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Thyroid Dysfunction in Acute Coronary Syndrome and its Relation to Morbidity and Mortality

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Abstract: ***Background: Thyroid hormones have important effects on the cardiovascular system through direct and indirect mechanisms. A typical pattern of altered thyroid hormone metabolism characterized by low T3 circulating levels has been described in patients with acute myocardial infarction, heart failure and in adults and children after cardiopulmonary bypass. We tried to evaluate the prevalence of thyroid dysfunction in patients with acute coronary syndrome (ACS) and to study the impact of these dysfunctions on morbidity and mortality among those subjects. Subjects and methods: A prospective cohort study conducting on 196 acute coronary syndrome patients divided into 98 patients with STEMI and 98 patients with NSTEMI or unstable angina (UA). They were subjected to full history and clinical examination and routine investigations, ECG, cardiac enzyme and APPACHE II score in addition to estimation of TSH, FT4 and FT3 using enzyme linked immunosorbent assay (ELISA). Results: The prevalence of thyroid dysfunctions in acute coronary syndrome were 23% from which the most prevalent thyroid dysfunction in this study is Euthyroid Sick syndrome (ESS) (68.9%) followed by Subclinical Hypothyroidism (24.5%) then Subclinical Hyperthyroidism (6.6%). Thyroid dysfunction in acute coronary syndrome increases relative risk of occurrence of shock, arrhythmia and reinfarction by 6.04, 2.05 and 1.67 fold respectively than euthyroid patients. Thyroid dysfunction in STEMI group increase relative risk of arrhythmia, reinfarction and Shock by 2.25, 2.4 and 8.3 fold respectively than euthyroid patients while it increases the arrhythmia and shock by 1.5 and 1.4 fold respectively with no impact on reinfarction in NSTEMI & unstable angina group. Significant increase in APACHE II score >14 and mortality in patients with thyroid dysfunction as compared to euthyroid patients. Thyroid dysfunction in acute coronary syndrome increase relative risk of death by 5.49 fold than euthyroid patients. Morbidity and mortality were significantly increased in Euthyroid sick syndrome (low T3 syndrome) in STEMI group with no significant difference in this respect in NSTEMI & unstable angina group. Conclusion: The prevalence of thyroid dysfunction in our cohort of ACS patients was 23%.most prevalent is ESS. UA, NSTEMI and STEMI patients were affected by ESS. ESS was significantly associated with all cause morbidity & mortality which was significant in STEMI group than NSTEMI & UA group.***

Keywords: Thyroid hormones, acute coronary syndromes, euthyroid sick syndrome

1. Introduction

Cardiovascular diseases have been studied in depth and recognized as a serious public health problem. According to data from the Ministry of Health, they are the leading cause of death in Brazil and third leading cause of hospital admission [(1)]. Cardiovascular diseases have similar pathophysiologic mechanisms which lead patient from risk factors, such as dyslipidemia, smoking and high blood pressure to congestive heart failure and finally to death [(2)].Thyroid hormones have a major impact on the cardiovascular system [(3)]. Thyroid diseases are associated with systolic and diastolic cardiac dysfunction, hypertension, and heart rhythm disorders. Overt hypo- as well as hyperthyroidism affect outcomes in patients with CAD. Even subclinical hyperthyroidism can be an independent risk factor for all-cause and cardiovascular mortality [(4)]. Subclinical hypothyroidism was recognized as an independent risk factor for atherosclerosis and myocardial infarction in elderly women [(5)]. Serum thyroid hormone levels have been described in several systemic non-thyroidal illnesses, among them acute heart diseases. The changes observed as "euthyroid sick syndrome", consisting of low total T3 and/or free T3, increased reverse T3 (rT3), and normal TSH, T4 and free T4 levels. These findings described by ***Kimura et al.*** [(6)] in acute myocardial infarction, affecting the prognosis. This change in thyroid function is thought to be associated with the mechanism involved in maintaining energy in face of altered systemic homeostasis caused by the acute ischemic event or directly related to inflammatory cytokines, acting as an inflammatory marker or both. The thyroid hormone system is rapidly down-regulated in acute myocardial infarction (AMI).This may be beneficial during acute ischemia. Patients with angina had higher levels of interleukin-6 and C-reactive protein and more depressed thyroid hormone system in early samples. Thyroid level depression in patients with angina may possibly have been present before the infarction process start [(7)] . Low T_3 concentrations are known to be major independent indicators of mortality in patients hospitalized for cardiac causes [(8)]. Determination of reverse T3 levels may be a valuable and simple aid to improve identification of patients with myocardial infarction who are at high risk of subsequent mortality [(9)]. The importance of recognizing "euthyroid sick syndrome" in coronary heart disease patients, suggesting an association with poor prognosis in patients with acute coronary syndrome [(10)]. Therefore, this study was designed to evaluate the prevalence of thyroid dysfunction in patients with acute coronary syndrome and to study the impact of these dysfunctions on morbidity and mortality among those subjects.

