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O. S. Khukhlina, T. M. Antofiichuk,
A. A. Antoniv, M. P. Antofiichuk
Higher state educational institution of Ukraine
«Bukovinian State Medical University», Chernivtsi

Intensity of liver parenchym fibrosis in patients with alcoholic and non-alcoholic steatohepatitis depending on the presence of dysmetabolic iron overload syndrome

Objective — to establish the features of iron homeostasis in patients with steatohepatitis of alcoholic and non-alcoholic etiology depending on the presence of dysmetobolic iron overload syndrome, to identify the probable link between ferrokinetics and markers of biochemical syndromes of steatohepatitis, the intensity of endotoxicosis and fibrosing reactions.

Materials and methods. The study was based on the clinical follow-up of 125 individuals, including 60 patients with nonalcoholic steatohepatitis and 65 patients with alcoholic steatohepatitis, 25 practically healthy individuals of appropriate age and gender. Depending on the indicators of iron homeostasis, the examined patients were divided into 4 groups: alcoholic steatohepatitis with dysmetabolic iron overload syndrome — 40 patients, 25 patients without dysmetabolic iron overload syndrome; 18 patients with non-alcoholic steatohepatitis and dysmetabolic iron overload syndrome and 42 patients — without dysmetabolic iron overload syndrome.

Results. In alcoholic steatohepatitis, activation of collagen anabolism processes was observed through the growth of protein-bound oxyproline in blood — in the presence of iron overload syndrome 2.5 times ($p < 0.05$), in the absence — 2.0 times ($p < 0.05$), as well as a significant increase in the intensity of collagen catabolism — by increasing the content of free oxyproline in blood, respectively — by 1.5 and 1.3 times ($p < 0.05$), which occurred due to a significant increase in collagenolytic activity of blood plasma (respectively in 1.6 and 1.4 times; $p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$) in all the cases. There was a significant increase in the content of hexosamines in blood: with iron overload syndrome 1.6 times ($p < 0.05$), in its absence — 1.5 times ($p < 0.05$), the content of sialic acids, respectively — 1.6 and 1.5 times ($p < 0.05$), and the accelerated degradation of fucoglycoprotein components of the extracellular matrix. In non-alcoholic steatohepatitis, activation of collagen synthesis processes with an increase in blood protein-bound oxyproline was established — in the presence of iron overload syndrome 1.6 times ($p < 0.05$), in the absence — 1.3 times ($p < 0.05$), as well as a slight increase in the intensity of collagen breakdown — with an increase in the content of free oxyproline in blood in non-alcoholic steatohepatitis with iron overload syndrome — 1.2 times ($p < 0.05$). There was also a significant increase in the content of hexosamines in blood: in the presence of iron overload syndrome by 1.3 times ($p < 0.05$), in its absence — by 1.2 times ($p < 0.05$), the content of sialic acids, respectively — in 1.4 and 1.2 times ($p < 0.05$), and the accelerated degradation of fucoglycoproteins.

Conclusions. The regularities of liver fibrosis progression in patients with alcoholic steatohepatitis with iron overload syndrome are inextricably linked with the activation of collagen anabolism, the increase in the intensity of collagen catabolism, which occurred due to a significant increase in collagenolytic activity of blood plasma. An important consequence of the activation of cytolysis and inflammation is a significant increase in the content of hexosamines in blood. In patients with nonalcoholic steatohepatitis, there was an activation of collagen synthesis, a slight increase in the intensity of collagen breakdown in the presence of iron overload syndrome, as well as a characteristic increase in blood hexosamines, and the accelerated degradation of fucoglycoproteins.

Key words: iron homeostasis, steatohepatitis of alcoholic etiology, steatohepatitis of nonalcoholic etiology, endotoxicosis.

Dysmetabolic iron overload syndrome (DIOS), which is currently an extremely important problem in internal medicine, is a pathological syndrome complex characterized by a steady increase in the content of elemental iron in the body with increased deposition in parenchymal organs, skin, bone marrow cells, resulting in toxic effects of iron [2, 3]. In contrast to hemochromatosis — a genetic disorder of iron metabolism [2, 7, 11], the development of DIOS is associated with congenital or acquired insufficiency of mechanisms of the regulation of iron excretion, accumulation in the population of mutations in genes of proteins that regulate iron metabolism; inefficient erythropoiesis and insufficient utilization of iron in the bone marrow, predominance of meat products in the diet; increasing life expectancy in the population, living in geo-zones with high iron content in soil, drinking water, the impact of harmful production factors in terms of industrial production [1, 3, 7—12]. The presence of DIOS is observed in various pathological conditions, including viral hepatitis B, C, alcoholic (AFLD) and non-alcoholic fatty liver disease (NAFLD) [10, 14—17, 21]. According to literature sources, DIOS is observed in 70—90 % of patients with alcoholism and is one of the likely adverse diagnostic criteria for alcoholic steatohepatitis (ASH) [13]. At the same time, DIOS also occurs in 20—30 % of cases of NAFLD [10, 17—19, 21].

Possessing powerful redox properties, iron is required for oxygen transport, the synthesis of deoxyribonucleic acids (DNA), activation of mitochondrial enzymes [1, 12]. As a metal with variable valence, iron in non-heme enzymes (catalase, peroxidase, cytochrome) neutralizes reactive oxygen species (ROS) [1]. At the same time, the increase in the Fe III pool can be a catalyst for the formation of a significant amount of ROS and an inducer of oxidative stress (OS) [3, 5]. During the transition of Fe III to Fe II, toxic free radicals are formed activating the processes of lipid peroxidation (LPO) and oxidative modification of proteins (OMP) [12]. A significant intensity of DIOS in the body makes it inhibit the work of its own antioxidant defense systems (ADS) and natural detoxification systems [4—6]. With excessive accumulation of iron in the depot organs, there is direct DNA damage and increased collagen formation [6].

