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RESEARCH ARTICLE

Mechanism Underlying the Formation of a Cluster of Metabolic Syndrome

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Abstract: ***Background:*** The concept of metabolic syndrome (MetS) as a cluster of risk factors of type 2 diabetes and cardiovascular diseases has undergone some evolutionary transformations over the past years. Integrating the autonomic dysfunction into the pathogenesis of MetS creates the possibility of including a range of nosologies affecting treatment and clinical manifestations of pathologies belonging to MetS into the MetS cluster. The purpose of this work is to determine the involvement of autonomic dysfunction in the pathogenesis of associated pathological conditions in patients and MetS.

Methods: A cross-sectional study was conducted. The sample consisted of 158 patients with metabolic syndrome. The patients underwent a physical examination, including BMI; a blood chemistry test with the determination of the hormonal status (insulin, testosterone, dihydrotestosterone); a 24-hour monitoring of blood pressure (BP); an assessment of heart rate variability; studies showing the presence of gastric reflux (pH-measurement) or its damaging impact (endoscopy); men were tested with the IPSS-QOL questionnaire and underwent transrectal ultrasound of the prostate and ultrasound of the bladder.

Results: It is revealed that because of MetS, the occurrence of cardiac autonomic neuropathy reaches 37.5%. Some features of gastroesophageal reflux disease in patients with MetS are shown. Regurgitation prevails in the structure of complaints. In case of fibrogastroduodenoscopy, an endoscopy-negative form of the disease occurs in 38%. According to the data of daily pH-measurement, when DeMeester score is high, in the supine position, 25% of the time accounts for alkaline reflux (pH > 7). It is found out that young men experience the enlargement of prostate volume and size; according to the IPSS questionnaire, the scores correspond to the initial manifestations of hyperplastic diseases of the prostate gland due to insulin resistance and normal level of androgens.

Conclusions: The paper demonstrates that the autonomic dysfunction of the nervous system (on a par with insulin resistance) is the main link in the development of MetS. This provides the basis for including the mentioned states – cardiac autonomic neuropathy, lower urinary tract symptoms, and gastroesophageal reflux disease – into the MetS cluster.

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1. INTRODUCTION

Metabolic syndrome (MetS) is a group of modifiable and interrelated risk factors in the development of cardiovascular diseases (CVDs) and type 2 diabetes [1]. Such a definition of MetS, taking into account that it ignores many factors that determine the absolute risk of CVDs, for example, age, sex, smoking, implies a thorough understanding of the etiology and pathogenesis of MetS. Otherwise, it is impossible to talk about the possibility of correction and, especially, prevention of cardiovascular complications. However, MetS pathogenesis is still under discussion. Most research blames abdominal visceral adipose tissue for causing MetS. Visceral adipocytes are characterised by high sensitivity to the lipolytic effect of catecholamines and low sensitivity to antilipolytic action of insulin. Intensive lipolysis in visceral adipocytes results in the release of a large amount of glycerin and free fatty acids (FFA) into the portal blood flow. FFAs are paid much attention in the pathogenesis of MetS [2]. FFAs are utilised in two ways. Firstly, they are used for synthesising very-low-density lipoprotein (VLDL) and triglycerides. Secondly, they activate gluconeogenesis, causing insulin resistance (IR). Actually, the results of nearly all studies conclude that IR is

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a general pathogenetic mechanism of the promotion and formation of the main MetS components [3, 4].

It should be mentioned that the predisposition to IR is a historically developed mechanism of adaptation to external conditions to maintain energy balance and proper functioning of organs and systems. IR, for a certain time, supports the body in a state between health and illness. Nevertheless, because of a sedentary lifestyle and chronic overeating of fats and other adverse factors, this mechanism becomes pathological and leads to the development of type 2 diabetes, hypertension, and atherosclerosis [5]. These very nosologies are involved in the current schemes of MetS pathogenesis. At the same time, a fairly logical pathogenetic chain is obtained in terms of the development of atherosclerosis – an excess amount of insulin stimulates the passage of constantly synthesised VLDL in the wall of the arteries and activates the capture of monocytes by cholesterol. Moreover, insulin stimulates the migration of smooth muscle cells to the intima and their proliferation. In the intima, smooth muscle cells and monocytes filled with VLDL form foam cells, which leads to the formation of an atheromatous plaque.

