Original Article

Association of free Tri-iodothyronine Level with Cardiogenic Shock and Prognosis in Patients Hospitalized with Acute ST-elevation Myocardial Infarction Treated with Streptokinase Therapy

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Abstract:

Background: Cardiogenic shock is the leading cause of death in patients with Acute ST-segment Elevation Myocardial Infarction (STEMI). Low free Tri-iodothyronine (FT3) levels are generally associated with poor prognosis in STEMI patients. This study was done to assess the association between FT3 levels and Cardiogenic shock in patients hospitalized with STEMI treated with streptokinase therapy.

Methods: This was an observational study of 140 patients of STEMI treated with streptokinase therapy in the department of cardiology, NICVD, Dhaka, Bangladesh from October 2018 to September 2019. The patients were divided into low FT3 (FT3 <3.5pmol/L; n = 70) and normal FT3 (FT3 e'' 3.5pmol/L; n = 70) groups according to FT3 levels measured within 24 hours after admission.

Results: During the index hospitalization period, 30 patients developed cardiogenic shock, 23(32.9%) in low FT3 group and 7(10.0%) in normal FT3 group. There were 17 deaths with 18.6% in low FT3 group and 5.7% in normal FT3 group (p=0.01). MACE occurred 45.7% in low FT3 group and 18.6%in normal FT3 group (p=0.001). The mortality in patients with cardiogenic shock was 43.3% compared to 3.6% in patients without cardiogenic shock. Multivariate logistic regression analysis showed FT3 level was an important predictor for cardiogenic shock in patients hospitalized with STEMI (p=0.01).

Conclusion: Low FT3 levels were strongly associated with cardiogenic shock in patients with STEMI. The FT3 level screening may be a simple and valuable way to predict Cardiogenic shock after STEMI.

Keywords: FT3, Cardiogenic shock, STEMI, MACE.

Conflict of Interest: There is no conflict of Interest.

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Introduction:

Thyroid hormones have a broad range of effects on the heart and vascular system. The precise mechanism of the thyroid hormones at cellular and molecular level on heart have been investigated and well characterized.[1]

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Free Tri-iodothyronine (FT3) is the only thyroid hormone transported into the myocyte and thereby plays a major role in cardiovascular haemodynamics, cardiac filling, and systolic contractility.[2] The observation that even minor sub-clinical alterations in thyroid hormone levels can lead to adverse effects on the cardiovascular system is now recognized.[3]

Thyroid hormones metabolism is altered in severe illnesses and is characterized by low FT3 levels and normal-to-low free Thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) levels which is known as the low-T3 syndrome or euthyroid sick syndrome.[4] The decline of FT3 level is caused either by increasing T3 catabolism or decreased conversion of the pro-hormone T4 into T3.[2] Inflammation, hypoxia, and oxidative stress modulate the activity of de-iodinase and thereby involve in the reduction of FT3 level.[5]

In acute myocardial infarction (AMI), the thyroid hormone system is rapidly down-regulated and it has tradi-tionally been interpreted as an adaptive process that reduces catabolism and conserve energy.[6] However, this theory is now challenged by clinical outcome data on baseline thyroid hormone dysregula-tion in AMI patients. Abnormal thyroid function tests, especially decreased FT3 have been shown to correlate with the severity of the disease and mortality in critically ill patients without prior known intrinsic thyroid diseases.[7,8] Furthermore, animal model studies showed that thyroid hormones have an important therapeutic role in limiting infarct size and improving myocardial function after AMI.[9]

Few clinical studies involving patients with AMI have addressed the possible correlation of thyroid hormone with the extent of myocardial injury. The Lower serum FT3 has been associated with increased serum levels of indicators of myocardial injury (troponin T and N-terminal pro-brain natriuretic peptide), as well as with lower left ventricular ejection fraction.[10] Lymvaios et al. (2011) also found a strong correlation of low FT3 with impaired left ventricular systolic function among AMI patients and describes FT3 levels as a predictor of ventricular functional recovery.[11]

