ORIGINAL ARTICLE

Relation between thyroid hormonal status, neutrophil-lymphocyte ratio and left ventricular systolic function in patients with acute coronary syndrome

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ABSTRACT

Aim To examine a relation of thyroid function, neutrophil-lymphocyte ratio (NLR) with left ventricular function measured through the left ventricular ejection fraction (LVEF) in patients with acute myocardial infarction treated with percutaneous coronary intervention (PCI).

Methods This prospective research involved 160 consecutive patients with acute myocardial infarction. Patients were divided into those with normal thyroid hormone status (n=80) and those with hypothyroidism (newly diagnosed) (n=80). Inflammatory parameters and parameters of hormonal status were taken for analysis: thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), and free triiodothyronine (FT3). All patients underwent transthoracic echocardiographic examination (TTE) five days upon admission, and left ventricular ejection fraction (LVEF) was analysed.

Results Significant difference between the two groups was verified in values of T3, T4, erythrocytes, haemoglobin, haematocrit, neutrophil, lymphocytes, NLR, C-reactive protein (CRP) and sedimentation rate. Patients with euthyroidism had a higher frequency of coronary single-vessel disease (p=0.035) and a significantly lower frequency of triple vessel disease (p=0.046), as well as a higher median value of LVEF (p=0.003). There was a significant correlation between LVEF with haemoglobin values (p=0.002), NLR (p=0.001), and CRP (p=001).

Conclusion The altered status of the thyroid gland in acute myocardial infarction is associated with the severity of the coronary blood vessel lesion, LVEF and correlates with inflammatory response.

Key words: myocardial infarction, prognosis, risk

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INTRODUCTION

Ischemic heart disease is differentiated in two directions, as a chronic form (stable angina pectoris) and as an acute form (acute coronary syndrome - ACS) (1). The term ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) (2). In 2018, the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction defined myocardial infarction, either STEMI or NSTEMI, as the presence of an acute myocardial injury, verified by elevated levels of myocardial necrosis enzymes, as a consequence of acute myocardial ischemia (the most severe forms of myocardial ischemia, if they are not quite short-term, can lead to myocardial infarction, which occurs distal to the site of critical narrowing of the coronary artery) (2). NSTEMI and STEMI are characterized as an increase in troponin above the >99th percentile of reference values (3). Poor therapeutic adherence is an important barrier to achieving optimal treatment goals and is associated with increased rate of major adverse cardiac events (MACE). Delayed follow-up of patients after acute myocardial infarction (AMI) results in a poorer short-term and long-term drug treatment (4,5).

Despite progress in the treatment of myocardial infarction, damage to the myocardium and subsequent remodelling of the left ventricle remain the main serious problems that affect the prognosis of patients, and in modern cardiology, the focus is on the prediction of a new cardiovascular incident, that is, on its primary and secondary prevention (4,5). For the functioning of the cardiovascular system, maintaining thyroid hormone homeostasis is of great importance (6). Triiodothyronine (T3) is a regulator of inotropic and lusitropic (relaxation) properties of the heart, thanks to its influence on myosin isoforms and especially on proteins that manage calcium (6). Thyroid hormones have a positive effect on oxidative stress after myocardial infarction. T3 and tetraiodothyronine or thyroxine (T4) reduce the levels of reactive oxygen species (ROS) induced by myocardial infarction (6). Hypothyroidism is linked to diastolic hypertension, dyslipidaemia, atherosclerotic plaque progression and instability and endothelial dysfunction (7). Also, in an acute incident, there are variations in thyroid plasma concentration, which themselves can affect the patient's prognosis as follows: inhibition of the 5′-deiodination of T4, resulting in increased plasma reverse T3 and decreased plasma T3 values, and in a lower metabolic clearance of T4; increased secretion of TSH (provoked by the lower T3 levels) resulting in increased thyroidal secretion of T4 and T3, which is then switched off by the negative feedback of thyroid hormones on the pituitary (8). In the experimental application of T3 and T4 in rats that suffered a myocardial infarction, there was a normalization of cardiac redox status and prevention of lipid peroxidation, which was associated with the alleviation of cardiac remodelling after ischemic injury (9) suggesting that oxidative stress may play an important role in the cardioprotective effect of T3 and T4.

