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CHANGES IN ADIPOCYTOKINES IN PATIENTS WITH ALCOHOLIC CIRRHOSIS OF THE LIVER ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE DEPENDING ON THE STAGE OF DECOMPENSATION*

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According to the literature, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are two hepatic diseases with similar pathogenetic mechanisms of the development, progression and histological characteristics [1]. Both ALD and NAFLD are associated with a lipid metabolism disorder. There are three main sources of excessive accumulation of lipids in the liver: increased lipolysis of visceral adipose tissue, accompanied by excessive intake of free fatty acids (FFA) from adipose tissue (59%), activation of de novo liver lipogenesis (26%) and high calorie and/or fat content in the diet (15%) [2, 3]. Excessive input of FFA in adipose tissue leads to «overloading» of fat cells that are no longer able to contain such an amount of FFA and the accumulation of fat in other tissues of the body that is not adapted for such function — in the liver, pancreas, muscles, etc. [4, 5]. Such ectopia and large amount of FFA in the body result in a decrease in insulin sensitivity and the development of glucose- and lipo-toxicity.

The consequence of these processes is a disorder of the synthesis of adipokines, which affect the metabolic processes and the formation of oxidative stress. Some adipocytes are proinflammatory cytokines, some are involved in the metabolism of glucose and lipids, and others affect the complement system and vascular hemostasis [6, 7]. Adiponectin, leptin and resistin are the most described adipokines whose role in the development and progression of diseases accompanied by lipid disorders is ambiguous and is still the subject of scientific research [8, 9, 10].

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The purpose of the research was to study the changes in adipocytokines in patients with ALD associated with NAFLD depending on the stage of decompensation.

MATERIALS AND METHODS

204 patients with diagnosed liver cirrhosis (LC) participated in the study. Among them, 78 patients were diagnosed with ALD at the stage of the LC (group I) and 126 patients had a combination of alcoholic liver cirrhosis (ALC) and NAFLD (group II). Among the patients in group I, there were 24 women and 54 men (53.2 ± 11.4) years old and average duration of the disease (5.9 ± 2.1) years; among patients of group II there were 22 women and 104 men (47.8 ± 9.4) years old and average duration of the disease (4.2 ± 2.7) years. Patients of groups I and II were subgrouped according to the compensation classes of LC by Child-Pugh score: IA (17 persons), IB (38 persons), IC (23 persons); IIA (44 persons), IIB (48 persons), IIC (34 persons). Diagnosis was verified using clinical and laboratory-instrumental methods.

The severity of the LC was assessed using the Child-Pugh score and the MELD score (Mayo Endstage Liver Disease, 2001). The level of leptin, adiponectin, resistin was determined by immunoassay using Human Leptin ELISA (Biovendor, Czech Republic), Human Adiponectin ELISA kit (Biovendor, Czech Republic), Resistin Human ELISA (Biovendor, Czech Republic) respectively.

Statistical processing of the obtained results was carried out using the software package Statistica v. 12.0, StatSoft, USA and Microsoft Exel. The following data of parametric statistics were used: the arithmetic mean (M) and the standard deviation (SD). For the analysis of dependencies, a method of correlation analysis with determining the Spirman rank correlation coefficient was used. Statistically significant differences were considered at $p < 0.05$.

RESULTS AND THEIR DISCUSSION

Analyzing the data of the clinical examination, it was found that the symptoms of astheno-vegetative, painful, dyspeptic, hepatorenal, hepatopulmonary syndromes, jaundice, medically uncontrolled ascites, signs of hepatic encephalopathy were more common in patients of group II of the corresponding classes, accompanied by changes in the Child-Pugh score and MELD score. In patients of group II, they were higher compared to those in group I at 22.74% and 31.18%, 21.06% and 17.78%, 13.72% and 15.98% of classes A, B, C respectively.

