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DYNAMICS OF SOLUBLE SELECTINS DURING OF THERAPY OF NON-ALCOHOLIC FATTY LIVER DISEASE

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ДИНАМИКА РАСТВОРИМЫХ СЕЛЕКТИНОВ НА ФОНЕ ТЕРАПИИ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

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The levels of E-, P- and L-selectins in blood were studied during therapy in 42 patients with non-alcoholic fatty liver disease (NAFLD). Patients were divided into three groups. In the first group (17 patients), the hepatoprotective agent was combined with pentoxifylline. In the second group (10 patients) combination of hepatoprotective agent and metformin was applied. In the third group (15 patients), only a hepatoprotective agent (Phosphogliv forte) was prescribed. When using both combined therapy regimens, there could be a decrease in the concentration of E- and P-selectins in blood with normalization of P-selectin levels. Monotherapy with Phosphogliv forte reduced plasma levels of E- and P-selectins, which did not reach control values. In cases of biochemical remission of NAFLD (normalization of aspartic and alanine aminotransferases), a decrease in the concentration of E- and P-selectins in blood was noted. At the same time, levels of P-selectin reached normal values. In patients with preservation of increased activity of aspartic or alanine aminotransferases in dynamics of treatment, only parameters of P-selectin decreased. Thus, against the background of NAFLD therapy, there is a positive dynamics of soluble selectins, which is more pronounced in cases of combined treatment regimens.

Keywords: non-alcoholic fatty liver disease, treatment, selectins, pentoxifylline, metformin, phosphogliv forte

Исследование динамики E-, P- и L-селектинов в крови у 42 пациентов с неалкогольной жировой болезнью печени (НАЖБП) на протяжении 12 недель терапии проводилось в трех группах. В 1-й группе (17 пациентов) применялся гепатопротектор в сочетании с пентоксифиллином, во 2-й группе (10 пациентов) использовалась комбинация гепатопротектора и метформина, больным третьей группы (15 обследованных) назначался только гепатопротектор (Фосфоглив форте). При применении обеих комбинированных схем терапии происходило снижение концентрации E- и P-селектинов в крови с нормализацией значений P-селектина. Монотерапия Фосфогливом форте приводила к уменьшению плазменного содержания E- и P-селектинов. В случаях биохимической ремиссии НАЖБП (нормализации аспарагиновой и аланиновой аминотрансфераз) отмечено снижение концентрации E- и P-селектинов в крови, при этом уровни P-селектина становились нормальными. У пациентов с сохранением в динамике лечения повышенной активности аспарагиновой или аланиновой аминотрансфераз уменьшались только показатели P-селектина. Таким образом, на фоне терапии НАЖБП отмечается позитивная динамика растворимых селектинов, более выраженная в случаях использования комбинированных схем лечения.

Ключевые слова: неалкогольная жировая болезнь печени, лечение, селектины, пентоксифиллин, метформин, Фосфоглив форте

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ALT – alanine aminotransferase
AST – aspartic aminotransferase
BMI – body mass index
ESR – erythrocyte sedimentation rate
GGT – gamma glutamyltranspeptidase
HOMA-IR – homeostasis model assessment – insulin resistance
ICAM-1 – intercellular adhesion molecule-1
NAFLD – non-alcoholic fatty liver disease
PECAM-1 – platelet/endotelial cell adhesion molecule-1
VCAM-1 – vascular cell adhesion molecule-1

To date, a strategy for the pharmacological correction of non-alcoholic fatty liver disease has not been developed, which is associated with the lack of evidence for the ability of drugs to reduce inflammation, cause a reversal of liver fibrosis, and improve prognosis. The main treatment recommendations for NAFLD include lifestyle and nutritional modifications aimed at increasing physical activity, reducing body weight and providing a reduction in liver steatosis and fibrosis, the severity of non-alcoholic steatohepatitis. In this regard, drug interventions in NAFLD are mainly aimed at correcting metabolic disorders (obesity, deviations in carbohydrate and lipid metabolism) and reducing oxidative stress [1, 2].