2. Subjects and Methods

This is prospective cohort study conducting in intensive care unit and CCU of internal medicine and cardiology departments and medical biochemistry department, Zagazig University. 196 patient diagnosed as acute coronary

syndrome by typical chest pain with ST-segment elevation in 2 or more contiguous leads or presumed new LBBB with elevated cardiac enzyme and classified as ST-segment elevation MI (STEMI), or ischemic ST-segment depression >0.5 mm (0.05mV) or dynamic T-wave inversion with pain or discomfort is classified as NSTEMI in case of elevated cardiac enzyme or UA in case of normal cardiac enzyme [(11)]. Patients were selected and divided according type of ACS into 98 patients with STEMI, 98 patients with NSTEMI &UA. All Patients were followed up for major cardiovascular adverse event (MCAE) which includes (arrhythmia, shock reinfarction) and mortality for 6 months. The mean age of the patients was 58.4 ± 9.56 years, 135 patients (68.9%) were males and 61 (31.1%) were females, 110 patients (56.1%) were diabetic,104 patients (53.1%) were hypertensive, 55 patient (28.1) were dyslipidaemic and 97 patients (49.5%) were current smokers**.**

Inclusion criteria: Patients with acute coronary syndrome above 30 years, irrespective of gender, race, ethnic group or clinical severity.

Exclusion criteria: Patients using corticosteroids, amiodarone, known thyroid disease or those who are taking thyroid drugs regularly**,** patients receiving any iodinated contrast agent within the previous two weeks, patients with established diseases, such as neoplasias, chronic renal failure, chronic obstructive pulmonary disease, liver cirrhosis, active infection and any conditions that are known to affect thyroid function tests.

Ethical Clearance: Written informed consent was taken from all patients to participate in this study. Approval for performing the study was obtained from ICU unit of internal medicine, cardiology and Medical Biochemistry departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval

Methods: All patients of this study were subjected to the following:

A) Full history taking:

Thorough history of the present illness and past history of previous hospital admission and any medical disorder with particular attention to hypertension, diabetes mellitus, cardiovascular disease, dyslipidemia, thyroid disorders, previous history of cardiac attack and family history of similar conditions.

B) Thorough clinical examination: With stress on:

- Blood pressure measurement after patient admission. It was measured by a mercury sphygmomanometer with the subject recumbent in bed, with the arm supported and positioned at the level of the heart. Mean blood pressure:

$$MAP \simeq \frac{(2 \times DP) + SP}{3}$$

- Pulse examination to show any abnormality and any special character.
- Temperature and respiratory rate.
- Cardiovascular examination.
- Other systems examination.

C) Routine investigations:

1. **Laboratory investigations**: CK-MB, troponin, CBC, LFT, KFT, lipid profile, PT, PTT, INR, ABG, RBS.
2. **Other investigation:** ECG, ECHO, other radiological investigations when need during stay in ICU.

D) Severity assessment: This was done by using the most commonly used scoring systems in ICU which is APACHE II score**.**

E) Special investigation: include measurement of serum TSH, FT4, FT3 levels by ELISA kits supplied by PRECHEK^{TM}.

3. Statistical Method

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data, the following tests were used to test differences for significance; Differences between frequencies (qualitative variables) in groups were compared by Chi-square test. Differences between means (quantitative variables) in two parametric groups were compared by Student's t-test and non parametric group by Mann Whitney Pearson correlation for parametric correlation. P value was set at <0.05 for significant results. Data were collected and submitted to statistical analysis [(12)].

