Uric Acid and NT-proBNP as Biomarkers of Cardiovascular Dysfunction in Hyperthyroidism and Hypothyroidism

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The various thyroid axis dysfunctions have cardiovascular consequences both in hyperthyroidism and in hypothyroidism. This cross-sectional study included hyperthyroid and hypothyroid female patients in whom uric acid and NT-proBNP were determined in relation to changes in clinical findings and some echocardiographic parameters. The results of our study suggest that NT-proBNP is a better predictor than uric acid, correlating with left ventricular diastolic dysfunction and systolic blood pressure variations.

Key words: uric acid, NT-proBNP, hyperthyroidism, hypothyroidism

The human natriuretic-peptide family is composed of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP was first discovered in 1980; it is secreted at atrial level, being a *28-amino acid* polypeptide [1]. BNP is derived from the *108-amino acid precursor proBNP* present in both cardiac ventricles and at lower levels in the atria. In response to volume expansion and myocyte stretch, proBNP is cleaved into the biologically active 32-amino acid peptide BNP and into the 76-amino acid NT-proBNP peptide by corin and furin enzymes. CNP is secreted by the vascular endothelium and has vasodilatory properties [1, 2]. Plasma BNP and NT-proBNP levels have been recommended for the assessment of diagnosis and prognosis in patients with heart failure, acute coronary syndromes, dyspnea of other causes, atrial fibrillation, systemic and pulmonary hypertension. NT-proBNP has higher stability and longer half-life compared to BNP [3,4]. Uric acid is a heterocyclic organic compound with the formula C5H4N4O3 (7,9-dihydro-1H-purine-2,6,8 (3H)-trione), with a molecular weight of 168 Daltons, which is excreted in urine. In humans it is the end product of purine metabolism by the intervention of numerous enzymes on purine nucleic acids adenine and guanine. Various evidences have associated elevated uric acid levels with diabetes mellitus, metabolic syndrome, subclinical atherosclerosis, cardiovascular and renal diseases [5-7].

Thyroid hormones, particularly T3, have shown beneficial cardiovascular effects by improving myocardial relaxation and reducing peripheral vascular resistance. The various thyroid axis dysfunctions [8] are accompanied by pathological cardiovascular changes[9], both in hyperthyroidism and in hypothyroidism. Moreover, after the discovery of the general physiological and pathological responses to stress, both in case of negative and positive responses, the stress concept was involved in the pathogenesis of many morbid, endocrine, metabolic or cardiovascular conditions. Clinical and subclinical thyroid changes are accompanied by autoimmune phenomena that can contribute to worsening of cardiovascular reactions and dysregulation of other endocrine systems, such as the hypothalamic-pituitary-adrenocortical axis [10-14].

Cardiovascular laboratory parameters have been insufficiently studied in the presence of certain endocrine dysfunctions. Changes in thyroid and cardiovascular status may be detected earlier by measuring such subclinical markers such as uric acid or atrial natriuretic peptides in parallel with the hemodynamic profile and echocardiographic parameters of systolic and diastolic myocardial dysfunction. In this regard, our study aimed to investigate the relationship between uric acid, NT-proBNP, thyroid hormones and some clinical or echocardiographic parameters of cardiovascular function in patients diagnosed with hyperthyroidism or hypothyroidism.

Experimental part

Material and methods

This cross-sectional study enrolled 94 patients divided into 3 groups according to thyroid stimulating hormone (TSH) and free thyroxine (fT4) level: 34 hypothyroid patients, 30 hyperthyroid patients and 30 euthyroid patients who served as controls. Patients were enrolled consecutively during clinic visits, after physical examination, thyroid ultrasound and thyroid hormone determinations. Patients with known major cardiovascular diseases (heart failure, valvular heart diseases, history of acute myocardial infarction, atrial fibrillation, cardiomyopathy), autoimmune diseases except for autoimmune thyroiditis, diabetes mellitus, liver or kidney disease, chronic ethanol or drug use, mental diseases were excluded. The control group

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consisted of healthy volunteers without thyroid and cardiovascular diseases, or diseases of other causes. Each patient signed the informed consent and the study protocol was approved by the local ethics committee.

The patients were assessed by physical examination followed by transthoracic echocardiography, thyroid ultrasound and laboratory tests.

Echocardiographic examination was performed with a AU3 Partner, Esaote Biomedica device, using a 2.5/3.5 Mhz transducer in the M, 2D, pulsed and continuous wave and color Doppler modes, following standard recommendations. For assessing the systolic function, the left ventricular ejection fraction (EF) was measured using the Simpson method, and for assessing the diastolic function the *E wave mitral peak maximum velocity*, A wave maximum velocity of late filling, E/A ratio and isovolumic relaxation time (IVRT) were measured.

Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (M3 Omron, Matsusaka Co. LTD, Japan) were measured.