The formation of DIOSs in patients with AFLD and NAFLD occurs due to a number of dysmetabolic factors, in particular, decreased synthesis of hepcidin, proteins that regulate iron metabolism (ferritin, transferrin, hepcidin, ceruloplasmin) in the liver due to hepatocellular insufficiency (HCI); dysregulatory redistribution of iron with accumulation in the cells of the liver, spleen due to portal hypertension, hypersplenism, portocaval blood shunting [20]. In obese patients, exogenous iron overload is not excluded with the daily consumption of large amounts of red meat, offal, wine, and other alcoholic beverages that stimulate the absorption of iron with food [3, 14, 18]. Prominent among the etiological factors of DIOS is the presence of hepatic steatosis, abdominal obesity, hyperglycemia and insulin resistance (IR), which significantly impair the functioning of transferrin due to its glycosylation, increased iron supply to the liver and ferritin synthesis [19]. The predominant accumulation of iron in hepatocytes, Kupffer cells in the perisinusoidal space triggers the processes of apoptosis, necrosis, collagen formation and is a trigger mechanism for the progression of hepatic steatosis to nonalcoholic steatohepatitis (NASH) with subsequent development of liver fibrosis (LF), liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [11, 14—17].

The analysis of the literature sources indicates a high interest of scientists in the likely impact of DIOS on the course of chronic viral hepatitis, liver cirrhosis of various etiologies [6, 13, 14] and so on. At the same time, the influence of hypersideremia, DIOS in general on markers of liver damage, the intensity of its fibrosis in patients with ASH and NASH are currently insufficiently studied, which determines the relevance of our study.

Objective — to establish the features of iron homeostasis in patients with steatohepatitis of alcoholic and nonalcoholic etiology depending on the presence of dysmetabolic iron overload syndrome, to identify a probable correlation between ferrokinetics and markers of biochemical syndromes of steatohepatitis, endotoxicosis and fibrosing reactions.

Materials and methods

125 patients were examined, including 60 on NASH and 65 patients with ASH, 25 practically healthy individuals of the corresponding age and sex. The examinations were performed in the gastroenterological and therapeutic departments of the Emergency Medical Service of Chernivtsi in 2015—2020. Among the examined patients with NASH there were 15 (25.0 %) male patients and 45 (75.0 %) female patients. The mean age of the examined patients was 46.3 ± 5.2 years. Among the examined patients with ASH, there were 56 male patients (86.2 %) and 9 female patients (13.8 %). The mean age of patients with ASH was 47.4 ± 5.1 years. The control group consisted of 25 practically healthy individuals (PHIs): male — 11 (44.0 %) and female — 14 (56 %). The mean age of PHIs was 41.3 ± 2.1 years.

The diagnosis of NASH and ASH was established in accordance with the unified clinical

guideline approved by the order of the Ministry of Health of Ukraine № 826 from 06.11.2014, in the presence of criteria for exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or drug genesis as a cause of cytolytic, cholestatic, mesenchymal-inflammatory syndromes, as well as the results of ultrasonography (USG) of the liver with shear wave elastography, AS-test Steato-test test, Fibro-test (BioRedictive, France). Additionally, in the diagnosis of steatohepatitis of alcoholic origin, anamnestic data on daily consumption of toxic doses of alcohol, consultation with a narcologist, availability of records in a narcological dispensary were taken into account.

The diagnosis of obesity was established according to the classification of the WHO International Working Group on Obesity (1997). Patients were measured for height and body weight, calculated body mass index (BMI) according to the Kettle formula: BMI = weight (kg)/height $(m)^2$.

The diagnosis of obesity was established when the BMI value is more than 30 kg/m^2.

The presence of DIOS was determined, in terms of ASH and NASH, by three of the following laboratory markers: increase in blood ferritin content of more than 300 μg/L in men and menopausal women and more than 200 μg/L in women of childbearing age; increase in serum iron content above reference values; decrease in total iron binding capacity blood serum; increase in iron saturation of transferrin by more than 45 %.

Depending on the indicators of iron homeostasis, the examined patients were divided into 4 groups. Among patients with ASH — DIOS was found in 40 patients (61.5 %), in 25 patients ASH was without DIOS (38.5 %) (Table 1). Among patients with NASH in 18 patients (30.0 %) was diagnosed with DIOS, in 42 people (70.0 %) NASH was without DIOS (see Table 1).

When patients were admitted to the hospital, the functional state of the liver was determined according to the approved list of enzyme activity, markers of pigment metabolism, mesenchymal inflammation, proteinogram, lipidogram, ionogram, calculation of the De Ritis Ratio, blood uric acid, urea, creatinine and creatinine.

Table 1. **Distribution of examined patients with steatohepatitis depending on the etiology and the presence of iron overload syndrome**

DIOS	PHIs (n = 25)	ASH (n = 65)	NASH (n = 60)
Yes	–	40 (61.5 %)	18 (30.0 %)
No	25 (100.0 %)	25 (38.5 %)	42 (70.0 %)

Iron homeostasis was studied by the content of iron, transferrin, ferritin in blood, the calculation of transferin saturation (TS):

TS = serum iron content : transferrin content · 3.9.

The intensity of endotoxicosis was studied by the content of medium molecular weight peptides (MMP) in blood by the method of NI Gabrielyan at a wavelength of 254 and 280 nm.

The intensity of liver tissue fibrosis was studied by changes in the metabolism of the following connective tissue components: the content of free according to S.S. Tetyanets (1985) and protein-bound oxyproline according to M.S. Osadchuk (1979), hexosamines by O.G. Arkhipova (1988), seromucoids, sialic acids using kits from the company *Danish Ltd* (Lviv), ceruloplasmin by the method of M.R. Revina (1976). The state of collagenolytic activity of blood plasma was studied by the intensity of azocol lysis with the help of reagents from *Danish Ltd* (Lviv).

