Levels of thyroid hormone, ferritin and testosterone in Acute Myocardial Infarction (AMI) patients in north India

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ABSTRACT

Background : Thyroid hormone plays a critical role in cardiomyocyte maturation and stress-related cellular responses like AMI. The inhibition of thyroid hormone receptor alfa (TRα) causes down regulation of this hormone in post-ischemic myocardium. On the other hand, ferritin, an inflammatory marker; and testosterone, a hormone which alters lipid profile, also play significant roles in pathogenesis of AMI. The objective of our study was to compare thyroid profile (total T3, T4 and TSH), ferritin, Vitamin B-12, folic acid and testosterone in newly diagnosed male cases of AMI with age-matched controls. We also contrasted these biochemical parameters between AMI subgroups with very low and low left ventricular ejection fraction (LVEF). **Methodology :**A cross-sectional study was conducted from September, 2012 to February, 2013 at a tertiary care hospital of north India. Newly diagnosed male AMI patients with positive clinical and ECG findings, and CPK MB > 25 U/L (spcetrophotometric method) and Troponin-I ultra > 2ng/ml (chemiimmunofluroscence method) were enrolled as cases (n=43). Cases were further sub-classified into those with very low LVEF (<35%, Group 1) and low LVEF (35-50%, Group 2). Serum was pooled at 12-24 hr of onset of symptoms and preserved at -20°C until analyzed. Serum TSH was measured with immunoradiometric assay; serum T3 and T4 were measured with radioimmuno assay. Serum ferritin, Vitamin B-12, folic acid and testosterone were also estimated (chemiimmunofluroscence method) in all cases. 40 age and sex matched controls were similarly examined. **Result :**AMI patients reported significantly lower T3, higher ferritin and lower testosterone level in comparison to control group. On the other hand, cases with lower LVEF (<35%) showed significantly lower value of CPK MB, T3, ferritin and testosterone. **Conclusion :**Our study found down regulation of T3 and testosterone levels, with raised higher ferritin levels in patients suffering from an acute attack of AMI.

Key words: AMI, Thyroid hormone, Ferritin, Testosterone.

INTRODUCTION

Stress-related acute health conditions like AMI are believed to alter thyroid hormone (TH) levels in otherwise euthyroid patients.[1] There are also evidences of alteration of serum ferritin and serum testosterone levels in AMI patients.[2,3] Changes in thyroid hormone and its neuro-endocrinal response to stress are termed as non-thyroidal illness or euthyroid sick syndrome, and this mechanism is poorly understood.[1,4] TH specially plays a critical role in cardiac cell differentiation as well as in post-ischaemic cardiac remodeling, cardiac contractility, and left ventricular function.[5,6] It is closely associated with many other cardiac diseases like heart failure, arterial hypertension, atherosclerosis and dyslipidemia.[5] Dysfunction of TH is found in ST segment elevated MI.[7] TH also regulates HSP (heat shock protein), which is cardio protective in nature. Thus it can control response to stress like in AMI.[8] Since AMI causes down regulation of TH receptor alfa 1 in post infracted heart, and ultimately induces the down regulation of TH; treatment with TH may be further beneficial in such cases.[9,10]

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The risk of AMI is also associated with iron store of our body[2], and heart failure patients often present with iron deficiency anemia with increased ferritin levels.[11]Hypothyroidism could result from deposition of iron in thyroid gland.[12] Therefore, a relation between thyroid hormone and iron storage might be playing an important role in pathogenesis of AMI. Even congenital hypothyroidism has been suspected to be associated with increased serum ferritin.[13]

Testosterone levels, on the other hand, are inversely related with risk of heart disease, and play an important role in causation of AMI. Low testosterone levels, causing alteration in lipid profile, is vividly related to coronary artery disease, and may be a leading cause of AMI.[3]

The objective of our study was to compare thyroid profile (total T3, T4 and TSH), ferritin, Vitamin B-12, folic acid and testosterone in newly diagnosed male cases of AMI with age-matched controls. We also contrasted these biochemical parameters between AMI subgroups with very low and low left ventricular ejection fraction (LVEF).

