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Metabolic preconditions for the formation and progression of steatohepatitis of alcoholic, mixed, non-alcoholic aetiology and their comorbidity with obesity and anaemic conditions

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Abstract. ***Background.*** *The urgency of the problem of comorbidity of alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) with anaemic conditions and the need for their differentiated correction is determined by the significant frequency of these diseases in the world and Ukraine and the presence of the syndrome of the mutual burden. Anaemia is a marker for the progression of steatohepatitis to liver cirrhosis, in which anaemic conditions is often a manifestation of hypersplenism with the increased destruction of red blood cells in the spleen, as well as frequent complications of liver cirrhosis caused by posthemorrhagic anaemia, which occurs due to bleedings from the oesophageal and gastric varices, portal hypertension and decreased biosynthesis of coagulation factors by the liver. The purpose of the study was to find out metabolic prerequisites for the formation and progression of steatohepatitis of alcoholic, mixed and non-alcoholic aetiology and comorbid anaemic conditions.* ***Materials and methods.*** *One hundred and twenty-five patients with steatohepatitis of alcoholic, non-alcoholic and mixed aetiology were examined for comorbidities of anaemic conditions with lipid metabolism and glycemic regulation disorders.* ***Results.*** *The results of investigations demonstrate hyperlipidemia (by 1.35–1.5 times) in patients with steatohepatitis of mixed aetiology and ASH, although in anaemic conditions, the content of blood total cholesterol and low-density lipoprotein (LDL) cholesterol decreased ($p < 0.05$). Increased blood levels of triglycerides (in the range of 1.6–2.2 times) and decreased blood levels of high-density lipoprotein cholesterol (by 1.45–1.55 times) in all groups of patients with steatohepatitis and comorbidity with anaemic conditions deepened ($p < 0.05$). In NASH with anaemic conditions, there is an increase in the blood LDL cholesterol and total cholesterol levels, with the rise of the atherogenic index by 2.8 times ($p < 0.05$). Patients with NASH and obesity have high values of glucose, insulin and degree of insulin resistance (by 2.6 times, $p < 0.05$), and with anaemic conditions, insulinemia and degree of insulin resistance are increased (by 2.9 and 3.0 times, respectively; $p < 0.05$). In patients with ASH and steatohepatitis of mixed aetiology associated with alcohol consumption, insulin deficiency is formed (by 1.4 and 1.2 times, $p < 0.05$), which develops in addition to anaemic conditions (blood insulin content is below the lower values by 1.8 and 1.6 times).* ***Conclusions.*** *The consequence of metabolic pathology (hyperlipidemia, hyperglycemia, insulin resistance), which developed under the comorbidity of steatohepatitis with anaemic conditions, was an increase in the degree of hepatocyte steatosis ($p < 0.05$).*

Keywords: *alcoholic steatohepatitis; non-alcoholic steatohepatitis; anaemia; blood lipids; glucose; insulin resistance; hepatocyte steatosis*

Introduction

The urgency of the problem of comorbidity of alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) with anaemic conditions (AC) and the need for their differentiated correction is determined by the significant frequency of ASH and NASH in the world and Ukraine and the presence of the syndrome of the mutual burden of this pathology [1, 2].

Anaemia is most commonly due to iron deficiency and/or inflammation, but vitamin deficiencies and, more infrequently, autoimmune haemolysis or drug-induced myelosuppression can be involved. In some cases, anaemia can be a complication of chronic liver disease, and in others as one of the first symptoms of the disease [3]. The pathogenesis of anaemia in fatty liver disease is quite complex. In patients with chronic liver diseases, several groups of

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aetiopathogenetic factors leading to the development of AC can be distinguished. The first group are factors related to liver disease and its complications, namely: a decrease in iron reserves in the body (as a result of bleeding from varicose veins of the esophagus and/or systemic hemorrhagic syndrome), hypersplenism with the development of pancytopenia, dysregulation of erythropoiesis (reduction of erythropoietin synthesis), violation of transferrin synthesis in hepatocytes, violation of iron accumulation [4, 5]. The second group is associated diseases, such as atrophic gastritis (Castle factor deficiency), chronic pancreatitis with secretory insufficiency. The third group are factors that do not have a direct relationship with liver disease, such as toxic damage to the bone marrow by ethanol and its decay products, a dietary factor (insufficient intake of iron and folic acid with food) [6].

