Thyroid Hormone Profile in Acute Coronary Syndromes

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Objective: To describe thyroid hormone profile in patients with acute coronary syndromes (ACS), divided into two groups: 1) unstable angina and/or non-ST-segment elevation acute myocardial infarction (UA/NSTEMI); 2) ST-segment elevation acute myocardial infarction (STEMI), as well as in patients that progressed or not to death, according to the groups.

Methods: Seventy ACS patients admitted to the coronary care unit of the Hospital dos Servidores do Estado, Rio de Janeiro, were prospectively studied. Blood samples were collected on day 1 and on days 4 and 7 following admission. Clinical evaluation and electrocardiograms were performed during hospitalization.

Results: Of the 70 patients admitted, 13 (18.6%) had "euthyroid sick syndrome" (ESS), a condition characterized by decreased serum T3 and/or free T3, increased serum reverse T3 (rT3), plus normal serum TSH, T4, and free T4. Patients belonging to the STEMI group showed early elevations, in addition to higher mean reverse T3 (rT3) and lower mean T3 and free T3 levels. In coronary heart disease patients that progressed to death, hormonal findings were consistent with those found in the ESS, with more expressive rT3 and T3 mean values.

Conclusion: Our results show the importance of recognizing the "euthyroid sick syndrome" in coronary heart disease patients, suggesting an association with poorer prognosis in patients with acute coronary syndrome.

Key words: Thyroid hormones, acute coronary syndromes, euthyroid sick syndrome.

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 the third leading cause of hospital admission[1].

Some studies have shown the effect of thyroid hormones on morbidity and mortality from heart failure[2-3], systemic arterial hypertension[4], atherosclerosis[5], dyslipidemia[6] and cardiopulmonary surgeries[7-8].

Serum thyroid hormone levels have been described in several systemic nonthyroidal illnesses, among them acute heart diseases. The changes observed in these situations have been classified 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 are seen in acute myocardial infarction, affecting the prognosis[9-10].

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[11] or directly related to inflammatory cytokines, acting as an inflammatory marker[12-13], or both.

The aim of this study was to evaluate potential changes in thyroid hormone profile in acute coronary syndromes at the time of diagnosis and compare them between two groups, based on therapeutic implications and distinct prognoses: unstable angina/non-ST-segment elevation acute myocardial infarction (UA/NSTEMI) and ST-segment elevation acute myocardial infarction (STEMI), as well as in patients that progressed or not to death.

Methods

A prospective observational study involving 70 patients consecutively admitted to the coronary care unit of a tertiary public hospital (Hospital dos Servidores do Estado do Rio de Janeiro) from September 2002 to December 2002. Inclusion criteria were patients with acute coronary syndrome, irrespective of gender, race, ethnic group, age, and clinical severity.

Exclusion criteria included patients using corticosteroids, amiodarone, or thyroid disease drugs regularly or who had received any iodinated contrast agent within the previous two weeks; patients with established diseases, such as neoplasias, chronic renal failure, chronic obstructive pulmonary disease requiring antibiotic therapy, liver cirrhosis, active infection, and decompensated diabetes mellitus, conditions that are known to affect thyroid function tests.

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Manuscript received May 8, 2005; revised manuscript received August 24, 2005; accepted August 29, 2005.

Patients enrolled in the study underwent clinical evaluation, consisting of medical history, physical examination, and electrocardiogram. After informed consent was obtained, blood samples were collected for laboratory tests on day 1 and on days 4, and 7 following admission. Thyroid hormones TSH, T3, T4, free T3 and free T4 were measured using the *Coat-a-Coat kit* from Diagnostic Products Corporation (DPC), using the chemiluminescent method, between a monoclonal antibody (specific) and a labeled antigen, forming an immune complex. Reverse T3 was determined by radioimmunoassay, using the Serono kit. Measured hormones and their respective reference values were: TSH (0.4 to 4 mU/mL), T3 (70 to 100 μg/dL), free T3 (1.5 to 4.1 pg/mL), T4 (4.5 to 12.5 μg/dL), free T4 (0.8 to 1.90 μg/dL), and rT3 (0.09 to 0.35 μg/mL).

