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A Study of Thyroid Profile and Sick Euthyroid State in Patients with Acute Coronary Syndrome

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Abstract
Back Ground: *Acute coronary syndrome (ACS) is still the commonest cause of morbidity and mortality in the cardiovascular disease (CVD) entity worldwide. Studies have shown the effect of thyroid hormones on morbidity and mortality from cardio-vascular events. The sick euthyroid state (SES) has been well associated in ACS affecting the prognosis.*
Aim & Objectives: *To study the prevalence of SES in patients with ACS, the thyroid profile in ACS and the outcome among the SES patients with ACS. Also to study the distribution of SES according to multiple variables in patients with ACS.*
Materials and Methods: *The one year study is carried out in our hospital and designed as cross sectional study. Study group included 155 patients diagnosed to have ACS. History, clinical examination and risk stratification is done. Blood samples, thyroid profile, serial ECGs and Echocardiography are done for all patients. Data is analyzed for prevalence by percentage and Chi-square tests used for P-values and significant correlations.*
Results: *Prevalence of SES in ACS is 25.5%.Statistically Significant P-values for High BMI, CRP positivity, worst outcome in SES group of ACS were observed, correlating well with several studies. Low T3 values and Increased rT3 value (sick euthyroid state) is correlating with the worst outcome in ACS.*
Conclusion: *Prevalence of sick euthyroid state (SES) is very common in patients with ACS. Almost one quarter of ACS patients had SES. SES significantly associated with high BMI, CRP positivity is associated with worst outcome. So, Sick euthyroid state is a strong prognostic indicator in ACS. The T3 and rT3 levels well correlated with the outcome.*
Keywords: *Sick euthyroid state, CRP-c reactive protein, Acute coronary syndrome.*

Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide and also in India[1]. Though thought to affect high income countries in the past, now it is the leading cause of morbidity and mortality even in low and middle income

countries as epidemiological transition[2]. CHD affects Indians with greater frequency and at younger age than counterparts, thereby having a greater economic impact also. Age standardized cardiovascular disease (CVD) death rates in people 30-69 years old are 180 per 100000 in Britain,280 per 100000 in China and 405 per 100000 in India[3]. Acute coronary syndrome which encompass unstable angina (UA), non st elevation myocardial infarction (NSTEMI) and st elevation myocardial infarction (STEMI) is still the commonest cause of cardiovascular disease with high morbidity and mortality although newer invasive and non-invasive therapeutic strategies are available and adapted. Demographic and health transitions, gene-environmental interactions and early life influences of fetal malnutrition are the likely causes of increased cardiovascular burden in India (Ghaffar,2004)[5].Lot of risk factors like diabesity, smoking, dyslipidemia, hypertension and alcoholism are associated with CVD. At this juncture, Thyroid hormone actions on heart is also to be taken care as it increases the number of beta adrenergic receptors ,enhances response to catecholamines, increases metabolic rate and oxygen consumption. So study related to Thyroid profile and sick euthyroid state in ACS is taken up.

Sick Euthyroid Syndrome(SES) is defined as disturbances in the circulating concentrations of Thyroid hormones and TSH assays arising in systemic non-thyroid illness without preexisting hypothalamic-pituitary-thyroid gland dysfunction and normalizing after recovery[5]. The common biochemical abnormality is low T3, normal T4 and increased rT3 though in certain situations like liver disorder and HIV infection where T4 is elevated. The mechanisms involved are changes in cytosolic factor (NADPH, glutathione), deiodinase expression, thyroid binding protein and inflammatory cytokines[3]. This sick euthyroid syndrome is well associated with acute coronary syndrome affecting the prognosis. Several studies have shown the effect of thyroid hormones on morbidity and mortality from heart failure,

systemic arterial hypertension atherosclerosis, dyslipidemia and cardiopulmonary surgeries. Sick euthyroid state is observed in most of the acute and chronic illnesses like sepsis, burns, CVD, gastro, pulmonary, renal diseases, surgery, malignancy and bone marrow transplant. SES, the low T3 syndrome was once believed as a beneficial adaptive mechanism has emerged as a strong prognostic determinant in chronic systolic heart failure for which the commonest cause is ACS.

