CHANGES IN CARBOHYDRATE METABOLISM 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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ABSTRACT

The purpose of the research was to study the changes in adipocytokines in patients with alcoholic liver cirrhosis (ALC) associated with non-alcoholic fatty liver disease (NAFLD) depending on the stage of decompensation. A significant increase in immunoreactive insulin, the HOMA-IR index and a decrease in the QUICKI index in patients II gr. in comparison with patients I gr. has been detected, indicating insulin resistance (p<0.05). On the basis of the results of the analysis of the correlation between the levels of leptin, adiponectin, resistin and carbohydrate metabolism, it was found that a stronger correlation was observed in patients suffering from ALC associated with NAFLD.

KEYWORDS  
alcoholic liver disease; non-alcoholic fatty liver disease; carbohydrate metabolism.

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Introduction. 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. With the global growth of obesity, fatty liver, which is characteristic to both diseases, becomes one of the most common among hepatic pathological changes throughout the world [1]. Both diseases have a staging – from simple steatosis (accumulation of fat in hepatocytes) to steatohepatitis (inflammation with balloon dystrophy of liver cells that initiates fibrosis) which can progress to fibrosis, cirrhosis, liver failure or hepatocellular carcinoma [2]. Staging of the pathological condition is the result of complex interaction, which involves the population of the liver cells (parenchymal and nonparenchymal), and pathological signals coming from other organs such as fatty tissue and the gastrointestinal tract. Such stimuli include the death of hepatocytes, biologically active substances and intestinal pathogens secreted by adipose tissue
which contribute to inflammation and fibrogenesis by activating macrophages (Kupffer cells), which, in turn, activate leukocytes and star cells (Ito cells, lipocytes) with subsequent excessive production of the extracellular matrix components [3].

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%) [4]. 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. [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].

Adiponectin, leptin and resistin are the most described adipokines. According to the literature, in patients with NAFLD the level of adiponectin decreases, and the level of leptin on the contrary – increases, which is due to metabolic processes in the adipose tissue [7]. Adiponectin is secreted entirely by adipose tissue and, to a lesser extent, by the placenta and it circulates in various isoforms: low molecular weight trimers, medium molecular weight hexamers and high molecular weight multimers [8]. Known links of adiponectin influence are the stimulation of lipid oxidation in the liver, induction of receptor of proliferation activation of peroxisomes, inhibition of lipogenesis and transformation of macrophages into foam cells, regulation of catabolism of fatty acids, cleavage of fatty acids with further reducing of triacylglycerides, inhibition of preadipocytes differentiation, anti-inflammatory and antiatherosclerotic (regulation of calcification of arteries ) properties, the effect on the cells of the hypothalamus with subsequent decrease in body weight, decrease in the synthesis of glucose by liver cells, increasing the sensitivity of cells to insulin; antioncogenic action is described [9, 10].

Leptin is also excreted primarily by adipose tissue, though its low levels are found in the placenta, skeletal muscles, epithelium of the stomach and mammary glands, in the brain, and, affecting the hypothalamus it suppresses the feeling of hunger, and thus controls body weight. However, in obesity and high leptinemia, there is a resistance of the hypothalamus to leptin [11]. The results of studies on the effect of leptin on insulin secretion and on the development of insulin resistance are still ambiguous. They prove that prolonged hyperleptinemia suppresses the expression of matrix ribonucleic acid of insulin. There is a direct dependence between the leptin level and the degree of insulin resistance. [12]. In addition, hyperleptinemia is accompanied by the development of inflammation in the vascular wall by affecting the activation of cellular immunity and the production of proinflammatory cytokines, which is accompanied by oxidative stress in endothelial cells and leads to the development of systemic hemostasis disorders [13]. Resistin was discovered in 2001 and called the “insulin resistance hormone”. It is secreted both by fatty tissue and macrophages. Recent studies have shown a positive correlation between resistin level and obesity, insulin resistance, chronic inflammation [14, 15, 16]. It has been found that its concentration increases with the differentiation of adipocytes, and it also has the ability to suppress adipogenesis and glucose uptake by cells. [17, 18]. The effect of resistin on the stimulation of inflammatory mechanisms, endothelial activation, and proliferation of smooth muscle cells in the vessels was described, which allows us to consider it as a marker for the development of systemic vascular disorders [19].

Thus, the role of adiponectin, leptin and resistin in the development and progression of diseases accompanied by carbohydrate metabolism disorders is ambiguous and is still the subject of scientific research.

The purpose of the research was to study the changes in carbohydrate metabolism 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; they underwent inpatient treatment in the gastroenterology department of the Ivano-Frankivsk Regional Clinical Hospital. 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 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).

A general-clinical examination, ultrasound examination of the abdominal cavity and esophagogastroduodenoscopy were performed. To detect the alcoholic aetiology of the disease, according to the recommendations of the World Health Organization, more than 2 doses of alcohol (1 standard dose = 10 g of ethyl alcohol) per day for women and more than 4 doses for men, were taken into account. CAGE (Cut, Annoyed, Guilty, Eye-opener), AUDIT (Alcohol Use Disorders Identification Test, 1989), the PAS questionnaire (post-alcohol syndrome developed by P.P Ogurtsov, A.B. Pokrovsky, A.E Uspensky), LeGo (P.M LeGo 1976) in the modification of O.B. Zharkov, 2000), ANI index (Alcoholic liver disease/non-alcoholic fatty liver disease index, 2006) were used. The control group included 20 practically healthy persons.