The potential impact of hormonal status on the course of myocardial infarction and heart failure may significantly impact future research on the individualization of myocardial infarction and heart failure treatment, depending on the patient's thyroid status. Considering the importance of thyroid hormones in the metabolism, the question arises whether their values can be important for the stratification of patients regarding the outcome and occurrence of MACE during and after AMI. There were no similar investigations in Bosnia and Herzegovina.

The aim of the study was to examine the association of thyroid function, neutrophil-lymphocyte ratio (NLR) with left ventricular function measured through ejection fraction of left ventricle (EFLV) in a patient with acute myocardial infarction treated with percutaneous coronary intervention (PCI).

PATIENTS AND METHODS

Patients and study design

This prospective research involved 160 consecutive patients with ACS that were hospitalized in the Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Centre of the University of Sarajevo during the period January-July 2022. The pa-

tients were divided into those with normal thyroid hormone status (n=80) and those with hypothyroidism (newly diagnosed) (n=80). Inclusion criteria were: age over 18 years, patients with ACS (STEMI or NSTEMI), elevated cardio specific enzymes for myocardial necrosis (creatine kinase (CK), creatine kinase-MB (CK-MB), cardiac troponin I), percutaneous coronary intervention (PCI) performed during hospitalization, and newly discovered hyper or hypothyroidism. Exclusion criteria were previous myocardial infarction, previous PCI or myocardial revascularization, primary cardiomyopathy, previous hypothyroidism or hyperthyroidism, diabetes mellitus, patients with chronic renal failure and creatinine >2.0 mg/dL (176.8μmol/L) and patients on a chronic haemodialysis program, pregnancy, malignant disease, treatment with amiodarone, patients with psychiatric diagnoses, patients who were not motivated to perform an interventional procedure.

An informed consent was obtained from all patients following an explanation of the purpose of the study. An ethical approval was obtained from the Ethical Committee of the Clinical Centre of the University of Sarajevo.

Methods

Inflammatory parameters (sedimentation rate, leukocytes, platelets, haemoglobin, haematocrit, neutrophils, lymphocytes, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), and fibrinogen) were measured at admission and 24-48 hours after the PCI procedure. Parameters of hormonal status, thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), and free triiodothyronine (FT3)) were taken within 24 hours of admission. The maximum values of inflammatory parameters were analysed. Reference ranges for evaluated laboratory parameters were: erythrocytes 4.34 -5.72 x10^{12}/L and 3.86 -5.08 x10^{12}/L for males and females respectively; leukocytes 3.4-9.7x10^{9}/L; haemoglobin 137-175 g/L in males and 119-157 g/L in females; haematocrit 0.41-0.53 % in males and 0.35-0.47% in females; platelets 158-424 x10^{9}/L for males and females; neutrophil granulocytes 44-72%; lymphocytes 20-46%; fibrinogen 2.0 -4.0 g/L; sedimentation 0 to 22 mm/h for males and 0 to 29 mm/hr for females; CRP up to 5.0 mg/L; T4 66-181 nmol/L; T3 1.3-3.1 nmol/L; TSH 0.27-4.20 μmol/mL; FT4 12.0-22.0 pmol/L; FT3 3.1-6.8 pmol/L.

Intrahospital complications were recorded (ventricular heart rhythm disorders, atrial tachyarrhythmias, acute heart failure and intrahospital death).

All patients underwent transthoracic echocardiographic examination (TTE) after five days of admission, and LVEF was measured by the Simpson method (10).

Statistical analysis

Tests of descriptive statistics were performed, with the display of measures of central tendency and dispersion. Each variable was tested for belonging to a normal distribution using the Kolmogorov-Smirnov test. Quantitative variables were compared by t-test with a correction for unequal variances where they were normally distributed. The Kruskal-Walli's test was used for the non-parametric analysis of the comparison of average values. Categorical variables were analysed with the χ2-test, with Yates's correction for continuity for 2x2 tables, or with Fisher's test for analyses in which cells were less than 5. A relative risk determination was calculated using the usual methodology with 2x2 tables. A statistical level of 95% ($p<0.05$) was taken as significant.