Anaemia is a marker of the progression of steatohepatitis to liver cirrhosis, in which AC is often a manifestation of hypersplenism with the increased destruction of erythrocytes in the spleen, as well as frequent complications of liver cirrhosis caused by posthemorrhagic anaemia, which occurs due to bleeding from varicose veins of the oesophagus, gastric, portal hypertension and decreased biosynthesis of coagulation factors by the liver [7, 8].

AC in ASH and NASH are not homogeneous in structure, and causes and therefore the management of such patients requires a differentiated approach [9]. Nevertheless, we have not found any report dedicated to the study of the effectiveness of ASH therapy for comorbidity with AC depending on the causes of their occurrence and the structure of anaemic conditions on the background of ASH in the available literature.

The purpose of the study is to establish metabolic prerequisites for the formation and progression of steatohepatitis of alcoholic, mixed (ME) and non-alcoholic aetiology and comorbid anaemic conditions.

Materials and methods

An open prospective study with an examination of 125 patients with steatohepatitis, including 60 with NASH and obesity of I–II degree compared to 65 patients with SH of alcoholic and mixed aetiology (25 patients with SH of mixed, including alcoholic, nature and 40 patients with ASH), 25 practically healthy individuals (PHIs) of the corresponding age and gender. The research was held in the therapeutic, gastroenterological, and haematology departments of Chernivtsi Emergency Hospital in 2015–2020. We examined 15 male patients (25.0 %) and 45 female patients (75.0 %) with NASH. The mean age 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 %) with average age 47.4 ± 5.1 years. Eleven (44.0 %) males and 14 (56 %) females were in the control group (the average age was 41.3 ± 2.1 years).

The verification of steatohepatitis of various aetiologies and anaemic conditions was done due to the ICD-10 classification. To confirm the diagnosis of NASH and ASH the unified clinical protocols approved by the order of the Ministry of Health of Ukraine No. 826 dated 06.11.2014 was used. Clinical guidelines of primary, secondary (specialized) medical care: Alcoholic hepatitis, Non-alcoholic steatohepatitis, European Association for the Study of the Liver, European Association for the Study of Obesity in the presence of criteria for excluding chronic diffuse liver damage of viral, hereditary, autoimmune or medicinal origin as the cause of cholestatic or cytolytic syndromes — ultrasound results. Biochemical FibroMAX test, which included Steato-test, ASH-test, NASH-test, and Fibro-test (BioPredictive, France) (Synevo laboratory), was used to determine the stage of liver fibrosis and the degree of hepatocyte steatosis as well as the differential diagnosis between NASH and ASH.

The diagnosis of anaemia was confirmed in accordance with the Order of the Ministry of Health of Ukraine No. 647 of July 30, 2010 On approval of clinical protocols for medical care to patients in the specialty Hematology, and with the clinical guidelines of primary and secondary (specialized) medical care Iron deficiency anaemia (November 2, 2015, No. 709).

The degree of compensation of carbohydrate metabolism was established by the level of fasting glucose, as well as by glucose tolerance test; insulin content in the blood by ELISA. The degree of insulin resistance (IR) was determined by the body mass index, index HOMA2-IR, which was calculated using the program HOMA Calculator Version 2.2.3 Diabetes Trials Unit (University of Oxford, UK). HOMA2-IR index values above 1.8 were regarded as IR.

The blood lipid spectrum was checked out by the content of total lipids, cholesterol (TC), triacylglycerols (TG) and high-density lipoproteins (HDL) in the blood using standard kits ACCENT-200 (PZ Cormay SA, Poland).