Aim

To study the prevalence of sick euthyroid syndrome (SES) in patients with acute coronary syndrome, the distribution of sick euthyroid syndrome according to age, gender, diabetes, hypertension, dyslipidemia, BMI, type of acute coronary syndrome, smoking, CRP status and to study the correlation between the thyroid profile and the outcome among the SES patients with ACS.

Materials and Methods

The study *Thyroid profile and Sick Euthyroid Syndrome in Acute coronary syndrome* is carried out in our institute. The study design is a cross sectional study. Period of study is over a year.

Inclusion criteria

Patients admitted with the diagnosis of ACS (UA, STEMI, NSTEMI) irrespective of their age, sex, race, ethnic group and clinical severity.

Exclusion criteria

- Patients with known CHD with or without ventricular dysfunction,
- Already known thyroid disorders
- Received iodinated contrast within last two weeks,
- Known Chronic Renal failure patient
- Patients with other acute illness like sepsis, DKA, respiratory failure and hepatic dysfunction
- On drugs like amiodarone, propronalol, corticosteroids and oral contraceptives which interferes thyroid function.

Study group included one hundred and fifty five (155) patients. Complete histories with risk factors, detailed physical examination including vital parameters were done. Risk stratification was done using TIMI scoring and Killips class. BMI Calculation (WHO criteria for Asian population), complete blood count, CRP (c-reactive protein), sugar, urea, serum creatinine, serum electrolytes, Lipid profile (ATP III guidelines), thyroid profile (T3,T4,TSH,FT3,FT4,rT3), serial ECGs, X-ray chest and Echocardiography was done for all patients as per the quality /standard methods. Thyroid profile was done in fasting state. TSH was estimated using Ultrasensitive chemi luminescent immune assay, T3, T4, FT3, FT4 by competitive chemi luminescent immune assay and rT3 by radio immuno assay. Reference values T3:70-100 µg/dl, fT3:1.5-4.1 pg/ml, fT4:0.8-1.90 ng/dl, T4:.5-12.5 µg/dl, TSH:0.42-5 mIU/ml, rT3:0.09-0.35 µg/ml. In ECG ST segment elevation/depression, pathological Q waves, T wave changes are taken as acute, evolving, evolved recent MI and unstable angina with features of prolonged (>20 minutes) anginal pain at rest, new onset angina, crescendo angina and post MI Angina are taken into consideration for ACS. In echocardiography regional wall motion abnormality and ventricular dysfunctions with ejection fraction is assessed. Diagnosis of SES/Low T3 syndrome is considered if T3 level is low and rT3 is elevated in this study. Statistical analysis done and bar diagrams, pie diagram, prevalence, percentages, group tabulations and Chi-square tests were established.

Results

The present study titled *Thyroid profile and Sick Euthyroid Syndrome in Acute coronary syndrome* is undertaken in the Department of Medicine and the Department of Cardiology over a period of one year. The results of the study are explained as follows:

The Table 1 and Figure 1 shows 25.2% (39/155) of patients with acute coronary syndrome had Sick euthyroid state. Remaining patients of ACS 74.8% (116/155) had normal thyroid profile. The Table 2 and Figure 2 shows prevalence of Sick euthyroid Syndrome among various types of ACS. Non ST elevation MI, ST elevation MI (anterior wall, anteroseptal, inferior wall), Unstable Angina is taken for and the observations are as follows:

21.6% (8/37) of patients with Unstable angina had SES.

25.8% (8/31) of patients with STEMI (IWMI) had SES.

34.3% (12/35) of patients with STEMI (AWMI) had SES.

33.3% (3/9) of patients with STEMI (ASMI) had SES.

18.6% (8/43) of patients with NSTEMI had SES

The Table 8 shows the Chi-square test done between various groups of ACS. When these values were analyzed there was no statistical difference of occurrence of SES with different type of ACS. The Table 3 and Figure 3 shows comparison study between group A (ACS with SES) and Group B (ACS with normal thyroid profile) on the basis of BMI. The results are given as follows:

57.1% of SES patients were obese {BMI of >27.5}

21.4% of SES patients were overweight {BMI of 23.0-27.4}

16.7% of SES patients had normal {BMI of 18.5-22.9}.