At admission (day one), an attempt was made to diagnose the "euthyroid sick syndrome". Subsequently, plasma thyroid hormone levels were compared in the UA/NSTEMI and STEMI groups on days 1, 4, and 7 and, later, in patients that progressed or not to death. In our sample, no differences were found in mean hormone levels, with respect to gender and age.

In the univariate analysis, continuous variables expressed as mean ± standard deviation were compared using the Student's t test (if homogeneity of variances was assumed) or the Mann-whitney test (if homogeneity of variances was not met). A two-tailed p-value < 0,05 was considered statistically significant (significance level = 5%). A database was created using Epinfo 2000.

This study was approved by the Research Ethics Committee of the Faculdade de Medicina da Universidade Federal Fluminense, under No 111/02, and was part of the Master's thesis submitted on April 23, 2005, at the Universidade Federal Fluminense.

Results

Table 1 shows general characteristics of the 70 patients admitted with acute coronary syndrome, of whom 39 (55.7%) had ST-segment elevation acute myocardial infarction (STEMI) and 31 (44.3%), unstable angina and/or non-ST-segment elevation myocardial infarction (UA/NSTEMI). Of the STEMI patients, 12 (30.8%) underwent chemical thrombolysis. In 70% of the patients, the first blood sample was drawn with delta-T > 12 hours of symptoms onset.

Seven patients (10%) died, six of them belonged to the STEMI group.

Table 2 shows mean thyroid hormone levels at the time of diagnosis on admission. Mean plasma reverse T3 was higher than reference values on days 1, 4 and 7, and was most marked on day 4. Mean levels of the other hormones were within the normal range.

TSH hormone distribution showed a broad dispersion in the sample, reflecting the high values of the standard deviation. Median TSH values on days 1, 4, and 7 were 1.28, 3.25, and 1.44, respectively.

Table 3 shows means and respective standard deviations of rT3, T3 and free T3 hormones on days 1, 4 and 7 days in the UA/NSTEMI and STEMI groups; p value corresponds to the difference between the two groups. Day one represents serial hormone determinations at admission. Italicized values indicate high mean plasma levels relative to reference values. There were no relevant changes in T4, free T4, and TSH hormones between the groups.

On analyzing table 3, we notice that mean plasma reverse T3 was higher than reference values in both groups of patients, and this trend was more marked in STEMI patients, yet no significant difference was found between the groups.

Mean plasma T3 and free T3 were within the normal range, with no significant difference between the groups. A decrease in mean plasma T3 was observed on days 1 and 4, respectively, in the STEMI group. With regard to mean plasma free T3, this trend was more marked in the STEMI group, on days 4 and 7, respectively.

Tables 4 and 5 show mean plasma rT3 and T3 based on deaths according to diagnosis of STEMI and UA/NSTEMI, with respective standard deviations and statistical significance. Highlighted values in Table 4 indicate mean plasma rT3 levels above reference values, and highlighted values in Table 5 indicate mean plasma T3 levels below reference values.

Discussion

Acute coronary syndromes are a serious condition that may affect thyroid gland homeostasis, with implications in terms of morbidity and mortality[14]. In our study, we sought do evaluate thyroid hormone plasma levels in patients with coronary heart disease and whether they characterized the "euthyroid sick syndrome", consisting of decreased T3 and/or free T3 levels, increased reverse T3 levels, and normal TSH levels. We compared findings between the unstable angina and/or non-ST-segment elevation acute myocardial infarction (UA/NSTEMI) and ST-segment elevation acute myocardial infarction (STEMI) groups. This two-group division was used

