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# The Relationship between the Simpathetic-Adrenal System and Immune Disorders Mediators in Patients with Metabolic Syndrome

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# ABSTRACT

**Introduction:** Functional condition of sympathy-adrenal system (SAS) and immune inflammation mediators in cases of metabolic syndrome (MS) has been studied. At the end of the 20th century, the concept of metabolic syndrome (MS) was proposed as a way to isolate a group of people who have several risk factors united by a single pathogenetic basis. MS belongs to the so-called "diseases of civilization" and is most common in economically developed countries.

**Method:** 65 patients have been examined. Increased activity of SAS, especially noradrenalin (NE) and activation inflammatory cytokines - IL-6, TNF-a have been revealed. It has been determined that high activity of SAS leads to immune disbalance of humoral immunity which proved to be the marker of MS progressing.

**Result:** When studying the daily excretion of catecolamines and DOPA in patients with arterial hypertension, a statistically significant increase in adrenaline (A) excretion was noted by 52.7% (p<0.001), which is 2.1 times higher than the control group (p<0.001). The highest indicators of the level of excretion A were observed in the group of patients with MS, which is 61.1% and, accordingly, 2.6 times higher than the control indicators.

**Conclusion:** The high activity of SAS leads to an immuno-imbalance of humoral immunity, which play an important role in the pathogenesis of MS.

Key Words: Sympatic-adrenal system, Immunne inflamatuon's mediators, Metabolic syndrome

# **INTRODUCTION**

At the end of the 20th century, the concept of metabolic syndrome (MS) was proposed as a way to isolate a group of people who have several risk factors united by a single pathogenetic basis. MS belongs to the so-called "diseases of civilization" and is most common in economically developed countries. The unifying basis of MS is primary insulin resistance (IR) and the associated systemic hyperinsulinemia (HI).<sup>1,2</sup> An important role in the development and progression of IR and HI and related metabolic disorders is played by neurohumoral disorders with an increase in the activity of the sympatic-adrenal system (SAS). However, under IR conditions, SAS hyperactivation leads to sympathetic stimulation of the heart, blood vessels, kidneys and the appearance of arterial hypertension (AH).<sup>3-5</sup>

The immune and neurohumoral systems are closely interconnected . Their interaction is carried out through various types of nerve fibers, which release neurotransmitters (adrenaline, norepinephrine, serotonin, etc.) and activate specific receptors of target cells. The close interaction of the neurohumoral and immune systems ensures the presence of receptors for norepinephrine (NE) on immune cells. The sympathetic nervous system (SNS) regulates the circulation and proliferation of lymphocytes, as well as their production of immunocompetent cells and other biologically active substances through the interaction of NE with immune cell receptors.<sup>6-8</sup>

MS changes the reactivity of the immune and neuroendocrine systems and disrupts the interaction between them. The initial immunodebalances in these patients make it difficult to form an adequate immune response. It is known that a violation of the interaction of the neurohumoral and immune systems of the body can contribute to the deterioration and progression of MS. Endogenous catecholamines (CA) are able to stimulate the production of pro-inflammatory cytokines and inhibit the production of anti-inflammatory cy-



tokines, suppress the Th1 response and cellular immunity, induce a switch to the Th2 response and stimulate humoral immunity. CA indirectly through  $\beta$ -adrenergic receptors are able to inhibit the production of the main anti-inflammatory cytokine interleukin-10 (IL-10). The pro-inflammatory effect can cause NE by activating  $\alpha$ -adrenergic receptors.<sup>9,10</sup>

Studying the role of SAS in the development of the immuneinflammatory response in MS and their interaction will allow a deeper understanding of the pathogenesis of MS, which will contribute to the development of pathogenetic approaches to its treatment. We aimed to study the relationship of the functional state of the sympatic-adrenal system and mediators of immune disorders in patients with metabolic syndrome.

# **MATERIALS AND METHODS**

The study included 65 patients (age from 35 to 57 years, on average 46.7  $\pm$  2.1 years), of which 40 revealed MS. All patients evaluated the state of carbohydrate metabolism (fasting glucose, fasting insulin); state of lipid metabolism (total cholesterol - TCh, triglycerides-TG, high density lipoproteins (HDL-C), low density lipoproteins (LDL-C). IR was calculated by the HOMA index. With a HOMA index> 2.77, patients were considered insulin resistant. Body mass index was calculated using the Ketle index.