The Table 9 shows the Chi-square test done to show the association between occurrence of SES and BMI. p value of 0.002 is significant. Thus there is an association between the occurrence of SES and High BMI. The Table 4 and Figure 4 shows comparison study between group A (ACS with SES) and Group B (ACS with normal thyroid profile) on the basis of CRP. The results are given as follows: 42.6% of CRP positive patients had SES but only 17.6% of CRP negative individuals had SES and with significant p value of 0.001 as shown in Table 10. The Table 5 and Figure 5 shows comparison study between group A (ACS with SES) and Group B (ACS with normal thyroid profile) on the basis of outcome. The results are

given as follows: Nine out of 155 patients expired. 21.9% of improved patients had SES where as 77.8% of patients who expired had SES with a significant p Value of 0.002 as shown in Table 11. Statistically insignificant difference is seen with respect to age, gender, diabetes, hypertension, dyslipidemia and smoking.

Thyroid profile and outcome among SES Patients with ACS is analyzed. Table 6 and Figure 6 shows correlation between T3 value and outcome. The mean Total T3 value for the patient who were improving during hospital stay was 77.62 (normal 70-100 micro/dl), where as the expired patients

had very low mean of 52.4. Table 12 shows the Independent samples-t test for this correlation with a p-value of 0.00.

The rT3 values are correlated with outcome as shown in Table 7 and Figure 7. The mean rT3 value for the patients who expired is 0.64 and in improved group it is 0.33.There is an association between the high rT3 value and worst outcome which is evident from the p-value of 0.000 as in Table 13.

Statistically indifferent correlation is seen between fT3, T4, fT4 and TSH values with outcome.

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Table 1: Prevalence of Sick euthyroid Syndrome (SES) in ACS:

SES	No. of cases	% of cases	Cumulative %
No	116	74.8	74.8
Yes	39	25.2	25.2
Total	155	100.0	

Table 2: Prevalence of Sick euthyroid syndrome among various type of ACS:

Type of ACS		Patients with SES group A	Patients with normal thyroid profile group B	Total
NSTEMI	Count	8	35	43
	%within Type of ACS	18.6%	81.4%	100%
	% within group	20.5%	30.2%	27.7%
STEMI (ASMI)	Count	3	6	9
	%within Type of ACS	33.3%	66.7%	100%
	% within group	7.7%	5.2%	5.8%
STEMI (AWMI)	Count	12	23	35
	%within Type of ACS	34.3%	65.7%	100%
	% within group	30.8%	19.8%	22.6%
STEMI (IWMI)	Count	8	23	31
	%within Type of ACS	25.8%	74.2%	100%
	% within group	20.5%	19.8%	20%
UA	Count	8	29	37
	%within Type of ACS	21.6%	78.4%	100%
	% within group	20.5%	25.0%	23.9%
Total	Count	39	116	155
	%within Type of ACS	25.2%	74.8%	100%
	% within group	100%	100%	100%

Table 3: BMI- group cross tabulation:

Body Mass Index (BMI)		Group		Total
		A- SES	B-Normal TP	
<18.5	Count	1	1	2
	% within BMI	50.0%	50.0%	100%
	%within group	2.6%	0.9%	1.3%
18.5-22.9	Count	8	40	48
	% within BMI	16.7%	83.3%	100%
	%within group	20.5%	34.5%	31.0%
23-27.4	Count	18	66	84
	% within BMI	21.4%	78.6%	100%
	%within group	46.2%	56.9%	54.2%
>27.5	Count	12	9	21
	% within BMI	57.1%	42.9%	100%
	%within group	30.8%	7.8%	13.5%
Total	Count	39	116	155
	% within BMI	25.2%	74.8%	100%
	%within group	100%	100%	100%

Table 4: CRP-group cross-tabulation

CRP		GROUP		Total
		A-SES	B-Normal TP	
Negative	Count	19	89	108
	%within CRP status	17.6%	82.4%	100%
	% within group	48.7%	76.7%	69.7%
Positive	Count	20	27	47
	%within CRP status	42.6%	57.4%	100%
	% within group	51.3%	23.3%	30.3%
Total	Count	39	116	155
	%within CRP status	25.2%	74.8%	100%
	% within group	100%	100%	100%

