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# NON-ALCOHOLIC FATTY LIVER DISEASE

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**ABSTRACT**

In recent decades, there has been an increase in non-alcoholic fatty liver disease (NAFLD), which not only leads to a decrease in the quality of life of patients, but also affects their life expectancy. Fatty hepatosis or non—alcoholic fatty liver disease (NAFLD, steatosis) is a disease in which excessive accumulation of fats (mainly triglycerides) is observed in the liver. Normally, there is a certain amount of fat in the liver, but when exposed to certain pathological factors, the balance between the synthesis and utilization of fats may be disturbed. The prevalence of NAFLD is higher among men and increases with age, due to socio-economic differences and lifestyle. In the general population of Western countries, the prevalence of NAFLD is 20-30%, of which 2-3% of cases have a progressive course of liver disease with transformation into non-alcoholic steatohepatitis (NASH), cirrhosis of the liver, hepatocellular carcinoma. The triglyceride content in NAFLD can reach 40% of the liver weight (at a rate of about 5%). NAFLD develops in three stages — steatosis, non-alcoholic steatohepatitis (NASH) and fibrosis. NAFLD often proceeds unnoticed, almost asymptomatic. The patient may not know for a long time about the presence of the disease, simply not paying attention to non-specific changes in well-being. It was found that the frequency of detection of NASH during biopsy in Western Europe and the USA is 7-9%. examination of large groups of patients with cryptogenic cirrhosis of the liver, which included an assessment of concomitant diseases and risk factors, allowed us to suggest that in 60-80% of cases of cirrhosis of unclear etiology is formed in the outcome of unrecognized NASH. The essence of the disease is liver obesity, the replacement of a normal healthy liver with fat, which leads to cirrhosis, like any other liver diseases, including viral hepatitis.The most significant risk factors are male

gender, obesity, increased waist circumference, metabolic syndrome, insulin resistance and type 2 diabetes mellitus (DM).

**Keywords:** non-alcoholic fatty liver disease, lifestyle, steatohepatitis, type 2 diabetes mellitus

## INTRODUCTION

In obese adult patients, the prevalence of NAFLD can reach 80-90%. This indicator is higher in patients with type 2 diabetes (30-50%), and in hyperlipidemia reaches 92%. Since these diseases have common pathogenetic mechanisms, they often combine and potentiate each other. The literature presents numerous data on possible pathogenetic mechanisms of liver damage in DM, as well as on the importance of the liver itself in the occurrence and progression of DM. The accumulation of free fatty acids in the liver leads to a violation of the permeability of cell membranes, including glucose, which increases the resistance of tissues to insulin, and also supports hyperglycemia. Most of us have only general ideas about the functions of the liver and believe that its main role is detoxification, that is, blood purification. This is certainly an important task, but only one of many. The liver is actively involved in metabolism and, in particular, in fat metabolism. It is in this organ that their splitting occurs with the release of energy. Unfortunately, liver cells are not only involved in fat metabolism, but also accumulate it, which leads to the development of a serious disease – non-alcoholic fatty liver disease (NAFLD), or fatty hepatosis. What is fatty hepatosis? Non–alcoholic fatty liver disease (NAFLD) is a disease that has many names: steatosis, steatohepatitis, fatty liver degeneration, fatty liver dystrophy, fatty hepatosis. However, its essence remains unchanged: due to the accumulation of fat in hepatocytes (liver cells) in an amount exceeding 5-10% of the liver weight, increased formation of free oxygen radicals begins, which can lead to the destruction of the cell membrane. As a result, inflammation begins in the organ (non-alcoholic steatohepatitis) and, as a result, cirrhosis and liver cancer can develop. There are 4 degrees of fatty hepatosis: 0 degree – small particles of fat are contained in separate groups of liver cells; I degree – the size of fat droplets in cells increases, separate foci of affected cells are formed (33% of affected hepatocytes in the field of vision); II degree – fat droplets of different sizes are contained in 33-66% of liver cells (small droplets, medium-drop, large-drop intracellular obesity); Grade III – fat "goes" beyond the cells, extracellular fatty formations are formed – cysts (diffuse large–drop obesity with extracellular localization) - more than 66% of the affected hepatocytes in the field of vision.Under IR conditions, the liver "overflows" with lipids

