UDC 616-002.17+616.36-004+616.36

CHANGES IN INDICATORS OF ENDOGENOUS INTOXICATION, IMMUNE-INFLAMMATORY REACTION AND ENDOTHELIAL DYSFUNCTION UNDER THE INFLUENCE OF TREATMENT OF PATIENTS WITH ALCOHOLIC LIVER CIRRHOSIS IN COMBINATION WITH OBESITY USING ADEMETHIONINE AND ARGININE GLUTAMATE

N.R. Matkovska

HSEE of Ukraine "IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY", Ivano-Frankivsk

The aim *of research was to investigate the effect of a complex treatment with ademethionine and arginine glutamate on the state of endogenous intoxication, immune-inflammatory reaction and endothelial dysfunction in patients with alcoholic liver cirrhosis (ALC) in combination with obesity.*

Methods. *215 patients, diagnosed with ALC, took part in the study, including 66 women and 149 men. 109 people had ALC with obesity and 106 people had ALC without obesity. Patients were divided into subgroups depending on the stage of decompensation according to Child-Pugh. Depending on the treatment protocol (b protocol – basic therapy, h protocol – basic therapy in combination with ademethionine and arginine glutamate), all patients were divided into subgroups.*

Results. *In patients of groups I and II who received the h protocol, at the stage of compensation, subcompensation and decompensation, the indicators of sorption capacity of erythrocytes (SCE), leukocyte index of intoxication (LII), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNFα), asymmetric dimethylarginine (ADMA) and the resistin level significantly improved ($p<0.05$). In patients of groups I and II, who received basic treatment, at the stage of compensation such indicators worsened, but no significant difference was observed before and after treatment ($p>0.05$). At the stage of subcompensation and decompensation in patients of groups I and II, who received basic treatment, SCE, LII, hs-CRP, TNFα, ADMA and the resistin level significantly worsened ($p<0.05$).*

Conclusions. *Inclusion in the complex treatment of ademethionine and arginine glutamate for obese patients with ALC helps to reduce the manifestations of endogenous intoxication, immune-inflammatory reaction and endothelial dysfunction.*

Key words: *alcoholic liver disease, liver cirrhosis,obesity, endogenous intoxication, inflammatory, endothelial dysfunction.*

Clinical and experimental pathology 2020. Vol.19, №3 (73). P.63-71.

DOI:10.24061/1727-4338. XIX.3.73.2020.9

E-mail: nmail4you@gmail.com

ЗМІНИ ПОКАЗНИКІВ ЕНДОГЕННОЇ ІНТОКСИКАЦІЇ, ІМУНОЗАПАЛЬНОЇ РЕАКЦІЇ ТА ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ПІД ВПЛИВОМ ЛІКУВАННЯ ХВОРИХ НА АЛКОГОЛЬНИЙ ЦИРОЗ ПЕЧІНКИ В ПОЄДНАННІ З ОЖИРІННЯМ З ВИКОРИСТАННЯМ АДЕМЕТІОНІНУ І АРГІНІНУ ГЛУТАМАТУ

Н.Р. Матковська

Мета роботи - *вивчення впливу комплексного лікування з використанням адеметіоніну та аргініну глутамату на стан ендогенної інтоксикації, імунозапальної реакції та ендотеліальної дисфункції у хворих на алкогольний цироз печінки (АЦП), поєднаний з ожирінням.*

Матеріали та методи. *У дослідженні взяли участь 215 хворих із діагностованим АЦП, серед яких було 66 жінок та 149 чоловіків. У 109 осіб діагностовано АЦП з ожирінням, у 106 осіб – АЦП без ожиріння. Пацієнтів поділили на підгрупи залежно від стадії декомпенсації за Чайльдом – П'ю, а також залежно від застосованого протоколу лікування (b протокол – базова терапія, h протокол – базова терапія, поєднана з адеметіоніном й аргініну глутаматом).*

Результати. *У хворих на АЦП в поєднанні з ожирінням спостерігається більш важчий перебіг захворювання, що супроводжується вираженішими клініко-лабораторними проявами. У пацієнтів I та II груп, що отримували h протокол, на стадії компенсації, субкомпенсації та декомпенсації показники сорбційної здатності еритроцитів (СЗЕ), лейкоцитарного індексу інтоксикації (ЛІІ), високочутливого С-реактивного білка (вч-СРБ), фактору некрозу пухлин альфа (ФНПа), асиметричного диметиларгініну (АДМА) та рівень резистину достовірно покращилися ($p<0.05$). У пацієнтів I і II груп, що отримували базове лікування, на стадії компенсації такі показники погіршилися, проте достовірної різниці у них до і після лікування не спостерігалося ($p>0.05$). На стадії субкомпенсації і декомпенсації у пацієнтів I і II групи, що отримували базове лікування, СЗЕ, ЛІІ,*

Ключові слова: *алкогольна хвороба печінки, цироз печінки, ожиріння, ендотеліальна дисфункція, запалення.*

Клінічна та експериментальна патологія 2020. Т.19, №3(73). С.63-71.

.

