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Thyroid Dysfunction and its Relation to Myocardial Performance among Patients with Acute Myocardial Infarction

Ahmed Hussein El Sherif

Professor of critical care medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Rania Mostafa Elhusseiny

Professor of critical care medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Hanan Elsayed Zaghla

Professor of critical care medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Abdelraof Fahmy Ahmed

Lecturer of critical care medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Mohammed Salah Ismail Youssef

Critical Care Specialist, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract--Background: The cardiovascular system is one of the most important targets on which thyroid hormones act, thyroid hormone has a major role in the cardiovascular system function and cardiac hemodynamics. Objectives: The primary aim of our study was to evaluate the prevalence of thyroid dysfunction in patients with acute myocardial infarction and to study the impact of these dysfunctions on in-hospital morbidity and mortality among those subjects. Patients and Methods: This study was conducted on one hundred critically ill patients admitted to the critical care department with the diagnosis of acute myocardial infarction in the period from April 2017 to January 2019. Results: According to thyroid profile, 78 patients (78%) had euthyroid status and the remaining 22 patients (22%) had thyroid dysfunctions which include: 12 patients (54.54%) were euthyroid sick syndrome, 7 patients (13.81%) had subclinical hypothyroidism, 3 patients (13.63%) had subclinical hyperthyroidism. Conclusion: Thyroid dysfunction in association with acute myocardial

infarction affect the myocardial performance and this was evident in our study by lower ejection fraction, higher initial killip class, higher wall motion score index, and increased myocardial performance index compared to those with normal thyroid status but it has no impact on the in-hospital mortality.

Keywords---thyroid dysfunction, myocardial performance, morbidity & mortality, acute myocardial infarction.

Introduction

Coronary artery disease (CAD), its acute form, and acute coronary syndrome (ACS) are the major cause of death all over the world ⁽¹⁾. Thyroid hormones have a major impact on the cardiovascular system ⁽²⁾. Subclinical hyperthyroidism can be an independent risk factor for all-cause and cardiovascular mortality ⁽³⁾.

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.* ⁽⁴⁾ in acute myocardial infarction, affecting the prognosis. Low T3 concentrations are known to be major independent indicators of mortality in patients hospitalized for cardiac causes ⁽⁵⁾.

The importance of recognizing "euthyroid sick syndrome" (ESS) in coronary heart disease patients, suggesting an association with poor prognosis in patients with acute coronary syndrome ⁽⁶⁾. Therefore, this study was designed to evaluate the prevalence of thyroid dysfunction in patients with acute myocardial infarction and to study the impact of these dysfunctions on morbidity and mortality among those subjects.

Patients & Methods

This was a prospective observational study that involved one hundred patients admitted with the diagnosis of acute myocardial infarction (STEMI & NSTEMI) irrespective of age, gender, race and clinical severity, during the period from April 2017 to January 2019 and followed up during the in-hospital stay. Written informed consent was taken from all patients to participate in this study. Approval for performing the study was obtained from critical care department, Cairo University.

Excluded from our study, Patients with known thyroid illness or receiving medications that can affect thyroid function tests (Amiodarone, Corticosteroids or received any iodinated contrast agent within the previous two weeks), or those with diseases that are known to affect thyroid function tests, such as chronic renal failure, liver cirrhosis, active infection, and diabetic ketoacidosis.

Each patient was subjected to:

Detailed history: Personal history, history of the present illness, past history of previous medical admission and any medical disorder with particular attention to thyroid disorders and to risk factors for developing coronary artery disease.

Clinical examination: Including general and cardiac examination

Electrocardiography: Resting standard 12 leads electrocardiogram to detect any findings consistent with CAD either ST elevation or depression or T wave inversion or pathological Q waves or new onset LBBB.

