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Thyroid Hormone Profile in Patients With Acute Coronary Syndrome

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Background: Thyroid hormone has the a major role in the cardiovascular system function and cardiac a As well as to maintain the cardiovascular homeostasis A slightly change ind thyroid status actually affects cardiovascular mortality hemodynamic. The background of this study was to define the prevalence of thyroid dysfunction in acute coronary syndrome (ACS).

Objectives: The primary objective was to define the prevalence of thyroid dysfunction in acute coronary syndrome, including Non-ST Segment Elevation Myocardial Infarction (NSTEMI), ST-segment Elevation Myocardial Infarction (STEMI), and unstable angina groups. The secondary objective was to determine any associations of thyroids function tests with cardiac catheterization and mortality.

Patients and Methods: In a prospective, observational, and cross section study, we enrolled 400 patients admitted at the coronary care unit of King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Venous blood samples were collected from patients for the evaluation of thyroid function (thyroids stimulating hormones, free triiodothyronine, and free thyroxin).

Results: Excluding those taking thyroid hormone preparations, 76.7% of patients admitted with acute coronary heart disease (ST-segment elevation myocardial infarction and Non-ST segment elevation myocardial infarction), and unstable angina had euthyroidism. Thyroid dysfunction was reported in 23.3% of patients with coronary heart disease. Overall hypothyroidism prevalence was 7.8%, while subclinical hyperthyroidism in our study was 2.7%. Overt hyperthyroidism and subclinical hyperthyroidism was reported 2.0% and 0.5%, respectively. Euthyroid sick syndrome was noticed in 41 (10.2%) of critically ill patients. The mortality rate was 9.8%; all death patients had low triiodothyronine (T3) syndrome and were associated with statistically significant low free triiodothyronine (FT3) ($P > 0.001$).

Conclusions: No significant variance was observed among patients underwent for cardiac catheterization, STEMI, NSTEMI, unstable angina, and atrial fibrillation with respect to FT4, FT3, and TSH levels during coronary care unit hospitalization based on their profile data.

Keywords: Thyroid Disease; Cardiac Catheterization; Unstable Angina; Cardiovascular Disease; Euthyroid Sick Syndrome

1. Background

Thyroid hormone has a major role in the cardiovascular system function and cardiac hemodynamic (1, 2), as well as to maintain the cardiovascular homeostasis (3). A slightly change in thyroid status affects ventricular function, serum cholesterol levels, and heart rate and rhythm, and increases risk of coronary artery disease and cardiovascular mortality (4). Nevertheless, the relation between anomalous thyroid function and cardiovascular effects remains indistinct (5).

Clinical sign characteristics of hyperthyroidism like tachycardia, higher cardiac output, myocardial contractility, systolic blood pressure, and basal metabolism, as well as tremor suggest a hyperadrenergic state. This is all due to the sensitivity to catecholamine compounds (6-8). Hypothyroidism instead, seems to evoke a hypoadrenergic state due to the presence of bradycardia, reduced basal metabolism and cardiac output, and the intracellular catecholamine production from circulation, which has been found to be lower during hypothyroidism (9-11).

The subclinical hypothyroidism and hyperthyroidism have recently been documented as clinical entities with negative effects on the cardiovascular system (12, 13). Subclinical hypothyroidism is categorized by normal serum levels of FT4 and FT3, and slightly elevated serum thyreotropin (TSH) concentrations. This condition is associated with an initial reduced systolic function, diastolic hypertension, increased systemic vascular resistance, an atherogenic lipid profile, and inflammatory condition (14). Subclinical hyperthyroidism is related to an increased risk of supraventricular arrhythmias, hypercoagulable state, and a mild decrease of coronary reserve. Recent studies correlate both subclinical hypothyroidism and hyperthyroidism with an increased threat of cardiovascular mortality (15, 16).

Particularly, subclinical hypothyroidism is associated with increased risk of coronary heart disease (CHD), heart failure (HF), and mortality in patients with higher TSH levels, mainly those with TSH levels ≥ 10.0 mIU/L. Conversely, subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality,

HF and atrial fibrillation, particularly in those with suppressed TSH levels < 0.10 mIU/L (17).

The "low T3 syndrome" is a profile of low serum triiodothyronine (T3), normal thyroxin (T4), and normal TSH that can be seen in acute or chronic illnesses. This syndrome leads to the similar changes in cardiac function (decreased maximal rate of contraction and relaxation) and gene expression (alteration in myosin heavy chain isoform expression) as does primary hypothyroidism. In patients with cardiac disease, this syndrome is a major cause of death (18, 19).