Table 5 : Outcome-group cross-tabulation

outcome		GROUP		Total
		A-SES	B-Normal TP	
Expired	Count	7	2	9
	%within CRP status	77.8%	22.2%	100%
	% within group	17.9%	1.7%	5.9%
Improved	Count	32	114	146
	%within CRP status	21.9%	78.1%	100%
	% within group	82.1%	98.3%	94.2%
Total	Count	39	116	155
	%within CRP status	25.2%	74.8%	100%
	% within group	100%	100%	100%

Table 6: Correlation between T3 value and outcome

	outcome	N	Mean	Standard deviation	Std. Error Mean
T3	Improved	146	77.6233	13.18313	1.09104
	Expired	9	52.4444	17.37895	5.79298

Table 7: correlation between rT3 value and outcome

	outcome	N	Mean	Standard deviation	Std. Error Mean
rT3	Improved	146	0.3317	0.13719	0.01135
	Expired	9	0.6433	0.14440	0.04813

Table 8: CHI-SQUARE test for prevalence of SES among ACS

	Value	df	P-Value
Pearson Chi-Square N of Valid Cases	3.101 155	4	.541

Table 9 : CHI-SQUARE test for BMI across SES/Normal TP

	Value	df	P-Value
Pearson Chi-Square N of valid cases	14.523 155	3	0.002

Table 10: CHI-SQUARE test for CRP across SES/Normal TP

	Value	df	P-Value
Pearson Chi-Square N of valid cases	10.836 155	1	0.001

Table 11 : CHI-SQUARE test for SES/Normal TP across Outcome

	Value	df	P-value
Pearson chi-square N of Valid cases	14.048 155	1	0.002

Table 12: Independent samples t-test for Mean T3 across outcome

	t-Test for Equality Means						
	t	df	P- value	Mean difference	Std. Error difference	95% confidence Interval of the Difference	
						Lower	Upper
T3	5.457	153	0.00	25.1788	4.61431	16.06286	34.29483

Table 13: Independent samples t-test for correlation between rT3 and outcome:

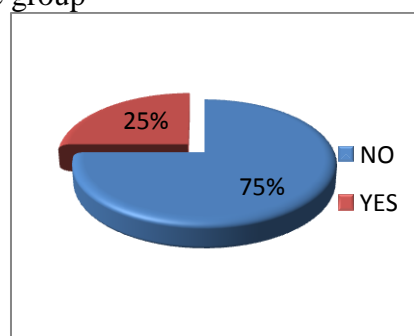|	t-Test for Equality Means						
	t	df	P- value	Mean difference	Std. Error Difference	95% confidence Interval of the Difference	
						Lower	Upper
rT3	-6.595	153	0.000	-0.3116	0.04725	-0.40497	-0.21827