As for type 2 diabetes, the main link of its pathogenesis is a developed IR accompanied by relative insulin deficiency even in the presence of compensatory hyperinsulinemia [6]. However, chronic hyperinsulinemia decreases the number of receptors on target cells (desensitisation develops). As a result, IR increases. β-cells of the pancreas gradually lose their ability to react to hyperglycemia. Thus, there is a relative insulin deficiency in the presence of compensatory hyperinsulinemia [7]. Prolonged active compensatory functioning of β-cells is accompanied by their decompensation; thereby, at the late stage of type 2 diabetes relative insulin deficiency turns to absolute, which dictates the need for the use of insulin therapy.

Talking about hypertension (HT), mechanisms that IR uses for its development are not fully disclosed. It is assumed that insulin acts on the membrane channels of cells that regulate the influx of sodium and calcium into a cell [8]. Under IR, insulin cannot reduce sodium influx into cells, which, probably, contributes to the development of HT. Furthermore, it is believed that hyperinsulinemia leads to the development of autonomic dysfunction, namely, to an increase in the activity of the sympathetic nervous system, mainly expressed through the inhibition of the activity of α2-adrenoceptors and I_1-imidazoline receptors [9]. Currently, there is reliable evidence of direct relation between SNS and excess body weight, in particular due to auto-, para, endocrine functions of adipose tissue – secretion of leptin, resistin, adipsin, adiponectin, free fatty acids, TNFα, insulin-like growth factor, plasminogen activator inhibitor, angiotensinogen, interleukins, prostaglandins, estrogens [10].

In clinical practice, MetS is a specific time and space model of polymorbidity, a set of CVDs and metabolic disturbances pathogenetically interrelated through insulin resistance or lipotoxicity. For example, polycystic ovary syndrome, which forms when hypersecretion of insulin stimulates the production of androgens by teka-cells of the ovaries, can be attributed to MetS; androgens disrupt the normal development of follicles, resulting in multiple atresia [11]; or NAFLD caused by the accumulation of an excessive amount of triglycerides and other cholesterol derivatives in hepatocytes [12]. Osteoporosis is a similar example. Adipocytes in the bone marrow can not only suppress osteoblastogenesis but induce bone resorption, since bone marrow adipocytes, as well as of any other localisation, release anti-inflammatory cytokines capable of stimulating osteoclasts [13]. Thus, the concept of MetS as a cluster of risk factors of type 2 diabetes and cardiovascular diseases have undergone some evolutionary transformations over the past years. Introducing autonomic dysfunction to the MetS pathogenesis as a factor of its progression opens up the possibility to include a whole range of nosologies into MetS that, by the superposition principle, exert mutual influence on the course and clinical manifestations of the pathologies included in MetS.

2. MATERIALS AND RESEARCH METHODS

In a clinic of Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Centre of the Russian Federation, a cross-sectional study was conducted. The sample consisted of 158 patients with MetS confirmed in accordance with the WHO recommendations (2009) by the presence of at least three out of five criteria:

- Abdominal obesity (for Caucasians – more than 94 cm for men and 80 cm for women);
- Triglycerides more than 1.7 mmol/L or drug therapy for hypertriglyceridemia;
- Decreased HDL (in men <1.0 mmol/L) or drug therapy for dyslipidemia;
- HBP > 130/85 mmHg or antihypertensive therapy of a patient with HBP in the case history;
- Increased level of fasting glycaemia or hypoglycemic therapy.

Patients aged 27 to 60 years old (median age 49.67±0.81 years old; 61 men and 97 women) signed an informed consent form to participate in the examination according to the WMA Declaration of Helsinki.