The pathogenesis of NAFLD involves complex interactions of genetic, demographic, metabolic, clinical, hormonal, and environmental factors. The main links in the pathogenesis of NAFLD include insulin resistance, oxidative stress, disorders in the production of adipokines, chemokines and cytokines, endothelial dysfunction, and imbalance of the intestinal microflora, accompanied by endotoxemia and an increase in the content of lipopolysaccharide in the blood [3]. Endothelial dysfunction initiates the development and promotes the progression of NAFLD, which is associated with the ability of sinusoidal liver endothelial cells to negatively affect the outcome of steatosis, inflammation, and fibrosis [4]. The increased expression of selectins on endotheliocytes and leukocytes, which occurs against the background of endothelial dysfunction, provides transendothelial migration of immune cells to loci inflammation. The relationship between increased plasma levels of adhesion molecules, including selectins, and the course of NAFLD and its histological picture was previously revealed [5–8].

The dynamics of selectins in treating NAFLD and associated metabolic disorders are not well understood, and the results of studies are often controversial. Thus, it was noted that NAFLD therapy with various drugs led to a decrease in the blood concentration of E-selectin, molecules of the superfamily of immunoglobulins, and normalization of the content of endotheliocytes circulating in the blood [5, 9, 10]. In obese women, on the background of two-month physical activity, there was a tendency to a decrease in plasma values of E- and P-selectins [11], and in cases of curcumin use, the content of VCAM-1 in the blood (but not ICAM-1, P- and L-selectins) decreased [12]. A decrease in body weight against the background of intensification of physical activity and diet in patients with obesity was characterized by a drop in plasma levels of E-selectin, ICAM-1, and VCAM-1, which was explained by an improvement in the bioavailability of nitric oxide [13]. However, the positive effects of physical activity on endothelial dysfunction in obesity have not been confirmed in several studies [14]. In addition, the impact on the profile of soluble selectins of drugs widely prescribed for NAFLD – pentoxifylline, metformin, and phosphogliv (glycyrrhizic acid), especially in the aspect of achieving remission of the disease, has not been studied in detail.

The aim was to study the effect of therapy for non-alcoholic fatty liver disease on the indicators of soluble selectins.

Material and Methods. During treatment, 42 patients with NAFLD (21 women, 21 men) aged 19 to 65 years (mean age 44.48±1.93 years) were examined. Inclusion criteria: NAFLD patients over 18 years of age; consent to participate in the study. Exclusion criteria included liver disease of other etiologies; alcohol consumption in hepatotoxic doses; intake during the last 12 weeks of hepatoprotectors, drugs that correct disorders of carbohydrate and/or lipid metabolism, glucocorticosteroids, non-steroidal anti-inflammatory drugs, antioxidants, immunosuppressive drugs, pentoxifylline; acute and chronic clinically significant somatic diseases in the period of exacerbation, malignant neoplasms; mental illnesses; alcohol or drug addiction.

Elevated serum levels of AST (68.52±4.30 U/l), ALT (83.81±5.09 U/l), GGT (99.24±13.44 U/l), increase in BMI (34.09±0.79 kg/m^2), HOMA-IR (4.92±0.33) were determined in patients with NAFLD. In 80.9 % of cases, hypertriglyceridemia, in 64.3 % – a reduced content of high-density lipoproteins was detected. Abdominal obesity, arterial hypertension, and metabolic syndrome were observed in 90.5 %, 47.6 %, and 80.9 % of patients, respectively.

Non-drug therapy for NAFLD included a sensible diet with a reduction in total calories, amount of animal fats, easily digestible carbohydrates, and an increase in physical activity, taking into account the condition of the cardiovascular system (daily aerobic exercise lasting at least 40–60 minutes), which provided weight loss (no more than 0.5–1.0 kg per week) [1].

Depending on the drug therapy, patients were divided into three groups. In the first group (17 patients), a hepatoprotector was used in combination with an endothelial protector (pentoxifylline 400 mg 3 times a day). In the second group (10 patients), a variety of a hepatoprotector and an insulin sensitizer (Metformin (Biosintez, Russian Federation) with dose titration up to 1–2 g per day) was used. In 15 cases (group III), drug therapy included the prescription of only a hepatoprotector (a combination of essential phospholipids and glycyrrhizic acid – Phosphogliv forte (Pharmstandard, Russian Federation), one capsule three times a day). The duration of therapy was three months.