вч-СРБ, ФНПα, ADMA та рівень резистину достовірно погіршилися (p<0.05). ***Висновки.*** *Включення в комплексне лікування хворих на АЦП, поєднаний із ожирінням, адеметіоніну та аргініну глутамату сприяє зменшенню проявів ендогенної інтоксикації, імунозапальної реакції та ендотеліальної дисфункції.*

Ключевые слова: *алкогольная болезнь печени, цирроз печени, ожирение, эндотелиальная дисфункция, воспаление.*

Клиническая и экспериментальная патология 2020. Т.19, №3 (73). С.63-71.
.

ИЗМЕНЕНИЯ ПОКАЗАТЕЛЕЙ ЭНДОГЕННОЙ ИНТОКСИКАЦИИ, ИММУНОВОСПАЛИТЕЛЬНОЙ РЕАКЦИИ И ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ ПОД ВЛИЯНИЕМ ЛЕЧЕНИЯ БОЛЬНЫХ С АЛКОГОЛЬНЫМ ЦИРРОЗОМ ПЕЧЕНИ В СОЧЕТАНИИ С ОЖИРЕНИЕМ С ИСПОЛЬЗОВАНИЕМ АДЕМЕТИОНИНА И АРГИНИНА ГЛУТАМАТА

Н.Р. Матковская

Цель работы - *изучение влияния комплексного лечения с использованием адеметионина и аргинина глутамата на состояние эндогенной интоксикации, иммуновоспалительной реакции и эндотелиальной дисфункции у больных с алкогольным циррозом печени (АЦП) в сочетании с ожирением.*

Материалы и методы. *В исследовании приняли участие 215 больных с диагностированным АЦП, среди которых было 66 женщин и 149 мужчин. У 109 человек диагностирован АЦП с ожирением, у 106 человек - АЦП без ожирения. Пациентов разделили на подгруппы в зависимости от стадии декомпенсации по Чайльд-Пью, а также в зависимости от примененного протокола лечения (b протокол - базовая терапия, h протокол - базовая терапия в сочетании с адеметионином и аргинина глутаматом).*

Результаты. *У больных с АЦП в сочетании с ожирением наблюдается болем тяжелое течение заболевания, сопровождающееся выраженными клинико-лабораторными проявлениями. У пациентов I и II групп, получавших h протокол, в стадии компенсации, субкомпенсации и декомпенсации показатели сорбционной способности эритроцитов (ССЕ), лейкоцитарного индекса интоксикации (ЛИИ), высокочувствительного С-реактивного белка (вч-СРБ), фактора некроза опухолей альфа (ФНОα), асимметрического диметиларгинина (ADMA) и уровень резистина достоверно улучшились (p <0.05). На стадии субкомпенсации и декомпенсации у пациентов I и II группы, получавших базовое лечение, СЗЕ, ЛИИ, уч-СРБ, ФНПα, ADMA и уровень резистина достоверно ухудшились (p <0.05).*

Выводы. *Включение в комплексное лечение больных с АЦП в сочетании с ожирением адеметионина и аргинина глутамата способствует уменьшению проявлений эндогенной интоксикации, иммуновоспалительной реакции и эндотелиальной дисфункции.*

Introduction

The main causes of liver damage are alcohol, viruses, non-alcoholic fatty liver disease (NAFLD). Today, it is estimated that about 10% of deaths among young and middle-aged people are related to alcohol consumption. Alcohol abuse is third among the causes of mortality among young people after tobacco and arterial hypertension and secondarily among the causes of liver transplantation in Europe. NAFLD is detected in 20–35 % of the adult population, both in industrialized and developing countries. This disease has a long asymptomatic course [2, 8]. The initial manifestations of NAFLD are fatty hepatosis and steatohepatitis. However, under unfavourable conditions, the pathological process is transformed into the liver cirrhosis (LC) and may lead to hepatocellular carcinoma [4, 12]. The basis of the development of the LC is the processes of fibrosis, necrosis, angiogenesis, which realize the steady progression of pathology through the cascade of systemic metabolic and immune-inflammatory reactions and lead to endotoxemia, the restructuring of the normal structure of the parenchyma and the vascular system of the liver with the formation of pseudo lobules, regeneration nodes, and the development of multiple organ failure [1, 10].

The liver interacts closely with fatty tissue, which is not only an energetic but also a powerful endocrine organ that expresses and produces a large number of biologically active polypeptides — adipokines. They act both on the local (autocrine and paracrine) and on the systemic (endocrine) level [5]. Among the cytokines and related proteins with endocrine function, the most well-known are leptin, tumor necrosis factor α (TNFα), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), visfatin, chemerin; among fibrinolytic proteins — plasminogen activator inhibitor-1 (PAI-1), tissue factors; among complement components and associated proteins — adipsin (or complement D factor), adiponectin, acylation-stimulating protein (ASP); among the lipids and proteins that influence lipid metabolism or transport — lipoprotein lipase, cholesteryl ester transfer protein, apolipoprotein E, non-esterified serum fatty acids; cytochrome P450-dependent aromatase and 17-β-hydroxysteroid dehydrogenase are the enzymes involved in steroid metabolism; among proteins of renin-angiotensin system, the most well-known is angiotensinogen; among other proteins — resistin, apelin, retinol-binding protein, obestatin, omentin, vaspin and others [3, 11, 13, 14].

