

## Artículo de investigación

**The role of metabolic syndrome in the course and outcome of NSAID-gastropathy**

Роль метаболического синдрома на течение и исход НПВП-гастропатии

El papel del síndrome metabólico en el curso y el resultado de la gastropatía por AINE

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Maxim V. Trushin<sup>124</sup>**Abstract**

Metabolic syndrome is a significant global problem. Many of these patients have to take NSAIDs for a long time as a baseline treatment for associated diseases, the side effects of which on the gastric mucosa known to many specialists. The purpose of the study was to determine the role of metabolic syndrome in the course and outcome of NSAID-gastropathy. Selected 84 patients from 44 to 69 years, divided into 3 groups: 1 group - 31 people with NSAID-gastropathy and MS, 2 group - 24 people with NSAID-gastropathy and without MS, 3 group - 33 patients with MS, taking NSAIDs without NSAID gastropathy. Clinical and anamnestic data were determined, anthropometric parameters were assessed, the biochemical blood test was performed to determine the lipid spectrum, fasting capillary blood glucose level and esophagogastroduodenoscopy (EGDS) – before and 4 weeks after therapy with proton pump inhibitors (PPI) for all subjects.

Data processing performed using the software package Excel, Anova and Statistica 10.

The process of GM erosions healing in subjects with MS and NSAID-gastropathy takes a longer period. The dominant factors in the development of erosive lesions are the levels of HDL cholesterol, degree of hypertension and H. pylori infection. Duration of treatment is mainly

**Резюме**

Введение. Метаболический синдром (МС) представляет собой существенную проблему для здравоохранения, сопоставимую с неинфекционной пандемией. Частое его сочетание с ишемической болезнью сердца (ИБС) и остеоартрозом диктует необходимость течения длительного времени назначать нестероидные противовоспалительные препараты (НПВП), что может сопровождаться развитием эрозивно-язвенного повреждения желудочно-кишечного тракта.

Целью работы было определение роли МС в течении и исходе НПВП-гастропатии. Материал и методы.

Материалы и методы. В динамике обследовано 84 пациента со стенокардией напряжения ПЖК в возрасте от 44 до 69 лет, получающие препараты ацетилсалициловой кислоты. Больные были разделены на 3 группы: 1-я группа – 31 человек с НПВП-гастропатией в сочетании с МС; 2-я

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influenced by LDL cholesterol levels, TG and TH levels, and the degree of AH. Conclusions. MS makes a negative contribution during NSAID gastropathy.

**Keywords:** NSAID-gastropathy, metabolic syndrome, NSAIDs.

группа – 24 человека с НПВП-гастропатией без МС; 3 группа – 33 пациента с МС в сочетании с хроническим гастритом, принимающие НПВП без развития эрозивно-язвенных повреждений желудка. Больные обследованы в динамике на протяжении месяца. Пациенты 1-й и 2-й группы с НПВП-гастропатией и 3-й группы с хроническим гастритом получали ингибиторы протонной помпы (ИПП) в суточной дозе 20 мг в течение месяца. При отсутствии эпителизации эрозий в течение месяца лечение ИПП пролонгировали еще на 4 недели. Результаты. Результаты эндоскопического исследования, проведенные через месяц показали, что в 1-й группе только у 10 из 31 человека отмечалось полное заживление эрозий; во 2-й – у 19 – из 24. Выводы. К способствующим манифестации НПВП-гастропатии следует относить наличие АГ, низкий уровень ЛПВП, и инфицированность *H. pylori*.