MATERIAL AND METHODS

This cross-sectional study was conducted from September, 2012 to February, 2013 at a tertiary care hospital of north India. Ethical clearance was obtained from the Institutional Ethical Committee. Informed written consent was obtained from each participant.

Forty three (n=43) cases were selected from among adult male patients presenting within 12-24 hours of onset of chest pain in the hospital emergency and admitted to the ICCU department. Female patients were not included in this study as they are more prone to thyroid disorders. All cases were patients with first episode for AMI, diagnostic ECG findings, LVEF < 50%, CPK MB > 25U/L and Troponin I ultra > 2 ng/ml. Patients with other acute disorders like any infectious disease, terminal disease, liver disease or other systemic disorders, endocrinal disorders, other cardiac diseases as well as patients on regular hormonal medication were excluded from this study. Patients with history of consuming vitamins (B-6, B-12 and folic acid) and iron supplements during the last 6 months were also excluded. Forty (n=40) age matched male controls were enrolled. Venous blood samples were obtained during admission (prior to any treatment) from the cases, and from all controls. Centrifugation was done; and serum samples were kept frozen at – 20°C until day of assay.

Serum thyroid stimulating hormone (TSH) was measured with immunoradiometric assay (IRMA, normal reference range = 0.3-5.0 microIU/ml). Serum triiodothyronine (T3, normal reference range = 70-200 ng/dl) and thyroxine (T4, normal reference range = 5.5-13.5 microgram/dl) were measured with radioimmuno assay (RIA). CPK-MB was measured by enzymatic method and assayed by spectrophotometer with kit supplied by SIEMEN (Immuno Inhibition, IFCC method kinetic, UV; normal reference range = 0-25U/L at 37°C). Trop-I ultra (reference range = 0-1.5ng/ml), serum ferritin (reference range = 22-322 ng/ml), folic acid (reference range >5.38ng/ml), Vitamin B-12 (normal range=215-911pg/ml), testosterone (normal range = 241-827 ng/dl) levels were measured with the ADVIA centaur CP assay by using direct chemiluminometric technologies.

We further sub-classified the cases were divided into two groups - Group 1 with LVEF <35% (n=21) and Group 2 with LVEF 35-50% (n=22)

The sample size was based on a pilot study at the current institution. With standard deviations of 27.85 and 34.98 in the two groups, a sample size of 33 subjects per group had a two-sided alpha error of 0.05 and 80% power to detect a mean difference of 21.8 between the AMI cases and controls. The sample size was calculated using the nMaster v1.0 software developed by the Department of Biostatistics, Christian Medical College, Vellore, India.

The statistical analysis was done using SPSS v.17.0 (SPSS Inc., Chicago, IL). Student's t test was performed to test significance of the mean differences for continuous variables. Two sided p value < 0.05 was considered as significant. Pearson correlation coefficient was also calculated.

RESULT

The mean age of AMI patients was 50.7 ± 15.6 years; while it was 47.9 ± 18.3 years for controls. All cases (n=43) were reported to have CPK MB level >25 U/L and Trop-I ultra > 2 ng/ml.

Table 1 demonstrates the comparison of thyroid profile, ferritin, Vitamin B-12, folic acid, and testosterone levels between the cases and controls. The mean serum T3 level among cases (62.14 ± 34.81) was significantly less ($p<0.0001$) than that in the control group (127.86 ± 43.70). However, no significant differences were obtained for serum TSH or T4 levels among the two groups; though mean TSH level was slightly on the higher scale for cases. Mean ferritin level was significantly high in cases (188.81

± 47.64) in comparison to controls (82.62 ± 30.75) (p< 0.001). However, we failed to find any significant difference in Vitamin B-12 and folic acid levels between cases and controls. On the other hand, serum testosterone levels were low among cases (257.07 ± 53.84), compared to controls (348.42 ± 49.10); this difference being statistically significant (p<0.001).