The normality of the distribution was checked using Lilliefors, Shapiro-Wilk tests and the method of direct visual evaluation of histograms of the distribution of eigenvalues. Quantitative values that had a normal distribution are presented as mean (M) ± standard deviation (S). 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 data that had a normal distribution, we used parametric tests with the assessment of Student's t-test, and Fisher's F-test. In the case of abnormal distribution, used: median test, calculation of the Mann-Whitney rank U-test, for multiple comparisons — Wilcoxon T-test (in the case of the study of dependent groups). Comparison of groups on qualitative signs and research of frequency of the revealed indicators was carried out by calculating the odds ratio (OR) using the program Past3.

The research was carried out taking into account the main provisions of the GCP (1996), the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964–2013), the Council of Europe Convention on Human Rights and Biomedicine (1997) Ministry of Health of Ukraine No. 616 of August 3, 2012, and a positive conclusion of the Commission on Biomedical Ethics of Bukovinian State Medical University (September 21, 2017). All patients signed an informed consent to participate in this research. The study protocol and the informed patient consent form were approved by the BSMU Biomedical Ethics Commission.

Results

Among the examined patients with alcoholic steatohepatitis anaemia was confirmed in 39.0 %, in patients with SH of mixed aetiology anaemia was found in 31.0 %, among patients with NASH in 20.6 % of cases. There we found the following types of anaemia in ASH patients: vitamin B_{12}-deficiency in 18.5 %, anaemia of chronic disease in 10.0 and acquired hemolytic anaemia (Zieve's syndrome) in 11.5 %. Due to the severity, we confirm a mild degree of anaemia (63 %), and 37.5 % of patients had moderate anaemia. The next types of anaemia were confirmed in patients with SH of mixed aetiology: vitamin B_{12}-deficiency in 15.0 %, anaemia of chronic disease in 9.0 and Zieve's syndrome in 7.0 % of patients.

Mild anaemia was registered in 63.5 % of cases, and moderate anaemia in 38.5 %. The structure of the anaemic syndrome in patients with NASH accompanied by obesity of I–II degree was as follows: vitamin B_{12}-deficiency anaemia in 14.0 %, anaemia of chronic disease in 5.7 %. 78.6 % of patients had mild anaemia and 22.4 % had moderate anaemia.

Analysis of the lipid spectrum of blood in patients with NASH revealed an increase in blood TG by 3.4 times and in AC by 3.7 times ($p < 0.05$) with a difference between groups ($p < 0.05$) (Table 1). In patients with ASH and ASH with AC the content of TG in the blood increased less intensively — by 1.6 and 2.0 times, respectively, compared with the indicator in control group ($p < 0.05$). In patients with SH the blood level of TG was increased 1.6 times, and in AC — 1.9 times ($p < 0.05$) with a significant difference between the groups ($p < 0.05$). Disruption of β-oxidation of fatty acids and lipogenesis, as well as enhanced lipolysis of deposited lipids in visceral fat depots lead to increased inflow of non-esterified fatty acids to the liver for use as energy material, TG biosynthesis, very-low-density lipoproteins in the form of neutral fats.

The second pathogenetic direction of established dyslipidemia in SH has established general hypercholesterolemia and a significant increase in blood LDL cholesterol (1.6 times in NASH, 1.7 and 1.8 times in NASH with AC, respectively) compared with the control group (Table 1). In patients with ASH and ASH with AC, LDL cholesterol and the content of cholesterol in the blood were increased less intensely: in ASH — 1.4 and 1.7 times, respectively, in ASH with AC — 1.3 and 1.4 times in comparison with the indicator in control group ($p < 0.05$).