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 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 severity of the LC was assessed using the Child-Pugh score and the MELD score (Mayo Endstage Liver Disease, 2001). The level of leptin, adeponectin, 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). To determine the significance of the differences between groups in the distribution, close to normal, t-criterion Student was used. 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.

Research results. Analyzing the data of the clinical examination, it was found that the symptoms of asthenov-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.

A significant increase in IRI in patients of group II (p <0.05) was one of characteristic features of carbohydrate metabolism, (Table 1). It was 3.72, 5.07 and 4.75 times higher than in group I of class A, B and C, respectively. The HOMA-IR index in people of group II significantly exceeded this indicator in group I of A, B and C classes at 4.60, 5.90 and 5.50 times respectively (p<0.05). The QUICKI index in patients of group II also significantly exceeded this indicator in patients of group I at 1.68, 1.68 and 1.64 times respectively (p<0.05). The level of HbA1c in patients of both groups was slightly increased, but there was no significant difference between the 1st and 2nd groups of the corresponding classes (p>0.05).
Table 1. Characteristics of carbohydrate metabolism 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 |
| IRI. mcU/ml | 5.89±0.32 | 6.23±0.39 | 23.16±1.46* | 6.21±0.42 | 31.52±1.97** | 6.13±0.49 | 29.11±2.21# |
| HOMA-IR | 1.05±0.06 | 1.19±0.05 | 5.47±0.18* | 1.21±0.07 | 7.14±0.26** | 1.20±0.09 | 6.61±0.21# |
| QUICKI | 0.681±0.004 | 0.627±0.005 | 0.373±0.004* | 0.583±0.005* | 0.347±0.003** | 0.576±0.003 | 0.352±0.004# |
| HbA1c.% | 4.63±0.18 | 4.98±0.22 | 6.37±0.16* | 5.07±0.19 | 6.24±0.16* | 5.12±0.15 | 5.82±0.14# |

Notes:
1) * – the probability of differences between groups IA and IIA (p<0.05);
2) ● – the probability of differences between groups IB and IIB (p<0.05);
3) # – the probability of differences between groups IC and IIC (p<0.05);
4) ▲ – the probability of differences between groups IA and IB (p<0.05);
5) ■ – the probability of differences between groups IB and IC (p<0.05);
6) ◻ – the probability of differences between groups IIA and IIB (p<0.05);
7) □ – the probability of differences between groups IIB and IIC (p<0.05);

The imbalance of adipocytokines was more obvious in patients suffering from ALC with concomitant NAFLD (Table 2). 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 significantly (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).

Table 2. 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** | 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** | 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** | 7.65±0.29* | 8.23±0.63# |

Notes:
1) * – the probability of differences between groups IA and IIA (p<0.05);
2) ● – the probability of differences between groups IB and IIB (p<0.05);
3) # – the probability of differences between groups IC and IIC (p<0.05);
4) ▲ – the probability of differences between groups IA and IB (p<0.05);
5) ■ – the probability of differences between groups IB and IC (p<0.05);
6) ○ – the probability of differences between groups IIA and IIB (p<0.05);
7) □ – the probability of differences between groups IIB and IIC (p<0.05).

Changes in the levels of resistin, leptin and adiponectin in both groups are associated with imbalance of carbohydrate metabolism. Correlation between levels of adipocytokines and indices of carbohydrate metabolism in group II was more obvious. The level of resistin is associated with carbohydrate metabolism disorders. In patients of group II the connection was more obvious. In particular, the correlations between the resistin level and IRI was the following: r=0.68, r=0.59, r=0.36 for classes A, B, C respectively; HOMA-IR – r=0.48, r=0.42, r=0.32 for classes A, B, C respectively; QUICKI – r=0.68, r=0.63, r=0.60 for classes A, B, C respectively; HbAlc – r=0.42, r=0.38, r=0.33 for classes A, B, C respectively. The correlation between carbohydrate metabolism and leptin level in patients of group II was as follows: for IRI – -0.69, -0.53 and -0.49 for classes A, B and C respectively; for HOMA-IR – -0.54, -0.41 and -0.33 for classes A, B and C respectively; for QUICKI – 0.63, 0.69 and 0.74 for classes A, B and C respectively; for HbAlc – -0.35, -0.33 and -0.31 for classes A, B and C respectively. The correlation between the adiponectin level and carbohydrate metabolism indices in patients of group II was: for IRI – 0.45, 0.38 and 0.36 for classes A, B and C respectively; for HOMA-IR – 0.36, 0.31 and 0.27 for classes A, B and C respectively; for QUICKI – -0.42, -0.38 and -0.37 for A, B and C classes respectively; for HbAlc – 0.31, 0.27 and 0.25 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 carbohydrate metabolism. Changes in carbohydrate metabolism were characterized by a significant increase in IRI, HOMA-IR score and a decrease in the QUICKI score in patients of group II compared to patients in group I, indicating insulin resistance (p<0.05).

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.

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. On the basis of the results of the analysis of the correlation between the levels of leptin, adiponectin, resistin and carbohydrate metabolism, it was found that a stronger correlation was observed in patients suffering from ALC associated with NAFLD. 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 manifestations.
2. Changes in carbohydrate metabolism (IRI, HOMA-IR index, QUICKI and HbAlc score) in patients with ALC associated with NAFLD indicate that they have insulin resistance.
3. Levels of leptin, adiponectin, and resistin in patients with ALC associated with NAFLD correlate with changes in lipid and carbohydrate 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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