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Amino-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Serum Levels in Females with Different Thyroid Function States

[Farklı Tiroit Fonksiyonlarına Sahip Kadınlarda Serum Amino-terminal Pro-Brain Natriüretik Peptit (NT-proBNP) Düzeyleri]

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ABSTRACT

Aim: Cardiovascular changes that accompany thyroid disorders could be stimulus for the release of BNP from heart ventricles. Different factors, including stress environment conditions, have important role in pathogenesis of thyroid disorders and could possibly affect this response. The aim of this study was to assess the relationship between NT-proBNP and thyroid hormones levels in females with different thyroid functional states.

Materials and methods: The study included 104 female patients, age 18-55 years, divided into three groups: hyperthyroid, hypothyroid and euthyroid (control). Serum NT-proBNP, FT3, FT4 and TSH levels were determined in all groups, but in hyper- and hypothyroid group before and after the adequate therapy aimed to the regulation of thyroid status. NT-proBNP concentration was determined by Electrochemiluminescent Immunoassay "ECLIA" method on Roche Elecsys 2010 system.

Results: Mean serum NT-proBNP level in hyperthyroid group, before the therapy was 99.35 pg/mL and was significantly higher compared to serum NT-proBNP levels in control (65.90 pg/mL) and hypothyroid group (56.82 pg/mL, $p<0.05$). After therapy, serum NT-proBNP levels significantly decreased in hyperthyroid (53.64 pg/ml, $p<0.01$) and significantly increased in hypothyroid group (69.95pg/mL, $p<0.04$). A significant correlation between serum thyroid hormones, TSH and NT-proBNP levels were observed in hyperthyroid patients, but in hypothyroid patients only between NT-proBNP and FT3 levels. Multiple regression analyses demonstrated that FT3 level was independently associated with serum NT-proBNP levels in hyperthyroid group, after normalization of thyroid status.

Conclusion: Thyroid hormones possibly effect BNP secretion and therefore affect the serum NT-proBNP level.

Key Words: amino-terminal pro-brain natriuretic peptide; NT-proBNP; females; hyperthyroidism; hypothyroidism

ÖZET

Amaç: Tiroit hastalıklarına eşlik eden kardiovasküler değişiklikler kalp ventriküllerinden BNP salınımı için uyarıcıdır. Tiroit hastalığının patogenezinde önemli rolü olan farklı etkenler içinden çevresel stres de, BNP salınımına karşı oluşan cevabı etkileyebilmektedir. Bu çalışmadaki amaç farklı tiroit fonksiyonlarına sahip kadın hastalarda NT-proBNP ve tiroit hormon düzeyleri arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Çalışma yaşları 18-55 arasında değişen 104 kadın hastayı içerir. Hastalar hipertiroit, hipotiroit ve ötiroit (kontrol) olmalarına göre üç gruba ayrıldı. Serum NT-proBNP, FT3, FT4 ve TSH düzeylerine tüm gruplarda bakılırken, hiper- ve hipotiroit olan gruplarda tiroit düzeyini regüle etmesi planlanan uygun tedavi öncesi ve sonrasında da hormon düzeyleri tespit edildi. NT-proBNP konsantrasyonları elektrokemilüminesans immun yöntem "ECLIA" metodu ile Roche Elecsys 2010 sisteminde çalışıldı.

Sonuçlar: Hipertiroit grupta ortalama serum NT-proBNP düzeyleri (99.35 pg/mL) kontrol (65.90 pg/mL) ve hipotiroidi grubu (56.82 pg/mL) ile karşılaştırıldığında tedavi öncesi değerler anlamlı olarak yüksek bulundu ($p<0.05$). Tedavi sonrasında ise serum NT-proBNP düzeyleri hipertiroidi grubunda (53.64 pg/ml, $p<0.01$) anlamlı olarak azaldı, hipotiroidi grubunda (69.95pg/mL, $p<0.04$) ise anlamlı olarak arttı. Hipertiroidi hastalarında serum tiroit hormonları, TSH ve NT-proBNP düzeyleri arasında anlamlı bir korelasyon gözlenirken, hipotiroidi hastalarında bu anlamlılık sadece NT-proBNP ve FT3 düzeyleri arasında görüldü. Çoklu regresyon analizinde ise hipertiroidi grubunda, FT3 düzeylerinin bağımsız olarak serum NT-proBNP düzeyleri ile tiroit düzeylerinde yapılan normalizasyon sonrasında ilişkili olduğu görüldü.