Laboratory tests: venous blood samples were obtained from all patients on arrival for: Routine labs: [CBC, liver function tests, kidney function tests, random blood sugar, Na⁺ & K⁺ levels, serum cardiac markers: troponin (cTn) and creatin kinase MB isoenzyme (CK-MB), and lipid profile: Total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)]. Thyroid function tests: TSH, FT4, FT3 levels were measured by using ELISA kits supplied by PRECHEK™ Measured hormones and their individual reference values were TSH (0.27 - 4.5mIU/mL), FT3 (1.7–4.2 pg/mL), and FT4 (0.8–1.8ng/dL). Based on their thyroid function tests, participants' characteristics were categorized into one of the following 6 groups: Euthyroidism was determined as a normal TSH dilution of (0.27 - 4.5mIU/L). Overt hypothyroidism was demarcated as a TSH ≥ 10 mIU/L and free T4 concentration level; less than normal. Subclinical hypothyroidism as having TSH concentration > 4.50 and <10 mIU/L with a normal free T4 concentration. Overt thyrotoxicosis was characterized by TSH concentration < 0.10 mIU/L with an elevated free thyroxin level. Subclinical hyperthyroidism was characterized by TSH concentration ≥ 0.10 and < 0.45 mIU/L, or < 0.10mIU/L with a normal free T4 concentration. Euthyroid sick syndrome is a condition characterized by decreased levels of FT4, FT3 and TSH.

Echocardiography

Two-dimensional echocardiography and Doppler examination were performed for all patients to evaluate left ventricular ejection fraction (LVEF %), wall motion score index (WMSI), myocardial performance index (MPI), and to detect any ischemic complications.

Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). Comparison between 3 groups was done using Kruskal-Wallis test (non-parametric ANOVA) then post-Hoc test was used for pair-wise comparison based on Kruskal-Wallis distribution. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results

Our study conducted on one hundred patients (50 males & 50 females) with mean age (54.3 ± 8.8) years. 57 patients admitted with acute ST elevation myocardial infarction (STEMI) and 43 patients with Non-ST elevation myocardial infarction (Non-STEMI). Among all patients studied dyslipidaemia was the most common risk factor (57 %) followed by hypertension (52 %), male gender (50 %), smoking (38 %), history of IHD (38 %), DM (23 %) & patients with positive family history of IHD (15 %) as shown in table (1).

According to thyroid profile, 78 patients (78%) had euthyroid status and the remaining 22 patients (22%) had thyroid dysfunction (figure 2) which include: 12 patients (54.54%) were euthyroid sick syndrome, 7 patients (13.81%) had subclinical hypothyroidism, 3 patients (13.63%) had subclinical hyperthyroidism, and none of the patients in our study had neither overt hypothyroidism nor overt hyperthyroidism (table 2).

From all cases studied 71 patients were presented with Killip 1 (71 %), 17 patients with Killip 2 (17 %), 8 patients with Killip 3 (8 %), and 4 patients with Killip class 4 (4 %). 50 % of patients have fair left ventricular ejection fraction (LVEF) $\geq 50\%$ and 50 % of patients have low ejection fraction (LVEF) $< 50\%$ with mean left ventricular ejection fraction (LVEF %) in studied patients was (51.6 ± 9.8) (ranges from 27 – 69 %). In studied patients the mean WMSI was (1.61 ± 0.38) (ranges from 1.0 – 2.56) as was calculated from 16-segment model of the left ventricle using 2D images.

In our study there was no significant difference between the type of myocardial infarction (STEMI & NSTEMI) and thyroid status (p value = 0.477). As shown in figure (6) the mean LVEF was significantly lower in patients with thyroid dysfunction than in patients with euthyroid state (45.0 ± 6.7 vs. 53.4 ± 9 , $p < 0.001$). Also patients with thyroid dysfunction had higher WMSI (1.87 ± 0.25 vs. 1.53 ± 0.83 , $p < 0.001$) (figure 7), and a higher myocardial performance index (MPI ≥ 0.45) (100.0% vs. 51.3%, $p < 0.001$) with mean MPI (0.555 ± 0.062 vs. 0.473 ± 0.117 , $p = 0.002$) (figure 8) than that of patients with normal thyroid profile.

Complications and thyroid status: Compared to patients in euthyroid state, patients with thyroid dysfunction have no significant increase in post MI angina (13.6 % vs. 11.5%, $p = 0.789$), mechanical complications (4.5% vs. 1.3%, $p = 0.390$), pericarditis & pericardial effusion (4.5 % vs. 0.0 %, $p = 0.220$), arrhythmias prevalence (13.6 % vs. 12.8 %, $p = 0.920$), and cardiogenic shock (4.5 % vs. 3.8 %, $p = 1.0$).