The BMI in patients of IA, IB, IC and IIA, IIB, IIC groups was (22.61 ± 2.15), (21.04 ± 1.52), (19.21 ± 1.63), and (34.56 ± 4.67), (30.83 ± 2.87), (21.35 ± 1.63) kg/м^2 respectively. The analysis of the BMI values showed a significant difference between the indicators in groups I and II, depending on the stage of compensation ($p < 0.05$).

Changes in the biochemical parameters of the lipid spectrum were manifested by an increase in blood levels of TC, LDLC, VLDLC, AC and TG in patients with a stage of compensation compared with control group. In patients of group II of each class by Child-Pugh, such indicators were higher than in patients of group I of the corresponding class ($p < 0.05$). With increasing decompensation, they decreased proportionally. HDLC in the blood of patients of both groups decreased with increasing decompensation; in patients of group II, the indicator was significantly lower compared to patients in group I ($p < 0.05$). 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 imbalance of adipocytokines was more obvious in patients suffering from ALC with concomitant NAFLD (Table 1). In particular, the content of leptin in the blood of patients of group II was higher compared to those in patients of group I of class A by Child-Pugh at 2.26 and 1.74 times respectively ($p < 0.05$). In patients of both groups of class C by Child-Pugh, the level of leptin did not differ signifi-

cantly ($p > 0.05$). Adiponectin content in patients of group II was lower in comparison with patients of group I of A and B class by Child-Pugh at 1.6 and 1.56 times respectively ($p < 0.05$). The significant difference between adiponectin levels in patients of both groups of class C was not found ($p > 0.05$). In patients of both groups, the level of resistin increased with increasing decompensation. In people of group II, the level of resistin was higher compared to patients of group I of A, B and C classes by Child-Pugh at 2.53, 2.04 and 1.65 times respectively ($p < 0.05$). The content of leptin was the highest in patients of both groups in stage A.

With an increase in decompensation, this indicator decreased in both groups. Adiponectin content was the lowest in persons of both groups of class A and with increasing decompensation it decreased. In people of group II, these changes significantly differed from those of patients in group I ($p < 0.05$).

Changes in the levels of resistin, leptin and adiponectin in both groups are associated with lipid imbalance. Correlation between levels of adipocytokines and indices of lipid metabolism in group II was more obvious. The correlation between the content of resistin in the blood and the level of TC in group II was as follows: $r = -0.54$, $r = -0.55$, $r = -0.67$ for classes A, B, C respectively; the level of TG – $r = -0.56$, $r = -0.47$, $r = -0.53$ for classes A, B, C respectively; HDLC – $r = -0.59$, $r = -0.66$, $r = -0.69$ for classes A, B, C respectively; LDLC – $r = -0.55$, $r = -0.58$, $r = -0.61$ for classes A, B, C respectively; VLDLC – $r = -0.43$, $r = -0.47$, $r = -0.63$ for classes A, B, C respectively; AC – $r = -0.39$, $r = -0.42$, $r = -0.57$ for classes A, B, C respectively; the content of adiponectin — $r = 0.62$, $r = 0.68$, $r = 0.73$ and leptin — $r = -0.59$, $r = -0.62$, $r = -0.65$ for classes A, B, C respectively. The correlation between lipid metabolism and leptin level in patients of group II was as follows: for TC — 0.84, 0.79 and 0.67 for classes A, B and C respectively; for HDLC — 0.71, 0.56 and 0.48 for classes A, B and C respectively; for LDLC — 0.47, 0.42 and 0.39 for classes A, B and C respectively; for VLDLC — 0.52, 0.38 and 0.33 for classes A, B and C respectively; for AC — 0.73, 0.64 and 0.53 for classes A, B and C respectively; for TG — 0.76, 0.62 and 0.59 for classes A, B and C respectively; for adiponectin — – 0.72, – 0.65 and – 0.61 for classes A, B and C respectively. The correlation between the adiponectin level and lipid metabolism indices in patients

Table 1

Characteristics of adipocytokines levels in patients with alcoholic liver cirrhosis associated with non-alcoholic liver disease

