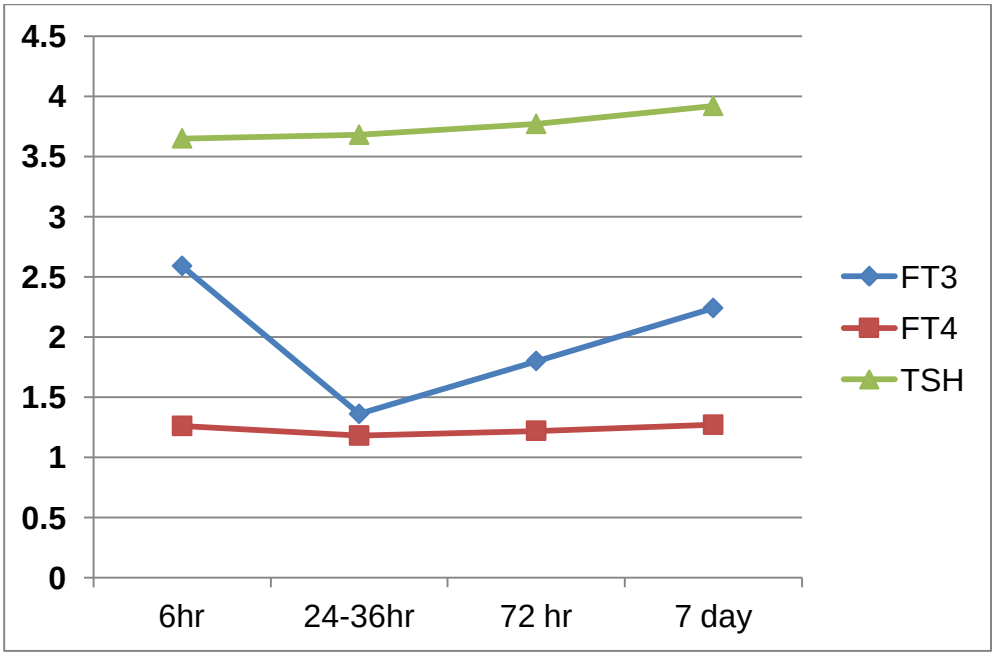
Parameter	Cases of ACS (n=100)				Control (n=100)	P value
	< 6hr (a)	24 –36 hr (b)	72 hr (c)	7day (d)	(e)	
FT3 (pg/ml)	2.59 ± 0.79	1.36 ± 0.68***	1.80 ± 0.67**	2.24 ± 0.76*	2.51 ± 0.70**	a vs b***, a vs c ***, a vs d**
FT4 (ng/ml)	1.26 ± 0.32	1.18 ± 0.30	1.22 ± 0.34	1.27 ± 0.32	1.21 ± 0.26	NS
TSH (µlU/ml)	3.65 ± 1.70	3.68 ± 1.69	3.77 ± 1.76	3.94 ± 1.79	3.24 ± 1.53	NS

FT3 P value of control (e) vs a **p >0.05** (NS), **NS**= not significant

***control (e) vs b and c **p < 0.000001**(very significant), *control (e) vs d **p < 0.05** (significant)

FT4 and TSH p value of control (e) vs a b c d is (NS) i e > **0.05**

FT3 within cases ***$p < 0.00001$, **$p < 0.001$



Graph 1: FT3, FT4, TSH values of cases at different time interval of ACS

Table 4:FT3, FT4, TSH in Subgroup STEMI and NSTEMI

Diagnosis	FT3(pg/ml)	FT4(ng/ml)	TSH(µlU/ml)
<6hr			
STEMI	2.52 ± 0.79	1.23±0.32	3.94±1.82
NSTEMI/UA	2.69 ± 0.77	1.30±0.30	3.19±1.38
P value	NS	NS	0.03
24 – 36 hr			
STEMI	1.29 ± 0.69	1.16±0.30	3.95±1.81
NSTEMI/UA	1.47±0.64	1.23±0.32	3.23±1.40
P value	NS	NS	0.03
72 hr			
STEMI	1.74±0.68	1.20±0.35	4.07±1.88
NSTEM/UA	1.89±0.63	1.27±0.32	3.28±1.43
P value	NS	NS	0.02
7 day			
STEMI	2.18±0.81	1.23±0.31	4.25±1.90
NSTEMI/UA	2.33±0.67	1.33±0.32	3.38±1.43
P value	NS	NS	0.01