and synthesizes a large number of very low-density lipoproteins (LDL), which are rapidly modified into low-density lipoproteins (LDL). However, the causes and relationships between the progression of liver fibrosis and impaired carbohydrate metabolism in patients with NAFLD combined with type 2 diabetes are insufficiently studied. It is a proven fact that fibrogenesis in the liver in NAFLD is associated with hyperglycemia and insulin resistance, leading to an increase in the level of free fatty acids and liver steatosis, and free radicals and proinflammatory cytokines lead to apoptosis of hepatocytes and activation of inflammatory cells with progression to liver fibrosis. the realization of fibrogenesis is carried out by enhancing hyperlipidemia, stimulating the production of pro-inflammatory cytokines, oxidative stress, and the development of insulin resistance. The first and most obvious cause of the development of fatty hepatosis is overweight. If the body mass index (an indicator that is calculated as body weight in kilograms divided by height in square meters) exceeds 30, then the probability of fatty hepatosis is up to 40%. Also, risk factors include: type 2 diabetes mellitus (from 15 to 60% of patients, according to various data, suffer from fatty hepatosis); hyperlipidemia (elevated blood lipids); hypercholesterolemia (elevated cholesterol in the blood). There are predictors that suggest a high risk of progression of NAFLD with the development of steatohepatitis and fibrosis, these include: female sex, body mass index (bMI) more than 28 kg/m$^2$, an increase in alanine aminotransferase (AlT) activity by 2 times or more, triglyceride (TG) levels more than 1.7 mmol/l, the presence of hypertension (AG), type 2 SD. The presence of more than two predictors indicates a high risk of liver fibrosis.

The "gold standard" for the diagnosis of liver diseases is a puncture liver biopsy, however, given the invasiveness of the procedure, non-invasive tests are proposed to assess the presence of fibrosis, according to the criteria of E. M. Brant. One of these tests is the NAFLD fibrosis score (NFS), a non–invasive system that identifies liver fibrosis in patients with NAFLD. The method was developed in 2007 by P. Angelo et al., at the Mayo Clinic. the test results are evaluated in numerical values and coordinated with widely used histological index scales used to assess the severity of the pathological process. The positive prognostic value is 90%. This test is recommended by experts in some countries as a first-line test.

The indicators included in the analysis are: age, hyperglycemia, body mass index, platelet count, albumin level and the ratio of aspartate aminotransferase and alanine aminotransferase (AST/ALT).

The NFS index < – 1.455 indicates the absence of significant fibrosis (F0-F1 fibrosis). Values in the range from 1.455 to 0.675 are uncertain, the so-called "gray zone". NFS index >0.675 is a predictor of fibrosis (F3-F4 fibrosis).

In patients with an NFS index < – 1.455, the course of NAFLD remains stable for many years and rarely progresses. The group of patients with severe fibrosis (NFS index >0.675) has a higher risk of liver cirrhosis and hepatocellular carcinoma. Patients who have entered the "gray zone" require careful monitoring and selection of therapy, followed by repeated testing. Depending on the quality of the therapy, patients from the "gray zone" can "move" both to the group with minimal manifestations of fibrosis and have disease progression.

The aim of the work is to study the relationship between impaired lipid metabolism and the degree of fibrosis in patients with NAFLD and in combination with Type 2 SD.