Indicators	Control, n = 20	Class of LC by Child-Pugh score					
		Gr. IA	Gr. IIA	Gr. IB	Gr. IIB	Gr. IC	Gr. IIC
		n = 17	n = 44	n = 38	n = 48	n = 23	n = 34
Resistin ng/ml	3.72 ± 0.26	4.23 ± 0.31	10.72 ± 0.52*	6.73 ± 0.21▲	13.74 ± 0.58•ß	9.68 ± 0.47▪	15.96 ± 0.69#□
Adiponectin µg/ml	8.46 ± 0.11	4.73 ± 0.06	2.96 ± 0.05*	5.12 ± 0.07▲	3.28 ± 0.08•ß	7.15 ± 0.07▪	7.31 ± 0.09#
Leptin ng/ml	7.92 ± 0.28	9.49 ± 0.51	21.47 ± 0.62*	8.91 ± 0.32	15.53 ± 0.75•ß	7.65 ± 0.29▪	8.23 ± 0.63#

Notes:
* the probability of differences between groups IA and IIA ($p < 0.05$);
• the probability of differences between groups IB and IIB ($p < 0.05$);
the probability of differences between groups IC and IIC ($p < 0.05$);
▲ the probability of differences between groups IA and IB ($p < 0.05$);
▪ the probability of differences between groups IB and IC ($p < 0.05$);
ß the probability of differences between groups IIA and IIB ($p < 0.05$);
□ the probability of differences between groups IIB and IIC ($p < 0.05$).

of group II was: for TC — – 0.65, – 0.58 and – 0.48 for classes A, B and C, respectively; for HDLC — – 0.48, – 0.51 and – 0.36 for A, B and C classes respectively; for LDLC — – 0.47, – 0.42 and – 0.33 49 for classes A, B and C respectively; for VLDLC — – 0.24, – 0.21 and – 0.17 for classes A, B and C respectively; for AC — – 0.46, – 0.39 and – 0.37 for classes A, B and C respectively; for TG — – 0.38, – 0.33 and – 0.30 for classes A, B and C respectively. The correlation between the level of adiponectin, the severity of the disease and the MELD index was more obvious in patients of group II.

Correlation analysis between the levels of resistin, leptin, adiponectin and the indices of the Child-Pugh score and the MELD score revealed a stronger connection among people in group II with an increase in decompensation. Thus, between the level of the resistine and the Child-Pugh score r = 0.52, r = 0.79, r = 0.84, and for the MELD score – r = 0.56, r = 0.72, r = 0.78 for classes A, B, C, respectively. Between the level of leptin and the indicator of the severity of the disease by Child-Pugh score and the MELD score, the correlation was as follows: for the Child-Pugh score — r = – 0.72, r = – 0.58, r = – 0,44, and for the MELD score — r = – 0.66, r = – 0.61, r = – 0.68 for classes A, B, C respectively. The relation between the level of adiponectin, the severity of disease and the MELD score was as follows for the Child-Pugh score — r = 0.69, r = – 0.49,r = 0.67, and for the MELD score — r = 0.73, r = 0.52, r = 0.34 for classes A, B, C respectively.

Thus, in patients with ALC associated with NAFLD, the course of the disease is more severe, it is accompanied by more severe clinical signs and disorders of lipid metabolism. As for the biochemical parameters of the lipid spectrum, higher levels of TC, LDLC, VLDLC, AC and TG were in patients of classes A and B compared to patients of class C. Patients of group II had higher rates than those in group I ($p < 0.05$). The content of HDLC in patients of group II was significantly lower in comparison with patients in group I ($p < 0.05$). Such changes, in our opinion, are associated with the progression of dysfunction of the liver as an organ that plays a central role in the regulation of the synthesis, degradation and deposition of cholesterol and lipoproteins. According to the literature, lowering TG levels in serum is associated with a decrease in their synthesis and a decrease in the processes of esterification; low level of VLDLC and LDLC is associated with a deficiency of microsomal triglyceride transferase protein and inhibition of cholesterol synthesis; a decrease in HDLC is associated with a decrease in the synthesis of apolipoprotein AI [4, 6].