RESULTS

The average age of patients was 61±11 years; in the group of patients with hypothyroidism it was 64 ± 10 and in patients with euthyroidism 58 ± 11 years ($p<0.001$). There were males predominated in the total sample, 111 (69.4%) ($p=0.002$), as well as in the group with euthyreosis, 65 (81.3%), in comparison with the group of patients with hypothyroidism, 46 (57.5%). A significant difference was verified in monitored parameters (T3, T4, erythrocytes, haemoglobin, haematocrit, neutrophil, lymphocytes, NLR, CRP, sedimentation). In accordance with coronary angiography, patients with euthyroidism were more frequently without the presence of coronary disease ($p=0.01$) and single-vessel disease ($p=0.035$), and less frequently with triple vessel disease ($p=0.046$). No statistically significant difference was verified between the groups in two-vessel and multivessel coronary disease occurrence. In both groups, two (2.5%) patients were diagnosed with myocardial infarction

with non-obstructive coronary arteries (MINOCA). A total of 58 (72.5%) patients with euthyreosis achieved complete resolution of the ST segment compared to 44 (55%) of those with hypothyroidism (p=0.02). Patients with hypothyroidism had a 38.9% higher relative risk for incomplete or absent ST-segment resolution after PCI.

The median value of LVEF in the group of patients with hypothyroidism was 40% (36-45%), while in the group with euthyroid hormone level it was 44% (40-48%) (patients with euthyroid hormone level had a higher median value LVEF) (p=0.003).

An indication for coronary artery bypass graft (CABG) during hospitalization was significantly more frequent (p=0.045) in the group of patients with hypothyroidism, 21 (26.3%), compared to euthyroid patients, 10 (12.5%).

The total number of in-hospital complications was significantly higher (p<0.001) within the group of patients with hypothyroidism, 42 (52.5%), in comparison with patients with euthyroid hormone level, 17 (21.3%).

Atrial tachyarrhythmia was also significantly more frequent (p=0.002) in the group with hypothyroidism, 15 (18.8%), than in the euthyroid group, two (2.5%). There was a significant correlation between EFLV with haemoglobin values (p=0.002), NLR (p=0.001), and CRP (p=001) (Table 1).

Table 1. Monitored parameters in two group of patients

Parameter	Euthyroidism (Mean ±SD) (n=80)	Hypothyroidism (Mean ±SD) (n=80)	p
Triiodothyronine (T3) (nmol/L)	1.96 ± 0.55	1.21±0.31	<0.001
Thyroxine (T4) (nmol/L)	111.40±20.83	103.82±24.0	0.034
Free triiodothyronine (T3) (pmol/L)	4.58±0.66	4.20±1.99	0.112
Free thyroxine (T4) (pmol/L)	16.82±2.69	16.28±4.08	0.325
Erythrocytes (x1012⁄L)	5.02±0.48	4.73±0.48	<0.001
Leucocytes (x109⁄L)	9.67±1.98	9.55±2.56	0.732
Platelets (x109⁄L)	225.35±68.56	240.65±67.56	0.157
Haemoglobin (g⁄L)	152.61±14.95	144.04±17.00	0.001
Haematocrit (%)	45.32±4.50	43.35±5.37	0.013
Neutrophils %	4.57±1.37	6.94±1.48	<0.001
Lymphocytes (%)	1.26±0.60	1.08±0.38	0.021
Neutrophil/lymphocyte ratio	4.10±1.47	6.76±1.65	<0.001
C-reactive protein (mg⁄L)	10.85±10.58	19.34±19.52	0.001
Fibrinogen (g⁄L)	4.62±2.46	4.55±2.20	0.858
Sedimentation (mm/h)	9.01±7.30	23.24±14.84	<0.001

SD, standard deviation;