Thyroid hormone homeostasis in patient of ACS

At the time of < 6hr after onset of pain there is no significant difference (p value >0.05) in the FT3 value of control and cases but at the time of peak of serum enzymes (24 – 36 hr after onset of pain) serum FT3 lower in both the subgroups (STEMI and NSTEMI/UA) as compared to the levels in controls. Serum FT3 levels increased gradually within subsequent hours and days without significant difference between the values within the two groups at any point of time. The FT3 level returns to the normal on the 7th day but not to the initial values (< 6hr values).There is no significant difference in the serum concentration of TSH and FT4 found between controls and cases (p > 0.05). FT4 serum levels remains normal and did not change significantly in both subgroups (p > 0.05 NS) While there is difference in TSH of STEMI and NSTEMI/UA. STEMI group having somewhat higher values of TSH than NSTEMI group but the values of TSH is within normal reference range.

Discussion:

Acute coronary syndromes are serious condition that may affect thyroid gland homeostasis, with the implication in terms of morbidity and mortality [3].In our study; we sought to evaluate thyroid hormone serum levels in patient with coronary heart disease and whether they characterized the "euthyroid sick syndrome ", consisting of decrease free T3 , normal TSH and free T4 levels. In most of the studies done on thyroid function in ACS, total T3 and total T4 are measured. In our study we tried to find out effect of ACS on homeostasis of free T3 and free T4 levels because we know that free (unbound) hormone is the active hormone which is available to its action by binding to the thyroid receptors present on cardiac myocytes. **Pavlou et al [3] and Friberg et al [4]** in their study evaluated thyroid function in patients of acute myocardial infarction. they reported that there is a rapid down regulation in the T3 levels in these patients. **Medha Rajappa and S.K.Sen** in their study on thyroid hormone status after acute myocardial in south Indians they get more decrease in the serum T3 levels at 24hr after onset of chest pain, serum T3 increased gradually within subsequent hours. The T3 levels returns to the normal on the 7th day. Serum concentration of total T4 and TSH remained within the normal range and did not change significantly in both groups. Also they found negative correlation in T3 levels with CK-MB levels.[1] In our study, on analysis of hormonal behaviour in patients admitted for coronary heart disease shows decrease mean serum free T3 levels as compared to the control group (p value < 0.00001), while the other hormones free T4 and TSH remained unchanged (Table IV). J Adawiyah **et al [2] (2010)** found the prevalence of NTIS **53%** out of 85 patients. **Franklin J.A, Gammage M.D, Ramsden D.B, [5] et al** in their study involving nine patient with acute myocardial infarction, compared with 27 healthy patients of control group, mean T3 , free T3 and T4 plasma levels at admission were lower, while those of free T4, TSH and reverse T3 were higher. At day 3, a sharp decline in mean plasma T4, free T3 and T3 found with statistical significance ($p < 0.05$), mean free T4 and TSH plasma concentration remain unchanged.

Our findings are consistent with the above study that is there is decline in free FT3 levels in patient at 24-36 hr and 72 hr after the onset of chest pain in ACS patients with statistical significance ($p < 0.05$), mean free TSH levels remain unchanged. Survivors in the AMI group had higher TT3, TT4 and lower FT3 and FT4 levels than controls. In AMI group, the non survivors had lower TT3 and FT3 levels than the survivors. These findings of above study supports the finding of our study that there is decrease in the FT3 levels in patient of AMI and this decrease in the levels of FT3 is proportional to the severity of AMI. This relation of FT3 in patient of AMI may be appearing to be independent prognostic factor in patients with AMI. [6]