The peculiarity of the adipocytokines was that with the progression of the LC, the level of leptin decreased, while the levels of adiponectin and resistin increased. Resistance to leptin is associated with fatty tissue as an endocrine organ and is characteristic for overweight patients, which is confirmed by higher levels of leptin in patients of group II. The higher content of leptin in patients of classes A and B is accompanied not only by the impaired liver function, but also by its increased release from adipose tissue. In patients of class C fat depot is exhausted, therefore the level of leptin decreases. Moreover, this decrease correlates with the severity of the disease and the prognostic MELD score. The level of adiponectin was lowered in class A patients and increased in patients with more severe course and correlated with severity of the disease and MELD score. Considering the hepatoprotective effect of adiponectin, some scientists believe that its elevated level reflects the anti-inflammatory response to liver damage, which depends on the severity of the disease [8, 9].

The level of resistin was increased in proportion to the deterioration of the liver function and correlated with the Child-Pugh score and the MELD score. The growth of resistin levels in patients of both groups with the progression of the disease is also associated with the degree of severity. Higher levels of resistin in patients of group II are accompanied by a more severe course of the disease. The revealed correlation between the levels of resistin, leptin and adiponectin with the degree of severity of the LC and the prognostic MELD score allows considering their changes for assessment of the severity of the LC and predicting the course of the disease.

CONCLUSIONS

1. Progression of liver cirrhosis in patients with ALC associated with NAFLD is accompanied by more severe clinical and laboratory manifestations.
2. Lipid metabolism in patients with ALC associated with NAFLD in the stage of subcompensation and decompensation is characterized by a decrease in levels of TC, HDLC, LDLC, VLDLC, and TG.
3. Levels of leptin, adiponectin, and resistin in patients with ALC associated with NAFLD correlate with changes in lipid metabolism, the severity of the LC, and prognostic score MELD, which allow their use in assessment of the severity and prediction of ALD associated with NAFLD.

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CHANGES IN ADIPOCYTOKINES IN PATIENTS WITH ALCOHOLIC CIRRHOSIS OF THE LIVER ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE DEPENDING ON THE STAGE OF DECOMPENSATION

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According to the literature, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are two hepatic diseases with similar pathogenetic mechanisms of the development, progression and histological characteristics. Both ALD and NAFLD are associated with a lipid metabolism disorder and a disorder of the synthesis of adipokines. Adiponectin, leptin and resistin are the most described adipokines whose role in the development and progression of diseases accompanied by lipid disorders is ambiguous and is still the subject of scientific research. The purpose of the research was to study the changes in adipocytokines in patients with alcoholic liver cirrhosis (ALC) associated with NAFLD depending on the stage of decompensation. The study included 204 patients. Among them, 78 patients (Gr. I) had ALC and 126 patients (Gr. II) had a combination of ALC with NAFLD. Patients were subgrouped according to compensation classes by the Child-Pugh score (A, B, C). With the progression of the liver cirrhosis the level of leptin decreased, while the levels of adiponectin and resistin increased. The higher content of leptin in patients of classes A and B is accompanied not only by the impaired liver function, but also by its increased release from adipose tissue. In patients of class C fat depot is exhausted, therefore the level of leptin decreases. Moreover, this decrease correlates with the severity of the disease and the prognostic MELD score. The level of adiponectin was lowered in class A patients and increased in patients with more severe course and correlated with severity of the disease and MELD score. The level of resistin was increased in proportion to the deterioration of the liver function and correlated with the Child-Pugh score and the MELD score. The revealed correlation between the levels of resistin, leptin and adiponectin with the degree of severity of the liver cirrhosis and the prognostic MELD score allows considering their changes for assessment of the severity of the liver cirrhosis and predicting the course of the disease.