The statistical analysis of the results was performed according to the type of study and the types of numerical data that were obtained. The normality of the distribution was checked using Liliefors, Shapiro-Wilk tests and the method of direct visual evaluation of histograms of the distribution of eigenvalues. The quantitative values that had a normal distribution are presented as mean (M) ± standard deviation (S). The discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of subjects). For the comparison of the data that had a normal distribution, we used parametric tests with the assessment of Student's t-test, Fisher's F-test. In the case of abnormal distribution, used: median test, calculation of the Mann–Whitney rank U-test, for multiple comparison — Wilcoxon T-test (in the case of the study of dependent groups). To assess the significance of the frequency of clinical manifestations of NASH and ASH depending on the DIOS, we used the method of calculating the odds ratio (OR) and determining its 95 % confidence interval. To assess the degree of dependence between variables, we used Pearson correlation analysis in the parametric distribution and Spearman's rank correlation coefficient in the case of the distribution of indicators that were significantly different from normal. For the statistical and graphical analyses of the obtained results we used software packages Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA).

Results and discussion

Analysis of iron homeostasis indicates a probable increase in serum iron in patients with NASH with DIOS — 1.7 times ($p < 0.05$) compared with PHIs,

and in the absence of DIOS — iron content corresponded to the reference values (Table 2) ($p > 0.05$).

In contrast to this data, in patients with ASH with DIOS, the increase in serum iron was more intense — 2.2 times ($p < 0.05$), however, and in the absence of DIOS in ASH, the iron content was significantly increased — 1.4 times ($p < 0.05$) in comparison with the indicator in PHIs though did not exceed the upper limit of norm, with the existence of a probable difference between similar groups of patients with NASH ($p < 0.05$) (see Table 2). The level of ferritin in the blood of patients with NASH with DIOS also exceeded the indicator in PHIs 2.7 times ($p < 0.05$), and in patients with ASH with DIOS — 4.3 times ($p < 0.05$) the presence of a probable intergroup difference ($p < 0.05$). In patients with NASH without DIOS, the ferritin content exceeded the index in PHIs by 1.3 times ($p < 0.05$), and in patients with ASH without DIOS — the excess was 1.6 times with the presence of an intergroup difference ($p < 0.05$) both between similar groups of patients with NASH and the groups of patients with DIOS ($p < 0.05$).

The results of the analysis of transferrin levels in patients with NASH with DIOS showed a significant excess of data in PHIs in 1.5 times ($p < 0.05$), and in patients with ASH with DIOS — 1.7 times ($p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$). In patients with NASH without DIOS, the transferrin content had only a tendency to increase ($p > 0.05$), and in patients with ASH without DIOS — the excess was 1.3 times with the presence of an intergroup difference ($p < 0.05$) as with a similar group patient with NASH, and with a group of patients with ASH with DIOS ($p < 0.05$).

The markers of transferrin saturation were increased in the observation groups of patients with NASH and ASH with DIOS: respectively in

Table 2. **Biochemical indicators of hepatocyte cytolysis activity, cholestasis, mesenchymal inflammation and hepatocellular insufficiency, indicators of iron homeostasis in patients with non-alcoholic and alcoholic steatohepatitis depending on the presence of iron overload syndrome**

Indicator	PHIs (n = 25)	NASH (n = 60)		ASH (n = 65)	
		DIOS (n = 18)	Without DIOS (n = 42)	DIOS (n = 40)	Without DIOS (n = 25)
ALT, U/L	22.8 ± 1.7	69.8 ± 2.8*	58.3 ± 2.4*#	82.4 ± 6.3*&	67.8 ± 4.8*&
AST, U/L	25.2 ± 1.5	57.2 ± 1.4*	41.6 ± 2.2*#	125.8 ± 5.8*&	102.0 ± 5.5*#&
De Ritis Ratio	1.1 ± 0.0	0.8 ± 0.0*	0.7 ± 0.0*#	1.5 ± 0.0*&	1.5 ± 0.0*&
Bilirubin general, μmol/L	14.1 ± 1.1	34.1 ± 1.5*	27.0 ± 1.7*#	48.3 ± 1.6*&	39.1 ± 1.3*#&
Bilirubin conjug., μmol/L	3.2 ± 0.2	8.6 ± 0.5*	6.4 ± 0.4*#	12.6 ± 0.8*&	10.3 ± 0.9*#&
Bilirubin uncong., μmol/L	10.9 ± 0.4	25.5 ± 1.2*	20.6 ± 1.1*#	35.7 ± 1.8*&	28.8 ± 1.2*#&
GGT, U/L	34.8 ± 5.3	127.7 ± 8.4*	106.2 ± 5.6*	261.5 ± 10.1*&	219.6 ± 9.8*#&
ALP, U/L	58.2 ± 4.1	106.9 ± 5.9*	83.8 ± 4.8*#	138.4 ± 6.3*&	112.0 ± 5.2*#&
LDH, U/L	164.5 ± 4.1	430.3 ± 12.7*	347.5 ± 10.5*#	568.9 ± 13.2*	498.5 ± 12.4*#&
Thymol test, RU	2.5 ± 0.1	4.7 ± 0.1*	3.9 ± 0.1*#	6.8 ± 0.1*&	6.3 ± 0.1*#&
Total protein, g/L	76.4 ± 4.3	59.6 ± 2.3*	67.3 ± 2.2*	54.2 ± 1.3*	57.5 ± 1.2*&
Albumin, g/L	43.1 ± 2.7	29.3 ± 1.1*	37.5 ± 1.3 #	27.6 ± 1.2*	31.7 ± 1.3*&
Uric acid, μmol/L	242.3 ± 8.2	332.9 ± 12.5*	308.4 ± 10.5*	512.8 ± 13.7*&	467.4 ± 12.4*&
Serum iron, μmol/L	17.6 ± 1.2	32.3 ± 1.2*	19.2 ± 1.1#	39.1 ± 0.9*&	25.6 ± 1.0*#&
Ferritin, μg/L	80.3 ± 5.8	219.8 ± 7.1*	103.7 ± 5.1*#	341.9 ± 4.3*&	227.6 ± 5.8*#&
Transferrin, g/L	2.4 ± 0.01	2.9 ± 0.01*	2.6 ± 0.01 #	3.3 ± 0.01*&	3.2 ± 0.01*#&
Transferrin saturation, %	27.6 ± 1.4	43.4 ± 1.3*	28.8 ± 1.4 #	46.2 ± 1.6*	31.2 ± 1.5#
MMP 254, RU/L	0.21 ± 0.00	0.35 ± 0.00*	0.30 ± 0.00*#	0.43 ± 0.00*&	0.39 ± 0.00*#&

