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Characteristics of clinical and biochemical changes in nonalcoholic steatohepatitis combined with cholelithiasis

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Abstract
The liver is one of the main organs for the regulation of carbohydrate, protein and lipid metabolism, glycogen deposition. Metabolic disorders in MS are always accompanied by changes in liver function. We have investigated the protein, lipid and carbohydrate profile of blood of 120 patients (divided into 3 groups) with nonalcoholic steatohepatitis in conjunction with the pathology of the gallbladder: calculous cholecystitis(1st group), non-calculous cholecystitis (2nd group); or without pathology of gallbladder (3rd group) to assess changes in metabolism and possible future clinical and functional changes specific to the presence of combined pathology. We discovered that gallstone disease affects the course of nonalcoholic steatohepatitis and accompanied by decompensation of carbohydrate, protein and lipid metabolism, as in patients of the third study group changes in clinical and laboratory parameters were the most insignificant compared to first group and second group.

Keywords: nonalcoholic steatohepatitis, calculous cholecystitis, non-calculous cholecystitis.

1. Introduction
Formation of integrative approach to the study of the pathogenesis and ways to optimize the diagnosis and treatment of many diseases are observed in modern medical science. Among these diseases there are gallstone disease (GSD), diabetes mellitus (DM), metabolic syndrome (MS), steatohepatitis [1, 2]. Practitioners focus on lipid status primarily in cardiovascular disease, atherosclerosis. But deep pathology of metabolism occur in the gastrointestinal tract, particularly in nonalcoholic steatohepatitis (NASH) [3]. Often this pathology is combined with gallbladder pathology, including non-calculous or calculous cholecystitis, which cause clinical, morphological and functional changes in hepatobiliary tract [4]. The liver is one of the main organs for the regulation of carbohydrate, protein and lipid metabolism, glycogen deposition. It is also a place for synthesis of very low-density lipoproteins (VLDL) [5]. Metabolic disorders in MS are always accompanied by changes in liver function. Decreasing of gluconeogenesis and increasing of the synthesis of fatty acids and lipoproteins are the consequence of reducing the sensitivity of hepatocytes to insulin.VLDL synthesis leads to an increase of lIipidemic and atherogenic index of blood, development (progression) of obesity [6, 7]. There is a direct correlation between insulin resistance, insulinemia, the level of low-density lipoprotein (LDL) and triglyceride concentrations in plasma. Thus, the pathology of the liver communicates with all components of MS [8, 9].
The number of publications and interest in this disease has increased significantly in recent years, but violations of lipid, protein and carbohydrate metabolism in patients are not studied enough. Scientific data studies on this subject, are often divergent, so the study of disorders of lipid metabolism has scientific and practical interest.

2. Material and methods of research
To assess changes in lipid, carbohydrate and protein metabolism and possible future clinical and functional changes specific to the presence of another pathology,we made laboratory analysis lipid profile of blood in patients with nonalcoholic steatohepatitis. Patients (study included women aged 36-74 years) were divided into three groups:
Group 1 - patients with nonalcoholic steatohepatitis combined with calculous cholecystitis (40 people);
2nd group - patients with nonalcoholic steatohepatitis non-calculous cholecystitis combined with (40 people);