Table 2 demonstrates comparison between the subgroups of AMI patients - Group 1 (n=21, very low LVEF) and Group 2 (n= 22, low LVEF). Patients in Group 1 recorded significantly higher mean level of CPK MB (148.48 ± 119.51) in contrast to Group 2 (62.28 ± 24.51) (p=0.004). Similar results were obtained with serum ferritin level, which was significantly higher in Group 1 (211.38 ± 52.66) compared to Group 2 (167.27 ± 30.05) (p= 0.002). Serum T3 was significantly lower in Group 1 (38.52 ± 16.16), compared to Group 2 (67.36 ± 29.09) (p<0.001). However, no such significant differences could be observed with TSH, T4, Vitamin B-12 and folic acid. Serum testosterone levels, on the other hand, were significantly lower in Group 1 (220.76 ± 43.76) in contrast with Group 2 (291.72 ± 37.37).

Figure 1 shows the correlation graph between CPK-MB and serum T3 levels, which were negatively and significantly correlated (Pearson correlation coefficient (r) =-0.427, p=0.005). Identical correlation graph (Figure 2) was obtained for serum ferritin and T3 (r = -0.370 p= 0.015). Figure 3 depicts a non-significant positive correlation between testosterone and T3 (r = 0.292, p= 0.057).

DISCUSSION

In the post-ischemic phase of AMI, remodeling of cardiac cells occur through various mechanisms. Internal cardiovascular regulation is one such important pathway where TH plays a critical role. Several experimental studies have demonstrated that TH affects cardiac hemodynamic and remodeling; as well as regulates genetic expression of some cardiac contractile proteins which combat stress through regulating different cardio protective molecules and cardiac metabolism. TH also regulates the molecular pathways of angiogenesis, myocyte differentiation and regeneration, which eventually improve myocyte shape and left ventricular function, ultimately leading to improved cardiac performance.[5,6,14]

Some studies have reported that TH can be used as a treatment modality in cases of heart failure since it partially recovers cardiac dysfunction by altering the heart chamber geometry.[5] According to several investigators, TH administration after AMI leads to decreased expression of beta myosine heavy chain (MCH), ultimately promoting ventricular wall thickening and preventing a hypothyroidism-like state.[15] TH administration also increases heat shock protein (HSP) content in patient's heart leading to prevention of AMI.[8] Klempere JD et al reported a decreased level of T3 in post surgical phase of coronary artery bypass surgery and noted that the condition improved after treatment with TH, which increased cardiac output in the post operative patients.[16] According

Table 1 : Comparison of the selected biochemical parameters between AMI cases and controls

	Cases (n=43) (mean ±sd)	Controls (n=40) (mean ±sd)	p-value
Serum TSH (0.3 - 5.0 microIU/ml)	5.31±3.98	4.14±2.27	0.107
Serum T3 (70-200 nanogram/dl)	62.14 ±34.81	127.86±43.70	<0.001
Serum T4 (5.5-13.5 microgram/dl)	7.87±2.24	8.32±2.98	0.44
Ferritin (22-322ng/ml)	188.81±47.64	82.62±30.75	<0.001
Vitamin B-12 (215-911pg/ml)	347.16±70.93	338.28±67.44	0.56
Folic acid (>5.38ng/ml)	7.76±8.07	6.75±1.37	0.43
Testosterone (241-827ng/dl)	257.07±53.84	348.42±49.10	<0.001

Figures in parenthesis indicate normal reference range values

Table 2 : Comparison of the selected biochemical parameters between AMI cases with very low LVEF (<35%) and low LVEF (35-50%)