4. Results

The mean age of the patients was 58.4 ± 9.56 years, 135 patients (68.9%) were males and 61 (31.1%) were females, according to thyroid profile, 151 patients (77%) had euthyroid status and 45 patients (23%) had thyroid dysfunction. The most prevalent thyroid dysfunction in study is Euthyroid Sick syndrome (ESS) (68.9%) followed by Subclinical Hypothyroidism (24.5%) then Subclinical Hyperthyroidism (6.6%). Significant increase in the occurrence of each of shock and mortality in thyroid dysfunction in comparison to euthyroid patients (P value <0.001, P value <0.0002 respectively) was detected. This study detected a significant increase of MCAE and mortality in thyroid dysfunction patients in STEMI group, while no significant difference in NSTEMI and UA group as compared to euthyroid patients. Thyroid dysfunction increases relative risk of occurrence of shock, arrhythmia and reinfarction by 6.04, 2.05 and 1.67 fold respectively than euthyroid function in acute coronary syndrome. Thyroid dysfunction increases relative risk of arrhythmia, reinfarction by 2.25 and 2.4 fold respectively than euthyroid function in STEMI group, while it increases the arrhythmia by 1.5 fold with no impact on reinfarction in NSTEMI and unstable angina group. Significant increase in MCAE and Mortality in sick euthyroid patients compared to euthyroid patients in acute coronary patient was noticed. Also, the study detected a significant increase in MCAE in euthyroid sick patients as compared to euthyroid patients in STEMI group (p=0.001), while there was no significant difference in NSTEMI and Unstable angina group (p=<0.557). There was a significant increase in mortality in sick euthyroid patients as compared to euthyroid patient in STEMI group (p=0.0001), while there was no significant difference in

NSTEMI and Unstable angina group (p= 0.577). By multivariate logistic regression it was found that: Diabetes mellitus is the most independent predictor of MCAE in acute coronary syndrome followed by sick euthyroid syndrome and APACHE II score (p= <0.001, p=0.027, p=0.042 respectively). By multivariate logistic regression it was found that APACHE II score is the most independent predictor of mortality in acute coronary syndrome patients followed by sick euthyroid syndrome (p=0.001, p=0.00).

Table 1: The thyroid function, type of dysfunction, MCAE and mortality of acute coronary syndrome patients

	Acute coronary syndrome (N=196)	
	Mean ± SD	Reference range
FT3	4.86 ± 1.75	(2.8-7.3 pmol/l)
FT4	9.01 ± 1.22	(8.5-22.5pmol/l)
TSH	1.57 ± 1.54	(0.4-5.5 µiu/ml)
	No	**%**
Thyroid function		
Euthyroid	151	77%
Thyroid dysfunction	45	23%
euthyroid Sick syndrome	31	15.8%
Subclinical Hypothyroidism	11	5.6%
Subclinical Hyperthyroidism	3	1.5%
MCAE		
Arrhythmia	27	13.7%
reinfarction	12	6.1%
Shock	14	7.1%
MORTALITY		
No	181	92.3%
Yes	15	7.6%

Table 2: prevalence of euthyroid sick syndrome as thyroid dysfunction

	Thyroid dysfunction (n=45)		Acute coronary syndrome
	No	%	%
Euthyroid Sick syndrome (ESS)	31	68.9	15.8%
Subclinical Hypothyroidism	11	24.5	5.6%
Subclinical Hyperthyroidism	3	6.6	1.5%

Table 3: Relative risk of thyroid disorders on arrhythmia, reinfarction and shock in patients with acute coronary syndrome

	Thyroid dysfunction	Euthyroid function	**RR**
Arrhythmia	16	11	
Sinus rhythm	135	34	2.05 fold
reinfarction	8	4	
No reinfarction	143	41	1.67 fold
Shock	5	9	
Hemodynamic stable	146	36	6.04 fold

Table 4: Comparison between patients with euthyroid function and patients with thyroid dysfunction in studied groups (STEMI and NSTEMI& UA) as regard the MCAE