In patients with SH the level of cholesterol and LDL cholesterol in the blood was increased 1.4 and 1.7 times, and in AC — 1.3 and 1.5 times ($p < 0.05$) with a significant difference between groups ($p < 0.05$) (Table 1). The increase in blood levels of cholesterol and the main class of atherogenic lipoproteins LDL contributes to progressive atherosclerotic vascular damage, including common hepatic and splenic arteries. The identified metabolic situation is an aggressive risk factor for the progression of hepatic steatosis, the development of tissue hypoxia, hepatocyte ischemia and other secondary metabolic disorders. An essential component of dyslipidemia is a probable decrease in blood levels of antiatherogenic lipoproteins HDL. Thus, in patients with NASH, the content of HDL in the blood was reduced 1.4 times, and in AC — 1.6 times ($p < 0.05$) with a significant difference between the groups ($p < 0.05$). In patients with ASH and ASH with AC the content of HDL in the blood was reduced by 1.5 and 1.6 times compared with control group ($p < 0.05$). In patients with SH, the content of HDL in the blood was reduced 1.4 times, and under AC — 1.5 times ($p < 0.05$) with a significant difference between the groups ($p < 0.05$). This fact contributed to the growth of the atherogenic index with maximum manifestations in patients with NASH — 2.8 and 3.5 times in NASH with AC, respectively, and 2.5 times — in ASH, 2.4 times in SH ME compared with control group ($p < 0.05$). Therefore, we can conclude that the indicators of lipid metabolism depend not only on the aetiology of steatohepatitis but also on the presence of comorbid anaemia.

Features of carbohydrate metabolism differed depending on the aetiology of SH, as well as the presence of comorbid pathology. Patients with NASH found a probable increase

Table 1. Blood lipid spectrum, glycemia and regulation of carbohydrate metabolism in patients with steatohepatitis of various aetiologies depending on the presence of comorbid anaemia (M ± m)

Indicator, units of measurement	PHIs, n = 25	Groups of examined patients					
		NASH, n = 47	NASH with AC, n = 13	ASH, n = 24	ASH with AC, n = 16	SH ME, n = 17	SH ME with AC, n = 8
TC, mmol/l	4.53 ± 0.07	7.45 ± 0.12[a]	7.87 ± 0.18[a,b]	6.23 ± 0.16[a]	5.83 ± 0.11[a,c]	6.36 ± 0.26[a]	5.92 ± 0.22[a,c]
HDL, mmol/l	1.33 ± 0.01	0.97 ± 0.03[a]	0.85 ± 0.01[a,b]	0.88 ± 0.02[a]	0.82 ± 0.05[a]	0.93 ± 0.04[a]	0.84 ± 0.03[a]
LDL, mmol/l	2.51 ± 0.14	4.07 ± 0.15[a]	4.40 ± 0.20[a]	4.20 ± 0.14[a]	3.60 ± 0.08[a,b,c]	4.35 ± 0.06[a]	3.68 ± 0.07[a,b,c]
TG, mmol/l	1.56 ± 0.05	5.39 ± 0.18[a]	5.83 ± 0.15[a,b]	2.52 ± 0.12[a,c]	3.18 ± 0.14[a,b]	2.50 ± 0.16[a,c]	3.05 ± 0.09[a,b,c]
AIP	2.46 ± 0.08	6.87 ± 0.09[a]	8.50 ± 0.12[a,b]	6.16 ± 0.09[a,c]	6.22 ± 0.08[a,c]	5.94 ± 0.08[a,c]	5.96 ± 0.08[a,c]
Fasting glucose, mmol/l	4.55 ± 0.11	5.87 ± 0.05[a]	5.73 ± 0.06[a]	5.74 ± 0.08[a]	5.58 ± 0.06[a]	5.64 ± 0.06[a,c]	5.58 ± 0.09[a]
Insulin, μIU/ml	9.84 ± 1.12	24.36 ± 2.22[a]	28.52 ± 2.14[a]	6.56 ± 0.49[a,c]	5.24 ± 0.56[a,c]	7.38 ± 0.77[c]	5.96 ± 0.46[a,c]
HOMA-IR	1.25 ± 0.04	3.18 ± 0.11[a]	3.67 ± 0.08[a,b]	0.88 ± 0.03[a,c]	0.71 ± 0.02[a,b,c]	0.97 ± 0.06[a,c]	0.81 ± 0.03[a,b,c]

Notes: [a] — the difference is probable in comparison with the indicator in control group of PHIs ($p < 0.05$); [b] — the difference is probable in comparison with the indicator in patients with SH without AS ($p < 0.05$); [c] — the difference is significant compared to patients with NASH ($p < 0.05$).