In adipose tissue, a large number of receptors is expressed, including insulin, glucagon, thyroid-stimulating hormone, glucocorticoid, androgenic, estrogenic, progesterone, leptin, apelin, IL-6 receptors, TNFα, gastrin/cholecystokinin-B, glucagon-like peptide-1, growth hormone, vitamin D, thyroid hormone, catecholamines and angiotensin II (type 1 and type 2). They are involved in various processes, including inflammation, immunological reactions, insulin sensitivity, liver steatosis and steatohepatitis [6].

The publications of the recent years show an ambiguous role of resistin in the pathogenesis of NAFLD. Adipokine, called the insulin resistance hormone, was discovered in 2001. However, it is secreted mainly by macrophages and, to a lesser extent, by fatty tissue. In addition to the differentiation of adipocytes, inhibition of adipogenesis and glucose uptake by cells, adipokine affects the stimulation of inflammatory mechanisms, activation of the endothelium, and proliferation of the smooth muscle cells in the blood vessels [15, 16, 17, 18].

This combination, especially at LC stage, becomes prognostically unfavourable for patients and leads to systemic complications, irritability and progression. In this regard, the methods to prevent progression, complications of LC and improve the life quality of such patients, are being sought. [9].

The aim of the study was to investigate the effect of complex treatment with ademethionine and arginine glutamate on the state of endogenous intoxication, immune-inflammatory reaction and endothelial dysfunction in patients with alcoholic liver cirrhosis (ALC) in combination with obesity.

Research methods

215 patients, diagnosed with alcoholic liver cirrhosis (ALC), took part in the study, including 66 women and 149 men aged (48.1±9.7) years and a median disease duration (5.8 ± 2.6) years. 109 people had ALC with obesity (group I) and 106 people had ALC without obesity (group II). Patients were divided into subgroups depending on the stage of decompensation according to Child-Pugh: class A – group IA (n=40), class B – group IB (n=39), class C – group IC (n=30) and IIA (n=39), IIB (n=36), IIC (n=31) groups, respectively; and also depending on the treatment protocol all patients were divided into subgroups (b protocol – basic therapy, h protocol – basic therapy in combination with intravenous administration of ademethionine and subsequent oral administration of ademethionine and arginine glutamate): patients receiving basic therapy were included in IAb (n=19), IBb (n=20), ICb (n=15), IIAb (n=22), IIBb (n=18), IICb (n=16) groups; patients who additionally received ademethionine and arginine glutamate were included in IAh (n=21), IBh (n=19), ICh (n=15) та IIAh (n=17), IIBh (n=18), IICh (n=15) groups.

Groups Ih and IIAh, in addition to the basic treatment, received intravenously 500 mg of ademethionine per day during two weeks, followed by oral administration of 500 mg of ademethionine and 1500 mg of arginine glutamate per day for 12 weeks.

Groups IBh and IIBh, in addition to the basic treatment, received intravenously 1000 mg of ademethionine per day for two weeks, followed by oral administration of 1000 mg of ademethionine and 3000 mg of arginine glutamate for 12 weeks.

Groups ICh and IICh, in addition to their basic treatment, received intravenously 1000 mg of ademethionine per day for two weeks, followed by oral administration of 1500 mg of ademethionine and 4500 mg of arginine glutamate per day for 12 weeks.

Diagnosis was verified using clinical and laboratory-instrumental methods in accordance with the order of the Ministry of Health of Ukraine No. 826 dated November 6, 2014, adapted clinical guidelines "Non-Alcoholic Fatty Liver Disease", 2014, adapted clinical guidelines "Alcoholic Liver Disease", 2014, adapted clinical guidelines " Liver Cirrhosis, 2017 (State Expert Centre of the Ministry of Health of Ukraine, Ukrainian Gastroenterology Association, Kyiv), recommendations of the European Association for the Study of Liver, Diabetes and Obesity (EASL-EASD-EASO, 2016), [7].

Exclusion criteria were liver cirrhosis of the viral, toxic and autoimmune genesis, metabolic diseases of the liver, oncological diseases, and the lack of individual consent of the patient to conduct the study. All patients were matched according to age and sex. The research was carried out in accordance with the ethical principles of conducting scientific research and principles of the Helsinki Declaration.