For laboratory tests venous blood samples were taken after a 12-hour overnight fast. After collection, blood samples were centrifuged and the plasma was stored in a freezer at -20ºC until measurements were made. Serum uric acid was determined by the colorimetric enzymatic method, reference range 3.5-5.7 mg/dL. Thyroid hormones were determined by the immunochemical method with electrochemiluminescence detection, levels of 0.2-4.2 mU/L for TSH and 0.8-1.7 ng/dL for fT4 being considered normal. Plasma levels of NT-proBNP were considered pathological when exceeded 125 pg/mL. For the NT-proBNP determination the immunoenzymatic method with monoclonal antibodies (ECLIA, USA) was used.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 16.0. Mean and standard deviation were calculated for all quantitative variables. In case of abnormal distribution of values, the differences were tested using the Mann-Whitney and Kruskal-Wallis tests. In other situations the ANOVA test was used. Statistical significance was established at $p < 0.05$. The interdependence relationship between the uric acid and NT-proBNP and the other variables was analyzed by the regression equation, calculating the Pearson correlation coefficient.

Results and discussions

The clinical, biochemical and echocardiographic characteristics of the study groups are presented in Table 1. The clinical parameters showed no significant differences between groups in terms of age and diastolic blood pressure levels. SBP increased significantly in both the hypothyroid (135.1 ± 10.3 vs 127.3 ± 8.6 mmHg, p = 0.004) and hyperthyroid group (154.6 ± 17.2 vs 127.3 ± 8.6, p <0.001). Hyperthyroidism had more significantly influenced HR than hypothyroidism: in hyperthyroidism a significant increase in HR (92.6 ± 10.9 vs 68.3 ± 5.9, p <0.001) was recorded, whereas in hypothyroidism there was a slight decrease in HR (64.8 ± 5.3 vs 68.3 ± 5.9, p = 0.013). Clear and statistically significant differences were found for thyroid hormone levels in patients with hypothyroidism and hyperthyroidism compared to controls. Echocardiographic assessment revealed that the EF was significantly lower in the hypothyroid patients compared to the controls (59 ± 5.8 vs 67.4 ± 6.8) and hyperthyroid patients (59 ± 5.8 vs. 65.7 ± 8.2). Changes in diastolic function indicated by a decreased E/A ratio and the increase in IVRT (230 ± 35 vs 164 ± 33 in the control group) were more significant in the hyperthyroid group. Compared to the control group, both hypothyroid and hyperthyroid patients had significantly elevated plasma NT-proBNP levels (48.7 ± 18.1 in the control group vs 115 ± 50.6 in the hypothyroid group and 240.4 ± 94.6 in the hyperthyroid group). Uric acid level was higher compared to the control group, the most significant increases being recorded in patients with hypothyroidism (4.6 ± 0.7 in the control group vs 5.9 ± 1.8 in the hyperthyroid group and 6.2 ± 1.8 in the hypothyroid group). Several studies have reported increased NT-proBNP levels in hyperthyroid patients. Some authors reported a more significant increase of NT-proBNP levels in patients with symptomatic hyperthyroidism than in subclinical hyperthyroidism. It has been demonstrated that antithyroid treatment does not influence NT-proBNP levels in patients with either Graves disease or toxic nodular goiter [3, 15-17]. Generally, the more thyroid dysfunction complicates with other conditions such as hypertension or heart failure, the higher the NT-proBNP levels might be [18, 19]. Arterial hypertension is greatly influenced by exposure to stress and poor economic conditions, which also influence the thyroid diseases [20]. Unlike other studies, our data show an increase in NT-proBNP in both hyperthyroid and hypothyroid patients. Similar findings

Table 1
BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Control	Hypothyroidism		Hyperthyroidism	
	Mean ± SD	Mean ± SD	p vs control	Mean ± SD	p vs control
Age (years)	45.7 ± 4.9	47 ± 5.1	p = 0.209	46.3 ± 4.8	p = 0.48
BMI (kg/m^2)	22.5 ± 2.1	29 ± 3.3	**p < 0.001**	24.5 ± 3.1	**p = 0.006**
HR (b/min)	68.3 ± 5.9	64.8 ± 5.3	**p = 0.013**	92.6 ± 10.9	**p < 0.001**
SBP (mmHg)	127.3 ± 8.6	135.1 ± 10.3	**p = 0.004**	154.6 ± 17.2	**p < 0.001**
DBP (mmHg)	77.1 ± 7.7	76.7 ± 6.5	p = 0.92	80.6 ± 7.8	p = 0.08
TSH (mU/L)	2.65 ± 0.8	6.8 ± 2.4	**p < 0.001**	0.14 ± 0.1	**p < 0.001**
fT4 (ng/dL)	0.96 ± 0.17	0.56 ±0.09	**p < 0.001**	1.91 ± 0.33	**p < 0.001**
Uric acid (mg/dl)	4.6 ± 0.7	6.2 ± 1.8	**p < 0.001**	5.9 ± 1.8	**p = 0.005**
NT-proBNP (pg/mL)	48.7 ± 18.1	115 ± 50.6	**p < 0.001**	240.4 ± 94.6	**p < 0.001**
EF (%)	67.4 ± 6.8	59 ± 5.8	**p < 0.001**	65.7 ± 8.2	p = 0.39
E (m/s)	0.54 ± 0.09	0.59 ± 0.1	**p = 0.042**	0.54 ± 0.1	p = 0.994
A (m/s)	0.45 ± 0.08	0.58 ± 0.08	**p < 0.001**	0.64 ± 0.1	**p < 0.001**
E/A	1.2 ± 0.05	1 ± 0.13	**p < 0.001**	0.85 ± 0.15	**p < 0.001**
IVRT (ms)	164 ± 33	168 ± 34	p = 0.64	230 ± 35	**p < 0.001**