3rd group - patients with nonalcoholic steatohepatitis with gallbladder pathology (40 people).
The control group included 40 healthy individuals, which diseases of the hepato-biliary system were not detected.
Verification of pathological conditions and somatic pathology was performed according to MKH10, classification of diabetes according to the WHO.
For research purpose in-patients gastroenterological department of Clinical Hospital of Ivano-Frankivsk. All patients body mass index (BMI) were measured. To verify the diagnosis of diabetes and NASH, determining the functional state of the liver using complex clinical laboratory, biochemical and instrumental methods.
To determine the status of carbohydrate metabolism, verify the diagnosis of "diabetes" glucose of blood serum was surveyed , glycosylated hemoglobin determination (HbA1c) a set of "Diabettest"were used, to determine the concentration of immunoreactive insulin - using a set of reagents done by Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus (Minsk). How to test IR was used homeostatic model NOMAIR (Nomeostasis model assessment), which is calculated by the formula: = NOMAIR insulin (nmol / L) x glucose (mmol / l) / 22.5.
To verify the diagnosis of nonalcoholic steatohepatitis of liver we used biochemical and instrumental methods, which made it possible to assess the functional state of the liver using standard conventional techniques. To determine the overall level of protein in serum using colorimetric biuret method. For study of pigment metabolism the method Yendrashyka, Klehhorna and Groff, which allows fractional determination of bilirubin. Aminotransferase (AST - aspartataminotransferase, ALT - alaninaminotransferase) serum was determined by colorimetric Raytmana and Frenkel. Thymol for Huerho and Popper defined to characterize the stability of the colloidal system of blood and specific assessment of the functional state of the liver. Determination of lipids in blood plasma include determination of total cholesterol (total cholesterol), triglycerides and HDL cholesterol (HDL cholesterol) enzymatic method using sets of firms' Olveks diagnosticum "(St. Petersburg). The upper limit of norm criterion considered in accordance with the recommendations of the Ukrainian Scientific Society of Cardiology (2008). The level of LDL cholesterol was calculated by the formula: LDL cholesterol = total cholesterol - (triglycerides / 5 + HDL cholesterol). Atherogenic factor (SC) was determined by the formula: SV = (total cholesterol - HDL cholesterol) / HDL cholesterol. All data are subjected to statistical analysis using the package Statistica 7.0 (StarSoft Inc., USA) [10, 11].

3. Results and Discussion

We have investigated the lipid profile of blood of 120 patients with nonalcoholic steatohepatitis in conjunction with the pathology of the gallbladder: total cholesterol serum triglycerides, HDL cholesterol, LDL cholesterol, atherogenic factor. In the analysis of disturbances were found signs of increase total cholesterol, hyperlipidemia, decrease HDL cholesterol of blood serum, increase LDL cholesterol and TG in all groups of examined patients with a tendency to increase in patients of the 1st group. In patients of the third group changes were significantly lower compared with the other two groups (Table. 1). The presence of comorbidity of gallbladder accompanied deepening dyslipidemia, increased concentrations of LDL cholesterol and triglycerides and decreased HDL cholesterol concentrations. Hyperinsulinemia promotes atherogenic dyslipidemia, enhances the proliferation of smooth muscle cells and fibroblasts, increases the activity of LDL receptors and endogenous cholesterol synthesis in the cells of the vascular wall and collagen - one of the main factors of liver damage.
The level of total cholesterol was significantly increased in all investigated groups compared with the control group. Highest level of total cholesterol was observed in patients of group 1. In patients with nonalcoholic steatohepatitis without combined pathology of the gallbladder total cholesterol level was moderately increased compared with the control group, but not out of norm. There was a high level of triglycerides in patients of the 1st group and moderately increased in patients of 2nd and 3rd groups compared to the control group, but in the normal range. HDL cholesterol level was reduced in all patients compared to control group. The possible reduction in HDL cholesterol were found in patients of group 1, moderate decrease - in patients of the 3rd group compared with the control group. The level of LDL cholesterol was elevated in all patients compared with the control group: in patients of 2nd and 3rd groups it remained in the normal range and was increased in patients of the 1st group. Significant increase in CA level was observed in all patients compared with the control group. The highest CA level have been found patients of 1st group , moderate - in patients of the 3rd. group.

Table 1: Indicators of lipid metabolism in patients with NASH in conjunction with GSD

Indicators	Nonalcoholic steatohepatitis in combination with calculous cholecystitis (n=30)	Nonalcoholic steatohepatitis in combination with non-calculous cholecystitis (n=30)	Nonalcoholic steatohepatitis without pathology of gallbladder (n=30)	Healthy (n=30)
GC,Mmol/l	7,68±0,14*	5,83±0,18*	6,50±0,03*	5,21±0,18
TG, Mmol/l	3,43±0,11*	1,71±0,83*	2,11±0,08*	1,22±0,15
HDL, Mmol/l	0,85±0,04*	0,93±0,05*	0,99±0,05*	1,10±0,05
LDL, Mmol/l	3,21±0,07*	2,20±0,09*	2,35±0,09*	1,72±0,13
AC	9,31±0,23*	6,50±0,12*	6,20±0,13*	3,81±0,14

Note: * - $p < 0,05$ when compared with the control group study

Based on the research of pigment and protein metabolism (Table. 2) have been established increased activity of ALT, AST, hyperbilirubinemia, total protein content in plasma was the 1st group was significantly reduced compared with the control group. In addition, in patients with nonalcoholic decreased compared with control group, but in patients with nonalcoholic steatohepatitis without pathology of the gallbladder level of total protein was normal, and in patients of steatohepatitis and calculous cholecystitis were found the highest degree of dysproteinemia. Reduction of total protein in

the blood indicates severe involvement of protein-synthetic function of the liver and usually it indicates a bad prognosis.