in fasting blood glucose (1.3 times, $p < 0.05$) compared with control group, which remained at this level and in comorbidity with AC ($p > 0.05$). The analysis of fasting glucose in ASH showed the same dependence: in the absence of AS fasting glucose exceeded the index in control group 1.3 times, and in ASH with AC 1.2 times ($p < 0.05$). Patients with SH ME found a probable increase in fasting blood glucose (1.2 times, $p < 0.05$) compared with control group, which remained at this level and in comorbidity with AC ($p > 0.05$). Analysis of blood insulin levels in patients with NASH revealed its significant increase (2.5 times, $p < 0.05$) compared with control group, and with the addition of AC the indicator exceeded the reference values by 2.9 times ($p < 0.05$) (Table 1). Evidence of a significant increase in the degree of IR in NASH was an increase in fasting HOMA-IR (2.6 times, $p < 0.05$), as well as a significant increase in HOMA-IR with the addition of AC in 3.0 times ($p < 0.05$) with a significant difference between these groups ($p < 0.05$). Thus, we concluded that the comorbidity with AC in the pathogenesis of NASH forms a powerful lipid distress syndrome on the background of a significant syndrome of IR (hyperinsulinemia, impaired glucose tolerance), which further contributes to the progression of hepatic steatosis and increase its degree.

Analysis of insulin in the blood of patients with ASH revealed a significant decrease (1.5 times, $p < 0.05$) compared with control group and with the addition of AC the rate was lower than control group, 1.9 times ($p < 0.05$) (Table 1). Simultaneously, the content of insulin in the blood of patients with SH ME was also reduced (1.3 times, $p < 0.05$) compared with control group and with the addition of AC the rate was lower than in control group, 1.7 times ($p < 0.05$). Thus, the phenomenon of IR in ASH and SH ME was not established, because fasting HOMA-IR was reduced compared to the reference values by 1.4 and 1.3 times, respectively ($p < 0.05$), and with the addition of AC decreased 1.8 and 1.6 times, respectively ($p < 0.05$) with a difference between these groups ($p < 0.05$). The latter fact may be connected with the formation of the endocrine dysfunction of the pancreas due to the chronic effects of alcohol.

The consequence of the metabolic (hyperlipidemia, hyperglycemia, IR) situation was an increase in the degree of hepatocyte steatosis (according to Steato-test) under the comorbidity of SH with AC. In patients with NASH without anaemia, S1 was dominated by the degree of hepatic steatosis (52.1 %), and in NASH with AC — S2 (37.5 %) ($p < 0.05$). In patients with ASH, S1 and S2 degrees of hepatic steatosis prevailed (63.5 and 28.4 %, respectively), and in ASH with AC — S2 and S3 (45.8 and 23.0 %) ($p < 0.05$). In patients with SH ME without comorbid pathology, S1 and S2 degrees of hepatic steatosis prevailed (53.7 and 36.2 %, respectively), and in SH ME with AC — S2 and S3 (61.5 and 27.0 %) ($p < 0.05$).

Discussion

Anaemia of chronic disease or inflammation may be secondary to autoimmune disorders, infections, chronic liver diseases, or malignancies. It is characterized by an immune activation with an increase in inflammatory cytokines and resultant increase in hepcidin levels [10, 11]. In addition, inappropriate erythropoietin levels or hyporesponsiveness to erythropoietin and reduced red blood cell survival contribute to the anaemia. Hepcidin being the central regulator of iron metabolism plays a key role in the pathophysiology of anaemia of chronic disease. Hepcidin binds to the iron export protein, ferroportin, present on macrophages, hepatocytes, and enterocytes, causing degradation of the latter. This leads to iron trapping within the macrophages and hepatocytes, resulting in functional iron deficiency [12, 13].

We collected scientific data on the frequency of comorbidity with anaemic conditions (according to retrospective analysis and examination) in patients with ASH, SH ME and NASH. For the first time the structure of anaemic conditions depending on the aetiology of steatohepatitis has been specified.

