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ASPECTS OF IMMUNOLOGICAL STATUS AND CARBON METABOLISM IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN CORRELATION WITH ITS FIBROUS TRANSFORMATION

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Introduction. Today, non-alcoholic fatty liver disease (NAFLD) is becoming more widespread worldwide [1]. NAFLD is diagnosed in almost half of the adult population, 25-30% of whom are at risk to progress to non-alcoholic steatohepatitis. Among the most important factors influencing the prognosis of NAFLD, tactics and effectiveness of treatment is the progression rate of fibrotic liver transformation [2]. According to recent studies, the prevalence of liver fibrosis in the world ranges from 6.9% to 19.0% [3]. Nowadays numerous researches are conducted that study the immune system role in the diseases of digestive organs, in particular a close connection has been established between disorders in the immune status and pathology developments in the hepatobiliary system [4,5,6]. It has been proved that the immune system can be suppressed as a result of the organism's intoxication caused by various reasons: toxins of microorganisms which cause the inflammatory process, toxic effect of antibacterial drugs used for the treatment [7]. In addition, it has been shown that these are cytokines that provide intercellular interaction in the immune system, communicate between the immune, endocrine, nervous and other systems, ensure their involvement in the organization and regulation of defence responses [8,9]. The content of serum pro- and anti-inflammatory cytokines shows not only the activeness of generalized inflammatory process, but also the effectiveness of treatment, predicts the course of the disease, the development of its complications [10].

Increasing TNF-α levels for a long time is known to inhibit the activity of type 1 T-helper cells and consequently the cellular immune response. On the one hand, TNF-α is necessary for the proliferation of hepatocytes and prevention of their apoptosis during liver regeneration, on the other, it is a mediator of hepatotoxicity during bacterial, viral and toxic stresses. In addition, the degree of increase in serum TNF-α content correlates with the morbidity [11].

Recent publications have shown that the level of IL-6 in serum is directly proportional to their concentration in the liver, indicating the grade of its inflammation [12,13]. In addition, isolated inflammatory cytokines from hepatocytes activate stellate cells [14].

Currently, scientists worldwide are conducting clinical validation of various elastographic methods to determine the stage of liver fibrosis. The study performed by Wong and co-authors [3] demonstrates the high accuracy of the shear wave elastography (SWE) method for the diagnosis of fibrosis and cirrhosis in patients with NAFLD, that being the case when stiffness is not affected by liver steatosis, necrosis, inflammation, or body mass index. However so far not sufficient attention has been paid in modern publications to highlighting the correlation between SWE and immunological status in patients with NAFLD.

Thus, the mechanisms underlying the development of NAFLD-induced structural changes in the liver still need clarification, and therefore the question of the role of the immune status in enhancing fibrotic processes remains topical.

Purpose of the investigation: to determine the special features of immunological status changes in patients with NAFLD depending on their stage of fibrosis.

Object and methods of investigation. The research involved 101 patients with NAFLD who were undergoing treatment at the Department of Liver and Pancreatic Diseases of «The Institute of Gastroenterology of NAMSU (National Academy of Medical Sciences of Ukraine)». Among the surveyed there were 32 men (31.7%) and 69 women (68.3%), the average age was (48.4±2.9) years. The control group included 30 apparantly healthy individuals. All the patients agreed to participate in the study. The materials submitted for publication do not violate the provisions of bioethics.

The diagnosis was verified on the basis of a thorough analysis of complaints, medical history, serological methods, ultrasound results, shear wave elastometry, liver steatometry and morphological studies, in accordance with the recommendations of international consensus.

Shear-wave elastography was performed on a Soneus P7 apparatus (Ukraine, Switzerland) with a 2-5 MHz convex sensor at a depth of 10-50 mm from the capsule. Then from these measurements the average values that characterized the liver stiffness in kilopascals (kPa) were determined. Ferraioli G threshold values were used to assess the fibrosis stage: F0 – stage 1 up to 6.5 kPa; F 2 stage – up to 7.1 kPa; F 3 stage – up to 8.7 kPa; F 4 stage – 10,4 or more on the METAVIR scale. In addition, the same apparatus was used to measure the ultrasound attenuation coefficient in dB/cm – a method of quantitative assessment of the liver steatosis degree.