Cardiogenic shock is the leading cause of death in patients with AMI and has a frequency of about 7-10%.[12,13] The incidence of CS has increased in recent years, while the exact reason is unclear, improved diagnosis and better access to healthcare are both likely contributory.[14] Cardiogenic shock caused by impairment of myocardial functions resulting in reduced cardiac output, end-organ hypoperfusion, and hypoxia which is evident clinically by presence of hypotension refractory to volume resuscitation and features of end-organ hypoperfusion. Despite all the advances in pharmacological, mechanical and reperfusion endeavors, in-hospital mortality in patients with cardiogenic shock continues to be as high as 50% to 80%.[15]

Although primary Percutaneous coronary intervention (PCI) strategy is recommended over fibrinolysis within indicated timeframe yet fibrinolysis is used widely as a means of revascularization in patients with acute STEMI especially in centres not offering primary PCI facilities in Bangladesh.[16] Cardiogenic shock occurs more amongst patients with ST-segment elevation myocardial infarction (STEMI vs NSTEMI, 7.5% vs 2.5%). It was observed that shock developed in 7.5% of patients with STEMI and in 2.5% of patients with non-ST-segment elevation myocardial infarction.[12]

Early identification of high risk patients helps to ensure appropriate therapies for their level of risk. Despite emerging innovative treatments, in-hospital mortality in patients with cardiogenic shock continues to be very high. Reduced FT3 along with other risk score could aid physicians to estimate risk of development of cardiogenic shock after acute STEMI more efficiently, improve their management and therefore contribute to reduce mortality and morbidity in STEMI patients.

Methodology

Study population

This prospective observational study was conducted at the department of Cardiology, NICVD, Dhaka, Bangladesh, from October 2018 to September 2019. A total of 140 cases were included in the study after considering the inclusion and exclusion criteria. The inclusion criterion was Patients with STEMI admitted in NICVD and treated with streptokinase therapy. The exclusion criteria were (1) History of Thyroid disease, overt Hypothyroidism or Hyperthyroidism, Amiodarone use within one month, (2) Previous myocardial infarction, Valvular, Congenital heart diseases and Cardiomyopathy, (3) Any severe co-morbidities (renal disease, previous stroke, COPD, anemia, malignancy, bleeding disorder. The study protocol was approved by the Hospital Ethics Committee. Informed written consent was obtained from the patients or a legal representative. Similar type of patient regarding age, sex, risk factors type of STEMI were selected to match both the groups as close as possible. Blood samples were collected within the first 24 h after admission. The serum levels of thyroid hormone (including FT3, FT4 and TSH) levels were measured by

Automatic Immune Assay System (Immunology Machine, Model Access 2, Beckman Coulter). The patients were divided into the low FT3 (FT3 <3.5 pmole/L; n=70) and the normal FT3 (FT3 e"3.5 pmol/L n=70) groups according to the FT3 levels. Baseline investigations (12 lead ECG, RBS, Serum Creatinine) and Echocardiography were carried out and noted.

Definition

Cardiogenic Shock was diagnosed as (1) systolic blood pressure <90 mmHg for >30 minutes or needed support to maintain blood pressure e"90 mmHg and evidence of end-organ hypoperfusion (decreased urine output, altered mental status and peripheral vasoconstriction).

Follow up

Routine follow-up was done every day during hospitalization period. The primary endpoint of this study was the development of cardiogenic shock and the secondary endpoint was all-cause death during hospitalization period.

Results:

The mean age of the patients was 61.8±12.5 years in low FT3 group and 58.6±12.7 years in normal FT3 group. The mean age of Low FT3 group was higher than Normal FT3 group which was not statistically significant (p=0.13). Regarding sex distribution, in Low FT3 group, 51 (72.9%) patients were male and 19 (27.1%) were female. In Normal FT3 group patients, 55 (78.6%) patients were male and 15 (21.4%) patients were female. Male female ratio was around 3:1. Statistically no significant association was seen in term of sex among the study groups (p=0.59) (Table I).