The logical consequence of joining AC to steatohepatitis was a decrease in lipid-synthesizing function of the liver in patients with ASH and SH ME, as evidenced by a decrease in blood levels of total cholesterol, LDL cholesterol with the addition of AC [14–16]. This fact indicates a serious decrease in the ability of the liver to synthesize *de novo* cholesterol and drugs of different classes in SH under the development of AC. At the same time, the content of TG and HDL cholesterol in the blood in all groups increased due to the comorbidity with AC. In NASH with the addition of AS, the content of cholesterol and LDL cholesterol in the blood also increased significantly, including a significant increase in AIP — the maximum among the comparison groups. The established direction of lipid metabolism disorders in ASH and SH ME is similar to NASH and is secondary in nature, because swaps in the lipid spectrum of the blood occur primarily due to increased biosynthesis of cholesterol and TG from ethanol, which enters the body in large quantities in alcoholism, and the comorbidity with AC processes of lipid anabolism are inhibited due to the development of hepatocellular insufficiency.

It has been established that the frequency of manifestations of a number of clinical syndromes of steatohepatitis prevailed in comorbidities with anaemia in patients with ASH and SH ME: astheno-vegetative, abdominal discomfort, splenomegaly, degree of hepatocyte steatosis [17, 18]. The frequency of astheno-vegetative syndrome, dyspepsia, cholestasis, abdominal discomfort, splenomegaly, the degree of hepatocyte steatosis significantly prevailed in patients with NASH due to comorbidity with AC [19]. Among the biochemical syndromes of SH with the comorbidity of NASH with AC, the frequency of hepatocellular insufficiency, impaired glucose tolerance ($p < 0.05$), hyperuricemia ($p < 0.05$) significantly prevailed.

It has first been studied that in patients with NASH on the background of grade I–II obesity with the addition of AC is characterized by an increase in insulinemia and insulin resistance ($p < 0.05$), and in patients with ASH and SH ME, insulin deficiency develops (decreased blood insulin; $p < 0.05$), which deepens under AC joining ($p < 0.05$).

Conclusions

In patients with ASH and SH ME, hyperlipidemia (within 1.4–1.8 times) has been established with a decrease in blood levels of total cholesterol, and LDL cholesterol on the

terms of AC joining ($p < 0.05$). Elevated blood levels of TG (in the range of 1.6–2.2 times) and decreased blood levels of HDL cholesterol (about 1.3–1.5 times) in all groups with comorbidity with AC deepened ($p < 0.05$). In NASH with AC, the content of total cholesterol and LDL cholesterol in the blood significantly increased, including a significant growth of the atherogenic index (2.8 times), the maximum among the comparison groups ($p < 0.05$).

For the course of NASH in the background of obesity is presented with an increase in fasting glucose (within 1.3 times), insulinemia (2.5 times) and the degree of insulin resistance (2.6 times, $p < 0.05$), and conditions of AC accession an increase in insulinemia and degree of IR (2.9 and 3.0 times, respectively; $p < 0.05$). In patients with ASH and SH ME associated with alcohol consumption, insulin deficiency is formed (1.4 and 1.3 times, respectively; $p < 0.05$), which progresses under AC presence (a decrease in blood insulin content by 1.8 and 1.6 times).

The consequence of the metabolic (hyperlipidemia, hyperglycemia, IR) situation, which developed under the comorbidity of SH with anaemic conditions, was an increase in the degree of hepatocyte steatosis. In patients with NASH without anaemia, S1 was dominated by the degree of hepatic steatosis (52.1 %), and in NASH with AC — S2 (37.5 %) ($p < 0.05$). In patients with ASH, S1 and S2 degrees of hepatic steatosis prevailed (63.5 and 28.4 %, respectively), and in ASH with AC — S2 and S3 (45.8 and 23.0 %) ($p < 0.05$). In patients with SH ME without comorbid pathology, S1 and S2 degrees of hepatic steatosis prevailed (53.7 and 36.2 %, respectively), and in SH ME with AC — S2 and S3 (61.5 and 27.0 %) ($p < 0.05$).