DISCUSSION

In patients with decreased thyroid hormone values, CRP and sedimentation values were elevated, indicating that these patients have an increased inflammatory response. In addition, haemoglobin, haematocrit and erythrocyte values were decreased. The number of intrahospital complications in patients with hypothyroidism was higher, and the LVEF itself was lower. Our data revealed that there was a significant correlation between LVEF with haemoglobin, NLR and CRP values. Research indicates CRP levels are elevated during progressive thyroid failure, which could be an additional risk factor for coronary heart disease in hypothyroid patients (11). Interestingly, assessing CRP and troponin levels, a prospective multicentre observational study by Jabbar et al. indicated a twofold higher risk of mortality in AMI patients with low serum T3 levels (though not on other forms of thyroid dysfunction), implying a potential therapeutic modality for this group of patients (12). However, in a study conducted by Wang et al. it was observed that, in STEMI patients, CRP levels were negatively correlated with FT3 but positively correlated with cardiac injury biomarkers, suggesting that the link between AMI and a decreased thyroid function profile could be well mediated by an inflammatory response (13). In our study, euthyroid patients were more frequently without the presence of coronary disease on coronary angiography, as well as with single-vessel disease; patients with hypothyroidism had a significantly higher relative risk for incomplete or absent ST-segment resolution after PCI. Wang et al. indicated that in AMI patients, there was an increased risk of revascularization and heart failure due to hypothyroid status, which was therefore considered to be an independent prognostic factor for major adverse cardiovascular events (14). Our study found that the patients with euthyroid hormone level had a higher median value of LVEF. Interestingly, in the study of patients with subclinical hypothyroidism and AMI it was suggested that thyroid replacement therapy did not substantially improve left ventricular ejection fraction (LVEF) during the follow-up period, thus not favouring the idea that patients with AMI should be treated for subclinical hypothyroidism (15). Moreover, in our study, the total number of in-hospital com-

plications was significantly more frequent within the group of patients with hypothyroidism. In particular, an indication for CABG during hospitalization was significantly more frequent in the group of patients with hypothyroidism. Similarly, an observational study evaluating the TSH and FT4 level of STEMI patients with previously unknown and untreated subclinical hypothyroidism (SCH), who underwent primary PCI, reported poor in-hospital outcomes compared to euthyroid patients; also, patients with SCH were more likely to have lower LVEF (equal to or less than 40%) level, contributing to short-term and long-term mortality (16,17). These findings in patients with hypothyroid status could be attributed to decreased nitric oxide availability, which may contribute to endothelial dysfunction, hampering flow-mediated vasodilation, as well as mitochondrial oxidative stress caused by elevated plasma inflammatory markers or by impaired left ventricular systolic function (16,18).

Furthermore, Li et al. found that, compared to euthyroid patients, STEMI patients with subclinical hyperthyroidism at admission, and those with low baseline T3 level, had a worse prognosis and an increased risk of in-hospital mortality (19).

Limitations of this study include the observational study design and a relatively small sample size. However, one of the study's strengths is that it evaluated relevant variables affecting thyroid function. Moreover, the prospective nature of our study allowed for the systematic collection of all pertinent data. The paper indicates the importance of thyroid hormone in the evaluation of the inflammatory process during AMI and indicates importance of thyroid hormone in MACE prediction.