The degree of endogenous intoxication was determined by the leukocyte index of intoxication (LII) calculated according to the Kal-Kalif formula: LII = [(4Mc + 3Yu + 2S + M) × (Pl + 1)] / [(Lymph + Mon) × (E + 1)], where Mc — myelocytes, Yu — young, S — stab, M — microxyphil, Pl — plasma cells, Lymph — lymphocytes, Mon — monocytes, E — eosinophils, and by the test of sorption capacity of erythrocytes (SCE). The basis of the SCE test is the ability of the red blood cells (as a universal absorbent) to absorb the vital stain (0.025% solution of methylene blue), which is determined by the photocolorimeter, and corresponds to the degree of endogenous intoxication. In the control group, SCE was (27.30 ± 1.56) %. The activity of the inflammatory process was evaluated by the content of high-sensitivity C-reactive protein (hs-CRP) and TNFα in the blood, which was determined using ELISA kit (Elabscience, USA), Human hs-CRP, Human TNF-alpha High Sensitivity ELISA (Biovendor, Czech Republic) according to manufacturer's techniques. Resistin level was determined by immunoassay using the Resistin Human ELISA kit (Biovendor, Czech Republic). The endothelial dysfunction was studied by content of asymmetric dimethylarginine (ADMA) in the blood, determined by the immune enzymatic method using ADMA High Sensitive ELISA (Biovendor, Czech Republic). In the control group, the levels of hs-CRP, TNFα, ADMA and resistin were (0.65 ± 0.02) mg/l, (17.38 ± 1.15) pg/ml, (0,46±0,01) mmol/l and (3.72 ± 0.26) ng/ml, respectively.

The severity of the LC was assessed using the Child-Pugh score and the MELD score (Mayo Endstage Liver Disease, 2001). The control group consisted of 20 healthy individuals, who were age and gender matched.

Assessment of patients was performed before and after 3 months from the beginning of treatment.

Statistical processing of the obtained results was carried out using the software package Statistica v. 12.0 (StatSoft, USA, trial) and Microsoft Excel. The average values are presented in the form (M±m), where "M" is the average value of the indicator, "m" is the standard error of the average. Student's t-test was used to determine the significance of differences between groups in a distribution close to normal. Differences at $p < 0.05$ were considered statistically significant.

The study is carried out according to the plan of the scientific works of Ivano-Frankivsk National Medical University and is a fragment of research work: "Diseases of internal organs in modern conditions, with combined pathology and lesions of target organs: features of the course, diagnosis and treatment", number of state registration: 0115U000995.

Results and discussion

Patients with signs of astheno-vegetative, painful, dyspeptic, hepatorenal, hepatopulmonary syndromes, jaundice, drug-induced ascites, manifestations of hepatic encephalopathy were more common in group I of the corresponding classes, which was accompanied by a more severe course of the ALC according to the Child-Pugh and MELD scores. In patients of both groups, they increased with increasing ALC decompensation. However, in patients of group I these values were higher compared to group II 7.23% and 28.42%, 13.62% and 17.14%, 14.62% and 18.57% of classes A, B, C, respectively ($p<0.05$), (Tables 1 is on page 76, Tables 2 is on page 77, Tables 3 is on page 78).

These results indicate a more severe course and more pronounced progression of liver failure in patients with a combination of ALD and obesity due to a more pronounced increase in inflammatory-necrotic process and fibrosis in the liver and accompanied by significant systemic changes in blood flow, more severe systemic immunoinflammatory response, which ultimately leads to the development of multiple organ failure with fatal consequences.

In all patients, SCE, LII, TNFα, hs-CRP, ADMA and resistin levels increased with increasing decompensation of the disease. There was a significant increase in SCE in patients of group I ($p<0,05$) compared with persons of group II. SCE in patients of group I was 1.20, 1.19 and 1.11 times higher than that of class A, B and C of group II, respectively. The LII index in patients of group I significantly exceeded this indicator in A, B and C classes patients of group II in 1.18, 1.16 and 1.07 times, respectively ($p<0.05$). hs-CRP in patients of group I significantly exceeded this figure in persons of group II by 1.58, 1.46 and 1.34 times of classes A, B and C, respectively ($p<0.05$). The level of TNFα in patients of group I significantly exceeded this figure in persons of group II in 1.49, 1.46 and 1.41 times of classes A, B and C, respectively ($p<0.05$). The level of resistin in patients of group I significantly exceeded this figure in persons of group II in 2.41, 1.78 and 1.86 times of classes A, B and C, respectively ($p<0.05$). The level of ADMA in patients of group I significantly exceeded this figure in patients of group II in 2.14, 1.93 and 1.45 times of classes A, B and C, respectively ($p<0.05$).

Three months after the prescribed course of treatment, clinical and laboratory manifestations improved in most patients receiving the h protocol, whereas in patients with the b protocol, deterioration was observed, especially at the stages of subcompensation and decompensation. In patients receiving basic treatment, the Child-Pugh and MELD scores deteriorated, indicating further disease progression and, consequently, a worsening of the mortality prognosis. Within 3 months from the beginning of treatment, 3 people died in group ICb and 2 people – in group IICb due to deterioration of patients' condition and the development of complications (in 2 patients of group IICb and 1 patient of group ISb liver failure was developed, 1 patient of group ICb group had mesenteric thrombosis, 1 patient of group IICb had bleeding from varicose veins).

In patients of groups I and II, who received the h protocol, at the stage of compensation, subcompensation and decompensation, the indicators of SCE, LII, hs-CRP, TNFα, ADMA and the resistin level significantly improved ($p<0.05$). In patients of groups I and II who received basic treatment, at the stage of compensation such indicators worsened, but no significant difference was observed before and after treatment ($p>0.05$). At the stage of subcompensation and decompensation in patients of groups I and II, who received basic treatment, SCE, LII, hs-CRP, TNFα, ADMA and the resistin level significantly worsened ($p<0.05$).