The examination included the analysis of complaints, case histories, and clinical check-ups. In physical examination, a general examination was carried. Growth (m) and body mass (kg) were measured. Body mass index (BMI) was calculated by the formula: body mass (kg)/growth $(m)^2$. Waist circumference and hip circumference were measured by centimeter and waist-to-hip ratio was calculated. Systolic and diastolic BP level was studied in accordance with international recommendations by means of a 24-hour monitoring of BP using Meditech ABPM-04 (Hungary). A blood chemistry test was done in serum with the use of common laboratory techniques. All male patients underwent urological examination – testing by the IPSS questionnaire – to determine their hormonal status. To quantify the disorders of urination and quality of life, the IPSS-QOL (International Prostate Symptom Score – Quality of Life) questionnaire was used, recommended by IV International Consultation on Benign Prostatic Hyperplasia. Transrectal ultrasound (TRUS) of the prostate, ultrasound of

the bladder (with the determination of the presence and amount of residual urine), kidneys and abdominal organs was carried out on the ultrasound scanner ClearVue 550 (USA). The patients' hormonal status –level of insulin, testosterone – was determined by ELISA using Lisa Scan EM (ERBA, the Czech Republic). Insulin resistance was calculated with HOMA-R, where HOMA-R = fasting glucose (mmol/L) x fasting insulin (μU/mL)/22.5. Values exceeding 2.27 were considered indicators of insulin resistance.

All the patients underwent a GERD examination in accordance with international recommendations on the presence of characteristic symptoms (heartburn and regurgitation) or on the basis of the results demonstrating the presence of gastroesophageal reflux disease (pH-measurement) or its damaging effect (endoscopy) [14]. The exclusion criterion was the presence of a gastric or duodenal ulcer, conditions after operations on the stomach, malignant neoplasms of any localisation, and prolonged intake of nonsteroidal anti-inflammatory drugs prior to the examination.

Heart rate variability (HRV) was analysed using the hardware and software complex Poly-Spectrum (Neurosoft, Russia). ECG recording for data analysis lasted 5 minutes in the supine position. HRV analysis in orthostasis lasted 5 minutes after the adaptation period. HRV results were recorded and interpreted in accordance with standards of measurement, physiological interpretation, and clinical use of heart rate variability developed by the task force of the European Society of Cardiology and the American Society of Pacing Electrophysiology [15]. Total power of the spectrum (TP), its high- (HF) and low frequency (LF) components were analysed. The establishment of the three frequency ranges is due to the difference in their formation: the range of very low frequencies reflects the functional state of supra-segmental structures; the low-frequency range – sympathetic; the high-frequency range – parasympathetic nerve system at the segmental level. The indicators were evaluated in view of absolute and relative values (%VLF, %LF, %HF) of the total power of each frequency range at the initial state and direction of their response to an active orthotest. $\%LF_{orthotest}/\%LF_{background}$ and $\%VLF_{orthotest}/\%VLF_{background}$ ratios were calculated. $\%LF_{orthotest}/\%LF_{background}$ ratio less than 1.0 in combination with the $\%VLF_{orthotest}/\%VLF_{background}$ coefficient over 1.0 indicated the development of cardiac autonomic neuropathy (CAN) [16].

To process the results, variational statistics methods were applied. Numerical indicators were expressed as the mean ± of a standard error of mean (M±m).

For processing the results, methods of variation statistics were used using the Statistica software. Continuous variables were checked for normality using a graphical representation of samples against the background of the Gauss curve, as well as the Kolmogorov – Smirnov criterion. Quantitative indicators were expressed as mean ± standard error of the mean (M ± m). For all statistical tests, the significance level was set at $p < 0.05$. For attributive and ordinal traits, intra- and intergroup differences were assessed using Student's t-test and Wilcoxon-Mann-Whitney t-test. For the comparison of qualitative signs, Fisher's angular transform method was used.

Is there any control group to compare with patients? It was better to compare the subjects with and without metabolic syndrome (suggestion).