Figure-1: SES/normal thyroid profile group
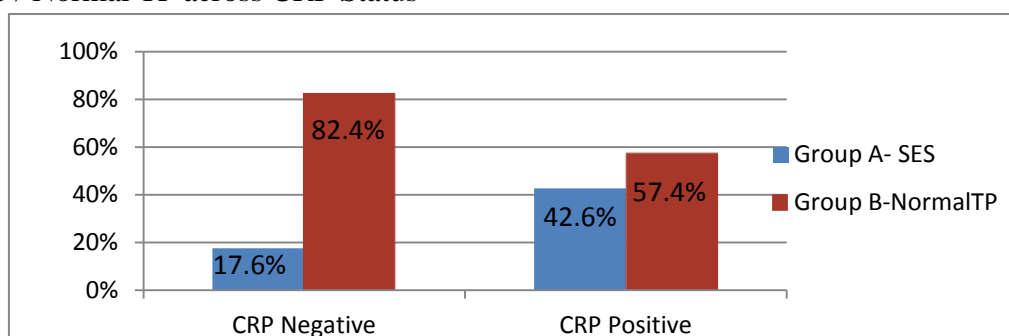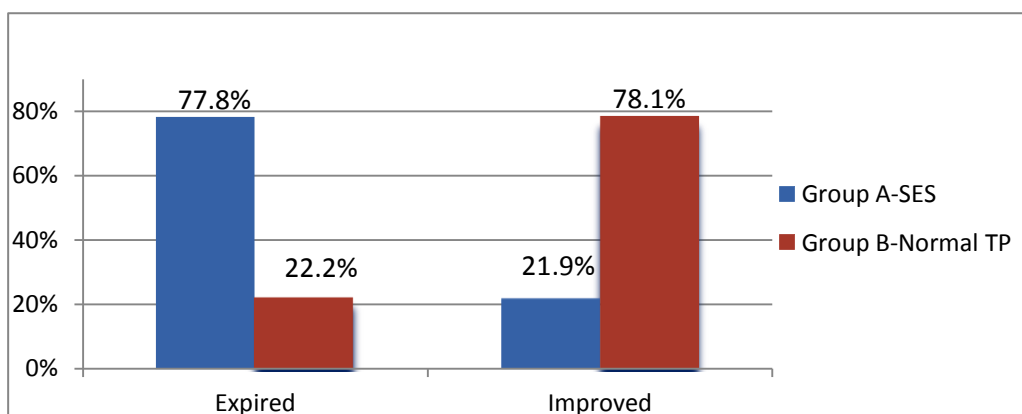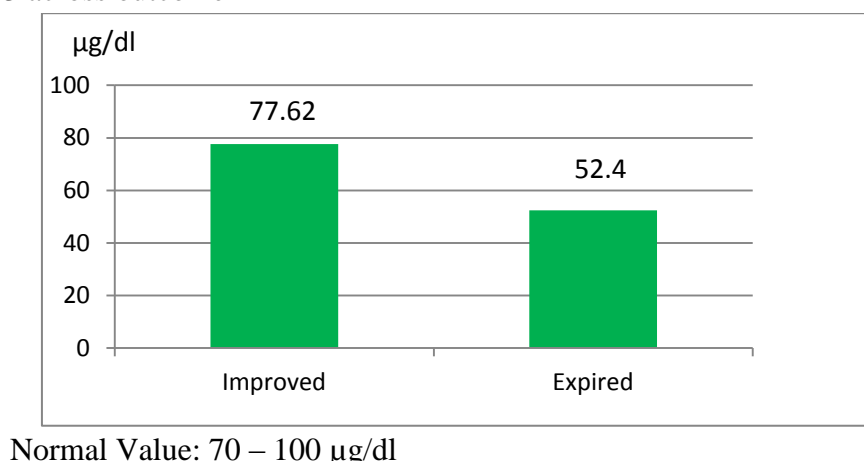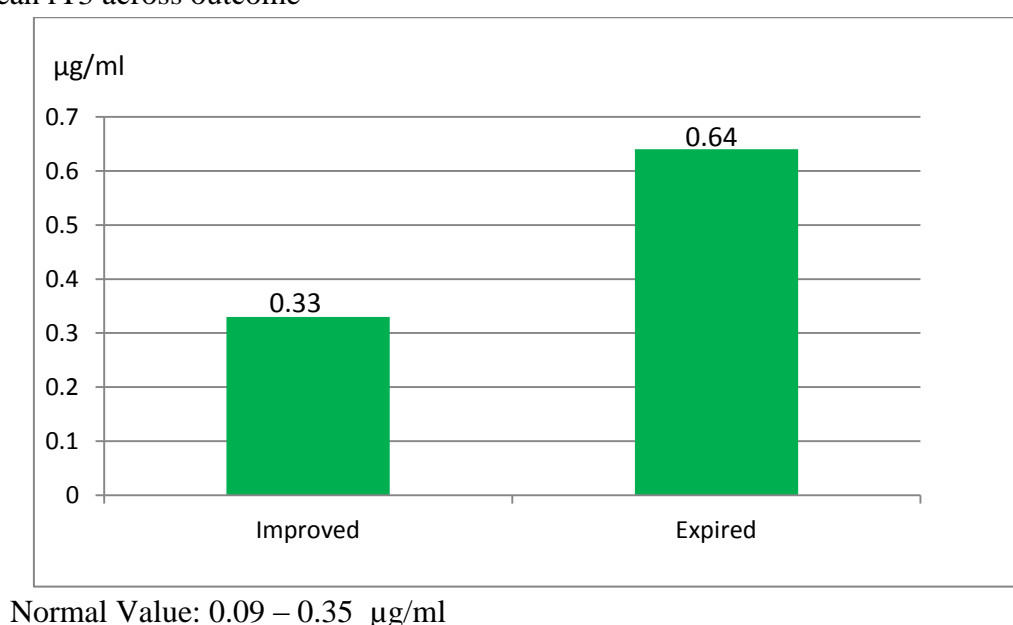