2. Objectives

The present study aimed to investigate the possible variations in thyroid hormone profile in acute coronary syndromes, Unbalanced Angina/Non-ST-segment Elevation Acute Myocardial Infarction (UA/NSTEMI), and ST-segment Elevation Acute Myocardial Infarction (STEMI) at the time of diagnosis, and also relations of thyroid function test (TFT) profile with cardiac catheterization, atrial fibrillation, and mortality in patients during CCU hospitalization at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia.

3. Patients and Methods

3.1. Design, Setting, and Patients

This is a prospective, observational, and cross section study comprising of 400 patients admitted to CCU at KAUH in Jeddah in two years duration (2012- 2013). The primary study objective was to determine the prevalence of thyroid dysfunction in Acute Coronary Syndrome (ACS): NSTEMI, STEMI, and unstable angina groups. Secondary objective was to determine any relationship between TFT profile and variables of cardiac catheterization, AF, and mortality. Patients with ACS, regardless of race, ethnic group, age, gender, and clinical severity were part of the inclusion criteria. However, patients under certain medications such as thyroid hormone preparations (thyroxin), antithyroid and corticosteroid drugs, or any other prescriptions that may affect the thyroid testing were excluded from this study.

A complete clinical evaluation, physical examination, medical history, and electrocardiogram were taken for the patients enrolled in the study. Venous blood samples were collected for the evaluation of thyroid function (TSH, FT3 and FT4) from day 1 to 4 after admission to CCU. Additionally, the following factors were considered to be cardiovascular risk factors: hypertension, age, gender, and diabetes mellitus. Measured hormones and their individual reference values were TSH (0.27 - 4.5 mIU/L), FT3 (12 - 22 pmol/L), and FT4 (12 - 22 pmol/L).

Based on their thyroid function tests, participants" characteristics were categorized into one of the following 6 groups:

1. Euthyroidism was determined as a normal TSH dilution of (0. 27 - 4.5 mIU/L).

2. Overt hypothyroidism was demarcated as a TSH ≥ 10 mIU/L oral free T4 concentration level; less than normal (< 12 pmol/L).

3. Subclinical hypothyroidism as having TSH concentration > 4.50 and < 10 mIU/L with a normal free T4 concentration.

4. Overt thyrotoxicosis was characterized by TSH concentration < 0.10 mIU/L with an elevated free thyroxin level.

5. Subclinical hyperthyroidism was characterized by TSH concentration ≥ 0.10 and < 0.45 mIU/L, or < 0.10 mIU/L with a normal free T4 concentration.

6. Euthyroid sick syndrome is a condition characterized by decreased levels of FT4, FT3 and TSH.

This study was approved by the Ethics Committee of KAUH (Code No. 238-14), Jeddah, Saudi Arabia. Informed consents were obtained from all participants and those with abnormal thyroid function tests were referred to an endocrinologist for further treatment.

3.2. Statistical Analysis

Data analysis was performed by SPSS Version 16 (SPSS Statistics, Chicago, IL USA).

Descriptive statistics was performed by calculating mean and standard deviation of numerical data, and extracting tables of frequency and percentages for categorical data. Chi-squared test and Fisher exact test were used when necessary. Mann Whitney U Test was performed as the test of significance for not normally distributed data after checking by Kolmogorov-Smirnov test of normality.

4. Results

General characteristics of 400 patients with acute coronary syndrome show at CCU of King Abdulaziz University Hospital in the western region of Saudi Arabia. A total of 103 (25.7%) participants had STEMI, 107 (26.7%) NSTEMI, and 142 (42.2%) unstable angina. Of STEMI patients, 58 (14.5%) underwent chemical thrombolytic therapy. Out of 400 patients, 181 (45.1%) underwent cardiac catheterization during hospitalization and 38 (9.5%) patients died (Table 1).

Figure 1 shows the frequencies of thyroid hormone abnormalities diagnosed during admission. Mean plasma levels of FT4, FT3, and TSH on admission for all 400 patients were 15.19 ± 3.898 pmol/L, 4.04 ± 1.257 pmol/L, and 3.17 ± 5.43 mIU/L, respectively. Hormone distribution (TSH) displayed a comprehensive diffusion in the sample, accompanying with high standard deviation (0.001- 81.8 mIU/L).