Purposely prescribing pentoxifylline is due to its positive effect on the manifestations of NAFLD in the form of a decrease in the synthesis of pro-inflammatory cytokines and reduction of oxidative stress [15]. Metformin has been used to correct insulin resistance syndrome. In addition, it has a beneficial effect on the course of NAFLD and can reduce sinusoidal endothelial dysfunction [5, 16]. The choice of phosphogliv as a hepatoprotector is associated with the ability of phospholipids and glycyrrhizic acid to stabilize and increase the plasticity of cell membranes, inhibit apoptosis and limit hepatocyte necrosis, improve lipid metabolism, as well as with antioxidant and anti-inflammatory effects [1, 17].

A Control group comparable in age and sex was formed by 60 practically healthy people (33 men, 27 women) aged 22 to 55 years (mean age 44.84±1.30 years).

The study of the plasma concentrations of E-, P-, and L-selectins before and after 12 weeks of treatment was carried out by enzyme immunoassay using kits from Bender MedSystems GmbH (Austria). The patients gave informed consent to the study. The ethics committee approved the study.

The results were statistically processed by SPSS Statistics 24 (IBM, USA). Quantitative values with a normal distribution are presented as mean±standard error of the mean. Student's t-test, Newman – Keuls test, paired Student's t-test, Pearson's linear correlation coefficient (r), and χ^2 test with Yates's correction for continuity were used. Differences were considered statistically significant at $p<0.05$.

Results and Discussion. In the dynamics of NAFLD treatment, there were noticed the following states: a statistically significant improvement in anthropometric parameters (decrease in body weight and BMI), a reduction in biochemical markers of the inflammatory process (AST, ALT, GGT, ESR, C-reactive protein), a decrease in HOMA-IR values and serum levels of triglycerides.

The concentration of E- and P-selectins in the blood decreased, and the levels of L-selectin did not change after 12 weeks of NAFLD therapy (Table 1). The dynamics of soluble selectins during treatment were associated with an improvement in anthropometric parameters, markers of inflammation and enzymes indicating liver damage: ΔE-selectin and ΔALT (r=0.41; p=0.006); ΔE-selectin and ΔGGT (r=0.44; p=0.003); ΔP-selectin and ΔALT (r=0.31; p=0.04); ΔP-selectin and ΔC-reactive protein (r=0.32; p=0.03); ΔL-selectin and ΔGGT (r=0.30; p=0.05); ΔL-selectin and ΔBMI (r=0.36; p=0.01); ΔL-selectin and Δbody weight (r=0.31; p=0.04). This indicates the relationship between the restoration of endothelial function with a decrease in the amount of adipose tissue, the intensity of inflammation (including in the liver tissue).

Table 1

Effect of treatment of NAFLD on levels of selectins in blood (M±SE)

Examined groups	Molecules of selectin family (ng/ml)		
	E-selectin	P-selectin	L-selectin
Control	40.88±2.83	103.60±5.32	4591.00±231.48
Patients with NAFLD:			
In total	89.26±3.75 * / 71.31±4.16 *,**	166.26±9.11 * / 128.31±7.75 *,**	5758.48±299.86 * / 5720.24±313.67 *
Group I	90.29±7.87 * / 65.53±8.47 *,**	165.65±11.71 * / 119.00±11.20 **	5868.24±398.21 * / 5908.24±556.52 *
Group II	89.60±6.40 * / 65.30±6.49 *,**	162.30±17.84 * / 111.70±11.50 **	5689.80±651.47 / 5419.00±699.94
Group III	87.87±4.15 * / 81.87±4.26 *,**,x	169.60±19.09 * / 149.93±14.82 *,**,x	5679.87±590.25 1 / 5708.00±434.12 1

Note: in the numerator – parameters before treatment, in the denominator – after treatment. 1 – F=3.5, p=0.035; * – p<0.05 in comparison with the control; ** – p<0.05 during treatment; x – p<0.05 in comparison with the values of patients of groups I and II after treatment (Student's t-test, Newman – Keuls test, paired Student's t-test).

In patients treated with combined regimens (hepatoprotector in combination with an endothelioprotector or insulin sensitizer), plasma values of E- and P-selectins were decreased, and L-selectin levels were not changed. In contrast, P-selectin values became normal by the end of therapy. Monotherapy with hepatoprotectors led to a decrease in the content of E- and P-selectins in the blood; however, their levels were higher than in patients of groups I and II (Table 1).