In-hospital mortality and thyroid status: Finally in our study the in-hospital mortality was 3.8% in patients with normal thyroid profile vs. 4.5% in those with thyroid dysfunction and there was no statistically significant difference between patients with thyroid dysfunction ($p = 1.0$) (table 3).

Table 1
CAD risk factors among all patients

Variable	Risk factors (N=100) %
Dyslipidemia	57
Hypertension	52
Male gender	50
Smoking	38
History of IHD	38
DM	23
Family history of IHD	15

Table 2
Thyroid function in study population

Thyroid function	N (%)	%
Euthyroid	78	78.0%
Thyroid dysfunction	22	22.0%
Euthyroid sick syndrome (ESS)	12 (54.5 %)	12%
Subclinical hypothyroidism (SCH)	7 (31.9 %)	7%
Subclinical hyperthyroidism	3 (13.6 %)	3%

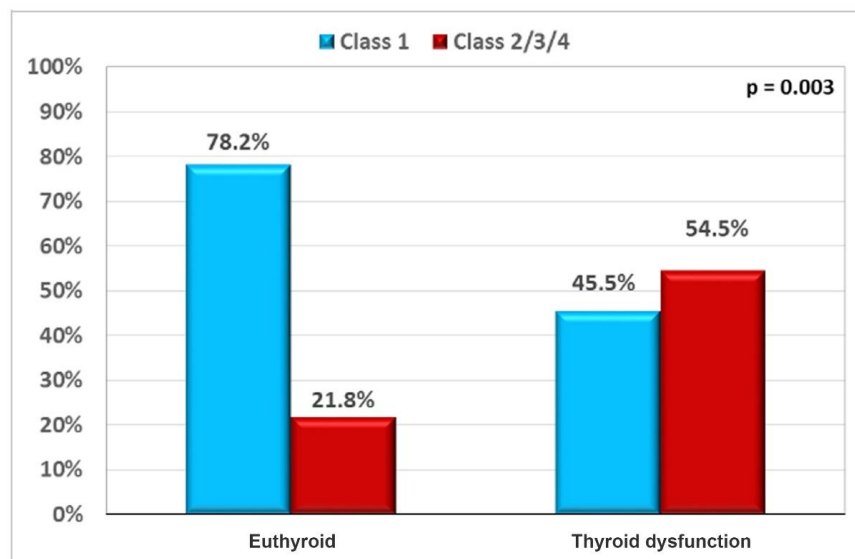