Note. * Changes are probable ($p < 0.05$) in comparison with the indicator in PHIs.
Changes are probable ($p < 0.05$) in comparison with the indicator in patients with steatohepatitis with DIOS.
& Changes are probable ($p < 0.05$) in comparison with the indicator in patients with NASH.

NASH — 1.6 times and ASH — 1.7 times ($p < 0.05$), which indicates the presence of dysmetabolic iron overload syndrome. Accordingly, in the compared groups — patients with NASH and ASH without DIOS, the TS indicators were within the reference values ($p > 0.05$).

The analysis of the activity of biochemical syndromes of ASH and NASH depending on the presence of DIOS showed the following patterns (see Table 2). The activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) cytolysis markers was predominant in patients with ASH, and in the middle of the group — in patients with DIOS. In particular, in patients with ASH with DIOS, ALT activity exceeded the indicator in PHIs by 3.6 times (against 2.9 times without DIOS) ($p < 0.05$), and AST activity exceeded by indicator in PHIs by 5.0 times (against 4.1 times without DIOS) ($p < 0.05$) with a significant intergroup difference ($p < 0.05$). Thus, the De Ritis Rario exceeded the value in PHIs in both cases by 1.4 times ($p < 0.05$). LDH activity in patients with ASH with DIOS exceeded the indicator in PHIs by 3.5 times (against 2.0 times without DIOS) ($p < 0.05$). A strong correlation was found between the content of iron in the blood and the activity of AST ($r = 0.61$; $p < 0.05$), the content of transferrin in the blood and AST ($r = 0.67$; $p < 0.05$), the content of blood ferritin and AST ($r = 0.75$; $p < 0.05$), blood ferritin and LDH ($r = 0.73$; $p < 0.05$) in patients with DIOS.

In patients with NASH, depending on the presence of DIOS analysis of cytolysis showed the following patterns (see Table 2). The activity of ALT and AST was also predominant in patients with manifestations of DIOS, but probably of lower intensity. In particular, in patients with NASH with DIOS, ALT activity exceeded the indicator in PHIs 3.1 times (against 2.6 times without DIOS) ($p < 0.05$), and AST activity exceeded the indicator in PHIs 2.3 times (against 1.7 times without DIOS) ($p < 0.05$) with a significant intergroup difference ($p < 0.05$). The De Ritis Ratio in patients with NASH depending on the presence of DIOS was significantly reduced by 1.4 and 1.6 times ($p < 0.05$), respectively, compared with the PHIs, which indicates the presence of a toxic component in the pathogenesis of NASH with DIOS and increase in AST activity due to toxic effects of iron. It is confirmed by the data of the analysis of lactate dehydrogenase (LDH) activity, which in patients with NASH with DIOS exceeded the value in PHIs by 2.6 times (against 2.1 times without DIOS) ($p < 0.05$). Correlation analysis of cytolysis markers with ferrokinetic parameters showed the presence of relationships between blood iron content and AST activity ($r = 0.41$; $p < 0.05$), blood transferrin content and AST ($r = 0.39$; $p < 0.05$), blood ferritin and AST ($r = 0.54$; $p < 0.05$), blood ferritin and LDH ($r = 0.57$; $p < 0.05$), in patients with DIOS.

An important marker of cytolytic syndrome is a violation of pigment metabolism (see Table 2). The content of total bilirubin and its fractions in the blood was higher in patients with ASH (increase in the range of 2.6—3.2 times; $p < 0.05$) and increased depending on the presence of DIOS (in the range of 3.3—3.9 times; $p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$). The fraction of direct bilirubin content in the blood increased the most at ASH ($p < 0.05$). The content of total bilirubin and its fractions in NASH was slightly lower compared with patients with ASH (increase in the range of 1.9—2.0 times; $p < 0.05$) and also increased in the presence of DIOS (in the range of 2.3—2.7 times; $p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$). Among the bilirubin fractions, the maximum increase in the blood content of the direct fraction ($p < 0.05$) was found.

The analysis of markers of cholestasis indicates the maximum manifestation of this syndrome in patients with ASH with DIOS (see Table 2). This is evident from an increase in blood direct fraction of bilirubin in DIOS — 3.9 times (vs. 2.7 times in its absence) ($p < 0.05$), as well as an increase in the activity of parietal enzymes: the activity of gamma-glutamyl transferase (GGT) exceeded PHIs in 7.7 times (against 6.4 times without DIOS) ($p < 0.05$), and activity of alkaline phosphatase (ALP) — exceeded indicator in PHIs in 2.4 times (against 1.9 times without DIOS) $p < 0.05$) with a probable intergroup difference ($p < 0.05$).