Key words: alcoholic liver disease; non-alcoholic fatty liver disease; cirrhosis.

ЗМІНИ АДИПОЦИТОКІНІВ У ХВОРИХ НА АЛКОГОЛЬНИЙ ЦИРОЗ ПЕЧІНКИ ПРИ ПОЄДНАННІ З НЕАЛКОГОЛЬНОЮ ЖИРОВОЮ ХВОРОБОЮ ПЕЧІНКИ ЗАЛЕЖНО ВІД СТАДІЇ ДЕКОМПЕНСАЦІЇ

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Метою роботи було вивчення змін показників адипоцитокінів у хворих на алкогольний цироз печінки (АЦП) при поєднанні з неалкогольною хворобою печінки (НАЖХП) залежно від стадії декомпенсації. Обстежено 204 пацієнти. Серед них у 78 осіб (I гр.) діагностовано АЦП та у 126 осіб (II гр.) було поєднання АЦП з НАЖХП. Пацієнтів було поділено на підгрупи залежно від класів компенсації за критеріями Чайльд-П'ю (A, B, C). Із прогресуванням цирозу печінки рівень лептину зменшувався, а рівні адипонектину та резистину зростали. Вищий рівень лептину був у пацієнтів II гр. У пацієнтів класу С жирові депо виснажені, тому рівень лептину знижується. Причому це зниження корелює зі ступенем важкості захворювання та прогностичним індексом MELD. Рівень адипонектину був знижений у осіб класу А і підвищувався у пацієнтів з більш важчим перебігом та корелював зі ступенем важкості захворювання та індексом MELD. Рівень резистину підвищувався пропорційно з погіршенням функції печінки та корелював із показниками Чайлд-П'ю і індексом MELD. Виявлені кореляційні зв'язки рівнів резистину, лептину та адипонектину зі ступенем важкості цирозу печінки та прогностичним індексом MELD дозволяють розглядати їх зміни для оцінки ступеня важкості цирозу печінки та прогнозування перебігу захворювання.

Ключові слова: алкогольна хвороба печінки; неалкогольна жирова хвороба печінки; цироз.

ИЗМЕНЕНИЯ АДИПОЦИТОКИНОВ У БОЛЬНЫХ С АЛКОГОЛЬНЫМ ЦИРРОЗОМ ПЕЧЕНИ ПРИ СОЧЕТАНИИ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ В ЗАВИСИМОСТИ ОТ СТАДИИ ДЕКОМПЕНСАЦИИ

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Целью работы было изучение изменений показателей адипоцитокинов у больных с алкогольным циррозом печени (АЦП) при сочетании с неалкогольной болезнью печени (НАЖБП) в зависимости от стадии декомпенсации. Обследовано 204 пациента. Среди них у 78 человек (I гр.) диагностирован АЦП и в 126 лиц (II гр.) было сочетание АЦП с НАЖБП. Пациентов разделили на подгруппы в зависимости от классов компенсации по критериям Чайльд-Пью (A, B, C). С прогрессированием цирроза печени уровень лептина уменьшался, а уровни адипонектина и резистина возрастали. Высший уровень лептина был у пациентов II гр. У пациентов класса С жировые депо истощены, поэтому уровень лептина снижается. Причем это снижение коррелирует со степенью тяжести заболевания и прогностическим индексом MELD. Уровень адипонектина был снижен у лиц класса А и повышался у пациентов с более тяжелым течением, а также коррелировал со степенью тяжести заболевания и индексом MELD. Уровень резистина повышался пропорционально с ухудшением функции печени и коррелировал с показателями Чайлд-Пью и индексом MELD. Выявленные корреляционные связи уровней резистина, лептина и адипонектина со степенью тяжести цирроза печени, а также с прогностическим индексом MELD позволяют рассматривать их изменения для оценки степени тяжести цирроза печени и прогнозирования течения заболевания.

Ключевые слова: алкогольная болезнь печени; неалкогольная жировая болезнь печени; цирроз.