This study presents only generalized results obtained from patients with MetS, in order not to overload the article. Separately, for each nosological form, there is published work, where there is confirmation of changes only in patients with MetS.

3. RESULTS AND DISCUSSION

The analysis was based on the results of the examination of 158 patients with MetS from 27 to 60 years old (the median age 49.67±0.81, 61 men and 97 women). All the patients with MetS were diagnosed with hypertension stages 1 and 2. The waist circumference exceeded 94 cm in men and 80 cm in women. As for the third criterion: 41% of the patients with MetS have dyslipoproteinemia; 34% suffer from impaired tolerance to carbohydrates. Various combinations of the symptoms were observed in 25% of the patients.

It is revealed that as the bodyweight increases, the background activity of sympathetic influences on the heart rate increases at rest with a decrease in the influence of supra-segmental structures (Table **1**). In response to the orthotest in patients with MetS, there is a decrease in sympathetic influences with an increase in supra-segmental structures to heart regulation. These changes become more pronounced with the increasing BMI. Greater impact of supra-segmental struc-

Table 1. HRV at rest and during orthotest in patients with MetS depending on BMI (M±m).

BMI, kg/m^2	%VLF (at rest)	%LF (at rest)	%HF (at rest)	%VLF (orthotest)	%LF (orthotest)	%HF (orthotest)	VLForthotest / %VLFbackground	%LForthotest / %LFbackground
25,0-29	55.10±2.65	20.55±1.93	18.39±2.22	53.38±3.41	28.13±2.63	14.46±1.23	1.01±0.06	1.23±0.12
30,0-34	56.02±3.05	23.68±2.06	20.34±2.56	55.19±3.44	26.48±3.07	12.29±0.87	1.16±0.19	1.09±0.12
35,0-39	54.23±4.50	25.92±2.84	19.69±4.09	61.43±5.09	25.64±3.14	11.50±4.42	1.29±0.13	1.07±0.14
≥40	54.00±10.28	26.33±5.67	21.67±8.93	66.50±6.96	24.50±4.60	11.00±4.65	1.35±0.28	0.87±0.48

tures on HRV providing automatic heart rate testifies to the increasing influence of the neurohumoral link; whereas the lack of response of the sympathetic division of ANS in response to the orthotest under initial hypersympathicotonia indicates that an increase in metabolic changes leads to a decrease in the sensitivity of the baroreflex and depletion of reserves for an adequate reaction in terms of automatic function support.

In our previous study, we examined 102 patients with MetS (75.5%) and 20 people diagnosed with hypertension (37.7.%) without verified MetS. The analysis of the examination results demonstrated that such a change in the automatic function support – the predominance of the central contour of heart rate regulation over the segmental during exercise in the presence of hypersympathicotonia at rest – leads to a series of clinical manifestations. There is definitely a clear relation between hypersympathicotonia and hypertension (HP). One of the main factors increasing BP in this situation is the activation of renal sympathetic nerves and RAAS. However, in the presence of the mentioned autonomic changes, HP has a specific daily BP profile proved in our research (Table **2**).

Table 2. 24-hour BP monitoring of patients with MetS.

Indicator	Value (M±m)
Averaged systolic BP for 24 hours, mmHg	142.92±2.89
Averaged diastolic BP for 24 hours, mmHg	92.38±2.18
Systolic BP time index for 24 hours, %	36.85±7.64
Diastolic BP time index for 24 hours, %	45.38±7.56
Systolic BP variability for 24 hours, mmHg	12.46±0.69
Diastolic BP variability for 24 hours, mmHg	11.00±0.58
Daily systolic BP index, %	10.85±0.98
Daily diastolic BP index, %	9.77±1.57

In the presence of such autonomic changes, HT has a number of specific features in a daily BP profile. They are a labile course of HT with spikes and valleys in blood pressure during the day and a decrease in the coefficient of average values of day/night BP, which is an important and independent factor of the high risk of cardiovascular events. Nevertheless, the development of cardiac autonomic neuropathy (CAN) is a more significant cardiovascular manifestation of the autonomic dysfunction associated with the manifestation of polyneuropathy in MetS. In literature, CAN is not described as a MetS component but many researchers think that it is a pitfall in diagnosis and treatment for cardiovascular pathologies in patients with MetS. This cohort of patients is not likely to feel a pain syndrome until the very late stages of the disease. Typical complaints often appear in the preinfarction state. Studying the patients with MetS demonstrates that 37.5% have CAN, which worsens the prognosis regarding the life expectancy of patients by 50%.