**Ключевые слова:** НПВП-гастропатия, стенокардия напряжения, метаболический синдром, НПВП.

## Resumen

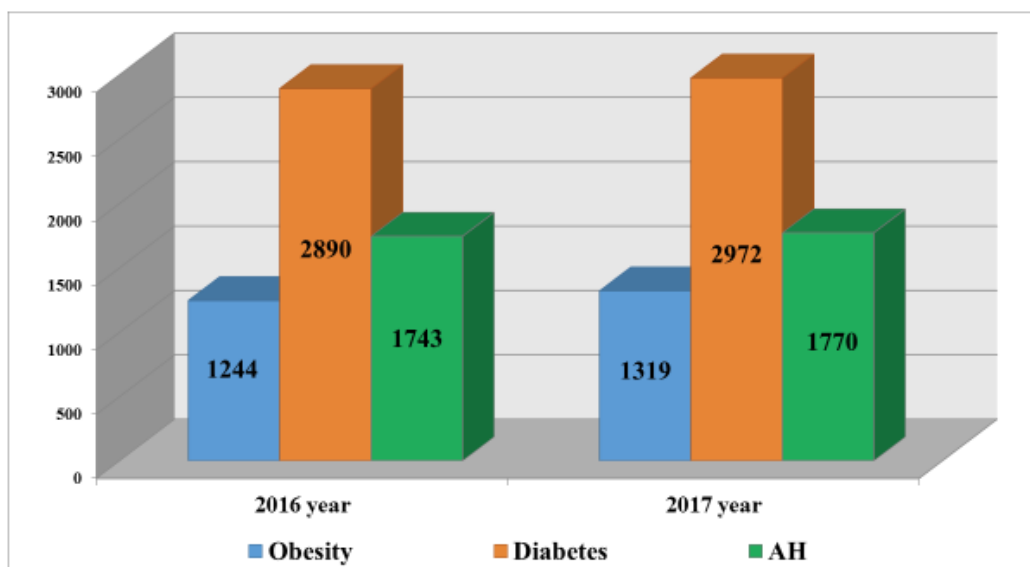
El síndrome metabólico (EM) es un problema importante de salud pública comparable a una pandemia no transmisible. Su combinación frecuente con enfermedad coronaria (CHD) y osteoartritis dictamina la necesidad durante mucho tiempo de recetar medicamentos antiinflamatorios no esteroideos (AINE), que pueden estar acompañados por el desarrollo de daño ulcerativo erosivo en el tracto gastrointestinal. El objetivo del trabajo fue determinar el papel de la EM en el curso y el resultado de la gastropatía por AINE. Material y métodos. En dinámica, se examinaron 84 pacientes con angina de pecho IIFK de 44 a 69 años, que recibieron preparaciones de ácido acetilsalicílico, divididos en 3 grupos: grupo 1 - 31 personas con gastropatía por AINE en combinación con EM; Grupo 2: 24 personas con AINE-gastropatía sin EM; Grupo 3: 33 pacientes con EM en combinación con gastritis crónica, que toman AINE sin el desarrollo de lesiones erosivas y ulcerosas del estómago. Los pacientes fueron examinados en dinámica durante un mes. Los pacientes del primer y segundo grupo con gastropatía por AINE y el tercer grupo con gastritis crónica recibieron inhibidores de la bomba de protones (IBP) en una dosis diaria de 20 mg durante un mes. En ausencia de epitelización de la erosión durante meses, el tratamiento con IBP se prolongó por otras 4 semanas. Resultados Los resultados de un examen endoscópico realizado un mes después mostraron que solo 10 de 31 personas mostraron curación completa de la erosión en el primer grupo, en el segundo grupo, de 24 en 24. Se pudo concluir que la presencia de hipertensión debe atribuirse a la manifestación de gastropatía por AINE, nivel bajo Infeción por HDL y *H. pylori*.