Cholestasis syndrome was also present in patients with NASH and its intensity increased with the accession of DIOS. Thus, there was an increase in blood levels of direct fraction of bilirubin in DIOS — 2.7 times (vs. 2.0 times in its absence) ($p < 0.05$), as well as an increase in GGT activity — 3.7 times 3.1 times without DIOS) ($p < 0.05$), ALP — 1.8 times (vs. 1.4 times without DIOS) ($p < 0.05$) with a probable intergroup difference ($p < 0.05$).

The correlation analysis of markers of cholestasis with ferrokinetic parameters showed the presence of the link between blood iron content and GGT activity (at ASH $r = 0.55$, NASH $r = 0.27$; $p < 0.05$), blood transferrin and GGT content at ASH $r = 0.51$, NASH $r = 0.25$; $p < 0.05$), blood ferritin and GGT ($r = 0.48$; $p < 0.05$) in patients with DIOS.

The activity of mesenchymal-inflammatory syndrome in patients with steatohepatitis prevailed in the alcoholic etiology of the process. Thus, with

ASH, an increase in the thymol test was recorded for DIOS — 2.7 times (against 2.5 times in its absence) ($p < 0.05$). At the same time, in NASH with DIOS the level of this indicator exceeded the data in PHIs by 1.9 times (against 1.6 times without DIOS) ($p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$).

The association of the development of hepatic cell insufficiency with DIOS syndrome in patients with ASH and NASH is confirmed by the frequency of this syndrome, calculated according to the theory of «chance ratio», according to which the manifestations of this syndrome were found in patients with ASH with DIOS 4.25 times more often (OR = 4.25 [CI 1.47—12.31]; $p < 0.05$) than in its absence. In patients with NASH with DIOS — the markers of hepatic cell insufficiency were observed 4.28 times more often (OR = 4.28 [CI 1.37—13.95]; $p < 0.05$) than in its absence. According to the study of biochemical markers of hepatic cell insufficiency, in patients with ASH found a probable decrease in blood total protein content by DIOS — by 29.1 % (vs. 24.7 % without DIOS) ($p < 0.05$), decrease in blood albumin content compared with the indicator in PHIs in 1.6 times for DIOS (against 1.4 times without DIOS) ($p < 0.05$), as well as an increase in blood content of MMP 254—2.0 times (against 1.9 times without DIOS) ($p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$). Along with these indicators, patients with ASH found a significant increase in the content of uric acid in blood, which is a natural antagonist and chelator of iron: for DIOS — 2.1 times (vs. 1.9 times without DIOS) ($p < 0.05$) with a probable intergroup difference ($p < 0.05$). Acquired hyperuricemia associated with alcohol abuse is a factor that partially eliminates the prooxidative effects of hypersideremia, provides ADS, which should be considered when assessing the overall toxic effects of excess iron on the human body.

Patients with NASH were characterized by a slightly less intense probable decrease in blood total protein content by DIOS — by 22.0 % ($p < 0.05$), a decrease in blood albumin content compared with the indicator in PHIs 1.5 times per DIOS (against 1.2 times without DIOS) ($p < 0.05$), as well as an increase in the content of MMP 254—1.7 times (against 1.4 times without DIOS) ($p < 0.05$) with the presence of a probable intergroup differences ($p < 0.05$). Along with these indicators, patients with NASH were found to have significant hyperuricemia: for DIOS — 1.4 times (vs. 1.3 times without DIOS) ($p < 0.05$) with a significant intergroup difference ($p < 0.05$). In this case, against the background of NASH and obesity, hyperuricemia is one of the manifestations and components of the metabolic syndrome and also compensates for the toxic effects of DIOS, strengthening the natural system of ADS [5, 18].

Analysis of the results of the study of the intensity of fibrosing reactions in the liver on the content of connective tissue metabolism of the extracellular matrix (Table 3) in the blood of patients with ASH and NASH depending on the presence of DIOS indicates that inflammatory, dysmetabolic processes and violations of ferrokinetics contribute to a significant imbalance of connective tissue metabolism components.

In particular, in patients with ASH, activation of collagen anabolism processes was found to increase protein-bound oxyproline in blood — in the presence

Table 3. **Indicators in the blood of protein and carbohydrate-protein components of connective tissue in patients with non-alcoholic and alcoholic steatohepatitis, depending on the presence of iron overload syndrome**

Indicator	PHIs (n = 25)	NASH (n = 60)		ASH (n = 65)	
		DIOS (n = 18)	Without DIOS (n = 42)	DIOS (n = 40)	Without DIOS (n = 25)
FibroTest, RU	0.18 ± 0.01	0.37 ± 0.01*	0.29 ± 0.01*#	0.47 ± 0.01*&	0.40 ± 0.01*#&
Protein-bound oxyproline, μmol/L	40.5 ± 2.4	63.2 ± 1.1*	52.3 ± 1.2*#	98.6 ± 1.5*&	79.2 ± 1.7*#&
Free oxyproline, μmol/L	12.3 ± 0.3	14.3 ± 0.5*	11.4 ± 0.2 #	18.9 ± 0.4*&	16.6 ± 0.2*#&
Hexosamines, μmol/L	5.4 ± 0.02	6.8 ± 0.1*	6.2 ± 0.1*	8.9 ± 0.1*&	8.2 ± 0.1*#&
Seromucoids, μmol/L	1.8 ± 0.02	2.5 ± 0.02*	2.2 ± 0.03*#	2.9 ± 0.01*&	2.7 ± 0.02*#&
Non-protein fucose, μmol/L	37.3 ± 5.7	66.3 ± 7.1*	59.45 ± 6.2*	95.6 ± 7.5*&	91.3 ± 6.8*&
Collagenolytic activity, RU	0.8 ± 0.01	0.9 ± 0.01*	0.6 ± 0.01*#	1.3 ± 0.01*&	1.1 ± 0.01*#&