## MATERIALS AND METHODS

We observed 48 patients aged 26 to 60 years. The first group included 28 (58.3%) patients with isolated course of NAFLD. In the second group, NAFLD was combined with type 2 diabetes in 20 (41.7%) patients. In all patients, the diagnosis was verified using instrumental (ultrasound) and clinical and laboratory research methods. To exclude the viral etiology of liver damage, markers of hepatitis B and C were determined by Pcr. The exclusion criteria were the use of alcohol or hepatotropic poisons in the anamnesis. Glucose, cholesterol, and especially triglycerides may also increase in the blood. For reference, the norms of AST content in men are up to 37 Units / l, in women – up to 31 Units / l, in children – up to 47 Units / l. ALT in a healthy body is contained in an amount of up to 41 units / l in men, up to 31 Units / l and up to 39 Units / l in women and children 6-12 years old, respectively. For infants and children under 6 years of age, the rate of indicators is higher and decreases with age. Ultrasound of the liver allows you to assess the increase in its size, as well as the heterogeneity of tissues affected by fatty hepatosis. Elastography can be attributed to non-invasive methods of studying liver structures. The technique aims to study the elasticity of liver tissues using ultrasound and allows you to estimate the volume of connective tissue growth. The functional state of the liver was assessed by the level of total bilirubin and its fractions (the endrashik– Cleggorn–Groff method), the activity of alkaline phosphatase (alkaline phosphatase) (using a photoelectric colorimeter kFk-2 for hydrolysis of n-nitrophenyl phosphate), AST and AlT (unified dinitrophenylhydrazine method of Reitman-Frenkel), thymol test (unified method), proteinograms (turbinometric method using a densitometer), lipid profile. As markers of lipid metabolism, the content of total cholesterol (ilka method), β-lipoproteins, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) in blood serum was studied (by

discelectrophoresis in polyacrylamide gel). The level of platelets in the blood serum was determined using a photoelectric colorimeter kFk-2.
The risk of fibrosis was calculated using the NFS formula.

**RESULTS**

When assessing the trophological status, overweight patients prevailed in both groups. the body mass index was less than 25 kg/m² in only 17.5% of patients in the group with isolated NAFLD and only 5% of patients in the group with a combination of NAFLD and type 2 diabetes. Whereas grade 2 obesity was observed in 7% and 50% of patients in each group, respectively. During the NAFLD fibrosis score in the first group of patients, the absence or minimal manifestations of fibrosis were detected in 71.6% of patients, while in patients of the second group – in 65% of patients (Table 1). 21.4% and 25% of patients were in the "gray zone", respectively. A high risk of liver fibrosis was found in 7% of patients with NAFLD and in 10% of patients with a combination of NAFLD and type 2 diabetes. The results obtained correspond to the literature data.

Table 1 Indicators of the degree of fibrosis

| NFS Fibrosis Assessment Range | NAFLD (n=28) | NAFLD+**DM** type 2 (n=20) |
|---|---|---|
| < – 1.455 (F0-F1 fibrosis) | 71.6% | 65% ** |
| from – 1.455 to 0.675 ("gray zone") | 21.4% | 25% |
| >0,675 (F3-F4 fibrosis) | 7% | 10% ** |

**Note: ** – p0.05 the significance of differences in comparison with patients of the first group.**

The risk of fibrosis in combination of NAFLD with type 2 diabetes is significantly higher ($p<0.05$) than in the isolated course of NAFLD, which further emphasizes the consistency and regularity of metabolic disorders.
In patients with NAFLD and NAFLD in combination with type 2 diabetes, there was a significant increase in AlT and AST levels relative to the control group ($p<0.001$), there were no significant differences between the first and second groups, although the level of aminotransferases was higher in patients with NAFLD (the first group).
Violation of lipid metabolism was detected in patients of two groups (Table 2). Total cholesterol, β-lipoproteins and triglycerides were significantly increased in both groups compared to the control group ($p<0.001$) and between groups ($p<0.05$). However, in the second group, the levels of these indicators were higher