Sonuç: Tiroit hormonlarının BNP salınımına etkisi serum NT-proBNP düzeylerini değiştirebilmektedir.

Anahtar Kelimeler: amino-terminal pro-brain natriüretik peptit; NT-proBNP; kadın; hipertiroidizim; hipotiroidizim

Introduction

Brain natriuretic peptide (BNP) is a cardiac neurohormone, composed of 32 amino acids, mainly secreted from the ventricles. Prohormone, pro brain natriuretic peptide (proBNP) is cleaved into the biologically active form BNP and amino terminal fragment of the prohormone NT-proBNP. Both peptides, BNP and NT-proBNP are presented in the plasma [1].

The basic stimulus for the BNP secretion is increased ventricular wall tension in response to sodium and water retention, volume expansion and elevated end diastolic volume [2]. It is well known that the synthesis and secretion of natriuretic peptides are under the complex control of neurohumoral and immune system. Increased BNP concentrations lead to reduction of blood pressure and plasma volume through coordinated action of the brain, adrenal glands, kidneys and blood vessels [3].

An increase of heart rate, total blood volume, left ventricular end-diastolic volume (LVEDV) and cardiac output in hyperthyroid state exerts the "stress" of the cardiac wall and could be possible stimuli for the secretion of BNP, and subsequently increased of the serum NT-proBNP level. Previous studies have shown the direct impact of thyroid hormones on BNP secretion and release, but presented results of theirs association are widely different [4-6]. Controversially, results of recent studies showed increased NT-proBNP levels in cardiac as well as in noncardiac patients with low T3 syndrome [7]. This study is different from the others because the fact that this female population we included were exposed to extremely long-lasting stress during the war period in Bosnia and Herzegovina. This surely was additional factor in pathogenesis of thyroid diseases and accompanying cardiovascular changes that also could possibly affect BNP response in this patient.

Accordingly, in this study we evaluated NT-proBNP levels in untreated patients with different thyroid functional states, exposed to stress during war period in Bosnia and Herzegovina. In addition, we evaluated natriuretic peptide before and after normalization of hormonal status in patients with thyroid dysfunctions.

Subjects and Methods

Subjects

All participants of our study were selected from the subjects who performed control of thyroid hormonal status at the Institute of Nuclear Medicine, Clinical Center of Sarajevo University, and who had never been treated for thyroid dysfunction state. Only women were included to avoid intersex variations.

After an overnight fast, all the women underwent full medical assessment, general laboratory examinations, electrocardiogram and echocardiography. The exclusion criteria were: presence of clinically evident cardiovascular diseases, renal diseases, pituitary/hypothalamic disorders, diabetes mellitus and pregnancy. Based on these criteria a study sample was formed which consisted of 104 patients and was divided into three, aged matched groups. According to the below criteria all patients had thyroid hormone levels that approved their overt hyperthyroid or overt hypothyroid status.

1. HYPERTHYROID GROUP consisted of 34 females, mean age 41.6±10.0 years. Overt hyperthyroidism was defined by serum TSH level <0.1 mIU/mL and increased serum FT4 level (>23 pmol/L).
2. HYPOTHYROID GROUP consisted of 35 females, mean age 49.1±4.3 years. Overt hypothyroidism was defined by serum TSH level >10 mIU/mL and decreased serum FT4 level (<10 pmol/L).
3. EUTHYROID (CONTROL) GROUP consisted of 35 females, mean age 43.7±8.8 years, with serum FT3, FT4 and TSH levels within the normal reference ranges.

Approval for the study was obtained by the local Ethics Committee (29-T-2940/04). All procedures on human subjects were performed in accordance with the latest version of Helsinki Declaration. All subjects included in the study signed an informed consent with careful explanation of the study procedures.