Significant deterioration in SCE, LII, hs-CRP, TNFα, ADMA and resistin levels in patients receiving basic treatment was accompanied by a deterioration in their condition and increased the risk of 3-month mortality.

In this study, to assess the effectiveness of a three-month treatment regimen with ademethionine and arginine glutamate in patients with ALC in combination with obesity, the indicators of SCE, LII, hs-CRP, TNFα, ADMA and resistine levels were used. Obese patients with ALC have a more severe course of the disease, accompanied by more pronounced clinical and laboratory manifestations. Increased SCE, LII, hs-CRP, TNFα, ADMA and resistin levels in all patients were revealed. In group I, such indicators significantly exceeded those in group II, according to the Child-Pugh class ($p<0.05$).

The inclusion of ademethionine and arginine glutamate in the treatment regimen for 3 months allowed to improve the general condition of patients, clinical and laboratory parameters and reduce the rate of disease progression, which is reflected in improved parameters of endogenous intoxication, immune-inflammatory response, endothelial dysfunction, reduction of the indicators of the Child-Pugh severity score and 3-month mortality MELD score.

Conclusions

1. Analyzing the results of the study, it has been found that with increasing ALC decompensation the degree of endogenous intoxication increases, which is accompanied by the development of immune-inflammatory response and endothelial dysfunction, as evidenced by elevated levels of SCE, LII, hs-CRP, TNFα, ADMA and resistin.

Table 1

Dynamics of endogenous intoxication, immune-inflammatory syndrome, endothelial dysfunction, disease severity indices and MELD score in patients with alcoholic cirrhosis with Child-Pugh stage A depending on the combination with obesity

Values	Control, n=20	ALC with obesity				ALC			
		IAb, n=19		IAh, n=21		IIAb, n=22		IIAh, n=17	
		Before treatment	After 3 month treatment	Before treatment	After 3 month treatment	Before treatment	After 3 month treatment	Before treatment	After 3 month treatment
SCE, %	27,32±1,56	45,96±0,67*	47,12±0,87*#	46,14±0,52*•	32,71±0,74*	38,26±0,76	39,76±0,87#	38,±0,82•	28,81±0,69
LII	0,59±0,16	1,82±0,07*	1,96±0,11*#	1,85±0,06*•	0,95±0,09*	1,54±0,08	1,64±0,06#	1,53±0,07•	0,74±0,05
hs-CCRP, mg/l	0,65±0,02	5,82±0,22*	6,15±0,19*#	5,85±0,15*•	1,69±0,09*	3,69±0,11	3,84±0,08#	3,72±0,13•	1,42±0,11
TNFα, pg/ml	17,38±1,15	61,43±2,52*	64,89±1,22*#	61,46±2,31*•	27,63±1,36*	41,23±1,54	43,61±1,42#	41,69±1,38•	23,34±1,29
Resistin, ng/ml	3,72±0,26	11.12±0.64*	12.24±0.75*#	11.21±0.44*•	6.11±0.17*	4.62±0.15	4.86±0.14#	4.69±0.19•	3.81±0.15
ADMA, mmol/l	0,46±0,01	3.46±0.09*	3.63±0.14*#	3.48±0.11*	2.17±0.08*	1.62±0.05	1.74±0.12#	1.65±0.07•	1.23±0.06
Child-Pugh score	-	5,76±0,11*	5,94±0,12*#	5,81±0,09*•	5,32±0,11	5,38±0,08	5,51±0,07#	5,39±0,09•	5,19±0,08
MELD score	-	13,64±0,92*	14,79±0,95*#	13,47±0,84*•	8,17±0,75	10,36±0,71	10,94±0,68#	10,54±0,86•	7,41±0,57

Notes:

*1) * – probability of difference of values between groups I and II ($p<0.05$);*

2) ● – probability of differences of values before and after treatment ($p<0.05$);

3) # –probability of differences of values between groups a and ah with treatment protocols ($p<0.05$).

Table 2

Dynamics of endogenous intoxication, immune-inflammatory syndrome, endothelial dysfunction, disease severity indices and MELD score in patients with alcoholic cirrhosis with Child-Pugh stage B depending on the combination with obesity