MCAE	**STEMI patients (N=98)**				**Test**	**p-value**
	Euthyroid function (N=71)		**Thyroid dysfunction (N=27)**			
	No	**%**	**No**	**%**	χ^2	
No	58	81.7%	8	29.6%	24.109	<0.001 (HS)
Yes	13	18.3%	19	70.4%		
Arrhythmia	8	11.3%	8	29.6%	2.28	0.140 (NS)
Re-infarction	3	4.2%	3	11.1%	1.614	0.204 (NS)
Shock	2	2.8%	8	29.6%	15.348	<0.001 (HS)
MCAE	**NSTEMI & unstable angina patients (N=98)**					
No	64	80%	13	72.2%	0.528	0.467 (NS)
Yes	16	20%	5	27.8%		
Arrhythmia	8	10%	3	16.7%	0.655	0.418 (NS)
Re-infarction	5	6.3%	1	5.6%	0.012	0.912 (NS)
Shock	3	3.8%	1	5.6%	0.122	0.726 (NS)

Table 5: Comparison between patients with euthyroid function and patients with euthyroid sick function in studied groups (STEMI and NSTEMI& UA) as regard the MCAE

MCAE	STEMI patients (N=98)				Test	p-value
	Euthyroid function (N=71)		Thyroid dysfunction (N=20)			
	No	%	No	%	χ^2	
No	58	81.7%	4	20%		
Yes	13	18.3%	16	80%	24.58	<0.001 (HS)
MCAE	NSTEMI & unstable angina patients (N=98)					
No	64	80%	8	72.7%		
Yes	16	20%	3	27.3%	0.309	<0.557 (NS)

Table 6: Comparison between patients with euthyroid function and patients with thyroid dysfunction in studied groups (STEMI and NSTEMI& UA) as regard the mortality:

Mortality	STEMI patients (N=98)				Test	p-value
	Euthyroid function (N=71)		Thyroid dysfunction (N=27)			
	No	%	No	%	χ^2	
Deceased	2	2.8%	9	33.3%	13.063	<0.0003 (HS)
Survive	69	97.2%	18	66.7%		
Mortality	NSTEMI & unstable angina patients (N=98)					
	Euthyroid function (N=80)		Thyroid dysfunction (N=18)			
Deceased	3	3.8%	1	5.5%		
Survive	77	96.2%	17	94.5%	0.095	0.757 (NS)

Table 7: Relative risk of thyroid disorders on mortality in patients with acute coronary syndrome

	Deceased	Survived	Total
Thyroid dysfunction	10	35	45
Euthyroid function	5	146	151
Total	15	181	196

RR=5.49 fold

Table 8: Comparison between patients with euthyroid function and patients with sick euthyroid function in studied groups (STEMI and NSTEMI& UA) as regard the Mortality

Mortality	STEMI patients (N=98)				Test	p-value
	Euthyroid function (N=71)		Thyroid dysfunction (N=20)			
	No	%	No	%	χ^2	
Deceased	2	2.8%	9	45%		
Survive	69	97.2%	11	55%	22.3	<0.0001 (HS)
Mortality	NSTEMI & unstable angina patients (N=98)					
Deceased	3	3.7%	1	45%		
Survive	77	96.3%	10	55%	0.3096	0.577(NS)

Table 9: Multivariate logistic regression of potential predictors of MCAE in acute coronary syndrome patients

Variables ǂ	β	SE	Adjusted OR*	95% CI	p (Sig.)
Diabetes mellitus	+2.520	0.535	12.426	(4.354 – 35.468)	<0.001 (HS)
Euthyroid sick syndrome	+1.622	0.731	5.063	(1.207 – 21.231)	0.027 (S)
APACHE II score	+0.088	0.043	1.092	(1.003 – 1.188)	0.042 (S)
Type (STEMI/Non STEMI)	+0.386	0.417	1.472	(0.650 – 3.333)	0.354 (NS)
CK-MB (IU/L)	0.000	0.002	1.000	(0.995 – 1.004)	0.910 (NS)
FT3	+0.037	0.157	1.038	(0.764 – 1.411)	0.811 (NS)
Subclinical hypothyroidism	+0.993	0.854	2.699	(0.506 – 14.394)	0.245 (NS)
Subclinical hyperthyroidism	+2.360	1.524	10.586	(0.534 – 209.841)	0.122 (NS)
Constant	-4.438				