Note. * Changes are probable ($p < 0.05$) in comparison with the indicator in PHIs.
Changes are probable ($p < 0.05$) in comparison with the indicator in patients with steatohepatitis with DIOS.
& Changes are probable ($p < 0.05$) in comparison with the indicator in patients with NASH.

of DIOS 2.5 times ($p < 0.05$), in the absence — 2.0 times ($p < 0.05$), and also a significant increase in the intensity of collagen catabolism — by increasing the content of free oxyproline in blood, respectively — by 1.5 and 1.3 times ($p < 0.05$), which occurred due to a significant increase in collagenolytic activity of blood plasma, respectively, in 1.6 and 1.4 times; $p < 0.05$) with the presence in all cases of a probable intergroup difference ($p < 0.05$). Excess iron is a potent inducer of collagen anabolism by perisinusoidal hepatic stellate cells (Ito cells), which are activated against the background of increased inflammatory activity, endotoxicosis and oxidative stress. We also found a significant increase in the content of hexosamines in blood: 1.6 times ($p < 0.05$), in its absence — 1.5 times ($p < 0.05$), the content of sialic acids, respectively — 1.6 and 1.5 times ($p < 0.05$), and accelerated degradation of fucoglycoprotein components of extracellular matrix (with an increase in the content of fucose not bound to protein — in 2.6 and 2.4, respectively) times ($p < 0.05$)). The obtained data, indicating an imbalance in the synthesis and degradation of extracellular matrix components, caused a significant increase in the integrated Fibro-test, which indicates the stage of liver fibrosis, for ASH with DIOS — 2.6 times compared with the PHIs ($p < 0.05$), for ASH without DIOS — 2.2 times ($p < 0.05$), with the presence in all cases of a probable intergroup difference ($p < 0.05$).

In patients with NASH, the patterns of liver fibrosis have their own characteristics (see Table 3). In particular, the activation of collagen synthesis processes with an increase in the blood of protein-bound oxyproline — in the presence of DIOS 1.6 times ($p < 0.05$), in the absence — 1.3 times ($p < 0.05$), as well as a slight increase in the intensity collagen breakdown — with an increase in the content of free oxyproline in the blood in NASH with DIOS — 1.2 times ($p < 0.05$). In NASH without DIOS, the content of free oxyproline in the blood tended to decrease ($p > 0.05$). Somewhat divergent data was obtained in the analysis of collagenolytic activity in NASH: for DIOS registered increase in collagenolytic activity by 12.5 % ($p < 0.05$), but in its absence collagenolytic activity in NASH was reduced by 25.0 % ($p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$). That is, the activated processes of collagen synthesis in NASH are accompanied by inhibition of its degradation with accumulation in extracellular matrix [4—6]. In patients with NASH, we also found a significant increase in the content of hexosamines in blood: in DIOS 1.3 times ($p < 0.05$), in its absence — 1.2 times ($p < 0.05$), the content of sialic acids, respectively — 1.4 and 1.2 times ($p < 0.05$), and accelerated degradation of fucoglycoproteins (the content of fucose not bound to protein in the blood increased — 1.8 and 1.6 times, respectively ($p < 0.05$)). The consequence of the registered processes was an increase in the integrated Fibro-test indicator for NASH with DIOS — 2.1 times compared to the indicator in PHIs ($p < 0.05$), for NASH without DIOS — 1.6 times ($p < 0.05$) with the presence of a probable intergroup difference ($p < 0.05$).

Conclusions

Alcoholic steatohepatitis is characterized by dysmetabolic iron overload syndrome, which is registered in 61.5 % of patients. DIOS on the background of ASH runs with the classic signs of hypersyderemia, hyperferritinemia, hypertransferinemia and a significant increase in the percentage of transferrin saturation with iron (respectively 2.3 times, 4.3, 1.4 and 1.7 times; $p < 0.05$), which causes relatively higher activity of hepatocyte cytolysis, mesenchymal inflammation, cholestasis and hepatocellular insufficiency compared with the course of ASH without DIOS ($p < 0.05$). For patients with ASH without DIOS is also characteristic, but less intense (respectively 1.5, 2.8, 1.3 times; $p < 0.05$) increase in blood iron, ferritin and transferrin.

In patients with non-alcoholic steatohepatitis on the background of obesity, the manifestation of DIOS was registered in 30.0 % of cases, in which hypersideremia, hyperferritinemia, hypertransferrinemia, increase in the percentage of TS (increase in 1.9, 2.7, 1.2 and 1, respectively), 6 times; $p < 0.05$), which led to a higher manifestation of biochemical syndromes of NASH under DIOS conditions with a higher degree of increase in aspartate aminotransferase activity in response to the toxic effects of iron, as indicated by a probable difference in De Ritis Ratio (respectively in DIOS — in 1.4 vs. 1.6 times; $p < 0.05$). The course of NASH without DIOS was characterized by hyperferritinemia ($p < 0.05$), which can be regarded as a marker of inflammatory activity.