Values	Control, n=20	ALC with obesity				ALC			
		IBb, n=20		IBh, n=19		IIBb, n=18		IIBh, n=18	
		Before treatment	After 3 month treatment	Before treatment	After 3 month treatment	Before treatment	After 3 month treatment	Before treatment	After 3 month treatment
SCE, %	27,32±1,56	68,32±0,87*•	76,36±0,92*#	68,51±0,84*•	38,31±0,79	57,14±0,58•	69,71±0,84#	57,22±0,65•	36,97±0,72
LII	0,59±0,16	2,23±0,09*•	2,51±0,07*#	2,26±0,07*•	1,73±0,11	1,93±0,15•	2,23±0,07#	1,92±0,11•	1,65±0,09
hs-CCRP, mg/l	0,65±0,02	10,53±0,63*•	13,27±0,72*#	10,56±0,71*•	7,08±0,19	7,21±0,21•	8,26±0,25#	7,25±0,16•	6,94±0,11
TNFα, pg/ml	17,38±1,15	84,63±3,51*•	95,27±2,85*#	85,27±3,48*•	60,02±3,13	58,16±2,43•	67,51±1,88#	58,98±1,45•	55,62±1,43
Resistin, ng/ml	3,72±0,26	13,57±0,74*•	14,76±0,82*#	13,62±0,68*•	7,15±0,51	7,63±0,17•	8,21±0,19#	7,65±0,21•	6,95±0,34
ADMA, mmol/l	0,46±0,01	4,31±0,09*•	5,43±0,09*#	4,35±0,11*•	1,96±0,08	2,23 ± 0,06•	2,46±0,09#	2,27 ± 0,08•	1,84±0,07
Child-Pugh score	-	8,73±0,19*•	9,17±0,15*#	8,82±0,12*•	5,47±0,14	7,69±0,17•	8,08±0,16#	7,81±0,11•	5,24±0,13
MELDscore	-	19,74±0,72*•	21,86±1,15*#	19,95±1,12*•	8,65±0,43	16,76±1,16•	19,64±1,27#	16,98±1,20•	7,92±0,56

Notes:

*1) * – probability of difference of values between groups I and II ($p<0.05$);*

2) ● – probability of differences of values before and after treatment ($p<0.05$);

3) # –probability of differences of values between groups a and ah with treatment protocols ($p<0.05$).

Table 3

Dynamics of endogenous intoxication, immune-inflammatory syndrome, endothelial dysfunction, disease severity indices and MELD score in patients with alcoholic cirrhosis with Child-Pugh stage C depending on the combination with obesity

Values	Control, n=20	ALC with obesity				ALC			
		ICb		ICh		IICb		IICh	
		Before treatment, n=15	After 3 month treatment, n=12	Before treatment, n=15	After 3 month treatment, n=15	Before treatment, n=16	After 3 month treatment, n=14	Before treatment, n=15	After 3 month treatment, n=15
SCE, %	27,32±1,56	94,73±0,78*•	112,56±0,51*#	95,01±0,81*•	61,39±0,67	85,11±0,74•	93,44±0,63#	85,23±0,67•	52,46±0,81
LII	0,59±0,16	2,73±0,08*•	2,95±0,09*#	2,94±0,06*•	2,43±0,08	2,55±0,06•	2,71±0,09#	2,58±0,07•	2,29±0,09
hs-CCRP, mg/l	0,65±0,02	14,76±0,53*•	16,26±0,75*#	15,71±0,67*•	10,32±0,83	11,04±0,61•	14,16±0,83#	11,12±0,79•	9,18±0,43
TNFα, pg/ml	17,38±1,15	98,63±5,67*•	115,81±6,05*#	99,45±4,93*•	84,22±3,48	70,21±3,14•	104,36±4,56#	71,16±2,87•	79,13±2,32
Resistin, ng/ml	3,72±0,26	15,87±0,74*•	18,85±0,96*#	15,89±0,81*•	10,08±0,88	9,48±0,22•	16,07±0,59#	9,51±0,18•	9,11±0,15
ADMA, mmol/l	0,46±0,01	5,08±0,11*•	5,31±0,08*#	5,13±0,07*•	3,52±0,09	3,51±0,06•	3,65±0,05#	3,56±0,08•	3,38±0,07
Child-Pugh score	-	13,98±0,61*•	15,38±0,52*#	14,21±0,64*•	7,84±0,41	12,52±0,67•	13,97±0,65#	12,81±0,53•	7,44±0,38
MELD score	-	27,43±1,19*•	30,13±1,21*#	28,13±1,23*•	17,52±1,15	23,65±1,02•	25,43±1,26#	23,71±1,11•	16,83±1,18

Notes:

*1) * – probability of difference of values between groups I and II (p<0.05);*

2) ● – probability of differences of values before and after treatment (p<0.05);

3) # –probability of differences of values between groups a and ah with treatment protocols (p<0.05).

2. Significantly higher levels of SCE, LII, hs-CRP, TNFα, ADMA and resistin were revealed in obese patients with ALC, which is accompanied by a more severe course of the disease.

3. Inclusion in the complex treatment of ademethionine and arginine glutamate for obese patients with ALC helps to reduce the manifestations of endogenous intoxication, immune-inflammatory reaction and endothelial dysfunction.

4. In patients with ALC in combination with obesity, the inclusion in the complex treatment of ademethionine and arginine glutamate helps to improve the course of the disease according to the Child-Pugh severity score and the MELD score.

Perspectives of the research

Studying of the efficacy of other hepatoprotectors in patients, who suffer from the liver alcohol cirrhosis combined with obesity.