Measurements

After the selection and inclusion of the patients in the study groups, blood samples were taken to determine the serum FT3, FT4, TSH and NT-proBNP levels. Hyperthyroid patients were treated with an adequate therapy (tiamazol, propylthiouracil, radioiodine I-131) to achieve euthyroid state. Criteria for achieving a euthyroid state were the decrease in FT3 and FT4 concentrations within the reference values. The therapy and therapeutic doses were individually adjusted. The average duration of therapeutic treatment was 5.60±0.89 months. Hypothyroid patients were treated with L-thyroxin therapy aiming to normalization of FT3, FT4 and TSH levels. Applied therapy and therapeutic doses were individually adjusted. The average duration of therapeutic treatment to achieve euthyroid state was 5.80±1.07 months. Control of hormonal status was done periodically. After the achievement of euthyroid state a blood sample was taken to determine the levels of NT-proBNP.

- NT-proBNP, FT3, FT4 and TSH measurements

Blood samples were collected in the fasting state, immediately put on ice and processed within 30 minutes. Thereafter, the obtained serum samples were kept frozen at -80°C. NT-proBNP, FT3, FT4 and TSH plasma levels were determined using electrochemiluminescence immunoassay "ECLIA" on Elecsys 2010 (Roche Diagnostic). All measurements were performed at the Institute of Nuclear Medicine, University of Sarajevo Clinics Center. This assay is an electrochemiluminoescent sandwich

immunoassay using two polyclonal antibodies directed at the molecule. The analytic range extends from 5-35.00 pg/mL. Functional sensitivity was <50 pg/mL, defined as the analytic lowest concentration that can be reproducibly measured with a between-run coefficient of variation 20%. Expected values for women, aged ≤ 50 years are 155 pg/mL.

Statistical analysis

For normal distributed variables, values are expressed as mean ± SEM. Differences in mean between groups were tested using a t-test, while the difference between related variables were tested using a t-test for paired samples. Correlation between continuous variables was tested with Spearman's rank correlation analysis. Multiple regression analysis was preformed for determining which variable was independently associated with NT-proBNP levels. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS statistical software system (version 16.0, SPSS Inc., Chicago, Illinois, USA).

Results

Basic anthropometric and physical examination data measured before the therapy are presented in Table 1. There were no statistically significant differences in BMI, heart rate and systolic and diastolic pressure values between study groups (Table 1).

Mean serum FT3, FT4 and TSH values significantly increased and decreased in hypothyroid and hyperthyroid group, respectively, after the therapy (Table 2). In control group mean FT3 concentration was 5.2 ± 0.21 nmol/L, FT4 15.3 ± 0.37 nmol/L and TSH 1.75 ± 0.23 mIU/mL. After the therapy there was no significant difference in mean FT3 and FT4 concentration between hypothyroid or hyperthyroid and control group. After the therapy TSH values remained significantly lower in hyperthyroid group compared to control group (p <0.05).

Mean serum NT-proBNP concentration in overt hyperthyroid group before the therapy was 99.35 pg/mL and was significantly higher compared to overt hypothyroid (56.82 pg/mL) and euthyroid group (65.90 pg/mL, p<0.05, Figure 1). Although the NT-proBNP concentration was lower (56.82 pg/mL) in overt hypothyroid group before therapy compared to euthyroid group (65.91 pg/ mL) the difference was not statistically significant.

After the therapy, a significant decrease (by 46%) in mean serum NT-proBNP concentration was observed in overt hyperthyroid group (99.35 pg/m L vs. 53.64 pg/mL) (p <0.01), while in overt hypothyroid group a significant increase (by 23%) in mean serum NT-proBNP level was observed (56.82 pg/mL vs. 69.95 pg/mL) (p<0.05) (Figure 2). After the therapy, there was no difference in mean serum NT-proBNP concentration between overt hyperthyroid, overt hypothyroid and control group. (Figure 3)

In hyperthyroid group before the treatment a significant positive correlation was found between serum FT3, FT4 and NT-proBNP (r=0.69 and r=0.63 respectively; p<0.01) and a negative correlation between serum TSH and NT-proBNP concentration (r=-0.58; p<0.01) (Table 3). In overt hypothyroid group before the treatment, a significant positive correlation was observed between serum FT3 and NT-proBNP (r=0.42; p<0.01) (Table 3) .