The mean RBS level was observed insignificantly higher in Low FT3 group and Normal FT3 group 8.1±3.4 vs. 7.3±2.9 mg/dl respectively (p=0.18). The mean serum creatinine was higher in Low FT3 group than Normal FT3 group (1.21±0.18 vs. 1.15±0.16 mg/dl) with statistical insignificant difference (p=0.06). The mean serum troponin I was higher in Low FT3 group than Normal FT3 group (28.2±19.6 vs. 19.8±16.1, p=0.007) with significant difference. It was observed that the mean LVEF% was significantly less in Low FT3 group than Normal FT3 group (43.45±4.83 vs 47.03±4.92, p=0.03) (Table I).

Distribution of study patients in respect to the site of MI showed similar frequencies in both group with no statistically significant association (Table II).

The mean level of FT3 was significantly lower in Low FT3 group than Group II (2.97±0.37 vs 4.25±0.48 pmol/L, p<0.001). The mean FT4 level was observed 13.22 ± 4.32 pmol/L in Low FT3 group and 14.64 ± 2.53pmol/L in Normal FT3 group with no statistical significance (p=0.12). TSH level is higher in Low FT3 group (2.26 ± 4.62 vs 1.45 ± 0.96) but without statistical significance (p=0.328) (Table III).

During the index hospitalization period, 30 patients developed Cardiogenic shock. Among them 23(32.1%)

Table-I

Baseline clinical, Biochemical and Procedural characteristics of study participants.

Characteristics	Group I (n= 70)	Group II (n=70)	p-value
Demographics			
Male – No. (%)	51 (72.9%)	55 (78.6%)	0.41^{ns}
Female – No. (%)	19 (27.1%)	15 (21.4%)	
Age (years)- mean±SD	61.8±12.5	58.6±12.7	0.002^{s}
CAD risk factors			
Diabetes mellitus– No. (%)	20 (28.6%)	16 (22.9%)	0.43^{ns}
Hypertension- No. (%)	37 (52.9%)		28 (40.0%)
0.12^{ns}			
Smoking- No. (%)	26 (37.1%)	35 (50.0%)	0.13^{ns}
Biochemical status			
RBS mmol/L (Mean ± SD)	7.3±2.9	8.1±3.4	0.18^{ns}
Serum creatinine mg/dl (Mean ± SD)	1.15±0.16	1.21±0.18	0.06^{ns}
Serum troponin I ng/ml (Mean ± SD)	19.8±16.1	28.2±19.6	0.007^{s}
Echocardiography			
LVEF (Mean ± SD)	47.03±4.92	43.45±4.83	0.003^{s}

p-value reached from Chi-square test and unpaired t-test.

Table-II

Distribution of the study patients according to site of MI (N=140).

Site of MI	Group I (n= 70)		Group II (n=70)		Total(n=140)		p value
	Number	%	Number	%	Number	%	
Anterior	35	50.0	33	47.1	68	48.6	0.73^{ns}
Inferior	14	20.0	20	28.6	34	24.3	0.23^{ns}
Extensive	14	20.0	11	15.7	25	17.9	0.51^{ns}
Inferior+RVI	7	10.0	6	8.6	13	9.3	0.77^{ns}

Group I: Acute ST

EMI patients with low FT3
Group II: Acute STEMI patients with normal FT3
Data were analyzed using Chi-Square Test.
ns = Not significant (p>0.05).

Table-III

Thyroid hormone status of the study patients (N=140).