**Palabras clave:** Gastropatía por AINE, angina de pecho, síndrome metabólico, AINE.

## Introduction

Currently metabolic syndrome (MS) is a problem comparable to the non-infectious pandemic. The results of selective studies in Russia have shown that 30% of the population is overweight, a quarter of them are verified with obesity

[Tokareva Z.N., 2010, p.10]. According to the 2017 statistical yearbook of the Ministry of Healthcare of the Russian Federation (RF), compared with 2016, Russians became “heavier” by 6%, 17% from them are the children (Fig. 1)



**Figure 1. The dynamics of the incidence of chronically non-communicable diseases in Russia in 2017 per 100 thousand people**

AH – arterial hypertension

[Polikarpov A.V., 2017, p.86]. The dynamics of obesity in the world is not encouraging. The data provided by World Health Organization (WHO) demonstrate the rapid increase of the body weight among adults and children. Thus, in 2016, more than 1.9 billion people over the age of 18 were overweight, over 650 million from them had the obesity [Jonathan Q Purnell, 2018].

According to the recommendations of the International Diabetes Federation in 2005 for the diagnosis of MS, the main component is an abdominal obesity (AO), waist measurement (WM) for men > 94 cm, for women > 80 cm; in combination with two or more of the following components: Arterial hypertension (AH), systolic blood pressure (SBP) level  $\geq 130$  mmHg and/or diastolic blood pressure (DBP)  $\geq 85$  mmHg; hypertriglyceridemia (HTG), with a TG concentration of > 1.7 mmol/L; low level of high-density lipoproteins (HDL) < 1 mmol/L for men and 1.3 mmol/L for women; hyperglycemia, with the fasting plasma glucose level  $\geq 6.1$

mmol/L. All of these components induce secondary disorders of the hemostatic system and lead to the early death of the working-age population from cardiovascular diseases [Almazov V.A., 1999, p.208; Mamedov M.N., 2005, p.41].

According to epidemiological data, over 30 million people in the world take NSAIDs, and most of them are over-the-counter [Alberti K.G., 2005]. Looking at the dynamics of chronic non-infectious diseases in Russia in 2017, an attention should be paid to an increase in the incidence of diabetes mellitus (DM) type II, obesity and coronary heart disease. Given this, we can assume a further increase in the consumption of NSAIDs [Polikarpov A.V., 2017, p.86].

NSAIDs are the first line medical group for the treatment of the pain syndrome and prevention of the cardiovascular disorders; they have the specific negative action on the mucous of all parts of the gastrointestinal tract due to inhibition

of prostaglandin synthesis (PG), leading to a significant reduction in its protective potential, causing damage on the background of the action of various exogenous and endogenous factors [Strachunsky L.S., 2017; Karateev A.E., 2018, p.1]. In this regard, the problem of the MS role in the context of comorbid pathology in the occurrence and course of NSAID-gastropathy deserves attention.

### Materials and methods

The 88 patients in the age from 44 to 69 years with Stable angina Class II were examined during 4 weeks. The subjects were divided into 3 groups. First group: 31 subject with NSAID-gastropathy and MS (8 male and 23 female, mean age  $57.9 \pm 6.0$  years), the second group: 24 subjects with NSAID-gastropathy without MS (11 male and 13 female, mean age  $53.5 \pm 7.6$  years), the third group: 33 subjects with MS, taking the NSAIDs without NSAID-gastropathy (14 male and 19 female, mean age  $62.7 \pm 8.9$  year). The prevalence of AH in the 1st group was 93.5%, in the 2nd group – 79%, in the 3rd group – 69%. Definition of erosive form of NSAID-gastropathy: defects of the gastric mucosa less than 5 mm in diameter, covered with a white necrotic mass [Uemura N, 2014, p.814].

Inclusion criteria were 3 or more diagnostic signs of MS:  $BMI \geq 25 \text{ kg/m}^2$ ,  $AH > 130 \text{ mmHg}$  and  $85 \text{ mmHg}$  or medically controlled hypertension, the level of fasting capillary blood glucose (CBG)  $> 5.6 \text{ mmol/L}$ , triglycerides (TG)  $> 1.7 \text{ mmol/L}$ ,  $HDL < 1.3 \text{ mmol/L}$ , NSAIDs consumption for more than 2 weeks. Exclusion criteria: erosive and ulcerative gastrointestinal lesions (GIT), not associated with the NSAIDs consumption, acute inflammatory diseases, pregnancy, systemic diseases.