Figure 1. Initial Killip classification and thyroid status in study population

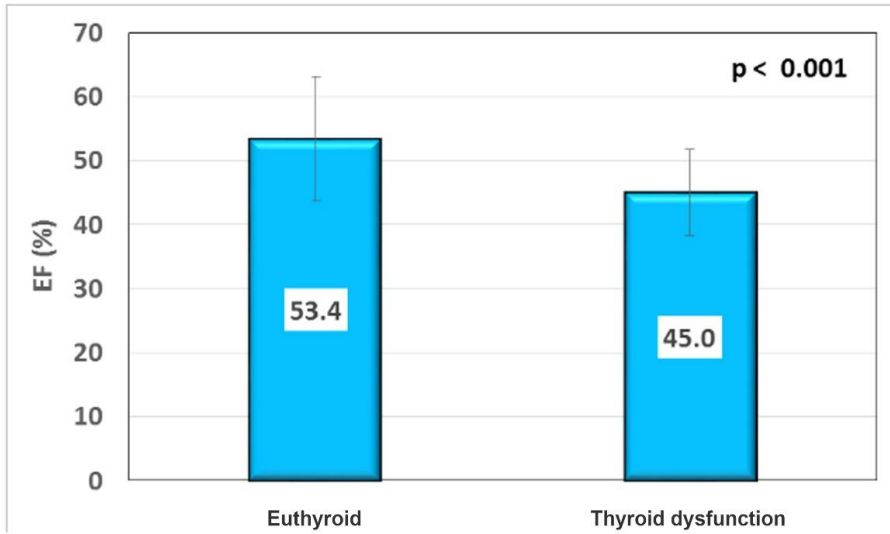


Figure 2. Mean LVEF %& thyroid status in study population

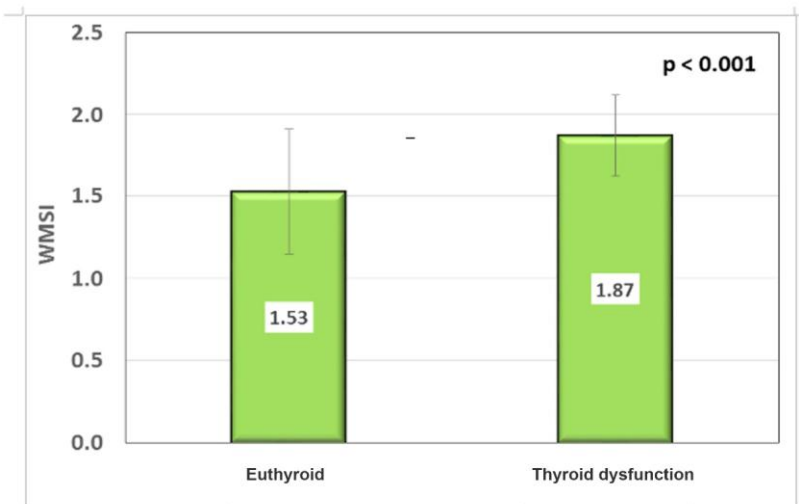


Figure 3. Mean WMSI and thyroid status in study population

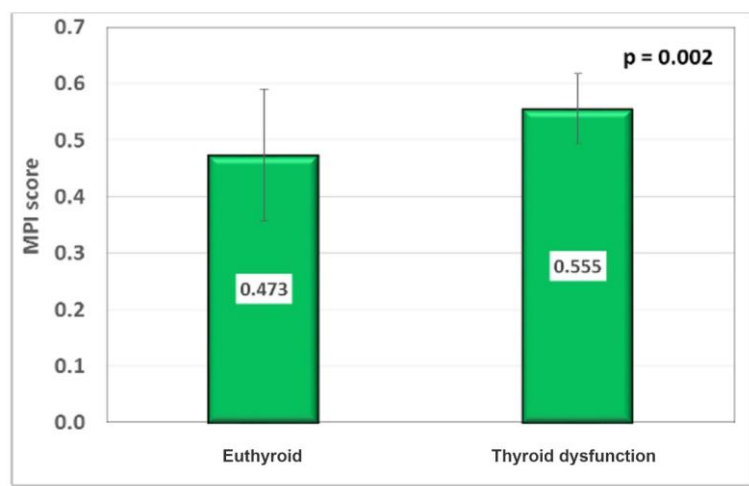


Figure 4. Mean MPI and thyroid status in study population

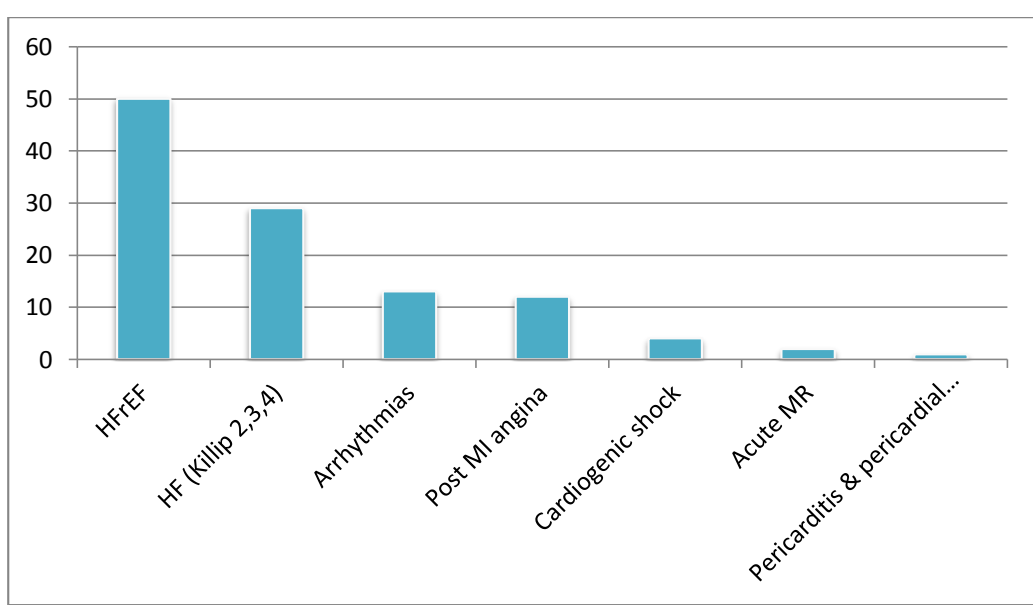


Figure 5. Frequency of complications among all patients

Table 3
In-hospital mortality and thyroid status

			Thyroid status		Total	P Value
			Euthyroid	Thyroid dysfunction		
Mortality	-Survivors	Count	75	21	96	1.0 (NS)
		%	96.2%	95.5%	96.0%	
	-Non-Survivors	Count	3	1	4	
		%	3.8%	4.5%	4.0%	
Total		Count	78	22	100	
		%	100.0%	100.0%	100.0%	