Figure 2: Prevalence of Sick euthyroid syndrome among various type of ACS
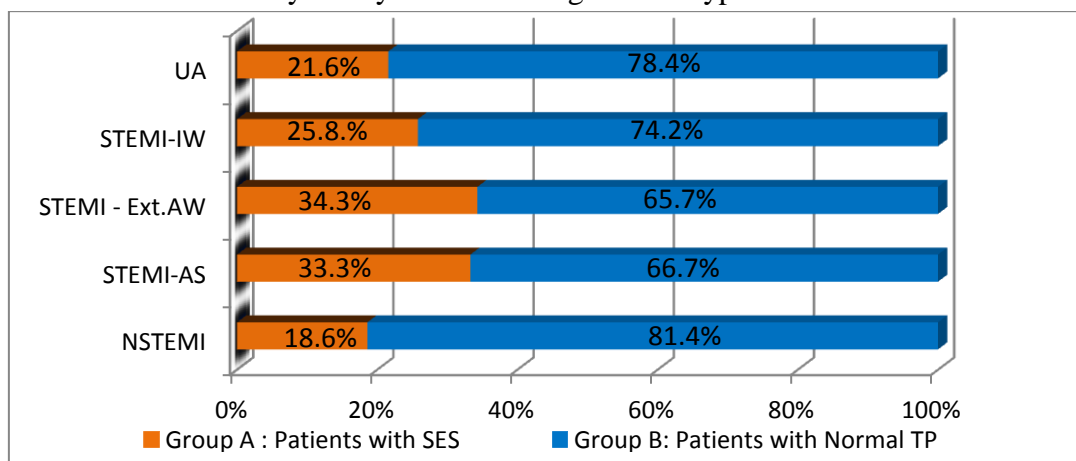
Figure 3: BMI across SES / Normal TP
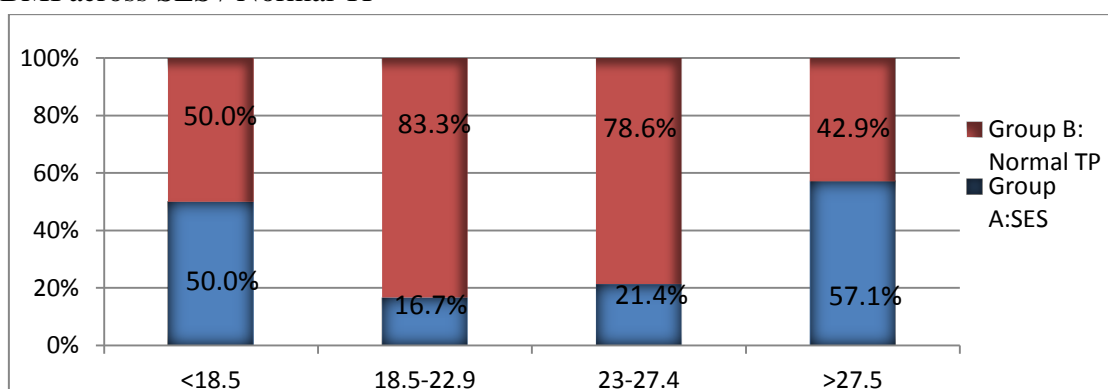
Figure 4: SES / Normal TP across CRP Status