Ethical approval. The research was carried out taking into account the main provisions of the GCP (1996), the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964–2013), the Council of Europe Convention on Human Rights and Biomedicine (1997) Ministry of Health of Ukraine No. 616 of August 3, 2012, and a positive conclusion of the Commission on Biomedical Ethics of Bukovinian State Medical University (No. 1, September 21, 2017).

Consent to participate. Written informed consent was obtained from the patients.

Data availability. Further data are available from the corresponding author on reasonable request.

References

1. Bekri S, Gual P, Anty R, et al. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. Gastroenterology. 2006 Sep;131(3):788-96. doi:10.1053/j.gastro.2006.07.007.

2. Tkach SM, Pankiv VI, Yuzvenko TY. Modern approaches to the management of patients with obesity (according to the materials of the Consensus of the American Gastroenterological Association in 2022). Clinical Endocrinology and Endocrine Surgery. 2023:1(81):47-57. doi:10.30978/CEES-2023-1-47. (in Ukrainian).

3. Bergamaschi G, Di Sabatino A, Corazza GR. Pathogenesis, diagnosis and treatment of anaemia in immune-mediated gastrointestinal disorders. Br J Haematol. 2018 Aug;182(3):319-329. doi:10.1111/bjh.15254.

4. Britton LJ, Subramaniam VN, Crawford DH. Iron and non-alcoholic fatty liver disease. World J Gastroenterol. 2016 Sep 28;22(36):8112-22. doi:10.3748/wjg.v22.i36.8112.

5. Hernandez Roman J, Siddiqui MS. The role of noninvasive biomarkers in diagnosis and risk stratification in nonalcoholic fatty liver disease. Endocrinol Diabetes Metab. 2020 Apr 5;3(4):e00127. doi:10.1002/edm2.127.

6. Hutchinson C. A review of iron studies in overweight and obese children and adolescents: a double burden in the young? Eur J Nutr. 2016 Oct;55(7):2179-97. doi:10.1007/s00394-016-1155-7.

7. Ntandja Wandji LC, Gnemmi V, Mathurin P, Louvet A. Combined alcoholic and non-alcoholic steatohepatitis. JHEP Rep. 2020 May 22;2(3):100101. doi:10.1016/j.jhepr.2020.100101.

8. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015 May 7;372(19):1832-43. doi:10.1056/NEJMra1401038.

9. Cappellini MD, Comin-Colet J, de Francisco A, et al; IRON CORE Group. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol. 2017 Oct;92(10):1068-1078. doi:10.1002/ajh.24820.

10. Docherty AB, Turgeon AF, Walsh TS. Best practice in critical care: anaemia in acute and critical illness. Transfus Med. 2018 Apr;28(2):181-189. doi:10.1111/tme.12505.

11. Fraenkel PG. Anemia of Inflammation: A Review. Med Clin North Am. 2017 Mar;101(2):285-296. doi:10.1016/j.mcna.2016.09.005.

12. Gangat N, Wolanskyj AP. Anemia of chronic disease. Semin Hematol. 2013 Jul;50(3):232-8. doi:10.1053/j.seminhematol.2013.06.006.

13. Pankiv VI. Features of prediabetes management in adolescents with excessive body weight and obesity. Mìžnarodnij endokrinologìčnij žurnal. 2022;18(8):436-439. doi:10.22141/2224-0721.18.8.2022.1222. (in Ukrainian).

14. Gangat N, Wolanskyj AP. Anemia of chronic disease. Semin Hematol. 2013 Jul;50(3):232-8. doi:10.1053/j.seminhematol.2013.06.006.

15. Gerjevic LN, Liu N, Lu S, Harrison-Findik DD. Alcohol Activates TGF-Beta but Inhibits BMP Receptor-Mediated Smad Signaling and Smad4 Binding to Hepcidin Promoter in the Liver. Int J Hepatol. 2012;2012:459278. doi:10.1155/2012/459278.

