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CARBOHYDRATE AND LIPID EXCHANGE CHANGES UNDER THE INFLUENCE OF TREATMENT OF PATIENTS WITH ALCOHOLIC LIVER CIRRHOSIS IN COMBINATION WITH OBESITY USING ADEMETHIONINE, ARGININE GLUTAMATE AND ROSUVASTATIN

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Abstract. In Ukraine, among the causes of death because of digestive tract diseases, alcoholic liver disease (ALD) has the second place. Due to the significant prevalence of obesity and the growing incidence of ALD, methods are being sought to prevent the progression of the pathological process in the liver, the occurrence of complications and to improve the quality of life of such patients.

The aim of the study: to examine the effect of complex treatment with ademethionine, arginine glutamate and rosuvastatin on changes in lipid and carbohydrate metabolism in patients with alcoholic liver cirrhosis (ALC) in combination with obesity.

Methods. The study included 156 patients diagnosed with ALC in combination with obesity, including 18 women and 138 men aged (45.3±8.9) years and a median duration of disease (5.1±2.8) years. Patients were divided into subgroups depending on the stage of Child-Pugh decompensation and depending on the applied treatment.

Results. At the stage of decompensation, lipid metabolism and leptin levels were low, which indicates the depletion of body fat depots as the disease progresses. It may be due to the progression of the liver dysfunction, as it is actively involved in regulating the formation, destruction and accumulation of fats. Changes in carbohydrate metabolism in patients with ALC in combination with obesity were characterized by a significant increase in IRI, HOMA-IR index and a decrease in the QUICKI index, indicating the presence of insulin resistance ($p<0.05$). In determining the adipocytokine values, it was found that in decompensated liver function, the leptin rates decreased and the levels of adiponectin increased. Higher leptin content in the stage of compensation and subcompensation is also associated with increased secretion of adipose tissue. At the stage of decompensation, fat depots are depleted, so leptin levels are reduced. This decrease is directly related to the Child-Pugh and MELD scores. Adiponectin levels were decreased in the stage of compensation and increased with the progression of the disease and correlated with disease severity and the MELD score. It is thought that an increased adiponectin level indicates the level of anti-inflammatory reaction in response to hepatocyte damage. Significant deterioration in carbohydrate metabolism, adiponectin and leptin in patients receiving basic treatment was accompanied by deterioration of their condition and increased the risk of 3-month mortality. After the course of treatment in patients of group receiving ademethionine, arginine, glutamate and rosuvastatin at the stage of compensation and subcompensation, the rates of lipid, carbohydrate metabolism, adiponectin and leptin significantly improved and differed from those in patients receiving basic treatment and combination of basic treatment, ademethionine and arginine glutamate ($p<0.05$). At the stage of decompensation in the scheme with the inclusion of rosuvastatin it was possible to normalize the levels of HDL cholesterol, VLDL cholesterol, atherogenic coefficient and leptin, reduce the levels of adiponectin, IRI, HOMA-IR, HbA1c and increase the QUICKI index, which was accompanied by a decrease in Child-Pugh severity score and 3 month mortality MELD score.

Conclusions. In patients with ALC in combination with obesity, the inclusion in the treatment of ademethionine, arginine glutamate and rosuvastatin helps to improve the course of the disease according to the lipid and carbohydrate metabolism, Child-Pugh and MELD scores.

Keywords: alcoholic liver disease; liver cirrhosis; obesity; adipocytokines; lipid metabolism.

Introduction. Mortality and life expectancy are influenced by factors such as hereditary factors, physiology, environmental conditions and behavioral factors. In particular, this applies to smoking, decreased physical activity, dietary factors, alcohol abuse. About 10% of deaths among young and middle-aged people are related to alcohol abuse. Alcohol consumption is the third leading cause of death among young people in Europe. In Ukraine, among the causes of death because of digestive tract diseases, alcoholic liver disease (ALD) has the second place [1, 2, 3, 4].

With the global increase in obesity, fatty degeneration of the liver is widespread throughout the world [5, 6, 7]. Liver damage has the following stages: steatosis

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(deposition of fat particles in liver cells), steatohepatitis (development of inflammation, balloon dystrophy of liver cells, accompanied by fibrogenesis). Progression of steatohepatitis is combined with fibrotic changes of varying degrees. Under adverse conditions, it progresses to liver cirrhosis, liver failure or hepatocellular carcinoma [8, 4]. This staging develops due to dysfunction of liver and stromal cells, inadequate signals from adipose tissue and gastrointestinal tract due to hepatocyte necrosis, secretion of adipose tissue biologically active substances and intestinal pathogens that promote inflammation and fibrogenesis through the activation of macrophages, which activate white blood cells and stellate cells with subsequent overproduction of extracellular matrix components [9, 10, 11].

Due to lipolysis, activation of fat synthesis in the liver and excessive consumption of high-calorie and fatty foods, the accumulation of lipids in the liver increases, that is accompanied by a decrease in insulin sensitivity. Due to this, there is an abnormal synthesis of adipokines, which affect metabolic processes, in particular disorders of lipid and carbohydrate metabolism, and the formation of oxidative stress [12, 13].