The subpopulation composition of lymphocytes was determined using the monoclonal antibodies of the firm «Sorbent TM» to molecules CD3, CD19, CD4, CD8, CD16. The mononuclear cells were isolated from the peripheral venous blood of patients in a density gradient of 1,077 g/cm. The immune status assessment was performed according to the guidelenes of R.V. Petrov (1992).

Circulating immune complexes (CICs) were determined by the method of V. Haskov (1977). During the investigation, sets of reagents of the company «Vector-

BEST» were used to measure the amount of TNF-α, IL-6, IL-10 and those of the company «DRG» Germany – to measure insulin in the blood serum. The enzyme-linked immunosorbent assay was performed using a «Stat Fax 303 Plus» analyzer (USA).

The insulin resistance score was estimated using the HOMA-IR index, which was calculated with the formula:

HOMA-IR = fasting plasma glucose (mmol/l) times fasting serum insulin (mU/ml) devided by 22.5.

Statistical processing of the results was performed using the software package «STATISTICA 6.1» (serial number – AGAR909 E415822FA). The median (Me), the lower (Q1), and the upper (Q2) quartiles were used to describe the data. The comparisons were performed using the non-parametric Mann-Whitney test. The statistical significance was assessed at no less than 95.0% (p <0.05). The degree of correlation between the variables was estimated using the Spearman's rank correlation coefficients (r).

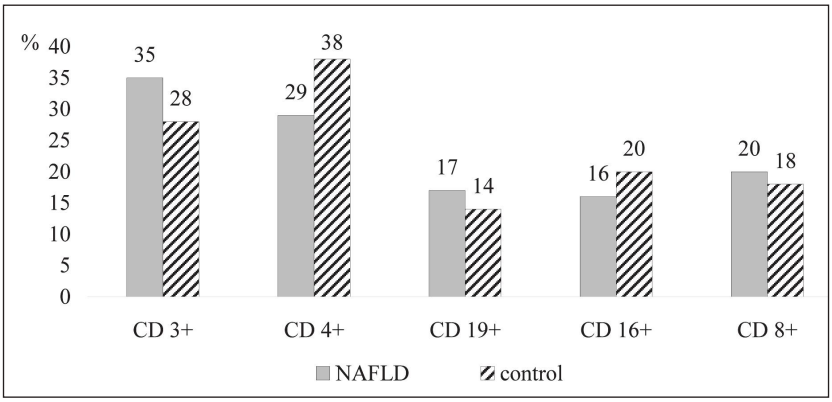

Figure 1 – Indicators of immune status in patients with NAFLD.

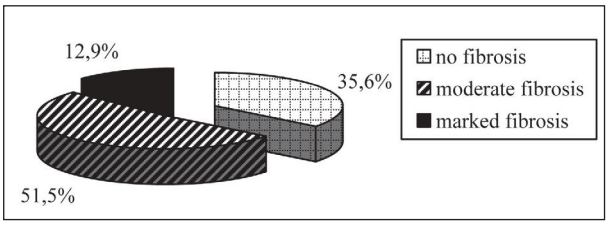

Figure 2 – Distribution of patients with NAFLD according to SWE results.

Research results. While analyzing the immunological indicators in patients with NAFLD it was found that the level of lymphocytes was increased in 38.6% of cases **(fig. 1)**. In 68.3% of patients a reduced relative content of CD3+ lymphocytes was detected. Given that cellular immunity is provided by sensitized T-lymphocytes, and in patients the content of T-cells is significantly reduced, we can assume that their immune response is of a depressive character.

In 61.4% of patients a significant decrease in the T-helper subpopulation was observed. It should be noted that the median of relative content in CD4+ lymphocytes decreased significantly by 1.3 times (p <0.05) as compared to the control group.

In 59.4% of patients with NAFLD, the CIC level was significantly increased (p <0.05) as compared to the control level.