Clinical and subclinical parameters	Uric acid		NT-proBNP	
	Hypothyroidism	Hyperthyroidism	Hypothyroidism	Hyperthyroidism
HR (b/min)	R = 0.166 p = 0.349	R = 0.103 p = 0.588	R = 0.196 p = 0.267	R = - 0.327 p = 0.078
SBP (mmHg)	R = - 0.71 p = 0.691	R = - 0.094 p = 0.620	R = - 0.133 p = 0.455	**R = - 0.585** **p = 0.001**
DBP (mmHg)	R = 0.051 p = 0.775	R = - 0.203 p = 0.282	R = 0.053 p = 0.766	R = - 0.309 p = 0.096
TSH (UI/ml)	R = 0.176 p = 0.320	R = - 0.100 p = 0.599	R = - 0.122 p = 0.492	R = 0.155 p = 0.414
fT4 (nmol/L)	R = 0.013 p = 0.944	R = 0.071 p = 0.708	R = 0.018 p = 0.918	R = 0.329 p = 0.076
EF (%)	R = 0.080 p = 0.655	R = 0.261 p = 0.164	R = 0.208 p = 0.237	R = - 0.128 p = 0.501
E (m/s)	R = 0.006 p = 0.973	R = - 0.203 p = 0.281	R = 0.117 p = 0.508	R = 0.150 p = 0.428
A (m/s)	R = 0.121 p = 0.495	R = - 0.023 p = 0.904	R = 0.117 p = 0.511	R = - 0.041 p = 0.831
E/A	R = - 0.134 p = 0.449	R = - 0.251 p = 0.180	R = - 0.011 p = 0.951	R = 0.132 p = 0.488
IVRT (ms)	R = - 0.111 p = 0.531	R = 0.165 p = 0.385	**R = - 0.656** **p < 0.001**	**R = 0.457** **p = 0.011**

Table 2
PEARSON'S CORRELATION ANALYSIS OF URIC ACID AND NT-PROBNP WITH THE CARDIO-VASCULAR PARAMETERS

were reported by authors who have shown that although hypothyroid patients *lack* the stimulatory *effect* of *thyroid hormones* on *BNP*, the proinflammatory status and endothelins may stimulate NT-proBNP release in hypothyroid patients [3, 21]. The data presented in our study do not refer to subclinical thyroid dysfunctions, the patients having pathological levels of both TSH and fT4 [12-22].

Our study supports the correlation between NT-proBNP and IVRT, positive in hyperthyroidism (R = 0.457, p = 0.011) and negative in hypothyroidism (R = - 0.656, p <0.001). NT-proBNP also correlated negatively with SBP levels in hyperthyroid patients (R = - 0.585, p = 0.001) (table 2). Uric acid levels did not significantly correlate with the studied parameters. These results suggest that NT-proBNP is a more sensitive marker of cardiovascular dysfunction associated with thyroid disease than uric acid. Changes seem to occur earlier in hyperthyroidism than in hypothyroidism, affecting blood pressure levels and left ventricular diastolic function. There have been studies that reported pathological NT-proBNP levels in patients with hyperthyroidism, even in the absence of echocardiographic changes [10].

On the other hand, Selvaraj S et al. determined the T3 level in patients with heart failure with preserved ejection fraction. T3 level was lower in 22% of these patients. The authors also suggest some plausible mechanisms by which low T3 level may lead to exacerbation of heart failure phenomena. For example, a low T3 level is associated with decreased expression of such proteins as alpha-sarcomericactinin, resulting in impaired left ventricular relaxation [10]. In an experimental model of rat heart failure, administration of T3 resulted in the improvement of left ventricular diastolic function [23]. From a clinical point of view, T3 administration in patients with low EF led to increased cardiac output and decreased systemic vascular resistance or symptom improvement in patients with dilated cardiomyopathy [10,24,25].

Conclusions

Our study revealed variations in uric acid and NT-proBNP levels in relation to some parameters of cardiovascular function in patients with hyperthyroidism or hypothyroidism. NT-proBNP is a more sensitive marker of blood pressure variations and diastolic dysfunction than uric acid, especially in patients with hyperthyroidism. Further studies are needed to evaluate the main mechanisms leading to cardiovascular disorders in thyroid dysfunction.

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