Discussion

Some studies have shown the effect of thyroid hormones on morbidity and mortality from heart failure (7, 8), systemic arterial hypertension (9), dyslipidemia (10) and cardiopulmonary surgeries (11). Therefore, we tried to evaluate the prevalence of thyroid dysfunction in patients with acute myocardial infarction (AMI) in intensive care unit and to study the impact of these dysfunctions on morbidity and mortality among those subjects.

According to thyroid profile, 78 patients (78%) had euthyroid status and the remaining 22 patients (22%) had thyroid dysfunction which include: 12 patients (54.54 %) were euthyroid sick syndrome (12 % of total population), 7 patients (13.81 %) had subclinical hypothyroidism (7 % of total population), 3 patients (13.63%) had subclinical hyperthyroidism (3 % of total population), and none of the patients in our study had neither overt hypothyroidism nor overt hyperthyroidism.

This was in line with *Khalil et al* (12). who studied 196 patients with ACS and the prevalence of thyroid dysfunctions 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%).

Our results were in line with *Kazim et al* (13) who reported that out of 457 acute coronary patient, 72 patients (15%) had thyroid dysfunction, The most frequent thyroid abnormality in our study was euthyroid sick syndrome (low T3 syndrome) and was found in 12.0 % of total population studied (54.5% of cases with thyroid dysfunction) which is consistent with *Wang et al* (14) who reported that the low-T3 syndrome was the most frequent pattern. Another study conducted by *Sabrinae et al* (15) reported out of 1026 acute cardiac patients, low T3 was found in 34.7%.

Regarding relation of thyroid dysfunction and the type of myocardial infarction, thyroid dysfunction was more prevalent in patients with STEMI (24.6%) than NSTEMI (18.6%) but with no significant difference (P value 0.477). This was supported by *Pimentel et al* (16) who found in their study that THs alterations were more evident in the STEMI group compared with the NSTEMI group, although this difference was not statistically significant.

The syndrome seems to occur more frequently in STEMI compared with NSTEMI patients, possibly because of their poorer early prognosis and the pathophysiologic features of the occlusive thrombus resulting in more myocardium at stake (17, 18).

Regarding lipid profile in our study, Serum total cholesterol levels were significantly higher in patients with thyroid dysfunction than in those with euthyroidism (218.4 ± 47.5 vs. 194.3 ± 51.0 , $p = 0.049$). We also noted higher levels of LDL-C, HDL-C, and triglycerides in patients with thyroid dysfunction compared to those with normal thyroid profile but with no significant difference between the two groups ($p = 0.207$, $p = 0.212$, $p = 0.456$) respectively.

Our results were consistent with *Duntas and Wartofsky* study in which SCH was associated with lipid profile abnormalities, especially increases in the concentrations of serum total and LDL cholesterol, but its effects on serum HDL-C and triglycerides concentrations were unclear (19, 20). As regards the myocardial performance, we found that patients with thyroid dysfunction having a reduced LVEF (EF < 50 %) were significantly more than that found in patients with euthyroidism (86.4% versus 39.7%, $p < 0.001$) and the LVEF was significantly lower in patients with thyroid dysfunction compared to patients with normal thyroid function (45.0 ± 6.7 vs. 53.4 ± 9 , $p < 0.001$). Also The WMSI was significantly higher in patients with thyroid dysfunction than in patients with normal thyroid function (1.87 ± 0.25 vs. 1.53 ± 0.83 , $p < 0.001$).