Variables	n = 70 (100%)
Gender:	
Male	42 (60%)
Mean age (years) ± standard deviation	62.5 ± 12.95
Previous diseases:	
Arterial hypertension	50 (71.4%)
Diabetes mellitus	13 (18.6%)
Coronary heart disease	23 (32.9%)
Delta-T for pain:	
< 6 hours	10 (14.3%)
Between 6 and 12 hours	11 (15.7%)
> 12 hours	49 (70%)
Type of ACS	
STEMI	39 (55.7%)
UA/NSTEMI	31 (44.3%)

Table 1 - Characteristics of patients with acute coronary syndrome

to investigate whether thyroid hormone levels would present a distinct behavior, because the STEMI group is associated with poorer prognosis, showing unique pathophysiologic features that determine the presence of occlusive thrombus and requiring reperfusion strategies, either by thrombolytics or mechanical recanalization.

Analysis of hormonal behavior in patients admitted for coronary heart disease showed increased mean plasma reverse T3, while the other hormones remained unchanged (Tab. 2). All patients taken into account, mean hormonal profile was not consistent with the "euthyroid sick syndrome". However, in the analysis of hormone plasma levels on the first day of admission, 13 patients (18.6%) showed serum concentrations consistent with those found in the "euthyroid sick syndrome". When the UA/NSTEMI and STEMI groups were compared, elevated mean rT3 concentration was more marked in the latter, but with no significant difference (Tab. 3).

Of the 70 coronary heart disease patients evaluated in this study, seven (10%) died within the first and seventh day of admission, when data and blood samples were collected. It must be emphasized that day 1 was considered the time of admission to the coronary care unit. In this study, the decision to exclude patients with prior thyroid diseases, decompensated diabetes mellitus, renal diseases, liver diseases, neoplasias, or using thyroid agents and amiodarone was intended to prevent their effect on thyroid hormone plasma levels. The fact that some changes in mean hormone concentrations did not reach statistical significance may be related to the sample size and to the lack of statistical power to detect such differences.

In our series, mean plasma reverse T3 in patients admitted was above the normal range on days 1, 4, and 7; and the highest mean was found 4 days after admission. As for the other hormones, namely TSH, T3, free T3, T4, and free T4, all means were within the normal range on days 1, 4, and 7.

When the two acute coronary syndrome groups were compared, mean plasma reverse T3 was above the normal range in both the UA/NSTEMI and STEMI groups on days 1, 4, and 7. The increase was higher in the latter group, but with

	TSH (mU/mol)	T3 (μg/dl)	T3L (pg/mL)	T4 (μg/dl)	T4L (μg/dl)	rT3 (μg/dl)
Day 1 n = 70	2.94 ± 6.49	78.03 ± 21.80	21.17 ± 0.61	8.39 ± 2.26	1.20 ± 0.36	*0.46 ± 0.25*
Day 4 n = 67	3.25 ± 7.89	79.53 ± 27.53	2.03 ± 0.61	8.76 ± 2.30	1.15 ± 0.22	*0.49 ± 0.22*
Day 7 n = 47	3.93 ± 9.47	81.92 ± 22.86	2.17 ± 0.57	8.96 ± 2.62	1.21 ± 0.27	*0.47 ± 0.20*

In italics, measurements above the reference value.

Table 2 - Mean and standard deviation for thyroid hormones during hospitalization

Diagnosis	T3 (μg/dL)	T3L (pg/mL)	rT3 (μg/dL)
Day 1 (mean ± standard deviation)			
UA/NSTEMI (n = 31)	79.78 ± 25.27	2.16 ± 0.57	*0.39 ± 0.17*
STEMI (n = 39)	76.64 ± 18.84	2.17 ± 0.64	*0.52 ± 0.29*
p value	0.64	0.87	0.09
Day 4 (mean ± standard deviation)			
UA/NSTEMI (n = 30)	86.29 ± 0.56	2.10 ± 0.61	*0.45 ± 0.16*
STEMI (n = 37)	74.05 ± 23.83	1.97 ± 0.62	*0.53 ± 0.26*
p value	0.13	0.62	0.40
Day 7 (mean ± standard deviation)			
UA/NSTEMI (n = 18)	78.51 ± 20.67	2.18 ± 0.65	*0.42 ± 0.22*
STEMI (n = 29)	84.03 ± 24.23	2.17 ± 0.52	*0.50 ± 0.19*
p value	0.38	0.80	0.13

Table 3 - Mean and standard deviation for hormones according to the UA/NSTEMI and STEMI groups

no significant difference. In both groups, the increase in mean plasma reverse T3 was higher on day 4.

