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CLINICAL RESEARCH

Natriuretic Peptide in Patients with Metabolic Syndrome

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Abstract

The present research aimed at studying the atrial and brain natriuretic peptide (NUP) levels in the blood plasma of patients with Metabolic Syndrome (MS). The research includes 52 patients in total, of which 40 patients with MS constitute the observation group while 12 conventionally healthy people comprise the control group. An increase in the NT-proBNP at 20% ($p<0.05$) and proANP at 67.8% ($p<0.05$) was observed in the blood plasma of the patients with MS. We observed a strong correlation between the atrium and brain NUP in the plasma and insulin and the insulin resistance index (IRI) that allows us to consider the NUP levels as the markers of early diagnosis of MS.

Keywords: *natriuretic hormones, metabolic syndrome, insulin resistance.*

Abbreviations: NUP, natriuretic peptide; **ANP**, atrial natriuretic peptide; **BNP**, brain natriuretic peptide; **MS,** metabolic syndrome; **IRI**, insulin resistance index**; TNF-α**, tumor necrosis factor-alpha.

Introduction

The potential use of the circulating NUP levels as biochemical markers of myocardial dysfunction severity and predictors of prognosis in patients with cardiovascular disease is now being widely discussed. Along with the traditional risk factors, new biomarkers of cardiovascular complications - NUP - have independent prognostic value for cardiovascular disease. At present, the NUP system is known to consist of ANP, BNP, C-natriuretic peptide and its renal form – urodilatin [1, 4, 3, 5]. Atrial and brain NUP are secreted by the myocardial cells in response to pressure by load and volume, and their biological effects include diuresis, natriuresis, vasodilation, suppression of the RAAS and endothelial systems. NUP is continuously released from the cardiomyocytes, although the relevant mechanical and / or neuroendocrine stimuli may increase the NUP secretion in diseases involving the right and left ventricles in pathological processes [2]. The hemodynamic effects of NUP include unloading the heart in response to the increased intravascular volume. Increase in their concentration levels in the blood indicates the breakdown of the cardiovascular system functioning. There is undoubted evidence of the natriuretic peptide system involvement in the pathophysiological mechanisms of hypertension (AH), myocardial infarction and atherosclerosis [3, 6]. Of scientific and clinical interest is the open-ended question of changing the NUP levels in the blood in patients with MS, which combines the pathology of the cardiovascular system with lipid and carbohydrate metabolism disturbances. It should be noted, however, that the data of the NUP levels and insulin resistance correlation are controversial [2, 4, 5].

The purpose of this study was to determine atrial and brain NUP levels in the blood plasma of MS patients and to establish their correlation with abdominal obesity, the parameters of carbohydrate and lipid metabolism.

Material and Methods

The study involved 52 people (38 women and 14 men, mean age 46.6 ±1.62 years).

A survey of patients was conducted in accordance with the Helsinki Declaration of the World Association "Recommendations for physicians involved in biomedical research involving human subjects" (2001), and after getting signed informed consent from the patients.

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For the diagnosis of MS, criteria relevant for the national guidelines RSSC (Russian Scientific Society of Cardiology) for diagnosis and treatment of MS (2009) were applied [6]. Exclusion criteria were chronic heart failure and coronary heart disease. In accordance with the criteria selected, the patients were divided into two groups: the control group (1st) included 12 apparently healthy persons; the observation group (2nd) which included 40 patients with MS.

A general clinical examination was performed, including anthropometry to identify abdominal obesity. The total cholesterol (TC), High-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were determined in the venous blood using the A-25 Biosystems Autoanalyzer (Germany) and the "Olveks" sets (Ukraine). Low-density lipoprotein cholesterol (LDL-C) was calculated according to Fridvald's formula. Fasting glucose and insulin were also determined, and the Homa index was calculated. The pro-ANP and N-terminal fraction of BNP (NT-proBNP) levels in plasma were determined by enzyme immunoassay (AxSYM, Norway) using the commercial kits (pro-ANP (1-98) and proBNP (1-108) of the "Bimedica GmbH" (Austria).

Statistical data processing was performed using the software package Statistica 6.0 for Windows. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between the two continuous variables. P value less than 0.05 was considered significant.

Results and Discussion

In all patients in the observation group, abdominal obesity was diagnosed. The Quetelet index in the examined persons was equal to 30.10 ± 0.87, a waist size for women – 93.66 ± 3.04, for men – 99.37 ± 4.41 (Table 1). Hypertension stage 1 was defined in 39.13% of persons; 56.52% of patients had stage 2 hypertension. On laboratory examination the cholesterol level in 56.5% of MS patients was increased by 27.6%, while the concentration of triglycerides in the blood serum - twice ($p<0.001$) in 34.78% of the persons, the values of atherogenic LDL-C were higher than the standard in 69.56% of cases, hypoalfacholesterolemia was detected in 63.5% of the patients.

Table 1.