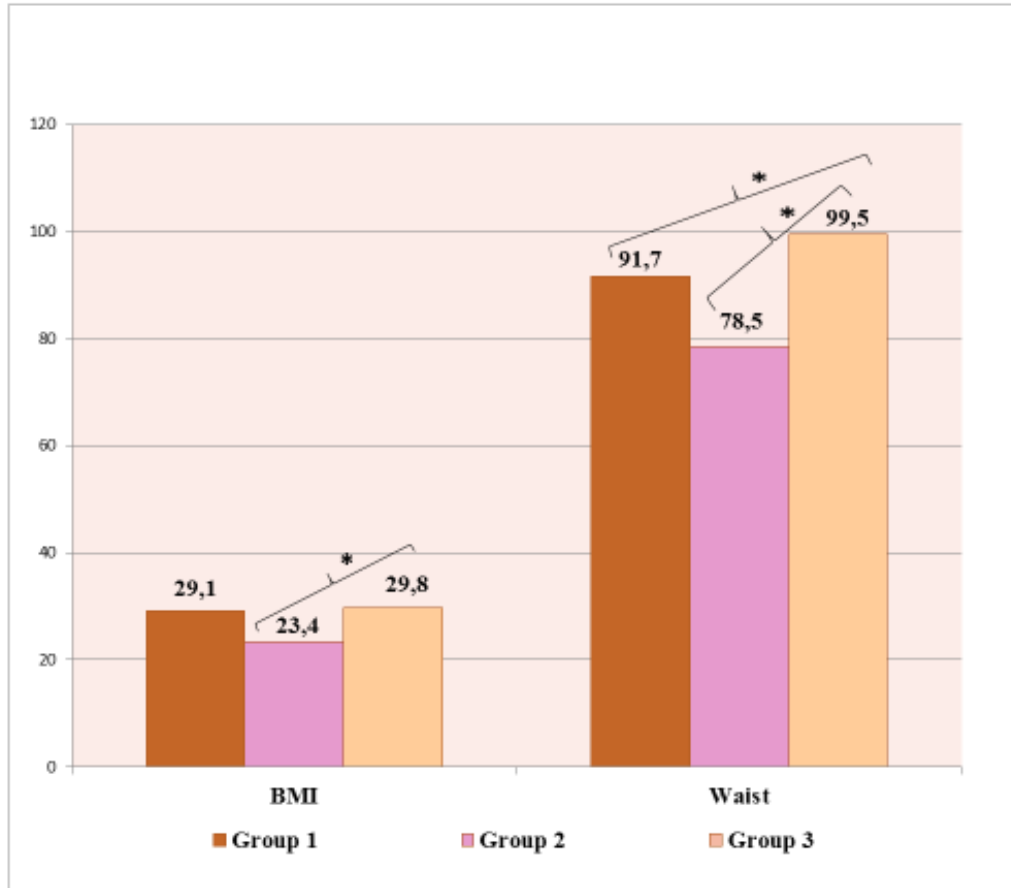
Clinical and anamnestic data were determined, anthropometric parameters were assessed, the biochemical blood test was performed to determine the lipid spectrum, fasting capillary

blood glucose level and esophagogastroduodenoscopy (EGDS) – before and 4 weeks after therapy with proton pump inhibitors (PPI) for all subjects. An intergroup analysis of the degree of the blood pressure increase and indicators of CBG, TC, LDL cholesterol and HDL cholesterol was performed. Statistical data processing was performed using the Excel, Anova, Statistica10 software package. Fisher criterion was used for comparison of the 1st and 2nd groups according to the frequency of erosions healing in the stomach.