Table 10: Multivariate logistic regression of potential predictors of mortality in acute coronary syndrome patients

Variables ǂ	β	SE	Adjusted OR*	95% CI	p (Sig.)
APACHE II score	+0.544	0.155	1.723	(1.271 – 2.336)	<0.001 (HS)
Sick euthyroid	+4.658	1.713	105.377	(3.669 – 3026.634)	0.007 (HS)
Type (STEMI/Non STEMI)	-3.190	1.852	0.041	(0.001 – 1.551)	0.085 (NS)
Sex (male/female)	-0.838	1.446	0.433	(0.025 – 7.360)	0.562 (NS)
Diabetes mellitus	-0.137	1.283	0.872	(0.071 – 10.773)	0.915 (NS)
Triglycerides (mg/dl)	-0.118	0.071	0.888	(0.773 – 1.021)	0.095 (NS)
HCO3- (mEq/L)	-0.040	0.088	0.961	(0.809 – 1.141)	0.650 (NS)
CK-MB (IU/L)	+0.005	0.008	1.005	(0.990 – 1.020)	0.528 (NS)
Subclinical hypothyroidism	-7.308	67.683	0.001	(0.000 – 2.739)	0.914 (NS)
Subclinical hyperthyroidism	-7.416	126.165	0.001	(0.000 – 1.482)	0.953 (NS)
Constant	+3.313				

5. Discussion

The cardiovascular system is one of the most important targets on which thyroid hormones act [(13)]. A typical pattern of altered thyroid hormone metabolism characterized by low T3 circulating levels has been described in patients with acute myocardial infarction, heart failure and in adults and children after cardiopulmonary bypass [(14)]. This low-T3 syndrome has commonly been interpreted by the medical community as an euthyroid sick syndrome, an adaptive compensatory and thus beneficial response that decreases energy consumption in diseased states [(15).] Therefore, we tried to evaluate the prevalence of thyroid dysfunction in patients with acute coronary syndrome (ACS) in intensive care unit of Zagazig university hospital and to study the impact of these dysfunctions on morbidity and mortality among those subjects.

The current study showed that 151 patients (77%) had euthyroid status and 45 patients (23%) had thyroid dysfunction which include: 31 patient euthyroid sick syndrome (68.9%), 11 patients had Subclinical Hypothyroidism with elevation of serum TSH & normal serum FT3, FT4 levels (24.5%) and 3 patients had Subclinical Hyperthyroidism with low TSH & normal serum FT4, FT3 levels (6.6%), this was in line with ***Kazim et al.*** [(16)] who reported that out of 457 acute coronary patient, 72 patients (15%) had thyroid dysfunction, also the same results in another study conducted by ***Sabrinae et al.*** [(17)] was reported. The overall prevalence of mild thyroid dysfunction was 43.6% of total acute cardiac patients. Out of them, 68 were subclinical hypothyroidism (6.6% of the total population), 23 subclinical hyperthyroidism (2.2%) and 356 Low T3 as ESS (34.7%) and ***Wang et al.*** [(18)] studied 582 patient with STEMI and they found that, 76 patients (13.06%) had abnormalities in thyroid function tests. The low-T3 syndrome was the most frequent abnormality. On the other hand in a study conducted by ***Adawiyah et al.*** [(19)], they reported that the prevalence of ESS was 53% in their cohort and this difference may be due to their small sample size as they did their study on 85 ACS patients only. Most frequent in our study was low T3 syndrome (euthyroid sick syndrome) 15.8 % from total patient and 68.9% of total thyroid dysfunction which is consistent with ***Wang et al.*** [(18)] who reported that the low-T3 syndrome was the most frequent pattern. Another study conducted by ***Sabrinae et al.*** [(17)] reported out of 1026 acute cardiac patients, low T3 was found in 34.7%. Also, ***Michele et al.*** [(20)] studied the cohort consisted of 1047 clinically and biochemically euthyroid patients underwent coronary angiography for suspected CAD and they found that 75% of the population had normal free T3 levels and the remaining 25% had low T3 syndrome;