Another manifestation of autonomic imbalance is the lower urinary tract symptoms (LUTS) affecting patients' quality of life.

In an early study, we analysed 64 men (30 MetS patients aged 36.47±2.52 years and 32 patients of comparable age 38.11±3.06 years without MetS). The results demonstrated that 90% of young men with MetS gained 1 to 9 points according to the IPSS questionnaire, whereas a mean score made up 5.73±0.70 points (Table **3**).

Table 3. IPSS-QOL questionnaire and hormonal status of male patients with MetS.

Indicator	Value (M±m)
IPSS, scores	5.73±0.70
Overall testosterone, ng/dl	6.75±0.42
Dihydrotestosterone, pg/ml	504.02±16.38
Insulin, μU/mL	7.31±0.69
HOMA-R index	2.12±0.11

Such a number of IPSS scores may be a marker of the hormone-metabolic ill health of a patient taking into account that one of the main mechanisms of a pathogenetic unity of MetS and LUTS is insulin resistance/hyperinsulinemia [17]. Androgen deficiency may serve as another mechanism. Its markers are the onset and progression of obesity and insulin resistance. However, in the conducted study, there was no decrease in the level of androgens – both testosterone and dihydrotestosterone – in patients with MetS. Moreover, testosterone levels exceeded the reference values in 16.7% of the patients. It should be noted that the dependence of levels of testosterone or dihydrotestosterone and concentrations of insulin, glucose, and insulin resistance index was not found. Probably, disorders in urological aspects in men may testify to the loss of visceral innervation of the bladder and to be a reflection of global autonomic dysfunction.

GERD is another nosology associated with MetS. It is known that obesity, even in the absence of diaphragmatic hernias, contributes to an increase in the frequency and duration of spontaneous relaxation of the lower esophageal sphincter, as the main pathogenetic factor of GERD [18]. Such impairment of the gastric motor function and emptying and a decrease in the tone of the lower esophageal sphincter in the absence of organic causes can be explained by dysregulation of the autonomic nervous system.

The research showed that the course of GERD in the presence of MetS has some specific features.

Earlier, we conducted a cross-examination of a population of 52 patients with GERD aged from 24 to 60 years old (mean age 44.86±1.50 years; 30 female and 22 male). Heartburn is thought to be one, if not only, of the major symptoms of GERD (80% of cases). However, analysing the complaints revealed that GERD at excessive body mass is characterised by an atypical course. More than half of the patients (56.3%) mainly complained about regurgitation, whereas 40.6% mentioned heartburn. During the endoscopy, the atypical nature of GERD under excessive body mass became even more pronounced. The endoscopy-negative form of the disease was diagnosed in 38% of the patients when clinical symptoms and morphological changes at the cellular level were not accompanied by esophagitis.