Urine and blood were taken for analysis on the 1st day of admission to the hospital before treatment. Biologically active amines were determined by daily urinary excretion of free and conjugated forms of catecholamines (CA) using the fluorimetric method modified by E.Sh. Matlina (1965). The determination of the activity of monoamine oxidase (MAO) in the blood serum was carried out by the colorimetric method A.V. Balaklevsky (1976). To determine the cytokine status, we studied the concentration of pro-inflammatory cytokines - interleukin-6 (IL-6), tumor necrosis factor (TNF- $\alpha$ ) and anti-inflammatory cytokine IL-10. The content of cytokines in blood serum was determined by the method of enzymelinked immunosorbent assay using test systems LLC "Cytokine" (St. Petersburg, Russia) on an enzyme-linked immunosorbent analyzer "Human" (Germany).

Statistical processing of the results was carried out using the Statistica-6 program.

# **RESULTS AND DISCUSSION**

All patients were randomized into three groups. Group I (control) consisted of 20 healthy individuals aged 35-45 years. Group II consisted of 25 patients with a diagnosis of arterial hypertension (AH) of the II-III stage, group III consisted of 40 patients with MS.

When studying the daily excretion of CA and DOPA in patients with AH, a statistically significant increase in adrenaline (A) excretion was noted by 52.7% (p<0.001), which is 2.1 times higher than the control group (p<0.001). The highest indicators of the level of excretion A were observed in the group of patients with MS, which is 61.1% and, accordingly, 2.6 times higher than the control indicators. Thus, the highest values of total A were recorded in group III (Table. 1).

The daily excretion of norepinephrine (NE) was also significantly increased in groups II and III. Thus, the content of NE in patients with hypertension is 63.2%, which is 2.6 times higher than the control indices (p<0.001). The indices of total NE in the group of MS patients were maximally increased in relation to other biogenic amines and 73.0% (3.7 times) higher than the control indices. Thus, the level of total NE in group IV turned out to be the highest (Table 1).

Data on the significance of insulinemia in the activation of SAS in MS patients were confirmed. A direct correlation was found between the daily excretion of NE with HI (r = 0.5730; p = 0.0001), as well as NE with BMI (r = 0.7374; p = 0.0001). A direct correlation dependence of daily excretion of NE with the level of SBP (r = 0.5327; p = 0.0001) and DBP (r = 0.3903; p = 0.0001) was revealed. The direct correlation of daily excretion of NE with the level of NE with the level of TG (r = 0.7723; p = 0.0001), oxidative stress (r = 0.6133; p = 0.0001) and the inverse correlation dependence of the increased level of NE with HDL-C (r = -0.6480; p = 0.0001).

The release of dopamine (DA) in this category of patients did not significantly change both in relation to the control group and in relation to other groups. Thus, the content of DA in patients with hypertension is reduced by 8.1% (p> 0.05) compared with the control parameters. The results of DA in MS patients also revealed a tendency to a slight decrease in indicators (Table 1).

The DOPA level was moderately increased in group II patients by 1.8 times compared with the control (p <0.01). The performance of the group of patients with MS was 86.8  $\pm$ 2.71 µg / day (Table 1), which is 51.8% higher than the control indicators (p <0.001).

Table 1: Indices of daily excretion of catecholamines
(CA) in healthy and patients with arterial hyperten-
sion (AH) and metabolic sindrom (MS) (mcg/day)

Groups Indicators		Healthy (n = 20)	Patients with AH (n = 25)	Patients with MS (n = 40)
Adrenalin	free	4.29 ± 0.33	8.9 ± 0.38 **	11.3 ± 0.45 **
	conjugated	3.9 ± 0.35	8.4 ± 0.32 **	9.72 ± 0.36 **
	total	8.13 ± 0.67	17.3 ± 0.70 **	21.02 ± 0.81 **

Groups Indicators		Healthy (n = 20)	Patients with AH (n = 25)	Patients with MS (n = 40)
Norepi- nephrine	free	8.1 ± 0.31	21.3 ± 0.63 **	27.6 ± 0.68 **
	conjugated	7.15 ± 0.36	20.1 ± 0.71 **	28.9 ± 0.81 **
	total	15.25 ± 0.67	41.4 ± 1.78 **	56.5 ± 1.48 **
	free	176.0 ± 9.07	149.5 ± 8.30 *	149.9 ± 8.75 *
Dopamine	conjugated	187.0 ± 7.30	190.4 ± 7.20 *	200.1 ± 9.2 *
	total	363.0 ± 16.40	339.9 ± 15.60 *	349.9 ± 17.95 *
DOPA		41.83 ± 2.47	78.8 ± 3.60 **	86.8 ± 2.71 **

\*p <0.05 and \*\*p <0.001 vs control group.