Peculiarities of the course of biochemical syndromes of steatohepatitis of alcoholic and non-alcoholic steatohepatitis with comorbidity with DIOS are higher cytolysis activity (with ASH — growth in the range of 3.6—5.0 times against 2.9—4.1 times in the absence of DIOS; $p < 0.05$; in NASH — in the range of 2.3—3.1 times against 1.7—2.6 times; $p < 0.05$); cholestasis (with ASH — increase in the range of 2.4—7.7 times against 1.9—6.4 times in the absence of DIOS, ($p < 0.05$), with NASH — in the range of 1.8—3.7 times against 1.4—3.1 times; $p < 0.05$); mesenchymal inflammation (with ASH — an increase of 2.7 times versus 2.5 times in the absence of DIOS ($p < 0.05$); with NASH — 1.9 times

versus 1.6 times; $p < 0.05$); hepatocellular insufficiency — at ASH — decrease in albumins in blood in 1.6 times against 1.3 times in the absence of DIOS, increase in the content of MMP 254 in 2.0 against 1.9 times accordingly ($p < 0.05$); at NASH — decrease in albumins 1.5 times vs. 1.2 times; $p < 0.05$, increase in the content of MMP 254 — 1.7 vs. 1.4 times; $p < 0.05$). A factor that partially opposes a number of damage mechanisms caused by excess iron is an increase in blood uric acid, which is a natural antagonist, iron chelator and a powerful antioxidant: in ASH for DIOS — 2.1 times (compared to 1.9 times without DIOS), with NASH — 1.4 to 1.3 times, respectively ($p < 0.05$)).

Regularities of progression of liver fibrosis in patients with ASH with DIOS are the activation of collagen anabolism (2.5 times vs. 2.0 times ($p < 0.05$) in the absence of DIOS), increasing the intensity of collagen catabolism (respectively in 1.5 vs. 1.3 times ($p < 0.05$), which occurred due to a significant increase in collagenolytic activity of blood plasma (1.6 and 1.4 times; $p < 0.05$, respectively). with DIOS there is a significant increase in the content of hexosamines in the blood: for DIOS 1.6 times versus 1.5 times ($p < 0.05$), the content of sialic acids, respectively — 1.6 versus 1.5 times ($p < 0.05$) and accelerated degradation of fucoglycoprotein components of extracellular matrix (respectively in 2.6 and 2.4 times ($p < 0.05$)). The imbalance in the synthesis and degradation of extracellular matrix components led to a significant increase in the Fibro-test for ASH with DIOS — 2.6 times versus 2.2 times ($p < 0.05$) in its absence.

In patients with NASH the following patterns of liver fibrosis were established: activation of collagen synthesis processes (in the presence of DIOS 1.6 times ($p < 0.05$), in the absence — 1.3 times ($p < 0.05$)), slight increase in the intensity of collagenolytic activity in NASH with DIOS — 1.2 times ($p < 0.05$); increase collagenolytic activity by 12.5 % ($p < 0.05$) for DIOS, however, in its absence, spacecraft in NASH was reduced by 25.0 % ($p < 0.05$). For patients with NASH is characterized by an increase in the content of HA in the blood: for DIOS 1.3 times ($p < 0.05$) versus 1.2 times ($p < 0.05$), sialic acid content, respectively — 1.4 versus 1.2 times ($p < 0.05$), and accelerated degradation of fucoglycoproteins (1.8 versus 1.6 times, respectively ($p < 0.05$)). The consequence of the registered processes was an increase in the integrated Fibro-test for NASH with DIOS — 2.1 times compared to the indicator in PHIs ($p < 0.05$), for NASH without DIOS — 1.6 times ($p < 0.05$).

The prospect of further research in this area is the development of methods for the treatment of iron overload syndrome in patients with steatohepatitis of various etiologies.

Conflicts of interest: none.
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О. С. Хухліна, Т. М. Антофійчук, А. А. Антонів, М. П. Антофійчук
Буковинський державний медичний університет, Чернівці

Інтенсивність фіброзування паренхіми печінки у хворих на алкогольний і неалкогольний стеатогепатит залежно від наявності синдрому перевантаження залізом

Мета — встановити особливості гомеостазу заліза у хворих на стеатогепатит алкогольної та неалкогольної етіології залежно від наявності синдрому перевантаження залізом, виявити можливу залежність між показниками ферокінетики і маркерами біохімічних синдромів стеатогепатиту, інтенсивності ендотоксикозу та фіброзоутворення в печінці.

Матеріали та методи. Матеріал досліджень — клінічні спостереження за 125 особами, з них 60 з неалкогольним стеатогепатитом, 65 з алкогольним стеатогепатитом, та 25 практично здорових осіб відповідного віку і статі. Залежно від показників гомеостазу заліза хворих розподілили на 4 групи: 40 пацієнтів з алкогольним стеатогепатитом і синдромом перевантаження залізом, 25 — з алкогольним стеатогепатитом без синдрому перевантаження залізом, 18 — з неалкогольним стеатогепатитом і синдромом перевантаження залізом, 42 — з неалкогольним стеатогепатитом без синдрому перевантаження залізом.

Результати. При алкогольному стеатогепатиті встановлено активацію анаболічного колагену по зростанню в крові рівня пов'язаного з білком оксипроліну: за наявності синдрому перевантаження залізом — у 2,5 разу ($p < 0,05$), за його відсутності — в 2,0 рази ($p < 0, 05$), а також істотне зростання інтенсивності процесів катаболізму колагену (при підвищенні в крові вмісту вільного оксипроліну — відповідно в 1,5 і 1,3 разу ($p < 0,05$)) унаслідок значного збільшення колагенолітичної активності плазми крові (відповідно в 1,6 і 1,4 разу; $p < 0,05$) з наявністю в усіх випадках статистично значущої ($p < 0,05$) міжгрупової різниці. Відзначено істотне підвищення вмісту в крові гексозамінів: при синдромі перевантаження залізом — у 1,6 разу ($p < 0,05$), за його відсутності — в 1,5 разу ($p < 0,05$), сіалових кислот — відповідно в 1,6 і 1,5 разу ($p < 0,05$) і прискорену деградацію фукоглікопротеїнових компонентів позаклітинного матриксу. При неалкогольному стеатогепатиті встановлено активацію процесів синтезу колагену з підвищенням у крові рівня пов'язаного з білком оксипроліну: за наявності синдрому перевантаження залізом — у 1,6 разу ($p < 0,05$), за його відсутності — в 1,3 разу ($p < 0,05$), а також незначну інтенсифікацію розпаду колагену — зі збільшенням вмісту в крові вільного оксипроліну при неалкогольному стеатогепатиті та синдромі перевантаження залізом у 1,2 разу ($p < 0,05$). Установлено також істотне підвищення в крові рівня гексозамінів: за наявності синдрому перевантаження залізом — у 1,3 разу ($p < 0,05$), за його відсутності — в 1,2 разу ($p < 0,05$), вмісту сіалових кислот — відповідно в 1,4 і 1,2 разу ($p < 0,05$) та прискорену деградацію фукоглікопротеїнів.