Список літератури

1. Allen AM, Kim WR. Epidemiology and Healthcare Burden of Acute-on-Chronic Liver Failure. Sem Liv Dis. 2016;36(2):123–6. doi: 10.1055/s-0036-1583201
2. Aller R, Burgueño Gomez B, Sigüenza R, Fernández-Rodríguez C, Fernández N, Antolín B, et al. Comparative study of overweight and obese patients with nonalcoholic fatty liver disease. Rev Esp Enferm Dig. 2019;111(4):256-63. doi: 10.17235/reed.2019.5926/2018
3. Ayeser T, Basak M, Arslan K, Sayan I. Investigating the correlation of the number of diagnostic criteria to serum adiponectin, leptin, resistin, TNF-alpha, EGFR levels and abdominal adipose tissue. Diabetes Metab Syndr. 2016;10(2 Suppl 1):S165–9. doi: 10.1016/j.dsx.2016.03.010
4. Bedossa P. Pathology of non-alcoholic fatty liver disease. Liver Int. 2017;37(Suppl 1):85–9. doi: https://doi.org/10.1111/liv.13301
5. Bekaert M, Verhelst X, Geerts A, Lapauw B, Calders P. Association of recently described adipokines with liver histology in biopsy-proven non-alcoholic fatty liver disease: a systematic review. Obes Rev. 2016;17(1):68–80. doi: 10.1111/obr.12333
6. Boutari C, Perakakis N, Mantzoros CS. Association of Adipokines with Development and Progression of Nonalcoholic Fatty Liver Disease. Endocrinol Metab (Seoul). 2018;33(1):33–43. doi: 10.3803/EnM.2018.33.1.33
7. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–1402. doi: https://doi.org/10.1016/j.jhep.2015.11.004
8. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism. 2016;65(8):1017–25. doi: https://doi.org/10.1016/j.metabol.2016.01.012
9. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51(7):629–650. doi: 10.1007/s00535-016-1216-y
10. Garbuzenko DV, Arefyev NO, Kazachkov EL. Antiangiogenic therapy for portal hypertension in liver cirrhosis: Current progress and perspectives. World J Gastroenterol. 2018;24(33):3738–48. doi: 10.3748/wjg.v24.i33.3738
11. Hadizadeh F, Faghihimani E, Adibi P. Nonalcoholic fatty liver disease: diagnostic biomarkers. World J Gastrointest Pathophysiol. 2017;8(2):11–26. doi: 10.4291/wjgp.v8.i2.11
12. Kim D, Kim WR. Nonobese fatty liver disease. Clin Gastroenterol Hepatol. 2017;15(4):474–85. doi: https://doi.org/10.1016/j.cgh.2016.08.028
13. Musso G, Cassader M, De Michieli F, Paschetta E, Pinach S, Gambino R, et al. MERTK rs4374383 variant predicts incident nonalcoholic fatty liver disease and diabetes: role of mononuclear cell activation and adipokine response to dietary fat. Hum Mol Genet. 2017;26(9):1747–58. doi: 10.1093/hmg/ddw400
14. Panera N, Corte CD, Crudele A, Stronati L, Nobili V, Alisi A. Recent advances in understanding the role of adipocytokines during non-alcoholic fatty liver disease pathogenesis and their link with hepatokines. Expert Rev Gastroenterol Hepatol. 2016;10(3):393-403. doi: 10.1586/17474124.2016.1110485
15. Shen C, Zhao CY, Wang W, Wang YD, Sun H, Cao W, et al. The relationship between hepatic resistin overexpression and inflammation in patients with nonalcoholic steatohepatitis. BMC Gastroenterology [Internet]. 2014[cited 2020 Oct 26];14:39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942781/pdf/1471-230X-14-39.pdf doi: 10.1186/1471-230X-14-39
16. Su CM, Huang CY, Tang CH. Characteristics of resistin in rheumatoid arthritis angiogenesis. Biomark Med. 2016;10(6):651–60. doi: 10.2217/bmm.15.125
17. Tanaka N, Masuoka S, Kusunoki N, Nanki T, Kawai S. Serum Resistin Level and Progression of Atherosclerosis during Glucocorticoid Therapy for Systemic Autoimmune Diseases. Metabolites [Internet]. 2016[cited 2020 Oct 26];6(3):28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5041127/pdf/metabolites-06-00028.pdf doi: 10.3390/metabo6030028
18. Zhang Q, Wang Y, Liu Y, Yang Q, Wang X, Wang Q, et al. Effects of telmisartan on resistin expression in a rat model of nonalcoholic steatohepatitis and insulin resistance. Zhonghua Gan Zang Bing Za Zhi. 2015;23(4):281–5. doi: 10.3760/cma.j.issn.1007-3418.2015.04.010