A study of the activity of the catalytic enzyme dezamination of biogenic amines of MAO revealed that in parallel with increase CA concentration in daily urine, there was significant decrease in MAO all groups of patients: from moderate (II group by 42,9; by 1,75 times, III - group pronounced by 71.5%; by 3,5 times .Reverse correlation of MAO with daily exretion of all CA fractions especially NA and A in patients with MS revealed (r=-0.5325; p=0,0001) (r=-0.4249; p=0.0001).This means that the level of CA in the urine increseas, which in turn leads to a decrease in MAO activity, thereby reducing the catalytic activity of thiz enzyme. Strengthening LPO processes also affects MAO activity. This suggests that the aggravation of pathological changes in the catalytic properties of MAO activity (Figure 1).



\* p<0.001 vs Healthy patient group

Figure 1: The activity of monoamine oxidase (MAO) in healthy and patients with arterial hypertension (AH) and metabolic sindrom (MS).

The immune system reacted with an disbalance of pro- and anti-inflammatory cytokines. In all groups of patients, an increase in pro-inflammatory cytokines was noted, so IL-6 increased from moderate (group II by 64.0%) to a sharp increase of more than 3.7 times in MS patients. The highest increases were observed in TNF- $\alpha$  - in the group of patients with MS up to 96.8 ± 9.6 pg / ml (4.3 times). Anti-inflammatory IL-10 had only a slight increase in both hypertensive patients (by 24.5%) and MS patients (1.7 times compared with the control). Apparently, this is due to a different immunological response to the chronic inflammatory process occurring in the vascular wall (Figure 2).

In MS patients, a positive correlation was found between IL-6 and elevated SBP (r = 0.5746; p = 0.0001), IL-6 and BMI (r = 0.6719; p = 0.0001), WC (r = 0.5993; p = 0.0001). A positive correlation was also found between the levels of IL-6 (r = 0.6719; p = 0.0001) and TNF-a (r = 0.6520; p = <0.0001) with an increase in daily excretion of NE.



\*p<0.05 and \*\*p <0.001 vs Healthy control group.

Figure 2: The content of immunocytokines in healthy patients with arterial hypertension (AH) and metabolic sindrom (MS).

MS is accompanied by an increase in the functional activity of SAS, especially NE. There was a direct correlation between the increase in daily excretion of NE with HI, NE with the body mass index, NE with the level of blood pressure, NE with the level of TG and the inverse correlation between the increase in daily excretion of NE with HDL-C. At the same time, in these same patients, a violation of the immune response was observed with an increase in pro-inflammatory cytokines - IL-6 and especially TNF-a. A direct correlation dependence of an increase in IL-6 and TNF-a levels with an increase in daily excretion of NE was revealed. The established correlation relationships between the content of CA and IL confirm the distinct influence of SAS activation on the state of the body's immune system in MS, being markers of disease progression. This necessitates the development of tactics of pathogenetically substantiated drug treatment of this category of patients.

The problem of the functional state of SAS in MS patients, its relationship with other clusters of the disease, in particular with the immune system, has become a subject of discussion in recent years. SAS and the immune system are closely interconnected. HI leads to a significant increase in the activity of the SNS, and in the first place SAS. Under IR conditions, overactive SNS leads to the appearance of hypertension and the development of MS due to sympathetic stimulation of the heart, blood vessels, and kidneys. On the other hand, endogenous CA can stimulate the production of cytokines and humoral immunity.

Studies have revealed an increased functional activity of SAS, especially NE and A in patients with MS. The increased activity of SAS is accompanied by a sharp decrease in the key MAO deamination enzyme with a change in its catalytic properties. The data obtained indicate that in patients with MS, HI leads to a significant increase in the activity of the SNS, and in the first place, SAS.<sup>9</sup> Under the conditions of IR, this leads to the appearance of hypertension and the development of MS due to sympathetic stimulation of the heart, blood vessels, and kidneys.<sup>7,8</sup> At the same time, in these same patients, a violation of the immune response was noted with an increase in pro-inflammatory cytokines, IL-6, TNF-a. The established correlation relationships between the content of CA and IL confirm the distinct influence of SAS activation on the state of the immune system.<sup>10-12</sup>

## CONCLUSION

Thus, the high activity of SAS leads to an immuno-imbalance of humoral immunity, which play an important role in the pathogenesis of MS, being markers of disease progression. This necessitates the development of tactics of pathogenetically substantiated drug treatment of this category of patients.

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