Due to the significant prevalence of obesity and the growing incidence of ALD, methods are being sought to prevent the progression of the pathological process in the liver, the occurrence of complications and to improve the quality of life of such patients [14, 15, 16].

The aim of the study: to examine the effect of complex treatment with ademethionine, arginine glutamate and rosuvastatin on changes in lipid and carbohydrate metabolism in patients with alcoholic liver cirrhosis (ALC) in combination with obesity.

Research methods. The study included 156 patients diagnosed with ALC in combination with obesity, including 18 women and 138 men aged (45.3±8.9) years and a median duration of disease (5.1±2.8) years. Patients were divided into subgroups depending on the stage of Child-Pugh decompensation: class A (n=57), class B (n=51), class C (n=48). Depending on the applied treatment, all patients were divided into groups: patients of group I (IA (n=22), IB (n=18) and IC (n=16)) received basic therapy; patients of group II (IIA (n=18), IIB (n=17) and IIC (n=16)) additionally received ademethionine and arginine glutamate; patients of group III (IIIA (n=17), IIIB (n=16) and IIIC (n=16)) additionally received ademethionine, arginine glutamate and rosuvastatin.

Groups IIA and IIIA, 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 IIB and IIIB, 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 IIC and IIIC, 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.

Groups IIIA and IIIB received additionally 20 mg of rosuvastatin orally per day for 12 weeks, and patients of group IIIC received an additional 10 mg of rosuvastatin orally per day for 12 weeks.

ALC was diagnosed in accordance with domestic and international clinical guidelines (Order of the Ministry of Health of Ukraine № 826 of 06.11.2014) "Unified clinical protocol of primary, secondary (specialized) medical care: non-alcoholic steatohepatitis", recommendations of the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO).

The study did not include patients with viral, toxic, autoimmune, metabolic liver cirrhosis, malignancies and those who did not consent to the study. The research followed the principles of ethics of scientific research and the Declaration of Helsinki.

The levels of total cholesterol (TC), lipoprotein cholesterol of high, low and very low density (HDLC, LDLC, VLDLC), atherogenic coefficient (AC), triacylglycerides (TG) were determined. The carbohydrate metabolism was evaluated for immunoreactive insulin (IRI) indicatros, glycosylated haemoglobin (HbA1c), HOMA-IR indexes (calculated using the formula HOMA-IR = (glycemia in the fasted state, mmol/l* insulin in the fasted state (mcU/ml))/22.5) and QUICKI (www.mdapp.co/insulin-sensitivity-quicki-calculator-324). The level of leptin and adiponectin was determined by immunoassay using Human Leptin ELISA (Biovendor, Czech Republic) and Human Adiponectin ELISA kit (Biovendor, Czech Republic) respectively.

In addition, the LC Child-Pugh severity score and the three-month MELD mortality score were determined. The control group included 20 healthy individuals. Assessment of patients was performed before and after 3 months from the beginning of treatment.

Statistical processing of the study results was performed using software 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. The reliability of the obtained data was evaluated by Student's t-test and correlation analysis was used.

Results and discussion. Changes in the biochemical parameters of the blood lipid spectrum in obese patients with ALC were manifested by increased blood levels of TC, LDL cholesterol, VLDL cholesterol, AC and TG at the stage of compensation and subcompensation compared with the control group. TC, LDL cholesterol, VLDL cholesterol, AC and TG in patients with the stages of compensation and decompensation significantly exceeded the indicators of the control group in 1.95 and 1.56, 1.62 and 1.33, 5.22 and 3.84, 4.61 and 3.28, 2.52 and 2.06 times, respectively ($p<0.05$). Lower values of TC, LDL cholesterol, VLDL cholesterol, AC and TG in patients with stages B and C according to Child-Pugh indicate more pronounced liver dysfunction in them. The content of HDL cholesterol in the blood decreased with increasing decompensation (Tables 1-3).

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Table 1

Dynamics of lipid and carbohydrate metabolism under the influence of complex treatment with ademethionine, arginine glutamate and rosuvastatin in patients with alcoholic liver cirrhosis in combination with obesity with stage A according to the Child-Pugh score, M±m