According to SWE results, a moderate fibrosis was diagnosed in 52 (51.5%) patients with NAFLD, while 13 (12.9%) patients were diagnosed with marked fibrosis **(fig. 2)**.

Patients with marked fibrosis showed a significant increase in the relative content of CD19+ lymphocytes of 1.6 times (p <0.05) and of 1.4 times (p <0.05) in patients with moderate fibrosis respectively, as compared with its level in the control group **(table 1).** In addition, patients with marked fibrosis have a tendency to a higher impairment level of T-cell immunity: a significant decrease in the level of CD3+ cells and the percentage of CD4+ lymphocytes was determined in 69.2% of cases, an increase in the content of CD8+ cells in 38.5% of cases. There was also registered a 1.5-fold increased serum level of CIC in patients with marked fibrosis (76.9% of cases) as compared to the group of patients with moderate fibrosis (56.8% of cases).

In the analysis of carbohydrate metabolism, a significant increase in insulin level by 1.5 times (p <0.05) was observed in patients with NAFLD as compared to the control group **(table 2).** The highest median values of insulin were observed in patients with severe fibrosis, as evidenced by the correlation between this index and liver stiffness according to SWE data (r = 0.42, p <0.05).

In addition, a significant increase in glucose levels of 1.5 times (p <0.05) and 1.3 times (p <0.05) has been observed in NAFLD patients with marked and moderate fibrosis respectively, as compared to the control group levels.

The HOMA-IR values in patients with NAFLD were above 3.0 and were significantly different from those in the control group. These changes were more pronounced in patients with marked fibrosis (p <0.05).

Table 1 – Indicators of immune status in patients with NAFLD depending on the severity of fibrotic liver transformation, Me (Q1, Q2)

Indicator		Moderate fibrosis (n=88)	Marked fibrosis (n=13)	Control group (n=30)
Leukocytes	10^9c/l	6,0 (5,0; 7,2)	6,0 (5,3; 6,7)	5,3 (4,2; 615)
Lymphocytes	%	35,0 (30,0; 39,8)*	31,0 (23,5; 38,0)*	28 (25; 33)
	10^9c/l	2,2 (1,6; 2,5)*	1,9 (1,7; 2,4)*	1,59 (1,32; 1,81)
T- lymphocytes (CD3+)	%	45,0 (41,0; 50,0)*	43,0 (40,0; 45,5)*	51 (47; 54)
	10^9c/l	0,90 (0,80; 1,2)	0,90 (0,70; 1,4)	0,75 (0,57; 0,)
T-helpers (CD4+)	%	29,0 (24,5; 32,0)*	28,9 (22,5; 33,0)*	38 (35; 41)
	10^9c/l	0,60 (0,50; 0,80)	0,49 (0,38; 0,80)	0,49 (0,43; 0,64)
T-cytotox. (CD8+)	%	20,0 (16,0; 24,0)	20,4 (15,0; 26,0)	18 (15,5; 21)
	10^9c/l	0,42 (0,32; 0,52)*	0,34 (0,30; 0,70)	0,28 (0,24; 0,37)
B-lymphocytes (CD19+)	%	16,0 (14,5; 23,0)	22,4 (16,5; 27,0)* #	14 (12; 17)
	10^9c/l	0,40 (0,31; 0,52)*	0,50 (0,31; 0,60)*	0,24 (0,2; 0,31)
T-killers (CD16+)	%	15,9 (11,5; 20,0)*	16,8 (9,1; 18,0)*	20 (14; 24)
	10^9c/l	0,30 (0,19; 0,46)	0,31 (0,19; 0,41)	0,3 (0,2; 0,42)
CD4+/CD8+		1,5 (1,3; 1,9)*	1,4 (1,15; 2,0)*	1,8 (1,65; 2,17)
CIC	a.u.	4,9 (3,4; 6,9)*	5,5 (2,9; 7,1)*	3,3 (2,15; 4,7)

Notes: 1. * – p <0.05 compared to the control group; 2. # – p <0.05 compared with moderate fibrosis.