4.1. Noticed on Data Analysis

A 307 (76.7 %) patients had Euthyroidism with acute coronary heart disease. Overt hypothyroidism was reported in 31 (7.8%) patients. One of the patients had severe hypothyroidism with thyroid hormone levels

of FT4 8.55 pmol/L, FT3 3.4 pmol/L, and TSH 81.8 mIU/L. Subclinical hypothyroidism was noticed in 11 (2.7%) patients. Overt thyrotoxicosis was seen in 8 (2.0%) patients (severe case with FT4 was 33.7 P mol /L and TSH 0.005 mIU/mL). Subclinical hyperthyroidism was noticed in 2 (0.5%) patients. And euthyroid sick syndrome, "low T3 syndrome" (a profile of low serum triiodothyronine (T3), normal thyroxin (T4), and normal TSH) was reported in 41 (10.2%) critically ill patients.

A total of 38 patients (9.8 %) died with ACS in the study group. euthyroid sick syndrome and FT3 was statistically significant low in death patient($P < 0.001$) (Table 2).

No statisitcally significant difference was observed in the TFT profile among patients underwent cardiac catheterization or had STEMI ,NSTEMI, unstable angina, and atrial fibrillation with respect to mean ± SD plasma of FT4, FT3 and TSH, and median (IQR) during CCU hospitalization.

5. Discussion

Acute coronary syndrome is a condition that should be taken very serious because of its significant effect on thyroid gland homeostasis with repercussions in terms of morbidity and mortality (1).

Excluding patients taking thyroid hormone preparations, 76.7% of patients who were admitted with acute CHD (STEMI and NSTEMI) and unstable angina had euthyroidism (20). Thyroid dysfunction was reported in 23.3% of patients with CHD. Overall prevalence of hypothyroidism was 7.8%; noticeably, it is four times more common in females than in males (23.4% vs. 6.9%). Hypothyroidism is commonly considered as a cardiovascular risk factor in many studies owning to its association with high serum LDL cholesterol. Hypercholesterolemia in hypothyroidism is possibly due to the reduction of catabolism of lipoproteins, as a result of decreased number of lipoprotein receptors (9, 10). Patients with hypothyroidism (both subclinical and overt) in our study groups had considerably higher total of LDL/cholesterol, greater than > 7 mmol/L (21, 22).

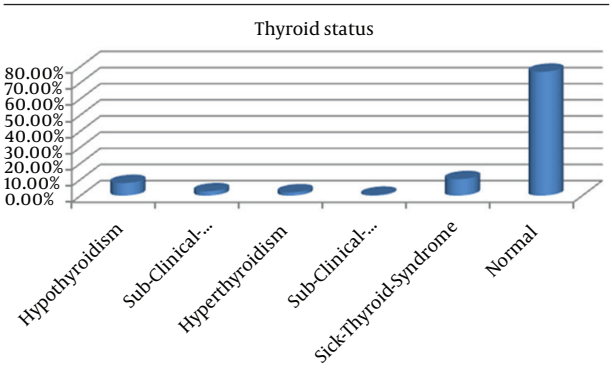

Figure 1. Percentage of Thyroid Hormone Abnormalities in CCU Admitted Patients

Table 1. Characteristics of Patients With Acute Coronary Syndrome [a,b]

Variable	Characteristic
Gender	
Male	123 (30.7)
Female	278 (69.3)
Age, y	59.9 ± 37.2
Previous disease	
Arterial hypertension	229 (57.1)
Diabetes mellitus	228 (65.8)
Coronary heart disease	360 (89.9)
Coronary heart disease	
STEMI	103 (25.7)
UA/NSTEMI	107 (26.7)
Unstable angina	142 (42.2)
Atrial fibrillation	21 (5.2)
Chemical thrombolytic	58 (14.5)
Cardiac catheterization	181 (45.1)
Death	38 (9.5)

[a] Abbreviations: NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST-segment elevation.
[b] Data are presented as No. (%) or Mean ± SD.

Table 2. Comparisons Between TFT Profile and Other Parameters [a]

TFT	FT4	FT3	TSH
Mean ± SD	15.19 ± 3.9	4 ± 1.26	3.18 ± 5.4
Median (IQR)	15 (4.7)	4 (1.39)	2.2 (2.48)
Cardiac catheterization	0.38	0.17	0.48
Death	0.88	> 0.001	0.32
Unstable angina	0.693	0.535	0.519
STEMI	0.583	0.305	0.757
NSTEMI	0.617	0.294	0.743
AF	0.919	0.641	0.7

[a] Abbreviations: NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST-segment elevation.