Values	Control, n=20	IA		IIA		IIIA	
		Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment
TC, mmol/l	3.49±0.31	6.78±0.21$^{\Delta}$	7.31±0.24$^{\Delta\blacklozenge}$	6.81±0.19$^{\Delta}$	6.53±0.22$^{\Delta}$*	6.82±0.16$^{\Delta}$	5.18±0.14$^{\Delta\bullet\#\blacklozenge}$
HDLC, mmol/l	1.43±0.09	1.14±0.08$^{\Delta}$	0.95±0.07$^{\Delta\blacklozenge}$	1.14±0.06$^{\Delta}$	1.16±0.05$^{\Delta}$*	1.13±0.06$^{\Delta}$	1.27±0.05$^{\Delta\bullet\#\blacklozenge}$
LDLC, mmol/l	2.82±0.17	4.58±0.13$^{\Delta}$	4.86±0.11$^{\Delta\blacklozenge}$	4.56±0.15$^{\Delta}$	4.29±0.14$^{\Delta}$*	4.59±0.15$^{\Delta}$	3.54±0.19$^{\Delta\bullet\#\blacklozenge}$
VLDLC, mmol/l	0.32±0.01	1.66±0.04$^{\Delta}$	1.79±0.05$^{\Delta\blacklozenge}$	1.67±0.06$^{\Delta}$	1.58±0.06$^{\Delta}$*	1.69±0.05$^{\Delta}$	1.26±0.07$^{\Delta\bullet\#\blacklozenge}$
AC	1.45±0.11	4.95±0.08$^{\Delta}$	6.69±0.07$^{\Delta\blacklozenge}$	4.97±0.09$^{\Delta}$	4.87±0.06$^{\Delta}$*	5.03±0.08$^{\Delta}$	3.08±0.05$^{\Delta\bullet\#\blacklozenge}$
TG, mmol/l	1.13±0.06	2.84±0.07$^{\Delta}$	3.14±0.08$^{\Delta\blacklozenge}$	2.87±0.07$^{\Delta}$	2.98±0.06$^{\Delta}$*	2.88±0.08$^{\Delta}$	2.67±0.09$^{\Delta\bullet\#\blacklozenge}$
Leptin ng/ml	7.92±0.28	21.69±0.55$^{\Delta}$	22.94±0.67$^{\Delta\blacklozenge}$	21.72±0.63$^{\Delta}$	12.43±0.61$^{\Delta\blacklozenge}$*	21.75±0.67$^{\Delta}$	11.03±0.69$^{\Delta\bullet\#\blacklozenge}$
Adiponectin µg/ml	8.46±0.11	2.86±0.11$^{\Delta}$	2.62±0.09$^{\Delta\blacklozenge}$	2.89±0.14$^{\Delta}$	5.62±0.13$^{\Delta\blacklozenge}$*	2.87±0.15$^{\Delta}$	6.28±0.16$^{\Delta\bullet\#\blacklozenge}$
IRI, mcod/l	5.89±0.32	23.48±1.25$^{\Delta}$	26.35±1.29$^{\Delta\blacklozenge}$	23.57±1.32$^{\Delta}$	6.48±0.21$^{\Delta\blacklozenge}$*	23.55±1.23$^{\Delta}$	5.98±0.27$^{\bullet\#\blacklozenge}$
HOMA-IR	1.05±0.06	5.37±0.09$^{\Delta}$	5.69±0.16$^{\Delta\blacklozenge}$	5.41±0.14$^{\Delta}$	1.17±0.04$^{\Delta\blacklozenge}$*	5.43±0.17$^{\Delta}$	1.07±0.04$^{\bullet\#\blacklozenge}$
QUICKI	0.681±0.004	0.375±0.005$^{\Delta}$	0.364±0.004$^{\Delta\blacklozenge}$	0.371±0.007$^{\Delta}$	0.663±0.005$^{\Delta\blacklozenge}$*	0.372±0.006$^{\Delta}$	0.675±0.008$^{\bullet\#\blacklozenge}$
HbA1c, %	4.63±0.18	6.31±0.12$^{\Delta}$	6.71±0.14$^{\Delta\blacklozenge}$	6.35±0.15$^{\Delta}$	4.91±0.07$^{\Delta\blacklozenge}$*	6.34±0.13$^{\Delta}$	4.74±0.08$^{\bullet\#\blacklozenge}$
Child-Pugh score	-	5.75±0.11	6.24±0.16$^{\blacklozenge}$	5.79±0.14	5.35±0.12$^{\blacklozenge}$*	5.82±0.16$^{\Delta}$	5.09±0.08$^{\bullet\#\blacklozenge}$
MELD score	-	13.59±0.76	15.21±0.81$^{\blacklozenge}$	13.48±0.87	8.79±0.21$^{\blacklozenge}$*	13.65±0.81$^{\Delta}$	6.79±0.34$^{\bullet\#\blacklozenge}$

Notes: 1) Δ – the probability of differences in values compared with the control group ($p<0.05$); 2) * – the probability of differences in values between groups I and II ($p<0.05$); 3) • – the probability of differences in values between groups I and III ($p<0.05$); 4) # – the probability of differences in values between groups II and III ($p<0.05$); 5) ♦ – the probability of differences in values before and after treatment ($p<0.05$)

Table 2

Dynamics of lipid and carbohydrate metabolism under the influence of complex treatment with ademethionine, arginine glutamate and rosuvastatin in patients with alcoholic liver cirrhosis in combination with obesity with stage B according to the Child-Pugh score, M±m