Table 2 – Indicators of carbohydrate metabolism in patients with NAFLD, Me (Q1, Q2)

Indicator	NAFLD (n=101)	Moderate fibrosis (n=88)	Marked fibrosis (n=13)	Control group (n=30)
Insulin, μIU/mL	16,5 (10,6; 19,4)*	15,8 (10,7; 25,4)*	22,2 (8,1; 30,7)* #	11,0 (2,3; 19,4)
Glucose,	4,8 (4,3; 5,9)	4,8 (4,3; 5,5)	6,1 (4,3; 6,2)* #	4,2 (3,8; 4,4)
HOMA-IR	3,8 (2,4; 4,5)*	3,3 (2,4; 4,8)*	4,5 (2,9; 4,6)* #	2,0 (1,3; 2,5)

Notes: 1. * – p <0.05 compared to the control group;2. # – p <0.05 compared to the group of patients with early fibrosis.

Table 3 – The level of pro- and anti-inflammatory cytokines in patients with NAFLD Me (Q1, Q2)

Indicator	NAFLD (n=101)	Moderate fibrosis (n=88)	Marked fibrosis (n=13)	Control group (n=30)
IL-6, pg/ml	2,8 (0,9; 5,5)	2,6 (1,0; 5,2)	5,5 (0,7; 11,0)* #	2,4 (0,2; 5,2)
IL-10, pg/ml	3,3 (1,2; 10,0)*	3,3 (1,4; 10,0)*	4,0 (0,7; 9,2)*	7,55 (4,3; 13,9)
TNF-α, pg/ml	1,1 (0,4; 5,1)* #	1,0 (0,4; 4,4)*	5,5 (0,7; 11,0)* #	0,5 (0,1; 3,8)
TNF-α/ІЛ-10	0,6 (0,1; 2,0)* #	0,6 (0,1; 1,3)*	1,4 (0,6; 3,8)* #	0,07 (0,05; 0,08)

Notes: 1. * – p <0.05 compared to the control group; 2. # – p <0.05 compared to the group of patients with moderate fibrosis.

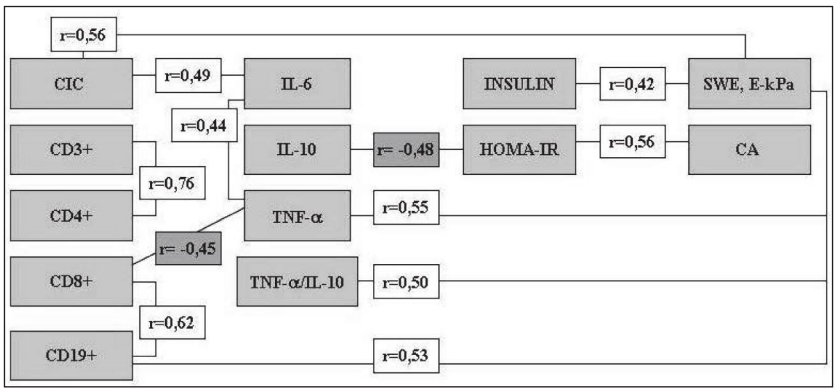

Figure 3 – Correlations detected in NAFLD patients.

When assessing the state of proinflammatory cytokines, it was found that the median value of IL-6 in the serum of patients with NAFLD was not significantly different from the control values, with its level increased 2.9 times (p <0.05) in patients with marked fibrosis as compared to the values for moderate fibrosis **(table 3).**

The concentration of TNF-α in patients with NAFLD is significantly higher by 2.2 times (p <0.05) as compared to the control group due to the significant increase of its content by 5.5 times in marked fibrosis.

As a result of determining the ratio between the pro-inflammatory and anti-inflammatory cytokines values (TNF-α / IL-10), changes in their balance toward proinflammatory cytokines were observed in patients with NAFLD as compared to the control group. The most pronounced shift is noted in patients with marked fibrosis.