Variable	Group I (n=70) Mean±SD	Group II (n= 70) Mean±SD	p value
FT3 (pmol/L)	2.97±0.37	4.25±0.48	<0.001^{s}
FT4 (pmol/L)	13.22±4.32	14.64±2.53	0.12^{ns}
TSH (mIU/L)	2.26±4.62	1.45±0.96	0.328^{ns}

Group I: Acute STEMI patients with low FT3
Group II: Acute STEMI patients with normal FT3
s = Significant (p<0.05)
ns = Not significant (p>0.05)
P value reached from unpaired t test.

in Low FT3 group and 7(10.0%) in Normal FT3 group. Cardiogenic shock occurred significantly more in Low FT3 group (p=0.001). There were 13 deaths with 18.6% in Low FT3 group and 5.7% in Normal FT3 group (p=0.01) (Table IV). Regarding Major Adverse Cardiac Event (MACE) which includes acute heart failure, significant arrhythmia, cardiogenic shock and cardiovascular death were higher in low FT3 group than normal FT3 group with statistically significant association (45.7% vs. 18.6%, p=0.001) (Table V).

The mortality in patients with cardiogenic shock was 43.3% compared to 3.6% in patients without cardiogenic shock. Mean hospital stay was observed more in patients with cardiogenic shock than without cardiogenic shock (5.29±1.65 vs. 3.67±1.01, p=0.001). (Table VI). The binary logistic regression analysis of Odds Ratio for characteristics of the subjects likely to cause Cardiogenic shock showed the low LVEF, elevated troponin I and low FT3 revealed to be significantly associated to develop Cardiogenic shock with the ORs being 1.89, 1.09 and 6.14 respectively (Table VII).

Table-IV

Comparison of FT3 by cardiogenic shock (n=140).

Variable	Cardiogenic shock (n=30) Mean±SD	No cardiogenic shock (n= 110) Mean±SD	p value
FT3 (pmol/L)	2.91±0.57	3.81±0.71	<0.001^{s}

s = Significant (p<0.05)
p value reached from unpaired t test.

Table-V

Comparison of patients by Major Adverse Cardiac Event (N=140).

MACE	Group I (n=70)		Group II (n= 70)		P value
	Number	%	Number	%	
Present	32	45.7	13	18.6	0.001[s]
Absent	38	54.3	57	81.4	

Group I: Acute STEMI patients with normal FT3
Group II: Acute STEMI patients with low FT3
p value reached from Chi Square test
s = Significant (p<0.05)

Table-VI

Multivariate regression analysis of predictors for Cardiogenic Shock (N=140).

Variables of interest	Regression coefficient (β)	Odds Ratio (OR)	95% CI of OR	p value
Agee"60 years	0.024	0.98	0.305 - 3.121	0.76[ns]
Smoking	0.245	1.42	0.242 - 8.182	0.11[ns]
Heart rate	1.378	2.78	1.783 – 55.107	0.03[s]
Serum creatinine	0.301	1.49	0.349 - 10.101	0.16[ns]
Low LVEF% <50%	0.402	1.89	1.211 – 11.913	0.02[s]
Elevated Troponin I	0.116	1.14	1.057 – 1.697	0.03[s]
Low FT3	1.332	3.43	1.008 – 11.644	0.01[s]

s = Significant (p<0.05)
ns = Not significant (p>0.05)

Table-VII

Comparison of outcomes by cardiogenic shock (n=140).

Variables	Cardiogenic shock (n=30)	No cardiogenic shock (n=110)	p value
Death No. (%)	13 (43.3)	4 (3.6)	<0.001[s]
Hospital stay (days)Mean ± SD	5.29±1.65	3.67±1.01	0.001[s]

s = Significant (p<0.05)
p value reached from Fisher's exact test and unpaired t test.