Values	Control, n=20	IB		IIB		IIIB	
		Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment
TC, mmol/l	3.49±0.31	5.44±0.29$^{\Delta}$	4.59±0.18$^{\Delta\blacklozenge}$	5.42±0.31$^{\Delta}$	4.16±0.22$^{\Delta\blacklozenge}$*	5.39±0.27$^{\Delta}$	3.73±0.24$^{\bullet\#\blacklozenge}$
HDLC, mmol/l	1.43±0.09	0.95±0.06$^{\Delta}$	0.79±0.04$^{\Delta\blacklozenge}$	0.94±0.05$^{\Delta}$	1.20±0.05$^{\Delta\blacklozenge}$*	0.93±0.06$^{\Delta}$	1.34±0.07$^{\bullet\#\blacklozenge}$
LDLC,mmol/l	2.82±0.17	3.74±0.14$^{\Delta}$	3.42±0.09$^{\Delta\blacklozenge}$	3.76±0.11$^{\Delta}$	3.24±0.06$^{\Delta\blacklozenge}$*	3.73±0.12$^{\Delta}$	3.06±0.07$^{\Delta\bullet\#\blacklozenge}$
VLDLC,mmol/l	0.32±0.01	1.26±0.04$^{\Delta}$	1.18±0.02$^{\Delta\blacklozenge}$	1.18±0.03$^{\Delta}$	0.84±0.01$^{\Delta\blacklozenge}$*	1.23±0.05$^{\Delta}$	0.35±0.03$^{\bullet\#\blacklozenge}$
AC	1.45±0.11	4.74±0.09$^{\Delta}$	3.21±0.04$^{\Delta\blacklozenge}$	4.76±0.07$^{\Delta}$	2.47±0.05$^{\Delta\blacklozenge}$*	4.80±0.07$^{\Delta}$	1.78±0.06$^{\Delta\bullet\#\blacklozenge}$
TG, mmol/l	1.13±0.06	2.31±0.07$^{\Delta}$	2.12±0.07$^{\Delta\blacklozenge}$	2.36±0.06$^{\Delta}$	1.87±0.08$^{\Delta\blacklozenge}$*	2.34±0.04$^{\Delta}$	1.65±0.05$^{\Delta\bullet\#\blacklozenge}$
Leptin ng/ml	7.92±0.28	15.43±0.76$^{\Delta}$	18.74±0.83$^{\Delta\blacklozenge}$	15.47±0.81$^{\Delta}$	10.32±0.92$^{\Delta\blacklozenge}$*	15.53±0.64$^{\Delta}$	8.86±0.38$^{\bullet\#\blacklozenge}$
Adiponectin µg/ml	8.46±0.11	3.31±0.07$^{\Delta}$	2.98±0.08$^{\Delta\blacklozenge}$	3.26±0.06$^{\Delta}$	5.42±0.09$^{\Delta\blacklozenge}$*	3.24±0.07$^{\Delta}$	6.12±0.08$^{\Delta\bullet\#\blacklozenge}$
IRI, mcod/l	5.89±0.32	28.62±1.18$^{\Delta}$	35.28±1.12$^{\Delta\blacklozenge}$	32.38±1.21$^{\Delta}$	17.14±1.14$^{\Delta\blacklozenge}$*	30.19±1.17$^{\Delta}$	13.61±1.07$^{\Delta\bullet\#\blacklozenge}$
HOMA-IR	1.05±0.06	7.11±0.19$^{\Delta}$	7.65±0.23$^{\Delta\blacklozenge}$	7.13±0.17$^{\Delta}$	3.06±0.14$^{\Delta\blacklozenge}$*	7.16±0.15$^{\Delta}$	2.11±0.18$^{\Delta\bullet\#\blacklozenge}$
QUICKI	0.681±0.004	0.349±0.005$^{\Delta}$	0.338±0.004$^{\Delta\blacklozenge}$	0.347±0.003$^{\Delta}$	0.524±0.006$^{\Delta\blacklozenge}$*	0.348±0.004$^{\Delta}$	0.571±0.006$^{\Delta\bullet\#\blacklozenge}$
HbA1c, %	4.63±0.18	6.36±0.15$^{\Delta}$	6.83±0.12$^{\Delta\blacklozenge}$	6.42±0.17$^{\Delta}$	5.73±0.11$^{\Delta\blacklozenge}$*	6.38±0.14$^{\Delta}$	5.41±0.15$^{\Delta\bullet\#\blacklozenge}$
Child-Pugh score	-	8.72±0.18	12.68±0.14$^{\blacklozenge}$	8.75±0.16	6.83±0.12$^{\blacklozenge}$*	8.83±0.19	5.81±0.15$^{\bullet\#\blacklozenge}$
MELD score	-	19.76±0.83	25.12±0.72$^{\blacklozenge}$	19.83±0.95	13.64±0.79$^{\blacklozenge}$*	19.91±0.38	9.43±0.64$^{\bullet\#\blacklozenge}$

Notes: 1) Δ – the probability of differences in values compared with the control group ($p<0.05$); 2) * – the probability of differences in values between groups I and II ($p<0.05$); 3) • – the probability of differences in values between groups I and III ($p<0.05$); 4) # – the probability of differences in values between groups II and III ($p<0.05$); 5) ♦ – the probability of differences in values before and after treatment ($p<0.05$).