In accordance with the results of correlation analysis, patients with NAFLD were found to have significant correlations between cellular and humoral immunity indicators, the cytokine level, carbohydrate metabolism and structural changes in the liver **(fig. 3).** In particular, the detected correlation between the HOMA-IR index values and the attenuation coefficient of the ultrasound (r = 0.56, p <0.01) has proved that NAFLD progression is accompanied by insulin resistance. At the same time, the development of fibrotic transformation in the liver occurs on the background of marked inflammation, as evidenced by the established positive correlations between the liver stiffness index according to SWE and the CIC level (r = 0.56, p <0.01), TNF-α content (r = 0.55, p <0.05) and the ratio value of proinflammatory and anti-inflammatory cytokines (r = 0.50, p <0.05).

Discussion. As a result of the investigation, the identified decrease in the relative indices of CD3+, CD4+, CD4/CD8 indicates a lack of cellular immunity in patients with NAFLD, especially in those with marked fibrosis. At the same time, the expression of activating antigens remains high, which indirectly indicates a disturbed signalling in the cells of the immune system. Lack of energy potential in lymphocytes, impaired maturation and differentiation in subpopulations of immunoregulatory cells are accompanied by a sharp change in the quantitative and functional parameters of immunocompetent cells, which is a major link in the pathogenesis of secondary immunodeficiency states in the fibrosis progression. The investigation has determined that fibrosis progression was associated with an increase of IL-6 and TNF-α levels. It is known from the literature that an increased level of pro-inflammatory cytokines does not induce the secretion of anti-inflammatory cytokines (IL-10), which leads to the excessive activation of macrophages, support of the inflammatory process and progression of fibrosis [15]. At the same time, with a favorable NAFLD development, the concentration of TNF-α decreases, so the study of serum concentration of this cytokine in the dynamics can be used to estimate the prognosis, in combination with other indicators [16].

The established correlations between immunological status indicators and insulin content, HOMA-IR and SWE data in patients with NAFLD indicate the feasibility of using immunological data as non-invasive diagnostic criteria for predicting the progression of structural liver changes and the insulin resistance.

Conclusions

1. The progression of liver fibrosis is accompanied by a lack of cellular immunity and an increase in the level of pro-inflammatory cytokines.

2. A significant imbalance between pro-inflammatory and anti-inflammatory cytokines (TNF-α / IL-10) has been detected in patients with marked liver fibrosis.

3. Significant fibrotic liver changes in patients with NAFLD occur on the background of profound disorders in the carbohydrate metabolism.

Prospects for further research. The development of the screening algorithm for the marked liver fibrosis in patients with NAFLD is considered to be a promising and important scientific direction, with consideration of the immunological status indicators.

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ОСОБЛИВОСТІ ІМУНОЛОГІЧНОГО СТАТУСУ ТА ВУГЛЕВОДНОГО ОБМІНУ У ХВОРИХ НА НЕАЛКОГОЛЬНУ ЖИРОВУ ХВОРОБУ ПЕЧІНКИ ЗАЛЕЖНО ВІД ЇЇ ФІБРОЗНОЇ ТРАНСФОРМАЦІЇ

Степанов Ю. М., Діденко В. І., Коненко І. С., Татарчук О. М., Петішко О. П.

Резюме. Сьогодні неалкогольна жирова хвороба печінки (НАЖХП) набуває все більшого поширення в усьому світі. *Мета:* визначити особливості змін імунологічного статусу у хворих на НАЖХП в залежності від стадії фіброзу. *Об'єкт і методи.* Обстежені 101 пацієнт з НАЖХП. Зсувнохвильову еластографію і оцінку коефіцієнта затухання ультразвуку виконано на апараті Soneus P7 (Україна, Швейцарія). Визначали субпопуляційний склад лімфоцитів, циркулюючі імунні комплекси, оцінювали інсулінорезистентність. *Результати.* Рівень лімфоцитів підвищений в 38,6% випадках; У 68,3% пацієнтів – знижений відносний вміст СД3+ лімфоцитів. У 59,4% хворих на НАЖХП рівень ЦІК був вірогідно підвищений (p<0,05) відносно рівня контролю. У хворих із вираженим фіброзом встановлено вірогідне підвищення відносного вмісту СД19+ лімфоцитів в 1,6 рази (p<0,05) та в 1,4 рази (p<0,05) в порівнянні із його рівнем в контрольній групі та у хворих із помірним фіброзом, відповідно. Виявлена кореляція між значеннями індексу HOMA-IR з коефіцієнтом затухання ультразвуку (r=0,56, p<0,01). Встановлена асоціацію між інсуліном із жорсткістю печінки за даними SWE (r=0,42, p<0,05). *Висновки.* У пацієнтів на НАЖХП прогресування фіброзу печінки супроводжується недостатністю клітинної ланки імунітету й підвищенням рівня прозапальних цитокінів. Для хворих на НАЖХП з вираженим фіброзом печінки характерний значний дисбаланс рівня прозапальних та протизапальних цитокінів (TNF-α/ІЛ-10). У хворих на НАЖХП спостерігались значні фіброзні зміни печінки відбуваються на тлі глибокого порушення вуглеводного обміну.