Table 1. Body mass index (BMI) and cardiovascular parameters in hyper- and hypo- thyroid groups before therapy and in euthyroid group

	Hyperthyroid Group (n=34)	Hypothyroid Group (n=35)	Euthyroid Group (n=35)
BMI	21.7±2.3	23.1±3.1	23.7±2.4
Systolic pressure (mmHg)	135.6±3.7	127.8±11.4	128.6±3.3
Diastolic pressure (mmHg)	69.7±11.3	80.3±7.3	76.7±3.4
Heart rate (beat/min)	85.1±9.3	80.3±2.7	78.6±5.7

Values are presented as mean±SEM

Table 2. Serum FT3, FT4 and TSH concentration in hypo-and hyperthyroid group before and after the therapy.

	Hypothyroid group (N=35)			Hyperthyroid group (N=34)		
	Before therapy	After therapy	p-value	Before therapy	After therapy	p-value
FT3 (nmol/L)	3.34±0.29	4.78±0.13	p<0.01	12.75±1.66	4.96±0.28	p<0.01
FT4 (nmol/L)	8.28±0.69	15.40±0.57	p<0.01	28.16±2.78	15.91±0.55	p<0.01
TSH (mIU/mL)	13.29±1.09	3.38±0.27	p<0.01	0.03±0.08	0.51±0.12	p<0.01

Values are presented as mean±SEM

Table 3. Correlation coefficients between NT-proBNP level and thyroid hormones in patients with dysfunctional thyroid states before and after the treatment and in euthyroid (control) group.

	Hyperthyroid group		Hypothyroid group		Euthyroid group
	Before treatment	After treatment	Before treatment	After treatment	Baseline
FT3	0.69*	0.34	0.42*	0.16	-0.09
FT4	0.63*	0.23	0.38	0.3	-0.05
TSH	-0.58*	0.13	-0.41	-0.18	0.16

*p<0.01

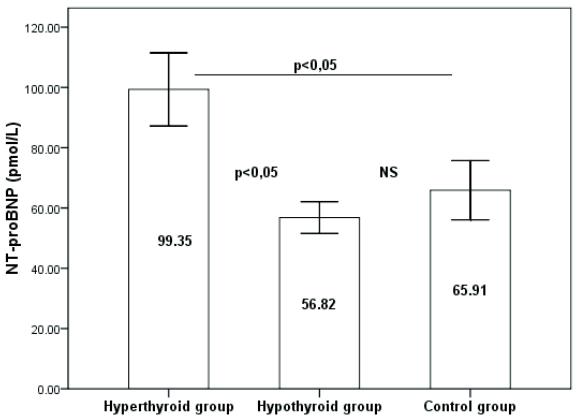

Figure 1. Mean serum NTproBNP concentration in overt hyper-, overt hypo- and euthyroid patients before therapy.

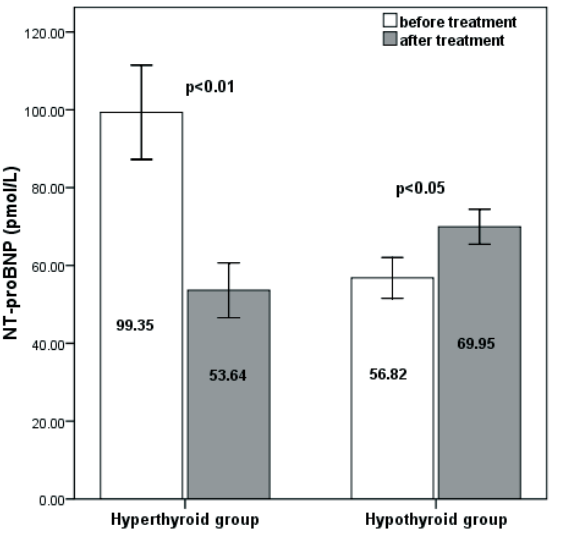

Figure 2. Mean serum NT-proBNP concentration overt hyperthyroid and overt hypothyroid group before and after the treatment.