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Table 3

Dynamics of lipid and carbohydrate metabolism under the influence of complex treatment with ademethionine, arginine glutamate and rosuvastatin in patients with alcoholic liver cirrhosis in combination with obesity with stage C according to the Child-Pugh score, M±m

Values	Control, n=20	IC		IIC		IIIC	
		Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment
TC, mmol/l	3.49±0.31	3.27±0.13	3.18±0.09	3.21±0.17	2.91±0.08$^{\Delta\blacklozenge*}$	3.24±0.11	2.79±0.09$^{\Delta\bullet\blacklozenge}$
HDLC, mmol/l	1.43±0.09	0.63±0.04$^{\Delta}$	0.54±0.02$^{\Delta\blacklozenge}$	0.67±0.03$^{\Delta}$	1.12±0.05$^{\Delta\blacklozenge*}$	0.65±0.02$^{\Delta}$	1.20±0.05$^{\Delta\bullet\#\blacklozenge}$
LDLC, mmol/l	2.82±0.17	2.85±0.09	2.76±0.08	2.87±0.08	2.58±0.07$^{\Delta\blacklozenge*}$	2.86±0.07$^{\Delta}$	2.53±0.05$^{\Delta\bullet\blacklozenge}$
VLDLC, mmol/l	0.32±0.01	0.44±0.03$^{\Delta}$	0.25±0.02$^{\Delta\blacklozenge}$	0.39±0.01$^{\Delta}$	0.33±0.01$^{\blacklozenge*}$	0.41±0.02$^{\Delta}$	0.31±0.02$^{\bullet\blacklozenge}$
AC	1.45±0.11	4.19±0.07$^{\Delta}$	4.89±0.12$^{\Delta\blacklozenge}$	3.79±0.09$^{\Delta}$	1.60±0.07$^{\blacklozenge*}$	3.98±0.06$^{\Delta}$	1.33±0.05$^{\bullet\#\blacklozenge}$
TG, mmol/l	1.13±0.06	1.75±0.07$^{\Delta}$	1.58±0.06$^{\Delta\blacklozenge}$	1.82±0.08$^{\Delta}$	1.42±0.07$^{\Delta\blacklozenge*}$	1.77±0.09$^{\Delta}$	1.27±0.05$^{\Delta\bullet\#\blacklozenge}$
Leptin ng/ml	7.92±0.28	6.71±0.28$^{\Delta}$	5.25±0.18$^{\Delta\blacklozenge}$	6.69±0.24$^{\Delta}$	7.22±0.18$^{\Delta\blacklozenge*}$	6.74±0.29$^{\Delta}$	7.65±0.21$^{\bullet\#\blacklozenge}$
Adiponectin µg/ml	8.46±0.11	15.76±0.93$^{\Delta}$	18.26±0.81$^{\Delta\blacklozenge}$	15.91±0.86$^{\Delta}$	12.76±0.75$^{\Delta\blacklozenge*}$	15.87±0.98$^{\Delta}$	10.43±0.94$^{\Delta\bullet\#\blacklozenge}$
IRI, mcod/l	5.89±0.32	26.56±1.67$^{\Delta}$	28.35±1.59$^{\Delta}$	26.75±1.71$^{\Delta}$	19.42±1.24$^{\Delta\blacklozenge*}$	26.83±1.52$^{\Delta}$	13.75±1.19$^{\Delta\bullet\#\blacklozenge}$
HOMA-IR	1.05±0.06	7.06±0.15$^{\Delta}$	7.44±0.13$^{\Delta\blacklozenge}$	7.09±0.17$^{\Delta}$	4.22±0.12$^{\Delta\blacklozenge*}$	7.12±0.13$^{\Delta}$	3.32±0.15$^{\Delta\bullet\#\blacklozenge}$
QUICKI	0.681±0.004	0.351±0.003$^{\Delta}$	0.345±0.004$^{\Delta}$	0.349±0.001$^{\Delta}$	0.531±0.005$^{\Delta\blacklozenge*}$	0.348±0.002$^{\Delta}$	0.594±0.005$^{\Delta\bullet\#\blacklozenge}$
HbA1c, %	4.63±0.18	5.87±0.19$^{\Delta}$	6.14±0.12$^{\Delta\blacklozenge}$	5.94±0.21$^{\Delta}$	5.34±0.09$^{\Delta\blacklozenge*}$	5.91±0.22$^{\Delta}$	5.12±0.16$^{\Delta\bullet\#\blacklozenge}$
Child-Pugh score	-	14.13±0.72	15.94±0.82$^{\blacklozenge}$	14.22±0.65	7.92±0.46$^{\blacklozenge*}$	14.4±0.89	6.72±0.34$^{\bullet\#\blacklozenge}$
MELD score	-	27.56±1.22	30.06±1.37$^{\blacklozenge}$	27.89±1.28	17.42±0.84$^{\blacklozenge*}$	28.07±1.14	12.49±0.95

Notes: 1) Δ – the probability of differences in values compared with the control group ($p<0.05$); 2) * – the probability of differences in values between groups I and II ($p<0.05$); 3) • – the probability of differences in values between groups I and III ($p<0.05$); 4) # – the probability of differences in values between groups II and III ($p<0.05$); 5) ♦ – the probability of differences in values before and after treatment ($p<0.05$).