In conclusion, the cardiovascular system is considerably and adversely impacted by the role of TSH, its absence, as well as alterations in thyroid hormone concentrations. In ACS patients, routine thyroid function testing before performing PCI should be done. The altered status of the thyroid gland in acute myocardial infarction is associated with the severity of the coronary blood vessel lesion, LVEF and correlates with inflammatory response. Routine analysis of the hormonal status of the thyroid gland along with other risk factors enables better screening of patients with a higher probability of developing in-hospital complications and a worse outcome in acute myocardial infarction.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Sirajuddin A, Mirmomen SM, Kligerman SJ, Groves DW, Burke AP, Kureshi F, White CS, Arai AE. Ischemic heart disease: noninvasive imaging techniques and findings. Radiographics 2021; 41:990-1021.
2. Bhatt DL, Lopes RD, Harrington RA. Diagnosis and treatment of acute coronary syndromes: a review. JAMA 2022; 327:662-75.
3. Begic E, Obradovic S, Jankovic S, Romanovic R, Djenic N, Dzudovic B, Jovic Z, Malovic D, Subota V, Stavric M, Ljuca F, Kusljugic Z. Increased C-reactive protein is associated with major adverse cardiovascular events after STEMI. Erciyes Med J 2020; 42:276-80.
4. Obradovic S, Begic E, Jankovic S, Romanovic R, Djenic N, Dzudovic B, Jovic Z, Malovic D, Subota V, Stavric M, Ljuca F, Kusljugic Z. Association of PC and AT levels in the early phase of STEMI treated with pPCI with LV systolic function and 6-month MACE. Acta Clin Belg 2020; 76:1-7.
5. Arambam P, Kaul U, Ranjan P, Janardhanan R. Prognostic implications of thyroid hormone alterations in acute coronary syndrome - a systematic review. Indian Heart J 2021; 73:143-8.
6. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116:1725–35.
7. Wiersinga WM, Lie KI, Touber JL. Thyroid hormones in acute myocardial infarction. Clin Endocrinol (Oxf) 1981; 14:367-74.
8. Ojamaa K, Kenessey A, Shenoy R, Klein I. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. Am J Physiol Endocrinol Metab 2000; 279:E1319-24.
9. Gray L, Chen F, Teeter EG, Kolarczyk LM, Smeltz AM. Evaluation of the Simpson's method to determine left ventricular ejection fraction using the transgastric two-chamber view. Semin Cardiothorac Vasc Anesth 2022; 26: 195-9.
10. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Müller B. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 2003; 166:379-86.
11. Jabbar A, Ingoe L, Thomas H, Carey P, Junejo S, Addison C, Vernazza J, Austin D, Greenwood JP, Zaman A, Razvi S. Prevalence, predictors and outcomes of thyroid dysfunction in patients with acute myocardial infarction: the ThyrAMI-1 study. J Endocrinol Invest 2021; 44:1209-18.

12. Wang WY, Tang YD, Yang M, Cui C, Mu M, Qian J, Yang YJ. Free triiodothyronine level indicates the degree of myocardial injury in patients with acute ST-elevation myocardial infarction. Chin Med J (Engl) 2013; 126:3926-9.
13. Wang W, Wang S, Zhang K, Chen J, Zhang X, Shao C, Li P, Tang YD. Hypothyroidism is associated with clinical outcomes in patients with acute myocardial infarction: subgroup analysis of China PEACE study. Endocrine 2021; 74:128-37.
14. Jabbar A, Ingoe L, Junejo S, Carey P, Addison C, Thomas H, Parikh JD, Austin D, Hollingsworth KG, Stocken DD, Pearce SHS, Greenwood JP, Zaman A, Razvi S. Effect of levothyroxine on left ventricular ejection fraction in patients with subclinical hypothyroidism and acute myocardial infarction: a randomized clinical trial. JAMA 2020; 324:249-58.
15. Izkhakov E, Zahler D, Rozenfeld KL, Ravid D, Banai S, Topilsky Y, Stern N, Greenman Y, Shacham Y. Unknown subclinical hypothyroidism and in-hospital outcomes and short- and long-term all-cause mortality among ST segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. J Clin Med 2020; 9: 3829.
16. Manolis AA, Manolis TA, Melita H, Manolis AS. Subclinical thyroid dysfunction and cardiovascular consequences: An alarming wake-up call? Trends Cardiovasc Med 2020; 30:57-69.
17. Ertugrul O, Ahmet U, Asim E, Gulcin HE, Burak A, Murat A, Sezai YS, Biter HI, Hakan DM. Prevalence of subclinical hypothyroidism among patients with acute myocardial infarction. Int Sch Res Notices 2011; 2011:810251.
18. Li MF, Wei ZT, Li S, Feng QM, Li JB. Association of mild thyroid dysfunction and adverse prognosis among Chinese patients with acute ST segment elevation myocardial infarction. Front Endocrinol (Lausanne) 2022; 13:879443.