Table 2: Indicators of protein and pigment metabolism in patients with NASH in conjunction with GSD

Indicators	Nonalcoholic steatohepatitis in combination with calculous cholecystitis (n=30)	Nonalcoholic steatohepatitis in combination with non-calculous cholecystitis (n=30)	Nonalcoholic steatohepatitis without pathology of gallbladder (n=30)	Healthy (n=30)
ALT, Mmol/l	0,88±0,14*	0,73±0,18*	0,65±0,03*	0,51±0,18
AST, Mmol/l	0,73±0,11*	0,61±0,83*	0,55±0,08*	0,43±0,15
General bilirubin, Mmol/l	15,85±0,04*	11,93±0,05*	11,09±0,05*	10,81±0,05
General protein, Mmol/l	53,21±0,07*	62,20±0,09*	66,35±0,09*	68,01±0,13

Note: * - $p < 0,05$ when compared with the control group study

In all patients with nonalcoholic steatohepatitis has been found a significant increase in levels of fasting blood glucose (FBG) compared with the control group, the highest level was observed in patients of group 1- 2.5 times higher than the normal range.

A stable increase of blood glucose level was accompanied by glycosylation of proteins (non-enzymatic formation of various compounds glucose with proteins) that causes damage to their structures and functions. HbA1c appeared as an integrated indicator of compensation of carbohydrate metabolism. The highest degree of increase HbA1c was observed in patients of the 1st group - nearly twice as patients of the 3rd group had normal level of HbA1c.

Was conducted determining the level of insulin in patients with nonalcoholic steatohepatitis combined with calculous, non-calculous cholecystitis and without gallbladder pathology. A significant decline of indicators was observed in patients the 1st group of study in comparison with the control group.

To diagnose IR we used homeostatic model NOMAIR. Significant increase of NOMAIR in comparison with the control group has been founded in patients with nonalcoholic steatohepatitis combined with non-calculous cholecystitis (1st group), and probable decrease - in patients of the 3rd group. Characteristics of carbohydrate metabolism in all study groups are shown in Table 3.

Table 3: Indicators of carbohydrate metabolism in patients with NASH in conjunction with GSD

Indicators:	Nonalcoholic steatohepatitis in combination with calculous cholecystitis (n=30)	Nonalcoholic Steatohepatitis in combination with non-calculous cholecystitis (n=30)	Nonalcoholic steatohepatitis without pathology of gallbladder (n=30)	Healthy (n=30)
FBG, Mmol/l	10,68±0,14*	8,83±0,18*	6,50±0,03*	3,87±0,18
HbA1c,%	9,43±0,11*	5,71±0,83*	5,11±0,08*	4,72±0,15
Insulin, Mmol/l	47,85±0,04*	73,93±0,05*	78,99±0,05*	88,10±0,05
Index, NOMAIR	26,21±0,07*	23,20±0,09*	22,35±0,09*	15,22±0,13

Note: * - $p < 0,05$ when compared with the control group study

4. Conclusion

We discovered that gallstone disease affects the course of nonalcoholic steatohepatitis and accompanied by decompensation of carbohydrate, protein and lipid metabolism, as in patients of the third study group (nonalcoholic steatohepatitis without pathology of the gallbladder) changes in clinical and laboratory parameters were the most insignificant compared to first group and second group.

Defining the carbohydrate and lipid metabolism makes it possible to judge about the metabolic state of the liver and its structural function in patients with nonalcoholic steatohepatitis and comorbidity of gallbladder. Adjunction of gall stone disease increase disorders of lipid metabolism, such as increasing content of total cholesterol, triglyceride, LDL cholesterol, decreased HDL cholesterol content, which has a crucial purpose in pathogenic changes of these pathologies. Therefore, determination of indicators has diagnostic value. The study of lipids is of scientific and practical interest to optimize the diagnosis and prognosis of nonalcoholic steatohepatitis in conjunction with cholelithiasis.

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