### Results

A comparative analysis revealed significant differences in anthropometric data ( $p < 0.05$ ). WM in subjects of the 3rd group ( $99.5 \pm 18.2 \text{ cm}$ ) exceeded the values of the same indicator in subjects of the 2nd group ( $78.5 \pm 6.8 \text{ cm}$ ) and 1st group ( $91.7 \pm 9.1 \text{ cm}$ ). It should be noted that BMI in subjects of the 3rd group ( $29.8 \pm 5.8$ ) significantly exceeded the value of the 2nd group subjects ( $23.4 \pm 1.8$ ), while in subjects of the 1st group no significant differences were found.

Indicators of total cholesterol in the groups were distributed as follows: in the 1st group –  $6.5 \pm 0.2 \text{ mmol/L}$ , in the 2nd group –  $4.1 \pm 0.1 \text{ mmol/L}$ , in the 3rd group –  $6.1 \pm 0.2 \text{ mmol/L}$ . The LDL cholesterol values were  $4.1 \pm 0.1 \text{ mmol/L}$  in the 1st group,  $3.1 \pm 0.1 \text{ mmol/L}$  in the 2nd group and  $3.8 \pm 0.2 \text{ mmol/L}$  in the 3rd group. The highest TG levels were observed in the 1st group ( $2.9 \pm 1.7 \text{ mmol/L}$ ), the lowest – in the 2nd group ( $1.2 \pm 0.2 \text{ mmol/L}$ ). The representatives of the 3rd group had TG values of  $1.6 \pm 0.4 \text{ mmol/L}$ . Significant differences of HDL cholesterol were noted, with the highest values detected in subjects of the 3rd group ( $2.1 \pm 0.4 \text{ mmol/L}$ ). It should be noted that the level of CBG in the 1st group was an average  $6.9 \pm 2.4 \text{ mmol/L}$ , in the 2nd group –  $4.9 \pm 0.5 \text{ mmol/L}$  and  $6.6 \pm 2.1 \text{ mmol/L}$  – in subjects of the 3rd group (Fig. 2).



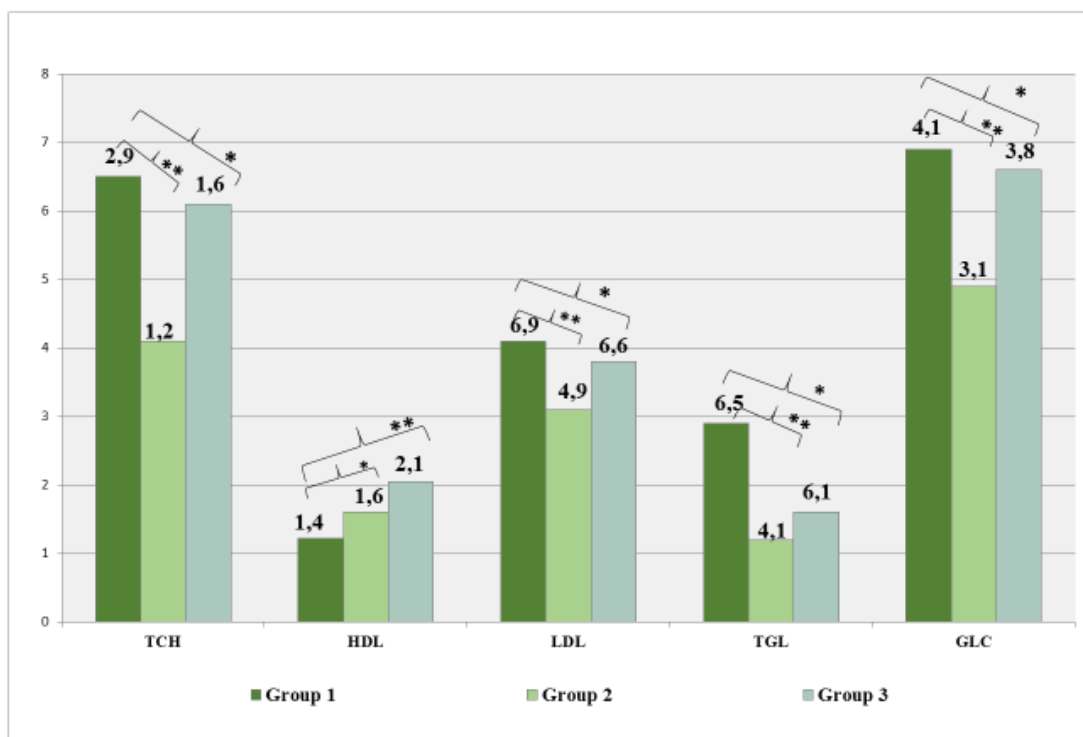
**Figure 2. Comparison of anthropometric indicators between groups**