Subclinical hypothyroidism prevalence in our study group was 2.7%, which is significantly low in comparison to other study groups. This low figure could be attributed to our definition of subclinical thyroid disease (when TSH values > 10 mIU/L for subclinical hypothyroidism), while in other study groups, the cut-point of TSH for subclinical hypothyroidism was TSH values > 6 mIU/L (23, 24).

Regarding subclinical hyperthyroidism and overt hyperthyroidism, our findings showed that the occurrence of overt hyperthyroidism and subclinical hyperthyroidism were 2.0% and 0.5%, respectively. In addition, all patients with atrial fibrillation in our study group had low TSH levels, either in the form of overt hyperthyroidism or endogenous subclinical hyperthyroidism, including those with TSH levels of 0.1 to 0.44 mIU/L (25, 26).

No statistically significant difference was observed in the TFT profile among patients underwent cardiac catheterization or had STEMI ,NSTEMI, unstable angina and atrial fibrillation with respect to mean (± SD) plasma level of FT4, FT3 and TSH, for median (IQR) during CCU hospitalization (27-29).

A total of 38 (9.8%) patients with coronary heart disease (CHD) in our study died. All of those patients had euthyroid sick syndrome and FT3 was statistically significant low in death patients (P < 0.001). Euthyroid sick syndrome is the term used to describe thyroid hormonal changes in critically ill patients. Euthyroid sick syndrome or Low T3 is the earliest manifestation followed by low T4 and finally low TSH, indicating diversity changes in the spectrum (30). Our study demonstrated that low T3 is an important marker of the severity of the illness and predicted mortality in CCU patients (31). Theoretically, these thyroid hormonal changes during sickness was related to a metabolic clearance rate of reverse T3 > greater than that of the marginal conversion of T4 to T3. Furthermore, euthyroid sick syndrome also relates to certain mechanisms, which cause underlying changes in production, delivery, clearance, affinity to carrier proteins, and response to targeting organs of thyroid (32). Deleterious effects on the heart muscle caused by increased peripheral vascular resistance and decreased cardiac output are effects of this syndrome of hormonal changes.

In another study by Cerillo et al. of 806 consecutive CABG patients, 19 (2.3%) died, and 64 (7.8%) patients experienced major complications during hospitalization; median reverse T3 level was higher in the group that progressed to death, with a significant difference (P = 0.0001) (33). Our recorded data suggested increased serious events (mortality) was associated with euthyroid sick syndrome (34, 35), which displays similar outcomes found in the other studies. Coceani et al. showed the FT3 levels were inversely related to CAD presence and an adverse prognosis on low T3 syndrome was conferred (28). A significant higher total mortality (log-rank 6.75, P = 0.009) as well as cardiac mortality (log-rank 8.26, P = 0.004) was seen among patients with low T3 syndrome (FT3 < 2.10 pmol/mL) (28). In Ozcan et al. study, out of 457 participants, 72 (15%) patients with thyroid dysfunction were detected. Death was reported more frequently (7% vs. 1% in the control group; P < 0.01) in the thyroid dysfunction group (35).

Study limitations included the relatively small percentage of patients with TFT abnormalities among CCU patients at KAUH. The definitions of subclinical thyroid disease as we determined (TSH values > 10 mIU/L for subclinical hypothyroidism), reduced the prevalence of subclinical hypothyroidism in our study group.

Definition of "Euthyroid sick syndrome" or "low T3 syndrome" consists of low FT4, low FT3, and low TSH. Reverse T3 was not measured in this study as its measurement equip was not available in our lab. This may underestimate euthyroid sick syndrome and the mortality associated with thyroid abnormality in CCU patients.

Thyroid hormone has an essential role in the cardiovascular homeostasis. Thus, mild forms of thyroid hormones disorders, even small variations of the thyroid hormone within the physiological range have been linked to adverse cardiovascular prognosis. The clinicians have to consider thyroid function test abnormalities as valuable coronary risk factors such as blood pressure, diabetic state, and cholesterol level during CCU hospitalization.

Our study showed that euthyroid sick syndrome, especially with low T3 is an important predictor of mortality in critically ill patients in CCU. However Low T4 and TSH did not increase the predictability of mortality in our study group.

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