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Table 2 Biochemical parameters of the liver

| Indicator, unit of measurement | NAFLD (n=28) | NAFLD+DM type 2 (n=20) | control group (n=10) |
|---|---|---|---|
| bMI, kg/m2 | 28,2±3,7# | 33,4±4,7# | 24,2±1,2 |
| AlT, units/l | 66,7±37,9# | 62,5±40,2# | 24,8±5,1 |
| AST, units/l | 54,0±28,8# | 59,7±36,2# | 22,9±5,7 |
| Oh, mmol/l | 5,9±0,83# | 6,77±1,0#* | 4,6±0,3 |
| β-lP, ed | 60,7±9,7# | 73,5±15,0#* | 40,6±10,6 |
| TG, mmol/l | 1,6±0,59 # | 2,3±0,68#* | 0,98±0,3 |
| HDL, mmol/l | 1,06±0,18# | 1,02±0,17# | 1,37±0,27 |
| LDL, mmol/l | 4,23±0,66# | 5,03±0,88# | 2,8±0,5 |
| VLDL, mmol/l | 0.5±0.23# | 0.62±0.53# | 0.28±0.13 |
| Albumins,% | 51,4±0,8 | 47,5±0,62 | 58±0,52 |
| α1-globulins,% | 8,1±0,17 | 8,32±0,22 | 8,17±0,19 |
| α2-globulins,% | 9,1±0,2 | 9,36±0,2 | 8,8±0,24 |
| β-globulins,% | 12,43±0,16 | 15,7±0,28 | 9,4±0,3 |
| γ-globulins,% | 18,4±0,24## | 19,9±0,23##* | 16,5±0,27 |
| Thymol sample, units. | 5,9±0,18## | 9,1±0,25##* | 2,11±0,08 |
| Thrombocyte, 109/l | 212±39 | 204±42 | 226±23 |

Note: * – p<0.05 reliability of differences between patients of the first and second groups; # – p<0.001 reliability of differences in comparison with the control group; ## – p<0.05 reliability of differences in comparison with the control group

than in the NAFLD group (p<0.05). This is consistent with the literature data on a higher proportion of NAFLD in patients with type 2 diabetes. In this case, the liver receives an excessive amount of fats and carbohydrates, which are converted into fatty acids, which are a substrate for the synthesis of triglycerides and very low-density lipoproteins that accumulate in hepatocytes. of the latter, due to the increased activity of triglyceride synthetase and triglyceride lipase, β-lipoproteins are synthesized. high-density lipoproteins were significantly (p<0.001) reduced in two groups of observations, due to the high level of triglycerides in the blood serum. however, a decrease in HDL levels in the second group was found in 30% of patients compared with the isolated course of NAFLD (22%). LDL and VLDL were significantly (p<0.001) increased in both groups compared with the control, however, significant differences in LDL and VLDL levels in groups 1 and 2 could not be detected.

Analysis of the protein spectrum indicators in patients of two groups revealed a significant (p<0.05) increase in gamma globulins, in the group with a combination of NAFLD and type 2 diabetes, compared with the indicators of the first group. The parameters of the thymol sample reflecting the change in the colloidal composition of proteins in the blood serum were significantly (p<0.05) increased in the first group

of patients compared with the control, and in the second group when compared with the control ($p<0.001$) and the first group ($p<0.05$). correlation analysis revealed positive associations between bMI and TG level ($r=0.64$; $p<0.001$) in the NAFLD group. The increase in the concentration of oH and TG in the group of patients with NAFLD and type 2 diabetes directly depended on bMI ($r=0.67$, $p<0.05$; $r=0.71$, $p<0.05$, respectively).

## CONCLUSIONS

1. NAFLD is a chronic progressive disease leading to the development of liver cirrhosis and hepatocellular carcinoma. The NAFLD fibrosis score test is a diagnostic non-invasive test for determining liver fibrosis and disease progression.
2. In NAFLD, lipid metabolism disorders correlate with the severity of liver fibrosis: the higher the dyslipidemia, the more likely it is to develop liver fibrosis.
3. With NAFLD in combination with type 2 diabetes, the risk of liver fibrosis increases.

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