Such changes in the lipid spectrum are associated with an increase in liver function disorders and correlate with the prognostic MELD criteria. The most obvious association was found in patients of group II of the class C: TC – r =-0.72, LDLC – r=-0.54, VLDLC –r=-0.63, AC – r=-0.67, TG – r=-0.56, HDLC – r=-0.69.

The characteristic features of carbohydrate metabolism were a significant increase in IRI, HOMA-IR index, QUICKI index and HbA1c in patients of all classes according to the Child-Pugh score ($p<0.05$). Thus, the values of IRI, HOMA-IR index and HbA1c in patients with stages A, B, C significantly exceeded those of the control group in 4.25, 5.13 and 1.37; 5.09, 6.78 and 1.38; 4.55, 6.74 and 1.27 times, respectively ($p<0.05$). The QUICKI index was lower compared to the control group in patients of classes A, B and C in 1.83, 1.96 and 1.95 times, respectively ($p<0.05$). The content of leptin in the blood decreased with increasing decompensation. In patients of classes A and B, it exceeded this indicator in the control group by 2.72, 1.94 times, respectively ($p<0.05$). In patients with the stage of decompensation, it was 1.18 times lower compared to the control group ($p<0.05$). The level of adiponectin in patients of classes A and B was lower compared to the control group by 2.95 and 2.59 times, respectively ($p<0.05$). In patients with the stage of decompensation, it was 1.87 times higher compared with the control group ($p<0.05$).

Changes in leptin and adiponectin levels in patients with ALC 1 in combination with obesity are associated with disorders of lipid metabolism and carbohydrate metabolism. Positive correlations were revealed between leptin level and TC (r=+0.84, r=+0.79 and r=+0.67 for stage of compensation, subcompensation and decompensation respectively), between leptin level and HDLC (r=+0.71, r=+0.56 and r=+0.48 for stage of compensation, subcompensation and decompensation respectively), between leptin level and LDLC (r=+0.47, r=+0.42 and r=+0.39 for stage of compensation, subcompensation and decompensation respectively); between leptin level and VLDLC (r=+0.52, r=+0.38 and r=+0.33 for stage of compensation, subcompensation and decompensation respectively); between leptin level and for AC (r=+0.73, r=+0.64 and r=+0.53 for stage of compensation, subcompensation and decompensation respectively); between leptin level and TG (r=+0.76, r=+0.62 and r=+0.59 for stage of compensation, subcompensation and decompensation respectively), between leptin level and QUICKI (r=+0.63, r=+0.69 and r=+0.74 for stage of compensation, subcompensation and decompensation respectively). Negative correlations were revealed between leptin level and adiponectin (r=-0.72, r=-0.65 and r=-0.61 for stage of compensation, subcompensation and decompensation respectively), between leptin level and IRI (r=-0.69, r=-0.53 and r=-0.49 for stage of compensation, subcompensation and decompensation respectively); between leptin level and HOMA-IR (r=-0.54, r=-0.41 and r=-0.33 for stage of compensation, subcompensation and decompensation respectively), between leptin level

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and HbAlc (r=-0.35, r=-0.33 and r=-0.31 for stage of compensation, subcompensation and decompensation respectively).

Positive correlations were revealed between adiponectin level and IRI (r=0,45, r=0,38 and r=0,36 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and HOMA-IR (r=0.36, r=0.31 and r=0.27 for stage of compensation, subcompensation and decompensation, respectively), between adiponectin level and HbAlc (r=0.31, r=0.27 and r=0.25 for stage of compensation, subcompensation and decompensation respectively).

Negative correlations were revealed between adiponectin level and TC (r=-0.65, r=-0.58 and r=-0.48 for stage of compensation, subcompensation and decompensation, respectively), between adiponectin level and HDLC (r=-0.48, r=-0.51 and r=-0.36 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and LDLC (r=-0.47, r=-0.42 and r=-0.33 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and VLDLC (r=-0.24, r=-0.21 and r=-0.17 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and AC (r=-0.46, r=-0.39 and r=-0.37 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and TG (r=-0.38, r=-0.33 and r=-0.30 for stage of compensation, subcompensation and decompensation respectively), between adiponectin level and QUICKI (r=-0.42, r=-0.38 and r=-0.37 for stage of compensation, subcompensation and decompensation respectively).