The MPI was significantly higher in patients with thyroid dysfunction than in patients with euthyroid state (0.555 ± 0.062 versus 0.473 ± 0.117 , $p = 0.002$). This was in same line with *Shilpa and Prashant* (21) who reported decreased left ventricular ejection fraction (LVEF %) significantly more in patients who had reduction of serum T3 ($p < 0.001$). *Adawiyah et al.* (22) noted significant difference in Killip's classification on day-1 between ESS and non ESS group ($p = 0.030$). In their study, more patients admitted with Killip's 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.

Recent evidence indicates that circulating T3 levels are an independent determinant of the recovery of left ventricular ejection fraction 6 months after acute myocardial infarction in humans. T3 levels may represent a predictor of the potential recovery of ventricular function (23). *Wang et al.* (14) showed that low FT3 levels were associated with high levels of markers of myocardial damage and with low LVEF after STEMI in Chinese patients. Nevertheless, the association between low FT3 levels and poor cardiovascular outcomes in patients with heart diseases remains controversial (24). A prospective study conducted by *Friberg et al.* (6) in 331 patients with AMI suggested that T3 was not a significant predictor of 30-day and 1-year death, but they showed that mortality was nevertheless high among patients with the most pronounced TH depression. Therefore, the clinical value of FT3 in patients with cardiovascular diseases remains to be determined using well-designed prospective studies (25).

In our study there was no significant increase of relative risk of post MI angina (13.6 % vs. 11.5%, $P = 0.789$), mechanical complications (4.5 % vs. 1.3%, $P = 0.390$), post MI pericarditis & pericardial effusion (4.5 % vs. 0.0 %, $P = 0.220$) in patients with thyroid dysfunction compared to patients with euthyroidism. Also we didn't find significant difference in prevalence of arrhythmia in patients with thyroid dysfunction compared to those patients with euthyroidism (13.6 % vs. 12.8 %, $P = 0.920$).

In contrast to our study, Adawiyah *et al.* ⁽²²⁾ found that ESS increase incidence of arrhythmia by 15. 6% than euthyroid patient this was 5%. Also Khalil *et al* ⁽¹²⁾ 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.* ⁽²⁶⁾ who reported that ESS had no significant increase of morbidity in NSTEMI and UA.

From all cases studied 4 cases developed cardiogenic shock 3 cases of them were in euthyroid state and the other one has thyroid dysfunction in the form of euthyroid sick syndrome (ESS). And there was no significant difference in relative risk of cardiogenic shock in patients with thyroid dysfunction compared to those patients with euthyroidism (4.5 % vs. 3.8 %, $P = 1.0$). In contrast to our study Khalil *et al* ⁽¹²⁾ found that 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.

In line with our study and regarding association between SCH and in-Hospital morbidity Helmy *et al* ⁽²⁷⁾ studied ACS patients, they have compared morbidity in both patients who had normal thyroid profile (euthyroid) vs. patients with subclinical hypothyroidism and they did not find a statistically significant difference. Morbidity was 34.6% in ACS patients with normal thyroid profile vs. 20% in those with SCH (p value 0.7). As regard the in-Hospital mortality in our study, mortality was 3.8% in patients with normal thyroid profile (euthyroid) vs. 4.5% in those with thyroid dysfunction and there was no statistically significant difference between the two groups (p value= 1.0).

In line with our study and regarding association between SCH and in-Hospital mortality in ACS patients, Helmy *et al* ⁽²⁷⁾ have compared mortality in patients who had normal thyroid profile (euthyroid) vs. those with subclinical hypothyroidism did not find a statistically significant difference between both groups. In contrast to our result, Adawiyah *et al.* ⁽²²⁾ reported that ESS in patients with ACS is associated with increased cardiovascular mortality and morbidity.

Limitations of study

This study showed some limitations, such as the small number of patients evaluated. In addition, some hormonal changes found might not have achieved statistical significance because the sample size lacked power. Reverse T3 was not measured in this study as its measurement equip was not available in our lab.

Conclusion

Thyroid dysfunction in acute myocardial infarction is highly prevalent as 22% of our patients experienced thyroid dysfunction. These dysfunctions were reported in both STEMI and NSTEMI subjects and the most frequent dysfunction was euthyroid sick syndrome (ESS).

Recommendation

Further studies are required with greater number of patients to detect thyroid dysfunction associated with acute myocardial infarction and emphasizes its effect on morbidity and mortality. Test for thyroid disorders in acute myocardial infarction may give predictor for risk of in-hospital morbidity in those subjects.

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