Biochemical remission of NAFLD was achieved in 52.4 % of patients during treatment: normalization of AST (69.36±4.33 U/l and 28.27±1.38 U/l, p<0.05) and ALT (78.36±6.36 U/L and 35.14±1.57 U/L, p<0.05). Despite a statistically significant decrease in their values, in 47.6 % of cases AST (67.60±7.81 U/l and 53.45±4.90 U/l, p<0.05) or ALT (89.80±8.05 U/l and 68.55±5.12 U/L, p<0.05) remained elevated. Cases of biochemical remission were usually observed in patients of groups I (45.4 %) and II (36.4 %), the absence of remission was more common in patients of the third group who received a hepatoprotector (55.0 %). The isolated use of the hepatoprotector was associated with unsatisfactory therapy results, while the effectiveness of combined regimens was much higher (c2=4.7; p<0.05).

In patients with biochemical remission of NAFLD (normalization of AST and ALT), the concentration of E- and P-selectins in the blood was decreased with the normalization of P-selectin values by the end of 3 months of treatment. In patients with no remission in the dynamics of therapy, the content of only P-selectin in the blood was decreased. At the same time, the values of E- and P-selectins became higher than in the group with positive results of treatment (Table 2).

Table 2

Interrelation of parameters of selectins in the blood with the results of NAFLD therapy (M±SE)

Examined groups	Molecules of selectin family (ng/ml)		
	E-selectin	P-selectin	L-selectin
Control	40.88±2.83	103.60±5.32	4591.00±231.48
Patients with NAFLD:			
Group I (remission «+»)	87.64±4.70 * / 58.64±5.28 *,**	163.64±10.40 * / 109.14±7.22 **	5459.82±380.14 * / 5563.18±517.85 *
Group II (remission «–»)	91.05±6.05 * / 85.25±4.98 *, x	169.15±15.61 * / 149.40±12.81 *,**, x	6087.00±469.99 * / 5893.00±341.78 *

Note: in the numerator – parameters before treatment, in the denominator – after treatment. * – p<0.05 in comparison with the control; ** – p<0.05 in the dynamics of therapy; x – p<0.05 compared with the parameters of group I patients at the end of treatment (Newman – Keuls test, paired Student's t-test).

Despite the enormous progress made in studying the pathogenesis of NAFLD, no case management algorithms have yet been developed. Lifestyle modification remains the most commonly recommended way to improve the flow of NAFLD [3]. The unproven effectiveness of traditionally used drugs makes it necessary to clarify new mechanisms of their action, which is interesting for searching for new drug treatment schemes.

According to our data, during therapy, a decrease in the plasma content of E- and P-selectins was observed, especially in patients with biochemical remission of NAFLD, in cases where P-selectin values were normalized. In patients with persistent hyperenzymemia, only the concentration of P-selectin in the blood decreased by the end of therapy. Combining therapy regimens (hepatoprotector & endothelial protector, hepatoprotector & insulin sensitizer) was accompanied by normalization of soluble P-selectin levels and a decrease in E-selectin values. Against the background of monotherapy with hepatoprotectors, the content of E- and P-selectins in the blood decreased but remained relatively higher than in groups I and II.

The positive effect of the selected treatment regimens is based on the inhibitory effect on the oxidative stress and endothelial dysfunction accompanying NAFLD, which is confirmed by a decrease in the expression of selectins. The dynamics of soluble selectins were associated with an improvement in anthropometric parameters (body weight, BMI), inflammation (ALT, GGT, and C-reactive protein), which emphasizes the possibility of leveling endothelial imbalance and reducing the severity of inflammation in the liver in the background of a decrease in the amount of adipose tissue.

NAFLD therapy has previously been shown to reduce the production of plasma endothelial markers (plasminogen activator inhibitor, endothelin-1, E-selectin, ICAM-1, VCAM-1, and PECAM-1) [5, 10]. Prescribing antibodies to L-selectin improved hepatic architectonic liver, reduced hepatocyte fat, decreased expression of interleukin-6, tumor necrosis factor-α, and fibrosis markers in the steatohepatitis model [18]. The beneficial effects of NAJBP therapy may be due to the restoration of adiponectin synthesis, inhibiting the endothelial expression of adhesion molecules. In turn, the lack of selectins restricts the interaction of immune cells with endothelium cells, thus reducing the likelihood of initiation and progression of non-alcoholic steatohepatitis.