BMI – body mass index

\* –  $P < 0.05$ .

In this study was performed a comparison in terms of the healing frequency against the background of therapy between the studied groups. The significant differences at the frequency of erosion healing were revealed between 1st and 2nd group ( $p < 0.01$ ). The percentage of successful healing was less in the

1st group (29%); in subjects of the 2nd group it was 79%. During the anamnestic data analysis an attention was paid to the presence of *Helicobacter pylori* infection in 30 subjects: 45.2% of people in the 1st group, 25.0% in the 2nd group, 30.3% in the 3rd group (Fig. 3).



**Figure 3. Comparison of blood parameters between groups**

TCH – total cholesterol

HDL – high density

lipoproteins

LDL – low density

lipoproteins

TGL – triglycerides

GLC – glucose

\*p<0.01

\*\*p<0.05

Thus, on the basis of the obtained data, it is possible to judge about the presence of factors that determine and slow down the reparative processes of the gastric mucosa (GM). The first are indicators of HDL, blood pressure and H. pylori infection, slowing reparation – high LDL, TG, TC, BMI, WM and blood CBG concentration.

### Discussion

A comparative analysis of anthropometric indicators revealed that the mean levels of BMI and WM in the 3rd group were higher than those in the 2nd and 1st groups. However, it is impossible to argue about the direct negative impact of high BMI and WM on the healing of GM by the results of our study due to the existing additional risk factors such as arterial hypertension (AH).

AH, as an integral part of MS, often provokes the development of erosive and ulcerative lesions of

the gastroduodenal region; their combination can vary from 3.4% to 50% [Almazov V.A., 2000, p.3]. Associated course of hypertension and acid-related diseases can have close pathogenetic relationships: these are systemic vascular disorders at the arterioles level, neuroendocrine changes, changes of homeostasis. The deterioration of vasomotor activity of smooth muscle cells of resistant vessels, increased tone and intravascular resistance of microvessels, reduced microcirculation efficiency and increased congestion in the venules, impaired ability of the endothelium to produce vasodilators; as a result – an intense response of the endothelium to the effect of humoral vasoconstrictors [Khlynova O.V., 2013, p.80; Smirnov, Yu. V., 1990, p. 48].

Increased blood pressure is a significant hemodynamic load on the vessel wall, leading to its damage and remodeling. On the other hand, an increase of arterial stiffness can develop at a normal level of blood pressure on the background

of atherosclerotic vascular damage, dyslipidemia, being a predictor of the further AH development [Nilsson P.M., 2013, p.1517]. For this reason, we paid attention to the biochemical parameters of the patients of the compared groups. The maximum TG level was noted in the 1st study group (2.6 mmol/L), the lowest – in the 2nd group (1.1 mmol/L;  $p < 0.05$ ). The maximum HDL cholesterol levels were recorded in the 3rd group, the minimum levels – in the 1st group.