none of the patients had increased levels of free T3. Mechanisms underlying the euthyroid sick syndrome are likely to be related to hormone changes in concentration, distribution, production, clearance, affinity to carrier proteins and response to target organs [(21)]. Some theories have been proposed to justify the "euthyroid sick syndrome", such as decrease in the extra thyroidal conversion of T4 to T3 secondary to lower extracellular clearance of T4 or reduced 5'deiodinase enzyme activity. Other mechanisms may be involved: reduced thyrotropin secretion, with decreased T3 and T4; thyroxine-binding globulin, albumin and the affinity of both to thyroid hormones may be reduced, impairing 5' monodeiodinase's action and T4 and T3 uptake, as well as these post-receptors action[(22)]. In contrast with our study ***Saurabh et al.*** [(23)] reported that euthyroid sick syndrome is the increase in free T4 level. Many theories explain increase free T4 in non thyroidal illness as T4-binding prealbumin (TBPA), and albumin are reduced during non thyroidal illness, there is studies postulate the existence of a binding inhibitor that could explain the observed alterations in free T4 fraction. In this study, we evaluate our patients during inhospital stay and after discharge for major cardiovascular adverse event (MCAE) and mortality during period of 6 month. It was found that 53 patients developed MCAE (27.0%) and 15 patient deceased (7.6%) as whole. However, there was a significant increase of MCAE and mortality (p value <0.0002) in acute coronary syndrome patients with thyroid dysfunction and ESS in comparison to euthyroid patients. These results were in consistent with ***Pimentel et al.*** [(24)] who studied 70 patients with both ST elevation and non-ST elevation myocardial infarction (NSTEMI). They found that in-hospital mortality of the euthyroid sick group was significantly higher than euthyroid subjects. Also, **Kazim *et al.*** [(16)] reported that thyroid dysfunction, particularly sick euthyroid syndrome, was found to be related to inhospital and long term mortality in patients with STEMI undergoing primary percutaneous intervention. ***Lazzeri et al.*** [(25)] found that the failure of intervention was also higher in patients with sick euthyroid syndrome on 641 STEMI patients. Moreover, ***Molinaro et al.*** [(26)] found that cardiac mortality was higher in the group with subclinical hypothyroidism and sick euthyroid syndrome in their study which was conducted on 1026 patient with acute cardiac disease for 3 month duration. Thyroid hormone (TH), apart from its "classical" actions on cardiac contractility and heart rhythm, appears to regulate various intracellular signaling pathways related to response to stress and cardiac remodeling. It affects cardiac remodeling by limiting reperfusion injury, and at later states, by inducing distinct changes in cardiac chamber geometry in a time dependent manner [(27)]. In the other hand, ***Bayrak et al.*** [(28)] noted no relationship between thyroid hormone levels and sudden cardiac death and major cardiovascular disorders at 3 and 6 months follow-up and this difference because the type of thyroid dysfunction in their study was mainly subclinical hypothyroidism and less frequent ESS. As regard to the type of cardiac insult the present study showed a significant increase in MCAE in thyroid dysfunction and also ESS patients in STEMI group (p<0.001) while there was no significant increase of MCAE in NSTEMI and unstable angina [(22)]. In contrast to our result, ***Rodrigo et al.*** [(29)] reported no significance difference between two groups as regard prognosis. Also, ***Adawiyah et al.*** [(19)] reported that ESS in patients with ACS is associated with increased cardiovascular mortality and morbidity and affects UA, NSTEMI and STEMI equally. This difference may be due to their small sample size which was done on 85 ACS patients and most of their patients had more killips class III and IV during hospital stay. In our study we found that thyroid dysfunction in acute coronary syndrome increases thee relative risk of occurrence of shock, arrhythmia and reinfarction by 6.04, 2.05 and 1.67 fold respectively than euthyroid patients. Similar result was reported by ***Adawiyah et al.*** [(19)] who found that ESS increase incidence of arrhythmia and re admission by 15. 6% and 22.2% than euthyroid patient which was 5% and 2% respectively. Our study found that thyroid dysfunction in STEMI group increase relative risk of arrhythmia, reinfarction by 2.25 and 2.4 fold respectively than euthyroid patients while it increases the arrhythmia by 1.5 fold with no impact on reinfarction in NSTEMI and unstable angina group which is consistent with ***Wartofsky et al.*** [(22)] who reported that ESS had no significant increase of morbidity in NSTEMI and UA. Also Thyroid dysfunction in STEMI group increase relative risk of Shock by 8.3 fold than euthyroid patients in comparison to 1.4 fold in NSTEMI and unstable angina group. This was in same line with ***Shilpa and Prashant*** [(30)] who reported decreased left ventricular ejection fraction (LVEF) significantly more in patients who had reduction of serum T3 (p<0.001). ***Pantose et al.*** [(31)] found significant correlation between total T3 and EF% (r=0.56, p=0.0004). ***Adawiyah et al.*** [(19)] noted significant difference in killips classification on day-1 between ESS and non ESS group (p=0.030). In their study, more patients admitted with killips class III and IV (cardiogenic shock) developed ESS and they concluded that thyroid hormones are important for the systolic as well as diastolic functions of the heart. When the thyroid hormone system is down-regulated in AMI, intracellular calcium handling is affected in a way that may contribute to myocardial stunning and reperfusion injury due to calcium overload. Furthermore, there is increased systemic vascular resistance leading to increased cardiac workload due to this down-regulation. If the heart is unable to cope with this, cardiac output and consequently LVEF is reduced. As regard mortality we found statistically significant increase in mortality among thyroid dysfunction patients and ESS (p <0.0003) and (p <0001) respectively in STEMI group as compared to NSTEMI and unstable angina group and thyroid dysfunction in STEMI group increase relative risk of mortality by 9.1 fold than euthyroid patients in comparison to 1.4 fold in NSTEMI and unstable angina group. This was in line with ***Wartofsky et al.*** [(22)] who reported that the importance of recognizing the "Euthyroid Sick Syndrome" in coronary heart disease patients, suggesting an association with poorer prognosis in patients with ST elevated myocardial infarction in form of increased mortality than those with NSTEMI and unstable angina. In contrast to these result, ***Adawiyah et al.*** [(19)] reported no significant difference between STEMI and NSTEMI and UA regarding mortality. This difference may be due to their patient had more killips class III and IV during hospital stay. A forward stepwise multivariate logistic regression analysis was conducted to determine the independent predictors of morbidity in ACS. It was found that hyperglycemia followed by euthyroid sick syndrome (ESS) and increase APPACHE II score > 14 are independent predictor of morbidity (odds