Висновки. Закономірностями прогресування фіброзу печінки у хворих на алкогольний стеатогепатит із синдромом перевантаження залізом є активація анаболічного колагену, зростання інтенсивності процесів катаболізму колагену внаслідок значного збільшення колагенолітичної активності плазми крові. Важливим наслідком активації цитолізу і запалення є істотне підвищення вмісту в крові гексозамінів. У хворих на неалкогольний стеатогепатит відзначено активацію процесів синтезу колагену, незначну інтенсифікацію розпаду колагену при синдромі перевантаження залізом, підвищення вмісту в крові гексозамінів і прискорену деградацію фукоглікопротеїнів.

Ключові слова: гомеостаз заліза, стеатогепатит алкогольної етіології, стеатогепатит неалкогольної етіології, ендотоксикоз.

О. С. Хухлина Т. Н. Антофийчук А. А. Антонив Н. П. Антофийчук
Буковинский государственный медицинский университет, Черновцы

Интенсивность фиброзирования паренхимы печени у больных алкогольным и неалкогольным стеатогепатитом в зависимости от наличия синдрома перегрузки железом

Цель — установить особенности гомеостаза железа у больных стеатогепатитом алкогольной и неалкогольной этиологии в зависимости от наличия синдрома перегрузки железом, выявить возможную зависимость между показателями феррокинетики и маркерами биохимических синдромов стеатогепатита, интенсивности эндотоксикоза и фиброзообразования в печени.

Материалы и методы. Материал исследований — клинические наблюдения за 125 лицами, из них 60 с неалкогольным стеатогепатитом, 65 с алкогольным стеатогепатитом, и 25 практически здоровых лиц соответствующего возраста и пола. В зависимости от показателей гомеостаза железа больных разделили на 4 группы: 40 пациентов с алкогольным стеатогепатитом и синдромом перегрузки железом, 25 — с алкогольным стеатогепатитом без синдрома перегрузки железом, 18 — с неалкогольным стеатогепатитом и синдромом перегрузки железом, 42 — с неалкогольным стеатогепатитом без синдрома перегрузки железом.

Результаты. При алкогольном стеатогепатите установлена активация анаболического коллагена по возрастанию в крови уровня связанного с белком оксипролина: при наличии синдрома перегрузки железом — в 2,5 раза ($p < 0,05$), при его отсутствии — в 2,0 раза ($p < 0,05$), а также существенное возрастание интенсивности процессов катаболизма коллагена (при повышении в крови содержания свободного оксипролина — соответственно в 1,5 и 1,3 раза ($p < 0,05$)) вследствие значительного увеличения коллагенолитической активности плазмы крови (соответственно в 1,6 и 1,4 раза; $p < 0,05$) с наличием во всех случаях статистически значимой ($p < 0,05$) межгрупповой разницы. Отмечено существенное повышение содержания в крови гексозаминов: при синдроме перегрузки железом — в 1,6 раза ($p < 0,05$), при его отсутствии — в 1,5 раза ($p < 0,05$), сиаловых кислот — соответственно в 1,6 и 1,5 раза ($p < 0,05$) и ускоренная деградация фукогликопротеиновых компонентов внеклеточного матрикса. При неалкогольном стеатогепатите установлена активация процессов синтеза коллагена с повышением в крови уровня связанного с белком оксипролина: при наличии синдрома перегрузки железом — в 1,6 раза ($p < 0,05$), при его отсутствии — в 1,3 раза ($p < 0,05$), а также незначительная интенсификация распада коллагена — с увеличением содержания в крови свободного оксипролина при неалкогольном стеатогепатите и синдроме перегрузки железом в 1,2 раза ($p < 0,05$). Установлено также существенное повышение в крови уровня гексозаминов: при наличии синдрома перегрузки железом — в 1,3 раза ($p < 0,05$), при его отсутствии — в 1,2 раза ($p < 0,05$), содержания сиаловых кислот — соответственно в 1,4 и 1,2 раза ($p < 0,05$), и ускоренная деградация фукогликопротеинов.

Выводы. Закономерностями прогрессирования фиброза печени у больных алкогольным стеатогепатитом с синдромом перегрузки железом являются активация анаболического коллагена, возрастание интенсивности процессов катаболизма коллагена вследствие значительного увеличения коллагенолитической активности плазмы крови. Важным следствием активации цитолиза и воспаления является существенное повышение содержания в крови гексозаминов. У больных неалкогольным стеатогепатитом отмечена активация процессов синтеза коллагена, незначительная интенсификация распада коллагена при синдроме перегрузки железом, повышение содержания в крови гексозаминов и ускоренная деградация фукогликопротеинов.

Ключевые слова: гомеостаз железа, стеатогепатит алкогольной этиологии, стеатогепатит неалкогольной этиологии, эндотоксикоз.

Контактна інформація

Антонів Альона Андріївна, д. мед. н., доцент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб
E-mail: antonivalona@ukr.net

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