A significant correlation with the increase in decompensation was observed between the levels of leptin and the Child-Pugh score (r=-0.72, r=-0.58 and r=-0,44 stage of compensation, subcompensation and decompensation respectively) and the MELD score (r=-0.66, r=-0.61, r=-0.68 for stage of compensation, subcompensation and decompensation respectively). A correlation was also found between the levels of adiponectin and the Child-Pugh index (r=0.69, r=-0.49 and r=0.67 stage of compensation, subcompensation and decompensation respectively) and the MELD score (r=0.73, r=0.52 and r=0.34 for stage of compensation, subcompensation and decompensation respectively).

After the course of treatment in patients of group III at the stage of compensation and subcompensation, the rates of lipid, carbohydrate metabolism, adiponectin and leptin significantly improved and differed from those in patients of groups I and II ($p<0.05$). At the stage of compensation, the carbohydrate metabolism rates, and at the stage of subcompensation, some rates of lipid metabolism (TC, HDL cholesterol, VLDL cholesterol) and leptin levels did not differ from such indicators in the control group ($p>0.05$). At the stage of decompression, LDL cholesterol, AC and leptin levels were low and did not differ from those in the control group ($p>0.05$). After the course of treatment, the rates of lipid metabolism, carbohydrate metabolism of adiponectin and leptin in patients of group III at stage C significantly improved ($p<0.05$).

In patients of group II at the stage of subcompensation after treatment, rates of lipid, carbohydrate metabolism, adiponectin and leptin significantly improved ($p<0.05$). In the compensation stage, the rates of carbohydrate metabolism, adiponectin and leptin significantly improved ($p<0.05$), and the rates of lipid metabolism also improved, but no significant difference was found after the course of treatment ($p>0.05$). In patients of group II at all stages of compensation there was a significant difference in lipid, carbohydrate metabolism, adiponectin and leptin compared with group I ($p<0.05$).

In patients of group I receiving basic treatment, at the stage of compensation, subcompensation and decompensation, such indicators deteriorated ($p<0.05$). Significant deterioration in carbohydrate metabolism, adiponectin and leptin in patients receiving basic treatment was accompanied by deterioration of their condition and increased the risk of 3-month mortality.

Thus, at the stage of decompensation, lipid metabolism and leptin levels were low, which indicates the depletion of body fat depots as the disease progresses. It may be due to the progression of the liver dysfunction, as it is actively involved in regulating the formation, destruction and accumulation of fats.

Changes in carbohydrate metabolism in patients with ALC in combination with obesity were characterized by a significant increase in IRI, HOMA-IR index and a decrease in the QUICKI index, indicating the presence of insulin resistance ($p<0.05$).

In determining the adipocytokine values, it was found that in decompensated liver function, the leptin rates decreased and the levels of adiponectin increased. Higher leptin content in the stage of compensation and subcompensation is also associated with increased secretion of adipose tissue. At the stage of decompensation, fat depots are depleted, so leptin levels are reduced. This decrease is directly related to the Child-Pugh and MELD scores. Adiponectin levels were decreased in the stage of compensation and increased with the progression of the disease and correlated with disease severity and the MELD score. It is thought that an increased adiponectin level indicates the level of anti-inflammatory reaction in response to hepatocyte damage.

The inclusion of ademethionine and arginine glutamate in the treatment regimen for 3 months allowed to improve laboratory parameters and reduce the rate of disease progression, which is reflected in improved carbohydrate metabolism, leptin and adiponectin and reduced Child-Pugh score and 3 month mortality MELD score. The inclusion of rosuvastatin in the treatment regimen for 3 months at the stage of compensation and subcompensation significantly improved lipid and carbohydrate metabolism, leptin and adiponectin levels compared with the group receiving only ademethionine and arginine glutamate ($p<0.05$). At the stage of decompensation in the scheme with the inclusion of rosuvastatin it was possible to normalize the levels of HDL cholesterol, VLDL cholesterol, AC and leptin, reduce the levels of adiponectin IRI, HOMA-IR, HbA1c and increase the QUICKI index, which was accompanied by a decrease in Child-Pugh severity score and 3 month mortality MELD score.

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Conclusions:

1. Changes in carbohydrate metabolism (IRI, HOMA-IR index, QUICKI index and HbAlc) in patients with ALC in combination with obesity indicate the presence of insulin resistance.

2. Leptin and adiponectin levels in patients with ALC in combination with obesity correlate with changes in carbohydrate metabolism, the severity of LC and the prognostic MELD score, which allows using them in the assessment of the severity and prediction of ALC in combination with obesity.

3. The inclusion in the complex treatment of ademethionine, arginine glutamate and rosuvastatin for obese patients with ALC helps to improve their fat metabolism, leptin, adiponectin and reduce insulin resistance.