References

1. Allen AM, Kim WR. Epidemiology and Healthcare Burden of Acute-on-Chronic Liver Failure. Sem Liv Dis. 2016;36(2):123–6. doi: 10.1055/s-0036-1583201
2. Aller R, Burgueño Gomez B, Sigüenza R, Fernández-Rodríguez C, Fernández N, Antolín B, et al. Comparative study of overweight and obese patients with nonalcoholic fatty liver disease. Rev Esp Enferm Dig. 2019;111(4):256-63. doi: 10.17235/reed.2019.5926/2018
3. Ayeser T, Basak M, Arslan K, Sayan I. Investigating the correlation of the number of diagnostic criteria to serum adiponectin, leptin, resistin, TNF-alpha, EGFR levels and abdominal adipose tissue. Diabetes Metab Syndr. 2016;10(2 Suppl 1):S165–9. doi: 10.1016/j.dsx.2016.03.010
4. Bedossa P. Pathology of non-alcoholic fatty liver disease. Liver Int. 2017;37(Suppl 1):85–9. doi: https://doi.org/10.1111/liv.13301
5. Bekaert M, Verhelst X, Geerts A, Lapauw B, Calders P. Association of recently described adipokines with liver histology in biopsy-proven non-alcoholic fatty liver disease: a systematic review. Obes Rev. 2016;17(1):68–80. doi: 10.1111/obr.12333
6. Boutari C, Perakakis N, Mantzoros CS. Association of Adipokines with Development and Progression of Nonalcoholic Fatty Liver Disease. Endocrinol Metab (Seoul). 2018;33(1):33–43. doi: 10.3803/EnM.2018.33.1.33
7. European Association for the Study of the Liver (EASL),

European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–1402. doi: https://doi.org/10.1016/j.jhep.2015.11.004

8. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism. 2016;65(8):1017–25. doi: https://doi.org/10.1016/j.metabol.2016.01.012

9. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol. 2016;51(7):629–650. doi: 10.1007/s00535-016-1216-y

10. Garbuzenko DV, Arefyev NO, Kazachkov EL. Antiangiogenic therapy for portal hypertension in liver cirrhosis: Current progress and perspectives. World J Gastroenterol. 2018;24(33):3738–48. doi: 10.3748/wjg.v24.i33.3738

11. Hadizadeh F, Faghihimani E, Adibi P. Nonalcoholic fatty liver disease: diagnostic biomarkers. World J Gastrointest Pathophysiol. 2017;8(2):11–26. doi: 10.4291/wjgp.v8.i2.11

12. Kim D, Kim WR. Nonobese fatty liver disease. Clin Gastroenterol Hepatol. 2017;15(4):474–85. doi: https://doi.org/10.1016/j.cgh.2016.08.028

13. Musso G, Cassader M, De Michieli F, Paschetta E, Pinach S, Gambino R, et al. MERTK rs4374383 variant predicts incident nonalcoholic fatty liver disease and diabetes: role of mononuclear cell activation and adipokine response to dietary fat. Hum Mol Genet. 2017;26(9):1747–58. doi: 10.1093/hmg/ddw400

14. Panera N, Corte CD, Crudele A, Stronati L, Nobili V, Alisi A. Recent advances in understanding the role of adipocytokines during non-alcoholic fatty liver disease pathogenesis and their link with hepatokines. Expert Rev Gastroenterol Hepatol. 2016;10(3):393-403. doi: 10.1586/17474124.2016.1110485

15. Shen C, Zhao CY, Wang W, Wang YD, Sun H, Cao W, et al. The relationship between hepatic resistin overexpression and inflammation in patients with nonalcoholic steatohepatitis. BMC Gastroenterology [Internet]. 2014[cited 2020 Oct 26];14:39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942781/pdf/1471-230X-14-39.pdf doi: 10.1186/1471-230X-14-39

16. Su CM, Huang CY, Tang CH. Characteristics of resistin in rheumatoid arthritis angiogenesis. Biomark Med. 2016;10(6):651–60. doi: 10.2217/bmm.15.125

17. Tanaka N, Masuoka S, Kusunoki N, Nanki T, Kawai S. Serum Resistin Level and Progression of Atherosclerosis during Glucocorticoid Therapy for Systemic Autoimmune Diseases. Metabolites [Internet]. 2016[cited 2020 Oct 26];6(3):28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5041127/pdf/metabolites-06-00028.pdf doi: 10.3390/metabo6030028

18. Zhang Q, Wang Y, Liu Y, Yang Q, Wang X, Wang Q, et al. Effects of telmisartan on resistin expression in a rat model of nonalcoholic steatohepatitis and insulin resistance. Zhonghua Gan Zang Bing Za Zhi. 2015;23(4):281–5. doi: 10.3760/cma.j.issn.1007-3418.2015.04.010

Відомості про авторів:
Матковська Н. Р. – канд. мед. наук, доцент кафедри терапії і сімейної медицини післядипломної освіти, Івано-Франківський національний медичний університет, Івано-Франківськ, Україна.
ORCID iD: https://orcid.org/0000-0002-9924-2127

Сведения об авторах:
Матковская Н. Р. – канд. мед. наук, доцент кафедры терапии и семейной медицины последипломного образования, Ивано-Франковский национальный медицинский университет, Ивано-Франковск, Украина.

Information about authors:
Matkovska N. R. – MD, PhD, Associate Professor of the Department of Therapy and Family Practice of postgraduate study faculty, Ivano-Frankivsk National Medical

Стаття надійшла до редакції 13.08.2020
Рецензент – проф. Ткачук С.С.