Ключові слова: неалкогольна жирова хвороба печінки, зсувнохвильова еластографія, лімфоцити, інсулінорезистентність.

ОСОБЕННОСТИ ИММУНОЛОГИЧЕСКОГО СТАТУСА И УГЛЕВОДНОГО ОБМЕНА У БОЛЬНЫХ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ В ЗАВИСИМОСТИ ОТ ЕЕ ФИБРОЗНОЙ ТРАНСФОРМАЦИИ

Степанов Ю. М., Диденко В. И., Коненко И. С., Татарчук О. М., Петишко О. П.

Резюме. Сегодня неалкогольная жировая болезнь печени (НАЖБП) получает все большее распространение во всем мире. *Цель:* определить особенности изменений иммунологического статуса у больных НАЖБП в зависимости от выраженности фиброза. *Объект и методы.* Обследованы 101 пациент с НАЖБП. Сдвиговолновую эластографию, оценку коэффициента затухания ультразвука проводили на аппарате Soneus P7 (Украина, Швейцария). Определяли субпопуляционный состав лимфоцитов, циркулирующие иммунные комплексы, оценивали инсулинорезистентность. *Результаты.* Уровень лимфоцитов повышен в 38,6% случаях. У 68,3% пациентов снижен относительное содержание СД3 + лимфоцитов. В 59,4% больных НАЖБП уровень ЦИК был достоверно повышен (p<0,05) относительно уровня контроля. У больных с выраженным фиброзом установлено достоверное повышение относительного содержания СД19 + лимфоцитов в 1,6 раза (p <0,05) и в

1,4 раза (p <0,05) по сравнению с контролем и в группе с выраженным фиброзом, соответственно. Выявлена корреляция между значениями индекса HOMA-IR с коэффициентом затухания ультразвука (r = 0,56, p <0,01). Установлена ассоциации между инсулином с жесткостью печени по данным SWE (r = 0,42, p <0,05). *Выводы.* У пациентов НАЖБП прогрессирования фиброза печени сопровождается недостаточностью клеточного звена иммунитета и повышением уровня провоспалительных цитокинов. Для больных НАЖБП с выраженным фиброзом печени характерен значительный дисбаланс уровня провоспалительных и противовоспалительных цитокинов (TNF-α / ИЛ-10). У больных НАЖБП наблюдались значительные фиброзные изменения печени происходят на фоне глубокого нарушения углеводного обмена.

Ключевые слова: неалкогольная жировая болезнь печени, сдвиговолновая эластография, лимфоциты, инсулинорезистентность.