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

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ЗМІНИ ПОКАЗНИКІВ ВУГЛЕВОДНОГО ТА ЛІПІДНОГО ОБМІНІВ ПІД ВПЛИВОМ ЛІКУВАННЯ ХВОРИХ НА АЛКОГОЛЬНИЙ ЦИРОЗ ПЕЧІНКИ В ПОЄДНАННІ З ОЖИРІННЯМ ІЗ ВИКОРИСТАННЯМ АДЕМЕТІОНІНУ, АРГІНІНУ ГЛУТАМАТУ ТА РОЗУВАСТАТИНУ

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Резюме. Мета дослідження: вивчення впливу комплексного лікування з використанням адеметіоніну, аргініну глутамату і розувастатину на зміни ліпідного та вуглеводного обмінів у хворих на алкогольний цироз печінки (АЦП) в поєднанні з ожирінням.

Матеріал і методи. У дослідженні взяли участь 156 пацієнтів з діагностованим АЦП в поєднанні з ожирінням, серед яких було 18 жінок та 138 чоловіків віком (45.3±8.9) років та середньою тривалістю захворювання (5.1±2.8) років. Пацієнтів було поділено на підгрупи залежно від стадії декомпенсації та залежно від застосованого лікування.

Результати. Достовірне погіршення показників вуглеводного обміну, адипонектину і лептину у пацієнтів, що отримували базове лікування, супроводжувалося погіршенням їх стану та підвищувало ризик 3-х місячної летальності. Після отриманого курсу лікування у пацієнтів групи, що отримувала адеметіонін, аргініну глутамат і розувастатин, на стадії компенсації і субкомпенсації показники ліпідного, вуглеводного обміну, адипонектину та лептину достовірно покращилися і відрізнялися від таких показників у пацієнтів, що отримували базове лікування та поєднання базового лікування, адеметіоніну та аргініну глутамат ($p<0.05$). На стадії декомпенсації у схемі із включенням розувастатину вдалося нормалізувати рівні ХС ЛПВЩ, ХС ЛПДНЩ, КА і лептину, знизити рівні адипонектину, IPI, HOMA-IR, HbA1c і підвищити рівень індексу QUICKI, що супроводжувалося зменшенням показників шкали тяжкості Чайльд-П'ю та індексу 3-х місячної летальності MELD.

Висновки. У хворих на АЦП в поєднанні з ожирінням включення в комплексне лікування адеметіоніну, аргініну глутамату та розувастатину сприяє поліпшенню перебігу захворювання за показниками ліпідного та вуглеводного обмінів, шкали тяжкості Чайльд-П'ю та індексу MELD.

Ключові слова: алкогольна хвороба печінки, цироз печінки, ожиріння, адипоцитокіни, ліпідний обмін.

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ИЗМЕНЕНИЯ ПОКАЗАТЕЛЕЙ УГЛЕРОДНОГО И ЛИПИДНОГО ОБМЕНОВ ПОД ВЛИЯНИЕМ ЛЕЧЕНИЯ БОЛЬНЫХ С АЛКОГОЛЬНЫМ ЦИРРОЗОМ ПЕЧЕНИ В СОЧЕТАНИИ С ОЖИРЕНИЕМ С ИСПОЛЬЗОВАНИЕМ АДЕМЕТИОНИНА, АРГИНИНА ГЛУТАМАТА И РОЗУВАСТАТИНА

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Резюме. Цель исследования: изучение влияния комплексного лечения с использованием адеметионина, аргинина глутамата и розувастатина на изменения липидного и углеродного обмена у больных с алкогольным циррозом печени (АЦП) в сочетании с ожирением.

Материал и методы. В исследовании приняли участие 156 пациентов с диагностированным АЦП в сочетании с ожирением, среди которых было 18 женщин и 138 мужчин в возрасте (45.3±8.9) лет и средней продолжительностью заболевания (5.1±2.8) лет. Пациенты были разделены на подгруппы в зависимости от стадии декомпенсации и в зависимости от применяемого лечения.

Результаты. Достоверное ухудшение показателей углеродного обмена, адипонектина и лептина у пациентов, получавших базовое лечение, сопровождалось ухудшением их состояния и повышало риск 3-х месячной летальности. После полученного курса лечения у пациентов группы, получавшей адеметионин, аргинина глутамат и розувастатин, в стадии компенсации и субкомпенсации показатели липидного, углеродного обмена, адипонектина и лептина достоверно улучшились и отличались от таковых показателей у пациентов, получавших базовое лечение и сочетание базового лечения, адеметионина и аргинина глутамат ($p<0.05$). В стадии декомпенсации в схеме с включением розувастатина удалось нормализовать уровни ХС ЛПВП, ХС ЛПОНП, КА и лептина, снизить уровни адипонектина, ИРИ, HOMA-IR, HbA1c и повысить уровень индекса QUICKI, что сопровождалось уменьшением показателей шкалы тяжести Чайльд-Пью и индекса 3-х месячной летальности MELD.

Выводы. У больных с АЦП в сочетании с ожирением включение в комплексное лечение адеметионина, аргинина глутамата и розувастатина способствует улучшению течения заболевания по показателям липидного и углеродного обменов, шкалы тяжести Чайлъд-Пью и индекса MELD.

Ключевые слова: алкогольная болезнь печени, цирроз печени, ожирение, адипоцитокины, липидный обмен.

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