Figure 5 : SES / Normal TP across Outcome

Figure 6 : Mean T3 across outcome

Normal Value: 70 – 100 µg/dl

Figure 7: Mean rT3 across outcome

Normal Value: 0.09 – 0.35 µg/ml

Discussion

ACS is one of the leading causes of morbidity and mortality worldwide. The thyroid hormonal changes could result in the functional derangement of the cellular metabolism affecting all the organs including heart. This study is carried out with the aim of assessing the prevalence of one of the thyroidal hormonal derangement in acute illness, the SES in patients with ACS. In this study of 155 ACS patients, an unadjusted prevalence of SES of 25.2% has been observed which is similar to Ramsden DB, et al[7] who reported 22.7%. When the prevalence of SES in different type of ACS is compared with non SES group this prevalence rate is not significant which is similar to Rodrigo Caetano Pimentel et al[8] but a study by Franklin JA et al reported that the incidence of SES is common in MI than in unstable angina. Distribution of SES in ACS patients and comparison study between Group A (ACS patient with SES) & Group B (ACS patients with normal thyroid profile) on age, in this study 33.3% were less than 40 years, 28.6% were between 41 and 60 years, 15.2% were more than 60 years of age. The significant difference may be due to the confounding factor BMI. Wiersinga WA et al[9] reported equal distribution in all age group. According to sex, 26.8% of females and 24.5% of males had SES. P value is > 0.05 which is insignificant which is similar to Luiz Maurino et al study .[10]

According to BMI, 57.1% of SES are obese, 21.4% are overweight and 16.7% are with normal BMI. P value is 0.002, a significant association between the prevalence of SES and high BMI and Kliridis PA et al study is with similar results[11.] According to diabetic state, 29.5% of diabetes had SES, 18.3% of non-diabetes had SES. Calculated p value is 0.120 and thus not significant which is similar to Langster W et al observation[12.] According to hypertension, both hypertensives and normotensives had equal prevalence of SES. With respect to dyslipidemia there is no statistical significance. According to CRP status, 42.6% of CRP positive ACS patients had SES but only 17.6% CRP negatives had SES. There is a strong association between CRP positivity status and the prevalence of SES. p value is 0.001 and is statistically significant. According to the outcome, in this study nine out of one fifty five expired and out of the nine, seven had SES when compared to two who were with normal thyroid profile. The p value is 0.002 a significant one implying the worst outcome. A study by Escosteguy et al showed similar results.

Study of correlation between Thyroid profile and the outcome among SES patients with ACS is discussed below: There is a significant correlation and hence low level of T3 is associated with worst outcome. Michele Coceani, MD et al reported similar observation[13].

In this study FT3 value neither changed nor affecting the outcome in SES as similar to the study by Wartofsky et al. T4 value correlation is not changed in this study but the study by Kotajima N et al reported T4 value get reduced in severe cases[14]. TSH value remain same in both worst outcome group and improved group in our study where the study by Tauber JL et al reported that in very sick condition T4 is low but the TSH remain normal.[15] There is an association between high rT3 value and worst outcome in our study where report by Utiger RD et al reveals that the rT3 is well associated with high mortality[16].

Conclusion

This study aimed at estimating the prevalence of sick euthyroid state in patients with ACS and also to find out its correlation with various risk factors like BMI, CRP, diabetes, hypertension, lipid profile, and smoking in CAD. Finally, the study is to correlate the thyroid profile with outcome of patients in ACS. The study sample included 155 Acute Coronary Syndrome patients admitted in ICCU and in Medical wards. Each of them was assessed clinically and by laboratory investigated. The initial treatment in the emergency department included the use of oxygen, aspirin, beta blockers, analgesics, nitroglycerin, thrombolysis and or heparin according to the diagnosis and their protocols. The primary observations are the prevalence of 25.2% of patients with acute coronary syndrome had sick euthyroid state. Sick euthyroid state occurred in all types of ACS with equal proportion. Sick euthyroid state significantly associated with High BMI, CRP positivity and this condition is associated with worst outcome. Sick euthyroid state did not significantly correlated with sex, diabetic state, hypertension, dyslipidemia and smoking. The T3 value well correlated with outcome i.e., low T3 is associated with worst outcome among SES patients. The rT3 value also well correlated with outcome i.e., high rT3 is associated with worst outcome among SES patients. Here by sick euthyroid state is also a strong prognostic indicator in ACS.

Conflict of interest

All authors contributed equally to the development and revision of this manuscript

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