The damaging effect of *H. pylori* infection has a dual nature: on the one hand, it is ulceration of the gastric mucosa and a greater vulnerability of epithelial cells, on the other – an increase of the gastric juice aggression, particularly the acidity. As a result of the interaction of these factors, the bacterium can penetrate deeper into the mucous membrane. It is also important that the restoration of proliferation after bacteria eradication in the antrum occurs quickly, but the healing of the stomach body is delayed for a longer time [Murakami K., 1997, p.184]. When comparing the two groups, it was noted that the frequency of complete healing of the GM in patients with hypertension in the 1st group is lower than in the 2nd group. Attention was also attracted by the fact that patients with a combination of AH, dyslipidemia and *Helicobacter pylori* did not undergo complete healing of the GM at the end of the observation period, that required a longer course of treatment. According to the literature data, gastrointestinal lesions (including acid-related pathology) are often observed in patients with diabetes. It has been established that diabetic neuropathy, characterized by the damage of various parts of the nervous system, especially those involved in the regulation of the gastrointestinal tract, was manifested by varying severity gastropathy. The presence of the 1st group patients with NSAID-gastropathy and MS with the lowest percentage of erosions healing in the GM (29%) was the confirmation of the aforementioned fact.

A separate role was allocated to the so-called perivascular adipose tissue (PVAT), which has an endocrine function, secreting many adipokines. An imbalance of these substances secretion occurs with obesity in PVAT. Increase of the leptin content in adipose tissue around the vessel stimulates neointimal growth, causes endothelial dysfunction along the protein kinase-C $\beta$ -dependent pathway, which has been confirmed in experimental conditions. A decrease of nitric oxide content and endothelial NO synthase was demonstrated as a response to a high leptin level of PVAT using the example of PVAT of the pig's epicardium with metabolic

syndrome and mice models with alimentary obesity. An imbalance of the leptin and adiponectin secretion in PVAT with obesity leads to suppression of the adenosine monophosphate kinase signal pathways and the mTOR cell growth protein, which is involved in the regulation of glucose metabolism [Fernández-Alfonso M.S., 2013, p.1; Simon C., 2013, p.338].

An interesting situation occurs with overweight and obesity after weight loss. The most unfavorable form of obesity is the abdominal type, associated with the endocrine and paracrine functions of adipose tissue, as well as with secretion of neuronal apoptosis-inhibiting protein, insulin resistance mediator, tumor necrosis-alpha factor (TNF- $\alpha$ ), which stimulates the synthesis of interleukin-1 and -6, leptin and ghrelin (regulators of eating behavior) [Mel'nichenko G.A., 2001, p.5; Kalantari S., 2017]. It has been shown that, in the case of overweight, the compensatory mechanisms switch on in the PVAT to restore the balance of pro- and anti-inflammatory cytokines, normalize the functioning of the endothelium and maintain normal vascular wall function. However, with a further increase in body weight, there is a "breakdown" of the compensation mechanisms and the progression of pathological changes in PVAT [Fernández-Alfonso M.S., 2013, p.1]. The duration of the adaptive response of PVAT with prolonged overweight without progression has not yet been established.

Therefore, it is possible to talk about common pathogenetic pathways in the development of hypertension, diabetes and the formation of metabolic vascular syndrome.

Thus, it is possible to single out characteristic systemic changes of the gastrointestinal tract of the same type, mainly due to local microcirculatory disorders, which can affect the reparative functions of the gastrointestinal tract.

## Conclusions

1. The process of GM erosions healing in subjects with MS and NSAID-gastropathy takes a longer period.
2. The dominant factors in the development of erosive lesions are the levels of HDL cholesterol, degree of hypertension and *H. pylori* infection.
3. Duration of treatment is mainly influenced by LDL cholesterol levels,

TG and TH levels, and the degree of AH.

4. No direct influence on the erosion reparation in the GM from the BMI and WM has been identified, but there is an indirect effect.
5. *H. pylori* infection contributes negatively to the GM erosions healing.

Conflict of Interest: The authors declare that they have no conflict of interest.

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