Discussion:

The mean age of study subjects was found 60.2±12.7 years. In the study by Zhang et al. (2012), the mean age 68.6±3.2 years was higher than that of our study. This disparity in distribution of age may be explained by the fact that Bangladeshis are prone to develop IHD which is often early in onset, follows a rapidly progressive course and having 5 -10 years earlier onset of first myocardial infarction.[16]

Regarding sex, the ratio of male and female patients was 3:1, however no statistically significant difference was seen between two groups. In Bangladesh, almost all of the studies related to coronary artery disease reported an overwhelming majority of male patients. This is probably due to fact that the females have less chance of CAD and less access to tertiary level care due to social issues.[17,18]

The mean serum troponin I was significantly higher in low FT3 group than normal FT3 group with significant difference (28.2±19.6 vs. 19.8±16.1, p=0.007). Troponin I correlate with severity of myocardial infarction and it is a traditional predictor of poor prognoses in patients with AMI.[19]

Regarding left ventricular ejection fraction, it is considered to be one of the major end points after treatment of

myocardial infarction and is strongly related to short and long-term survival. The mean left ventricular ejection fraction was significantly less in Low FT3 group than Normal FT3 group (43.45±4.83 vs 47.03±4.92, p=0.03). The results showed that FT3 was positively correlated with LVEF and revealed that the cardiac function is impaired in the low FT3 state in STEMI patients. This finding in our study was supported by previous studies done by Lymvaios et al. (2011) and Wang et al. (2013).[10.11]

In our study, we observed significantly more patients developed Cardiogenic shock in Low FT3 group than Normal FT3 group (37.1% vs 10.0%, p= 0.001). We found FT3 was independently associated with the increased development of Cardiogenic shock in hospitalized STEMI patients. Although multiple studies have established the risk profiles of cardiogenic shock, the associations of thyroid hormones with cardiogenic shock haven't been reported but multiple studies showed a low FT3 level is associated with the severity of STEMI.[19,20]

Considering the in-hospital death, 18.6% patients with Low FT3 died during their hospital stay, on the contrary 5.7% patients with normal FT3 were died. There was statistically significant difference in terms of mortality between two groups of patients (p=0.01). We found Major Adverse Cardiac Event (MACE) were higher in Low FT3 group than Normal FT3 group with statistically significant association (45.7% vs. 18.6%, p=0.001). We found more endpoint events, including cumulative deaths and MACE in the low FT3 group. These findings are consistent with relevant studies done by song et al. (2018), Lazzeri et al. (2012) and Zhang et al. (2012).[7,19.20,]

Among the patients with cardiogenic shock, the mortality was 43.3% compared to 3.6% in patients without cardiogenic shock. This high mortality rate in patients with cardiogenic shock following STEMI is consistent with previous studies.[21,22]

Thyroid hormones exert direct effects on hemodynamics, including increasing cardiac contractility, decreasing vascular resistance and so on. A low FT3 state after AMI changes the transcription of many cardiac structural and functional genes.[23] These changes in the expression of cardiac genes are also characteristic of pathological cardiac remodeling after myocardial infarction.[24] In addition, thyroid hormones are powerful regulators of vasculature in the adult myocardium; therefore, a low FT3 state would inhibit neovascularization in cardiac tissue after AMI, which would accelerate cardiac pathologic remodeling and heart failure.[25] These changes in a low FT3 state would accelerate pathological cardiac remodeling and worsen the cardiac function, which would lead to short and long-term adverse cardiac events. In this study we found that Low FT3 level is associated with increased development of Cardiogenic shock in comparison to normal FT3 level in Streptokinase treated STEMI patients.

This study has several limitations. Firstly, it's a single centre, small scale study with limited sample size. Secondly, FT3 levels were not measured at various time points and the changes of thyroid hormone over time after AMI are unknown.

Conclusion:

Low free Tri-iodothyronine (FT3) levels are strongly associated with cardiogenic shock development in Streptokinase treated STEMI patients. Measurement of FT3 levels may be a valuable and simple way to identify high-risk STEMI patients. These results provide useful insights into the management of patients with STEMI.

Death rate was significantly higher in patients with cardiogenic shock than without cardiogenic shock (43.3% vs. 3.6%, p<0.001). Mean hospital stay was observed more in patients with cardiogenic shock than without cardiogenic shock (5.29±1.65 vs. 3.67±1.01, p=0.001).

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