ratio=12.426, 5.063 and 1.092) respectively. This is in agreement with ***Drazner et al., Adawiyah et al., Molinaro et al. and Saurabh et al.*** [32, 19, 26 and 23] who reported that ESS predicts the risk of MCAE than euthyroid patients. Also, we found that APACHE II score > 14 and the presence of ESS (p= 0.007) are most independent predictor of mortality in ACS in our study. This is in agreement with ***Drazner et al., Giorgio et al., Adawiyah et al., Lazzeri et al. and Molinaro et al.*** [32,33,19,25,26] who found that low-T3 syndrome is a strong predictor of death in cardiac patients and might be directly implicated in the poor prognosis of cardiac patients. The APACHE II score is the most commonly used predictor of mortality in intensive care patients. This score involves 12 routine physiological measurements, age and previous health status. It ranges from 0 to 71 points and correlates with the severity of illness [34]. However, this score does not consider hormonal responses to illness, particularly serum levels of cortisol and thyroid hormones, which have been shown to be highly associated with mortality in critically ill patients [35]. Therefore, we can consider that the most important predictor of mortality in ACS is the presence of ESS in those subjects.

6. Conclusion and Recommendations

We can conclude that the thyroid dysfunction in our cohort of ACS is highly prevalent as 23% of our patients experienced thyroid dysfunction and these dysfunction were reported in both STEMI and NSTEMI&UA subjects and the most frequent dysfunction was ESS and ESS was significantly associated with all cause morbidity and mortality but more significant in STEMI group than NSTEMI &UA group. We recommend:

1. Test for thyroid disorders in acute coronary syndrome can give predictor for risk of morbidity and mortality in those subjects.
2. The addition of thyroid dysfunction to APACHE II score for measurement of severity and predict mortality on those subjects of ACS.
3. There is a need for further studies designed to answer the question whether restoration of euthyroidism might influence morbidity and mortality or not?

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