	Group 1 (LVEF <35%) (n=21) (mean ± sd)	Group 2 (LVEF 35-50%) (n=22) (mean ± sd)	p-value
CPK MB	148.48±119.51	62.28±24.51	0.004
Serum TSH (0.3 - 5.0 microIU/ml)	2.55±1.39	3.55±2.89	0.156
Serum T3 (70-200 nanogram/dl)	38.52±16.16	67.36±29.09	<0.001
Serum T4 (5.5-13.5 microgram/dl)	7.48±2.11	8.10±2.29	0.363
Ferritin (22-322 ng/ml)	211.38±52.66	167.27±30.05	0.002
Vitamin B-12 (215-911 pg/ml)	327.19±62.36	366.22±74.68	0.07
Folic acid (>5.38 ng/ml)	6.56±1.65	8.91±11.17	0.342
Testosterone (241-827 ng/dl)	220.76±43.76	291.72±37.37	<0.001

Figures in parenthesis indicate normal reference range values

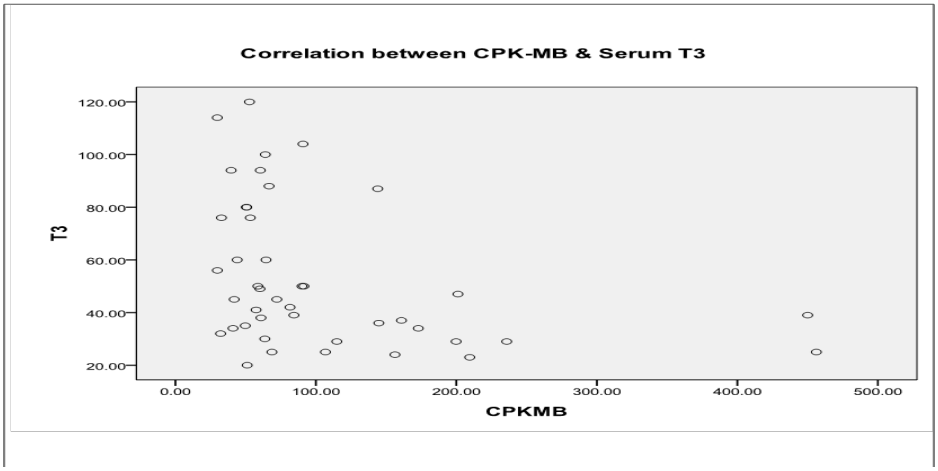

Figure 1: Correlation between CPK MB and serum T3 levels in AMI patients (n=43) (r = -0.427, p=0.005)

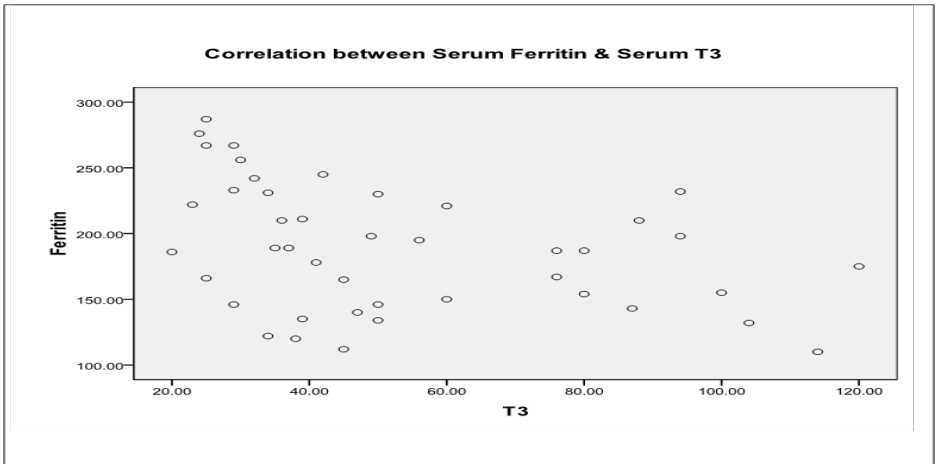

Figure 2: Correlation graph between serum ferritin and T3 in AMI patients (n=43) (r = -0.370, p=0.015)