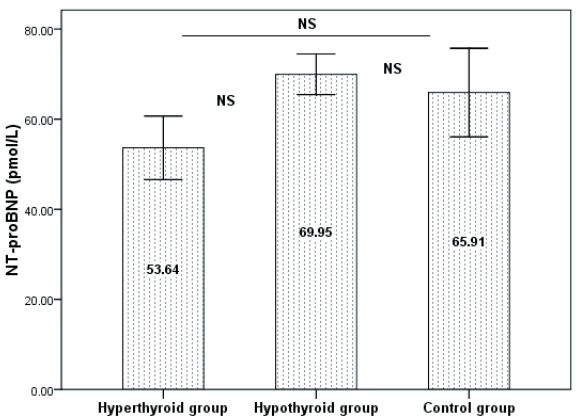

Figure 3. Mean serum NT-proBNP concentration in overt hyperthyroid and overt hypothyroid group after treatment and in euthyroid (control) group.

After the therapy no significant correlation between FT3, FT4, TSH and NT-proBNP concentration had been found in any of the study group (Table 3).

Using a multiple regression analysis with NT-proBNP as the dependent variable and FT3, FT4 and TSH as the independent ones, only FT3 remained independently associated with

NT-proBNP levels in overt hyperthyroid patients (ß = 0.667, p = 0.024), while in overt hypothyroid patients there was no independent association between thyroid hormones and NT-proBNP levels.

Discussion

Our results showed that the mean NT-proBNP concentration in hyperthyroid and hypothyroid group as well as in control group was below cut-off reference value of 155 pg/ml. However, the mean NT-proBNP serum concentration in the hyperthyroid group before the therapy was significantly higher compared to hypothyroid and control group. Although the NT-proBNP concentration was lower in hypothyroid group before therapy compared to values in control (euthyroid) group, the difference was not statistically significant.

Most of the symptoms that accompany dysfunctional thyroid states are the result of direct or indirect effects of thyroid hormones on the heart and blood vessels [8]. Previous studies have shown the presence of functional and structural myocardial changes in overt but also in subclinical form of dysfunctional thyroid disorders [9, 10]. Cardiovascular complications are the most common causes of death in these patients and their early diagnosis and adequate therapeutic treatment are of great clinical significance.

All patients included in this study had been exposed to stress period during the war. The study performed at Department of Physiology during the war had shown that female patients had hyper reactive cardiovascular response [11]. Our results showed differences in heart rate and mean systolic and diastolic pressure values between study groups, but were not statistically significant. Obtained values were expected, except mild higher heart rate values in hypothyroid group. It is well known that hypothyroidism is accompanied by lower heart rate and reduced left ventricular systolic and diastolic function [12]. We could suppose but not conclude that higher heart rate values in hypothyroid patients could be partly provocated by enhanced symphatic activity due to long-lasting stress period. We suppose that thyroid functional disorder in patients exposed to long-lasting stress triggers similar vegetative response regardless of the overt hypo or hyper thyroid function. For final conclusion profound studies in large sample should be done.

N-terminal pro-brain natriuretic peptide (NT-proBNP) as an inactive component of proBNP is an important indicator of left ventricular dysfunction during increased cardiac wall stress and could be a potential humoral marker of early cardiac dysfunctional changes in patients with thyroid functional disorders [2]. Previous studies have shown that BNP and NT-proBNP concentration changes in different thyroid functional states, but the results are conflicting [4-7]. Our study also showed that, adequate therapy aimed to the regulation of thyroid status had led to significant changes in serum NT-proBNP concentrations in hyperthyroid as well as in hypothyroid patients. Serum NT-proBNP levels significantly decreased in hyperthyroid patients upon achievement of euthyroid state, while in hypothyroid patient's serum NT-proBNP level significantly increased after the treatment. Our results are in concordance with the results of Kohno et al. [13] who found increased BNP levels in hyperthyroid patients compared to the healthy (euthyroid) subjects. In the same study, the authors measured plasma BNP concentration in thyroxin-induced hypothyroid as well as in propiltiouracil-induced hyperthyroid rats. They found a significant increase of plasma BNP concentration in hyperthyroid rats but significant decrease in hypothyroid rats. They also showed that plasma BNP concentration was significantly correlated with T4 in hyperthyroid patients and in rats. Shultz et al. [14] have assessed the concentration of NT-proBNP in patients with various dysfunctional thyroid states (clinical hyper- and hypothyroidism, and subclinical hyper-and hypothyroidism). These results showed four times higher serum NT-proBNP concentration in hyperthyroid patients compared to hypothyroid. Appropriate treatment and achieved euthyroid state led to significant increase in NT-proBNP level in hypothyroid and a significant reduction in hyperthyroid patients.