The probable mechanisms for the transient decrease in serum FT3 levels are multifactorial and can be attributed to:

1. Decrease hepatic conversion of T4 to T3.espesially in advanced heart failure, as a result of decreased in activity of 5' monodeiodinase. This decreased activity also reduces peripheral conversion of T4 to T3,diverting it to inactive reverse T3 pathway
2. An expanded blood volume of distribution
3. A short half life T3 [7.8]

Serum interlukin-6 (IL-6), which has been shown to be increased in the low T3 syndrome,appears to inhibit the hepatic monodeiodinase activity [7].Cardiac myocytes in border zone of reperfused viable myocardium, monocytes and macrophages produce IL-6, which may mediate the change in serum T3 levels after an AMI [8].High catecholamine levels are known to cause low T3 syndrome [9].The changes in blood levels of thyroid hormone in the euthyroid sick syndrome might be due to high levels of blood catecholamines generally found in patient with AMI. **Rodrigo Caeteano Pimentel and his co-workers (2006)** in their study patients belonging to the STEMI group showed early elevations, in addition to higher mean reverse T3 and lower meanT3 and free T3 levels. No significant difference in the FT3, FT4 and TSH levels found between STEMI and NSTEMI/UA groups. [10] In compare to above study, changes in the levels of FT3, FT4 between STEMI and NSTEMI/UA group are similar in our study. In STEMI group

decrease in FT3 levels is marked as compared to NSTEMI group but there is no significant difference between these two subgroups ($p > 0.05$). In patient with acute myocardial infarction, it has been postulated that down regulation of the thyroid hormone system may be an advantage if it is present when AMI strikes because the O_2 demand of the myocardium may be reduced, when metabolic rate is diminished. [11] Whether the euthyroid sick syndrome is an advantage after AMI whendamage has occurred and heart failure might be emerging may be questioned. Circumstances make it adequate to hypothesize that; changes in thyroid hormone levels may be deleterious. Thyroid hormones affect ventricular function through stimulation of sarcoplasmic calcium adenosine triphosphatase (ATPase) activity and expression [5]. This ATPase is responsible for removal of calcium from cytosol in diastole, allowing uncoupling of actin-myosin cross-bridging. It is therefore important for diastolic function of the heart. It also regulates the quantity of calcium in sarcoplasmic reticulum available for systolic contraction and is thus hereby also important for systolic function of the heart [12] When the thyroid hormone system is down regulated in short term in AMI, intracellular calcium handling is affected in a way that may con-tribute to myocardial stunning and reperfusion injury due to calcium overload [13]. Furthermore, down regulation of the thyroid hormone system leads to increase in systemic vascular resistance and increased cardiac after load. If the heart is unable to cope with this, cardiac output will be reduced. Clinical implication of this study is related to a better knowledge of role of thyroid hormone metabolism in non thyroidal illnesses, such as acute coronary syndrome. The hormonal profile characterized by the "euthyroid sick syndrome" seems to be associated with patho- physiological features and the prognosis of diseases, and further studies are needed to prove assumption. With prospective studies on larger patient materials, the cause and consequence of euthyroid sick syndrome in ACS can be further clarified. This biochemical marker, in addition to others, can be helpful in predicting the outcome of our patients with coronary artery disease.

Conclusion:

In our present study we came to conclusion that there is decrease in mean serum FT3 levels in patient of ACS without significant changes in FT4 and TSH as compared to controls. i e **Euthyroid Sick Syndrome**", a condition characterised by decreased serum T3 and/or free T3, plus normal serum TSH, T4 and free T4.There is no significant difference found in changes in thyroid hormone profile in STEMI and NSTEMI group. This down regulation of FT3 is transient in patient of ACS without complication and returns to normal or near to normal by the 7^{th} day. Thus we concluded that, the thyroid hormone system is rapidly down regulated in acute coronary syndrome. The degree of free T3 decrease is proportional to the severity of cardiac damage and may have a possible prognostic value. Thus, freeT3 serum levels may contribute to the elaboration of an ACS severity index.

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