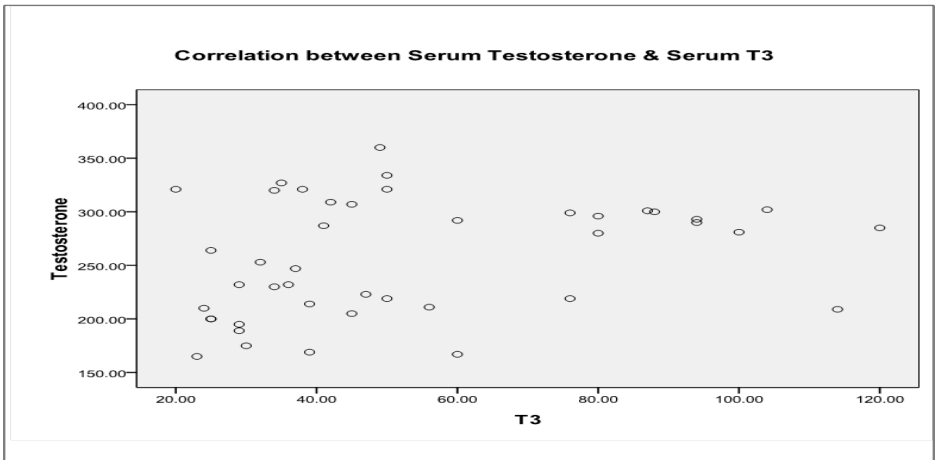

Figure 3: Correlation graph between serum testosterone and serum T3 in AMI patients (n=43) (r = 0.292, p=-0.057)

to another school of researchers, T3 administration significantly improves left ventricular function through plasma membrane mediated mechanisms.[14]

Pantos C et al reported a suppression of TH α1 receptor in post ischemic myocardium which could be the reason of hypothyroidism-like state leading to congestive cardiac failure (CCF) in post ischemic cardiac tissue. They proposed this process might be partly through mammalian target of rapamycin (mTOR) dependant pathway.[17] Kalofoutis C et al had found that AMI in diabetic rats is caused by down regulation of TH receptor. TH treatment was protective in such cases as it increased the ejection fraction percentage of the ischemic heart. Some others believe that this down regulation of TH starts much before initiation of the infarction process. [18,19]

In our study, we observed total serum T3 levels to be significantly reduced in AMI patients after 12-24 hr of onset of symptoms. Serum T3 was also negatively and significantly correlated with CPK-MB levels. We may hence probably consider a hypothyroid-like state in acute myocardial infarction; or in other words, there may be a strong indication of down regulation of thyroid hormones during this acute phase. Mechanisms for the transiently low serum T3 levels in acute cases might be due to decreased hepatic and peripheral conversion of T4 to T3, especially in advanced heart failure patients, since the activity of 5' monodeiodinase enzyme level is low. There is a probability of T3 being diverted to inactive rT3, increasing its level in serum. Low T3 would eventually increase the level of TSH from pituitary, leading to increased T3 and T4 level in serum. But this increased TH level finally imparts a negative feedback to pituitary and TSH would not increase further.[10,20]

Zhang et al commented that T3 being a more bioactive hormone than T4 and TSH, exerts an effect on myocardial contractility as well as peripheral arterial resistance. It has been concluded that inflammation and hypoxia in heart muscles of AMI patients cause decreased level of fT3. The low fT3 level is a strong predictor of a short- and long-term poor prognosis in AMI.[21] On the other hand some researchers observed that lower FT3 level correlates with higher level of cardiac markers and lower left ventricular ejection fraction (LVEF). Therefore low T3 might be a predictor for myocardial injury in AMI. In this study, FT3 level showed significantly negative correlation with both CKMB and cTnI. Down-regulation of T3 was probably associated with myocardial injury in AMI cases.[22]