Mean plasma T3 and free T3 was lower in the STEMI group on day 4, but with no significant difference. This finding suggests that the greatest hormonal changes occurred on day 4, data consistent with that found in the literature, because in patients with uncomplicated acute coronary syndrome, from day 5 on mean T3 and free T3 return to normal range

In a study with 16 acute myocardial infarction patients divided into two groups according to serum CKMB, an enzyme marker, both treated with chemical thrombolysis, serial measurements of thyroid hormones were performed at 2, 4, 6, 8, 12, and 72 hours after admission. Mean T4, free T4, T3, free T3, and TSH plasma levels were normal up to day 3, while mean reverse T3 plasma level was statistically significantly higher ($p < 0.05$) from first measurement to 72 hours after admission[15].

Despite an early increase in the rT3 hormone alone compared with the other hormones, and a decrease in mean plasma T3 on days 1 and 4 plus in free T3 on days 4 and 7, respectively, this profile may suggest the presence of "euthyroid sick syndrome" in the STEMI group, associated with a poorer prognosis.

In another study involving 95 patients with acute myocardial infarction and 19 patients with unstable angina patients divided into two groups, according to the use or not of beta-blockers and thrombolytics, there was a significant decline ($p = 0.05$) in mean plasma T3 and an increase in reverse T3; mean free T3, T4, free T4, and TSH remained unchanged in all the patients during the first five days following admission. These findings were consistent with those found in the "euthyroid sick syndrome". No significant difference between unstable angina and acute myocardial infarction was found in thyroid hormone plasma levels[14]. Our criticism regarding this study is that beta-blockers affect peripheral conversion of T4 to T3.

In yet another study involving nine patients with acute myocardial infarction, compared with 27 healthy patients of a control group, mean T3, free T3, and T4 plasma levels at admission were lower, while those of free T4, TSH, and reverse T3 were higher. At day 3, a sharp decline in mean plasma T4, free T3, and T3 was found, with statistical significance ($p < 0.05$). The highest mean plasma reverse T3 was observed on day 4, with statistical significance ($p < 0.05$). Mean free T4 and TSH plasma concentrations remained unchanged[9].

Increased plasma reverse T3 has been described in several

Endpoint	Day 1	Day 4	Day 7
STEMI (mean ± standard deviation)			
Death	*0.66* ± 0.29	*0.99* ± 0.42	*0.68* (1 case)
Non-death	*0.51* ± 0.30	*0.48* ± 0.18	*0.44* ± 0.19
p value	NS	NS	NS
UA/NSTEMI (mean ± standard deviation)			
Death	*0.17* (1 case)	-	-
Non-death	*0.39* ± 0.20	*0.46* ± 0.16	*0.43* ± 0.23
p value	NS	NS	NS

NS- non-significant; in italics, mean above the reference value.

Table 4 - Mean and standard deviation of the rT3 hormone (μg/mL), according to the diagnosis and endpoint

Endpoint	Day 1	Day 4	Day 7
STEMI (mean ± standard deviation)			
Death	*68.75* ± 22.29	*45.02* ± 10.05	*44.30* (1 case)
Non-death	*79.06* ± 14.90	*77.56* ± 22.62	*84.03* ± 24.23
p value	NS	*p = 0.006*	NS
UA/NSTEMI (mean ± standard deviation)			
Death	*68.04* (1 case)	-	-
Non-death	*79.78* ± 25.27	86.29 ± 30.56	78.51 ± 20.67
p value	NS	NS	NS

NS- non-significant; in italics, mean lower than the reference value.