16. Yefimenko TI, Mykytyuk MY. Non-alcoholic fatty liver disease: time for changes. Mìžnarodnij endokrinologìčnij žurnal. 2021;17(4):334-345. doi:10.22141/2224-0721.17.4.2021.237350. (in Ukrainian).

17. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017 Jan;66(1):6-30. doi:10.1136/gutjnl-2016-312288.

18. Milic S, Mikolasevic I, Orlic L, et al. The Role of Iron and Iron Overload in Chronic Liver Disease. Med Sci Monit. 2016 Jun 22;22:2144-51. doi:10.12659/msm.896494.

19. Nemeth E, Ganz T. Anemia of Inflammation. Hematology/Oncology Clinics of North America. 2014;28(4):671-681. doi:10.1016/j.hoc.2014.04.005.

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Метаболічні передумови формування та прогресування стеатогепатитів різної етіології при супутньому ожирінні й анемічних станах

Резюме. ***Актуальність.*** Актуальність проблеми коморбідності алкогольного стеатогепатиту (АСГ) і неалкогольного стеатогепатиту (НАСГ) з анемічними станами та необхідність їх диференційованої корекції визначається значною частотою цих патологій у світі та Україні, а також наявністю синдрому взаємообтяження. Анемія є маркером прогресування стеатогепатиту в цироз печінки, при якому анемічні стани часто є проявом гіперспленізму з посиленим руйнуванням еритроцитів у селезінці, а також частим ускладненням цирозу печінки, спричиненим постгеморагічною анемією, що виникає внаслідок кровотечі з варикозно розширених вен стравоходу, шлунка, портальної гіпертензії та зниження біосинтезу факторів згортання крові печінкою. ***Мета дослідження:*** встановити метаболічні передумови формування й прогресування стеатогепатиту алкогольної, змішаної і неалкогольної етіології та коморбідних анемічних станів. ***Матеріали та методи.*** Обстежено 125 хворих на стеатогепатит алкогольної, неалкогольної та змішаної етіології з анемічними станами й порушеннями ліпідного обміну і регуляції глікемії. ***Результати.*** Результати досліджень свідчать про гіперліпідемію (у 1,35–1,5 раза) у хворих на стеатогепатит змішаної етіології та АСГ, хоча за умов приєднання анемічних станів уміст загального холестерину (ХС) та холестерину ліпопротеїнів низької щільності (ЛПНЩ) у крові знизився ($p < 0,05$). Підвищення рівня тригліцеридів у крові (у межах 1,6–2,2 раза) і зниження рівня холестерину ліпопротеїнів високої щільності (у 1,45–1,55 раза) в усіх групах хворих зі стеатогепатитом та коморбідністю з анемічними станами ставали більш вираженими ($p < 0,05$). При НАСГ з анемічними станами спостерігається зростання в крові рівнів ХС ЛПНЩ та загального холестерину з підвищенням індексу атерогенності у 2,8 раза ($p < 0,05$). У пацієнтів із НАСГ й ожирінням високі значення глюкози, інсуліну та ступеня інсулінорезистентності (у 2,6 раза; $p < 0,05$), а при приєднанні анемічних станів посилюються інсулінемія та ступінь інсулінорезистентності (у 2,9 та 3,0 раза відповідно; $p < 0,05$). У хворих на АСГ і стеатогепатит змішаної етіології, пов'язані із вживанням алкоголю, формується дефіцит інсуліну (у 1,4 та 1,2 раза; $p < 0,05$), що відбувається на додаток до приєднання анемічних станів (уміст інсуліну в крові менше нижніх значень у 1,8 та 1,6 раза). ***Висновки.*** Наслідком метаболічної патології (гіперліпідемія, гіперглікемія, інсулінорезистентність), що розвинулася в умовах коморбідності стеатогепатиту з анемічними станами, стало підвищення ступеня стеатозу гепатоцитів ($p < 0,05$).

Ключові слова: алкогольний стеатогепатит; неалкогольний стеатогепатит; анемія; ліпідний спектр крові; глюкоза; інсулінорезистентність; стеатоз гепатоцитів