The NT-proBNP levels observed in our hyperthyroid group were lower compared to the results by Shultz et al. [14]. The probable cause for the observed discrepancies could be due to the fact that our hyperthyroid patients had also lower FT4 and FT3 levels.

The results of our study are in accordance with the results of Christ-Crain and et al. [15] who determined the serum NT-proBNP and proANP concentrations in 161 patients with different thyroid functional states. The authors showed statistically significant higher serum NT-proBNP and proANP concentration in hyperthyroid patients compared to hypothyroid and euthyroid patients. Application of L-thyroxin during a period of 48 weeks in patients with subclinical hypothyroidism led to, although insignificant, increase in NT-proBNP concentration.

Regardless of the fact that mean NT-proBNP concentration of all our study groups was below the upper reference values prior the therapy, we believe that the determined significant differences between groups, as well as the influence of therapy on serum NT-proBNP level indicate a significant effect of thyroid hormone secretion on BNP secretion and release, and thus the serum NT-proBNP level. The hypothesis is supported with the results observed in our study that

NT-proBNP levels significantly correlated with thyroid hormones in patients with dysfunctional thyroid states. Regression analysis confirmed an independent association between FT3 and NT-proBNP levels only in hyperthyroid patients, while in hypothyroid patients no independent association between thyroid hormones and NT-proBNP level emerged.

Our results are consistent with those of Schultz et al. [14] as well as with results of Ozmen et al [16]. Shultz et al. [14] found a significant correlation between the NT-proBNP and FT3, FT4 and TSH levels in all dysfunctional thyroid states (clinical hyper- and hypothyroidism and subclinical hyper- and hypothyroidism). Recent study of Ozmen et al. [17] showed a significant higher level of serum NT-proBNP level in hyperthyroid patients in comparison with hypothyroid and euthyroid patient groups. Serum NT-proBNP and thyroid hormones were correlated in all patients (hyper- and hypothyroid).

Our results support conclusions of some studies and the fact that thyroid hormone stimulate secretion of BNP *in vitro* and *in vivo* [13] and thereby serum NT-proBNP levels. Comparing results obtained in our study with the results of other previously cited studies we did not find any declination in NT-proBNP levels that could lead to the assumption that stress period which our patients were exposed influence this response. That could be also partly caused by long period passed from the exposition to the stress.

Described changes in the NT-proBNP levels in our hyperthyroid patients showed the existence of some "negative feedback loop" between the thyroid hormone and BNP secretion, suggested also in some other studies [17,18]. Specifically, BNP has significant diuretic and natriuretic effects, leading to a decrease in filling

pressure as well as in the left ventricular end-diastolic volume, which significantly reduces the overload in the hyperthyroid state. This peptide also increases permeability of capillary bed. B-type natriuretic peptide has direct effects in the kidney and leads to suppression of renin-angiotensin-aldosterone system, which further reduces the total blood volume, venous return and cardiac output. All those effects certainly have a role in the regulation of hemodynamic changes in this thyroid dysfunctional state but also could control the progression and magnitude of the hypertrophic response thereby limiting cardiac fibrosis, chamber remodelling, and progression to cardiomyopathy [17]. Thyroid hormone-induced myocardial hypertrophy is notably deficient in accompanying fibrosis [19] where important role could have BNP.

Conclusion

We believe that thyroid hormones influence the secretion of BNP and thereby affect the serum concentration of NT-proBNP, where BNP has an important role in regulation of the altered hemodynamic changes in hyperthyroid state. Due to the possible protective roles of BNP on the cardiovascular system in the hyperthyroid state, further research should be directed toward assessing the possibility for its therapeutic application in order to improve the hemodynamic changes and prevent the development of cardiovascular complications.

Conflict of interest:

Authors have no conflict of interest.

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