Clinical and laboratory characteristics of healthy persons and patients with MS

Parameters	Groups	
	control n=12	MS patients n=40
SBP, mmHg.	117.44±2.71	165.00±3.03**
DBP, mmHg.	72.44±2.78	103.91±2.10**
Quetelet index, U	28.25±0.81	30.10±0.87
Waist size Male/Female, sm	81.33±3.33 73.25±2.38	99.37±4.41** 93.66±3.04**
Fasting glucosa, mmol/L	5.81±0.14	6.12±0.17
Insulin, mcU/ml	9.43±1.44	16.42±1.70**
Homa index, U	2.40±0.80	4.70±0.65*
TC, mmol/L	4.95±0.18	6.32±0.24
TG, mmol/L	1.08±0.19	2.45±0.35**
HDL-C, mmol/L	1.35±0.14	1.05±0.05
LDL-C, mmol/L	3.11±0.12	4.42±0.45*
pro-ANP, nmol/mL	1.46±0.24	2.45±0.80*
NT-proBNP, fmol/mL	7.5±0.21	9.12±0.18*

***Note**: * - p <0.05 and **- P <0.001 - between control group and MS patients.*

Insulin resistance (IR) was set at 86.5% of the patients by the Homa index, which was increased by 1.9 times ($p<0.05$), but it was not accompanied by hyperinsulinemia, and only 11.5% of patients with severe hyperinsulinemia showed IR ($p<0.001$). The level of NT-proBNP in MS patients showed that the concentration of the NUP studied exceeded that in the control group by 20% ($p<0.05$). The most pronounced changes were found in MS patients at the level of pro-ANP.

To determine the relationships between plasma concentrations of the atrial and brain NUP and the clinical and biochemical markers of MS, a correlation analysis was performed, where r <0.4 - are the weak links, r = 0.4-0.6 is the average connection and r >0. 6 - are the strong bonds (Table 2).

Table 2.

Correlations between laboratory parameters and natriuretic peptide in patients with MS

Parameters	Natriuretic peptide			
	control		MS patients	
	NT-proBNP	pro-ANP	NT-proBNP	pro-ANP
	r	r	r	r
Insulin	-0.23	-0.33	-0.73	0.55
Homa index	-0.21	-0.34	-0.78	0.57
TC	0.42	-0.13	0.01	-0.05
TG	0.08	-0.38	-0.29	0.01
LDL-C	0.49	-0.12	-0.08	0.34
HDL-C	0.03	0.25	0.27	-0.20
SBP	0.20	-0.32	-0.31	0.34
DBP	0.23	-0.08	-0.34	0.24
Weight	0.23	-0.45	-0.42	0.27
Quetelet index	-0.02	-0.45	-0.66	-0.21

***Note**: Bold and italics type marked a strong connection, only bold type marked an average connection (p <0.05).*

In the control group, strong and significant relationships between clinical and laboratory parameters and the peptides studied were not established. However, in the group of patients with MS, medium and strong significant associations were formed between the NUP and laboratory parameters of carbohydrate metabolism: NT-proBNP correlated with the insulin levels ($r = 0.55$; $p > 0.05$) and IRI ($r = 0.57$; $p > 0.05$), pro-ANP correlated with the insulin levels ($r = -0.73$; $p > 0.05$) and IRI ($r = -0.78$; $p > 0.05$). The correlation between the Quetelet index and the amount of plasma NT-proBNP changes was identified in MS patients, which was proved by the formation of the links of medium strength ($r = 0.66$; $p > 0.05$).

Results of the clinical studies, significant correlations between the NUP and insulin levels, and IRI enable us to ascertain the relationship between the atrial and brain NUP levels in the blood plasma with changes in the metabolic processes in MS patients.

The main criterion of the metabolic syndrome - abdominal obesity- leads to insulin resistance, and further development of the metabolic changes plays a significant role. It is known that visceral fat synthesizes a number of hormones and bioactive substances (leptin, free fatty acids, angiotensin, etc.) [1, 5, 8]. It is important to note that in abdominal obesity, adipocytes are a source of proinflammatory cytokines. The literature highlights the effect of the cytokines on the myocardium, mainly tumor necrosis factor-alpha (TNF-α), which has directly damaging effects on the cardiomyocites, due to the presence of the expressed so-called «death receptors» on the surfaces of adult cardiomyocytes. TNF-α binds to the aforementioned receptors and initiates the process of apoptosis [9].

Today, we know that the reasons for the exchange and functional impairment in MS are insulin resistance and compensatory hyperinsulinemia. Insulin resistance leads to endothelial dysfunction and an imbalance in the vasoactive mediators leading to the enhanced secretion by the vasoconstrictors. Hyperinsulinemia acting on the kidneys and the hypothalamic-pituitary system increases the activity of the sympathetic nervous system, which in turn triggers the cascade of reactions leading to the heart and vascular remodeling. In MS the renin-angiotensin-aldosterone system (RAAS) is activated, increasing the total peripheral vascular resistance leading to the development of hypertension [5, 7, 8]. Thus, in MS the NUP level in the blood plasma increases. This process is due to the activation of the RAAS and sympathetic nervous system, a violation of the endothelial function of the blood vessels, an imbalance in the vasoactive mediators [5, 8] and increased cytokine secretion [9]. In this case, the remodeling of the heart occurs not only by hemodynamic overload, but also due to the influence of the humoral factors. Myocardial injury occurs during the active release of NUP. The natriuretic hormone counteracting the effect of the prior mentioned factors enables the neurohormonal protection of the heart.

Thus, the connection between the plasma levels of the atrial and brain NUP and the components of MS allows us to consider NUP levels as markers for the early diagnosis of MS.

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Atrial natriuretic peptide (ANP) is a cardiac hormone with pleiotropic cardiovascular and metabolic properties including vasodilation, natriuresis and suppression of the renin-angiotensin-aldosterone system. Moreover, ANP induces lipolysis, lipid oxidation, adipocyte browning and ameliorates insulin sensitivity. Studies on ANP genetic variants revealed that subjects with higher ANP plasma levels have lower cardio-metabolic risk.Â The metabolic effect of sacubitril/valsartan was tested in patients with cardio-metabolic disease. In a post-hoc analysis of the PARADIGM trial, subjects with heart failure and diabetes or HbA1c â‰¥ 6.5% who were randomized to sacubitril/valsartan had a better glycemic control than subjects receiving enalapril [69].