The synonym for non-thyroidal illness is low T3 syndrome, where the remaining thyroid parameters like T4 and TSH are within the normal range, or may be on a slightly lower scale. T3 level is usually inversely related with the severity of disease.23 Contradictory findings have been reported by Asvold BO *et al,* who found no association between thyroid function level and myocardial infarction risk in AMI patients.[24,25] According to Eber B et al, thyroid profile could not be considered as marker of left ventricular dysfunction in acute phase of AMI.[26] Some researchers have further postulated that the hypothyroid state might be sometimes advantageous as it would decrease metabolic demand of the myocardium.10 Low T3 is considered as an important risk factor for low cardiac output in patients undergoing CABG (coronary artery bypass grafting).[27]

Iqbal et al reported an association between total iron store of the body and risk of AMI.[12] Serum ferritin is the best indicator of iron storage. Oxidative stress created by increased iron store of the body might be an important factor of coronary artery disease leading to AMI. Increased oxidized LDL level due to free radical formation by iron and increased rate of lipid per oxidation are important factors of reperfusion injury of the cardiac myocardium, which may eventually lead to atherosclerosis causing AMI.[2] Increased ferritin levels are associated with both cardiomyopathy as well as subclinical hypothyroidism. Deposition of iron in thyroid gland might be another reason for hypothyroidism in patients with AMI.[12]

In the current study, we observed that serum ferritin levels were significantly increased in newly diagnosed AMI patients who presented with significantly low levels of T3. Severe cases of myocardial infarction (Group 1, LVEF<35%) presented with significantly lower level of T3 and higher levels of feritin in comparison to the low LVEF group (Group 2, LVEF 35-50%).

Patients with heart failure and cardiomyopathy usually presents with hormonal imbalance affecting growth hormone, insulin like growth factor 1 and testosterone. According to Bell JR et al, males are more prone to cardiovascular events earlier in life. They suggested that testosterone has some inotropic actions, and modulate Ca^{2+} channels in myocardium expressing androgen receptors. According to them, testosterone can improve acute post-ischemic outcomes and facilitate myocardial function and survival in chronic post-infarction.[28] Militaru et al described the beneficial effects of exogenous testosterone on the atherosclerotic process. Exogenous androgens decrease serum levels of HDL-cholesterol, plasminogen activator type 1, lipoprotein (a), fibrinogen, insulin, leptin, visceral fat mass, and reduce the chances of infraction in cardiac tissue. They concluded that low endogenous testosterone

level was associated with a higher short-term mortality acute myocardial infarction.[3]

In our study we observed significantly low testosterone levels in AMI cases, and it was more pronounced in patients with LVEF <35%. Testosterone level was also positively correlated with serum T3, but it was not significant. Therefore, low testosterone levels may be considered as a marker to check the severity of AMI.

We had to work in a resource-restricted setting, and it might have been better to measure rT3, fT3 and fT4 as well as soluble (sTfR) transferrin receptor and full hormonal profile including growth hormone, IGF-1 and estrogen in AMI cases. Ideally, a seven–day follow-up in the cases would have been better predictive of detailed pathogenesis of AMI.

CONCLUSION

Notwithstanding the few limitations, our study found low T3, testosterone and higher ferritin levels in patients suffering from an acute attack of AMI. These levels are also varying with the severity of the disease. Certainly, larger prospective studies are warranted to corroborate this finding, and to understand the role of thyroid hormone, ferritin and testosterone as well as their interrelations in pathogenesis of AMI. Exogenous thyroid hormone and testosterone, or their agonists might be considered in management of AMI. Role of iron chelators in the control of AMI warrants further exploration.

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CONFLICT OF INTERESTS

We, the authors of the article titled "Levels of thyroid hormone, ferritin and testosterone in Acute Myocardial Infarction (AMI) patients in north India" hereby declare that we have no conflict of interest.

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