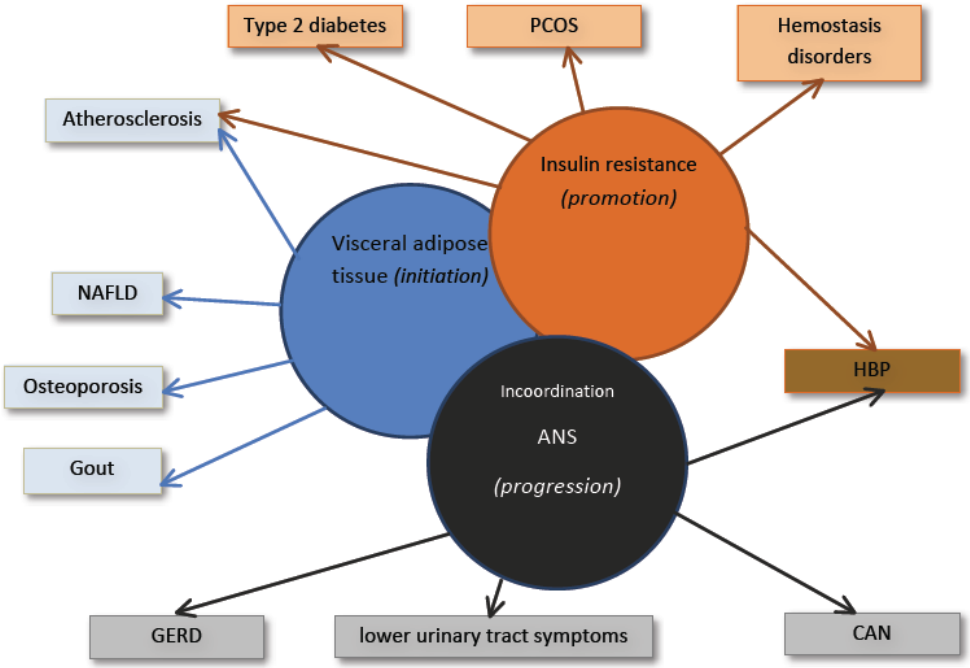

Fig. (1). The pathogenesis of nosological manifestations of the metabolic syndrome.

DeMeester was used to analyse pH-grams in the esophagus. In the study, the recommended indicators were supplemented by an assessment of identical parameters for pH greater than 7.

During the daily pH-measurement in the patients with MetS and GERD, including its erosive variants, it was found out that some patients do not have pathological by the quantity and length refluxes with pH<4. In some cases, the development of heartburn did not coincide with the recorded refluxes. At the same time, the percentage of refluxes in the supine position was high with pH>7-25,22±5,48%, which testifies to a significant contribution of alkaline refluxes to GERD development in this group of patients.

Thus, autonomic dysfunction at MetS determines a labile course of HT, underlies CAN and clinical manifestations of LUTS and GERD, which gives rise to the inclusion of the indicated pathological conditions in the MetS cluster. This dictates the need to consider the pathogenesis of MetS in terms of initiation-promotion-progression, as outlined in Fig. (**1**).

CONCLUSION

We suggest considering MetS not as a cluster of risk factors of the development of CVDs and type 2 diabetes but as a conglomerate of nosologies united by common pathogenesis. It leads to the need to consider CAN, GERD, and LUTS as MetS components rather than associated states. In such a case, developing common diagnostic criteria and inclusion of the diagnosis of metabolic syndrome into the list of medical standards is crucial. From the perspective of evidence-based medicine, it is desirable to conduct multi-centered studies to develop a multifactorial method of treatment with the combined use of drugs of different pharmacological classes to achieve the necessary therapeutic effect.

LIST OF ABBREVIATIONS

BMI	=	Body mass index
CAN	=	Cardiac autonomic neuropathy
CVDs	=	Cardiovascular diseases
ECG	=	Electrocardiogram
FFA	=	Free fatty acids
GERD	=	Gastroesophageal Reflux Disease
HF	=	High frequency
HRV	=	Heart rate variability
HT	=	Hypertension
IPSS-QOL	=	International Prostate Symptom Score – Quality of Life
IR	=	Insulin resistance
LF	=	Low frequency
LUTS	=	Lower urinary tract symptoms
MetS	=	Metabolic syndrome
TP	=	Total power of the spectrum
TRUS	=	Transrectal ultrasound
VLDL	=	Very-low-density lipoprotein

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This Study Protocol was approved by the Local Ethics Committee Federal State Research Institution Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk, Russian Federation №12 of 2016.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study involving human participants was in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants prior to the investigation.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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