Table 5 - Mean and standard deviation of the T3 hormone (μg/mL), according to the diagnosis and endpoint

nonthyroidal illnesses, including acute myocardial infarction. This elevation, when associated with low plasma T3 and/or free T3 and normal plasma TSH, characterizes the "euthyroid sick syndrome"[16]. Serum concentration of this hormone helps to differentiate hypothyroidism from euthyroid sick syndrome, because in the first there is a decline in serum reverse T3, while in the latter there is an increase in serum reverse T3[17]. By definition, this syndrome only exists in the absence of primary disorder of the hypothalamus and pituitary and thyroid glands.

One of the hypotheses postulated to explain the early change in this hormone in relation to the other hormones in nonthyroidal illnesses, is that the metabolic clearance rate of reverse T3 is greater than that of the peripheral conversion of T4 to T3[18].

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[19]. This syndrome's hormonal changes cause increased peripheral vascular resistance and decreased cardiac output, with deleterious effects on the heart muscle[9].

In a study with 114 patients with acute coronary syndromes divided into acute myocardial infarction and unstable angina, sharp decrease in mean plasma T3 and sharp increase in reverse T3 were found in coronary heart disease patients; these changes were significantly different ($p = 0.03$) in those with complications associated with the disease, including rhythm disturbances and heart failure. This hormonal profile is consistent with the "euthyroid sick syndrome". Hormonal variations were independent of the use of thrombolytics and beta-blockers[14].

In patients that progressed to death, compared with survivors, there was a significantly different decrease in mean plasma T3 and free T3 ($p = 0.003$ and $p = 0.04$) and a significantly different increase in mean plasma reverse T3 ($p = 0.002$) on day 4. TSH, T4 and free T4 values were within the normal range. Changes in mean thyroid hormones levels in patients that progressed to death were consistent with serum concentrations found in the "euthyroid sick syndrome", which was present on days 4 and 7, with higher mean plasma reverse T3 and lower mean plasma T3 and free T3 on day 4.

In another study involving 165 patients with acute myocardial infarction, 16 (10%) died within one week of admission; median reverse T3 level was higher in the group that progressed to death, with a significant difference ($p = 0.004$) and was associated with higher short- and long-term mortality rate, regardless of other risk factors[20].

Some theories have been proposed to justify the "euthyroid sick syndrome", such as decrease in the extrathyroidal conversion of T4 to T3 secondary to lower extracellular clearance of T4 or reduced 5'deiodinase enzyme activity[21]. 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[2] and T4 and T3 uptake, as well as these post-receptors action[17]. All the above may be directly affected by catecholamine levels[23]. These mechanisms corroborate the hypothesis of the thyroid gland adapting its metabolism according to the disease involved, characterizing the "euthyroid sick syndrome" The fact that serum TSH levels are unchanged or little changed is likely to be explained by two theories: failure of the hypothalamic-pituitary axis to respond to the low serum T3 concentration and/or suppressed TSH secretion due to normal or little elevated serum T4[24].

Evidence in our study points, therefore, in the same direction of that found in the other studies mentioned herein. Our data suggest that greater hormonal changes are associated with more severe events (STEMI and death).

The limitations of our study are related to operational and economic issues, which affected the sample size. Some hormonal changes found might not have achieved statistical significance because the sample size lacked power. Other statistical techniques would have contributed to further our understanding of the variation and distribution of hormonal measurements. Moreover, the sample size precluded the use of multivariate analysis.

The clinical implications of this study are related to a better knowledge of the role of thyroid hormone metabolism in nonthyroidas systemic illnesses, such as acute coronary syndrome. The hormonal profile characterized by the "euthyroid sick syndrome" seems to be associated with pathophysiological features and the prognosis of these diseases, and further studies are needed to prove assumption.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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