ASPECTS OF IMMUNOLOGICAL STATUS AND CARBON METABOLISM IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN CORRELATION WITH ITS FIBROUS TRANSFORMATION

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Abstract. Today, non-alcoholic fatty liver disease (NAFLD) is becoming more widespread worldwide. NAFLD is diagnosed in almost half of the adult population, 25-30% of whom are at risk to progress to non-alcoholic steatohepatitis. Among the most important factors influencing the prognosis of NAFLD, tactics and effectiveness of treatment is the progression rate of fibrotic liver transformation. *Purpose of the investigation:* to determine the special features of immunological status changes in patients with NAFLD depending on their stage of fibrosis. *Object and methods of investigation.* The research involved 101 patients with NAFLD who were undergoing treatment at the Department of Liver and Pancreatic Diseases of «The Institute of Gastroenterology of NAMSU (National Academy of Medical Sciences of Ukraine)». Among the surveyed there were 32 men (31.7%) and 69 women (68.3%), the average age was (48.4±2.9) years. Shear-wave elastography was performed on a Soneus P7 apparatus (Ukraine, Switzerland). Then from these measurements the average values that characterized the liver stiffness in kilopascals (kPa) were determined. Ferraioli G threshold values were used to assess the fibrosis stage. In addition, the same apparatus was used to measure the ultrasound attenuation coefficient in dB/cm – a method of quantitative assessment of the liver steatosis degree. The subpopulation composition of lymphocytes was determined using the monoclonal antibodies of the firm «Sorbent TM» to molecules CD3, CD19, CD4, CD8, CD16. The mononuclear cells were isolated from the peripheral venous blood of patients in a density gradient of 1,077 g/cm. The immune status assessment was performed according to the guidelenes of R.V. Petrov (1992). Circulating immune complexes (CICs) were determined by the method of V. Haskov (1977). During the investigation, sets of reagents of the company «Vector-BEST» were used to measure the amount of TNF-α, IL-6, IL-10 and those of the company «DRG» Germany – to measure insulin in the blood serum. The enzyme-linked immunosorbent assay was performed using a «Stat Fax 303 Plus» analyzer (USA). HOMA-IR = fasting plasma glucose (mmol/l) times fasting serum insulin (mU/ml) devided by 22.5. *Research results.* While analyzing the immunological indicators in patients with NAFLD it was found that the level of lymphocytes was increased in 38.6% of cases. In 61.4% of patients a significant decrease in the T-helper subpopulation was observed. It should be noted that the median of relative content in CD4+ lymphocytes decreased significantly by 1.3 times (p <0.05) as compared to the control group. In 59.4% of patients with NAFLD, the CIC level was significantly increased (p <0.05) as compared to the control level. According to SWE results, a moderate fibrosis was diagnosed in 52 (51.5%) patients with NAFLD, while 13 (12.9%) patients were diagnosed with marked fibrosis. The highest median values of insulin were observed in patients with severe fibrosis, as evidenced by the correlation between this index and liver stiffness according to SWE data (r = 0.42, p <0.05). In addition, a significant increase in glucose levels of 1.5 times (p <0.05) and 1.3 times (p <0.05) has been observed in NAFLD patients with marked and moderate fibrosis respectively, as compared to the control group levels. The HOMA-IR values in patients with NAFLD were above 3.0 and were significantly different from those in the control group. These changes were more pronounced in patients with marked fibrosis (p <0.05). In accordance with the results of correlation analysis, patients with NAFLD were found to have significant correlations between cellular and humoral immunity indicators, the cytokine level, carbohydrate metabolism and structural changes in the liver. In particular, the detected correlation between the HOMA-IR index values and the attenuation coefficient of the ultrasound (r = 0.56, p <0.01) has proved that NAFLD progression is accompanied by insulin resistance. At the same time, the development of fibrotic transformation in the liver occurs on the background of marked inflammation, as evidenced by the established positive correlations between the liver stiffness index according to SWE and the CIC level (r = 0.56, p <0.01), TNF-α content (r = 0.55, p <0.05) and the ratio value of proinflammatory and anti-inflammatory cytokines (r = 0.50, p <0.05).

Conclusions. The progression of liver fibrosis is accompanied by a lack of cellular immunity and an increase in the level of pro-inflammatory cytokines. A significant imbalance between pro-inflammatory and anti-inflammatory cytokines (TNF-α / IL-10) has been detected in patients with marked liver fibrosis. Significant fibrotic liver changes in patients with NAFLD occur on the background of profound disorders in the carbohydrate metabolism.

Key words: nonalcoholic fatty liver disease, shear wave elastography, lymphocytes, insulin resistance.

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