Anti-inflammatory potentials of pentoxifylline are associated with the inhibition of endothelial adhesive formation [19]. Thus, in the case of ischemic heart disease, pentoxyphyllin contributed to a decrease in ICAM-1 and VCAM-1 levels in the blood [20], and in the case of NAFLD, it caused a reduction in VCAM-1, ICAM-1 levels and normalization of RESAM-1 [10].

Metformin also has a beneficial effect on the expression of adhesive molecules in NAFLD. Its use in patients of NAJBP led to a decrease in plasma values of E-selectin, ICAM-1, VCAM-1, and RESAM-1 [5, 10], with the achievement in some cases of normal values of ICAM-1 in the blood [10]. The drug's ability to inhibit the expression of ICAM-1, VCAM-1 in type 2 diabetes mellitus [21], E-selectin, and ICAM-1 in case of the polycystic ovarian syndrome [22], has been noted.

The beneficial effect of metformin on selectins is associated with the correction of the level of glycemia and the restoration of tissue sensitivity to insulin, which is confirmed by the normalization of endothelial expression of adhesion molecules, nuclear factor-κB, interleukin-8, decrease in the production of reactive oxygen species, and an increase in the release of nitric oxide [23]. The disappearance of insulin resistance while intaking metformin improved insulin binding to platelet receptors and reduced cell activity and platelet expression of P-selectin [24]. In addition, metformin inhibits the expression of inducible. It enhances the expression of endothelial nitric oxide synthase, leveling endothelial dysfunction in the liver and inhibitory effect on stellate cells [16], which explains its possible antifibrotic effect.

The ability of hepatoprotectors to correct endothelial dysfunction in NAFLD is confirmed by the positive dynamics of the content of circulating endotheliocytes while taking α-lipoic acid [9], as well as the levels of ICAM-1, VCAM-1, PECAM-1 in the blood in cases of using phosphogliv [10]. Glycyrrhizic acid has antioxidant, anti-inflammatory, antiviral, antitumor, and immunoregulatory properties [25], which are based on inhibiting the expression of pro-inflammatory cytokines, reactive oxygen species, nuclear factor-κB, and adhesion molecules [26]. In a model of alcoholic hepatitis, glycyrrhizic acid reduced the secretion of vascular endothelial growth factor, ICAM-1, and P-selectin [27]. The anti-inflammatory effects of glycyrrhizic acid had previously been demonstrated in models of diabetes mellitus [28], psoriasis [29], and enteritis [30].

This way, therapeutic measures at NAFLD improve anthropometric status, lipid and carbohydrate metabolic rate, inflammation (S-reactive protein, SRE, AsAT, AlAT, GHT), and endothelial mediators. It can be assumed that the positive dynamics of selectins against the treatment background reflect the reversion of inflammatory processes in the liver. Combined therapy regimens have a more pronounced corrective effect for endothelial dysfunction, which is the reason for their inclusion in the management algorithms of patients with NAFLD.

Conclusions

1. With the treatment for NAFLD, there is a positive dynamic of soluble selectins, more pronounced in cases of using combined treatment regimens (a combination of a hepatoprotector with an endothelial protector or an insulin sensitizer).

2. The achievement of biochemical remission of NAFLD is characterized by the normalization of P-selectin parameters and a decrease in the blood levels of E-selectin. In the absence of remission, only a reduction in the levels of P-selectin in the blood is observed.

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THE TREATMENT OF METABOLIC SYNDROME IN PATIENTS WITH MORBID OBESITY

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СОВЕРШЕНСТВОВАНИЕ МЕТОДОВ ЛЕЧЕНИЯ МЕТАБОЛИЧЕСКОГО СИНДРОМА НА ФОНЕ МОРБИДНОГО ОЖИРЕНИЯ

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The prospective study of 35 patients aged 28 to 59 years with MO was performed. Patients underwent laparoscopic gastroplication according to the original method. The QOL of patients was studied by comparing the questionnaire results and special research methods. The achieved decrease in body weight as a result of laparoscopic gastric plication, correction of concomitant disorders in dependent organs and systems, and normalization of metabolic process indices allows us to