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POSSIBILITIES OF CORRECTION OF LIPID-PHOSPHOLIPID DISORDERS IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS AGAINST OBESITY AND PATHOLOGY OF THE BILIARY TRACT

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Abstract. Possibilities of correction of lipid-phospholipid disorders in patients with non-alcoholic steatohepatitis against obesity and pathology of the biliary tract. Filippova A.Yu. *High priority in the pathogenesis and treatment of non-alcoholic steatohepatitis (NASH) is given to disorders of lipid-phospholipid fractions, which are directly related to the functioning of hepatocytes. The aim of the study was to evaluate the effect of various complex treatment regimens on lipid-phospholipid fractions in patients with NASH in combination with obesity (OB) and pathology of the biliary tract (BT) according to a 6-month follow-up. 52 patients with NASH in combination with OB and BT pathology were examined. The control group consisted of 20 practically healthy individuals. The effect of complex treatment (preventive and therapeutic measures) on the indicators of lipid-phospholipid fractions in patients with NASH in combination with obesity and pathology of the biliary tract was studied. Changes in the indicators of serum lipid-phospholipid fractions were detected before treatment in all observation groups, which were accompanied by phospholipids (PL), phosphatidylcholine and sphingomyelin decrease and a significant increase in PL lysoforms – lysophosphatidylcholine and phosphatidylethanolamine, triglycerides, cholesterol esters (from $p<0.05$ to $p<0.001$). Combination therapy with the inclusion in the standard treatment of ursodeoxycholic acid and arginine glutamate in the comorbid course of NASH can be considered as a promising direction in the treatment of this category of patients, which can improve indicators of lipid-phospholipid fractions and stabilize the hepatocytes' membrane (from $p<0.05$ to $p<0.001$).*

Реферат. Возможности коррекции липидно-фосфолипидных нарушений у пациентов с неалкогольным стеатогепатитом на фоне ожирения и патологии билиарного тракта. Филиппова А.Ю. *Большое значение в патогенезе и лечении неалкогольного стеатогепатита (НАСГ) уделяется нарушениям липидно-фосфолипидных фракций, которые имеют непосредственное отношение к процессам функционирования гепатоцитов. Цель исследования – оценить влияние различных схем комплексного лечения на показатели липидно-фосфолипидных фракций у пациентов с НАСГ в сочетании с ожирением (ОЖ) и патологией билиарного тракта (БТ) по данным 6-месячного динамического наблюдения. Обследовано 52 пациента с НАСГ в сочетании с ОЖ и патологией БТ. Контрольная группа состояла из 20 практически здоровых лиц. Исследовано влияние комплексного лечения (профилактических и лечебных мероприятий) на показатели липидно-фосфолипидных фракций у больных с НАСГ в сочетании с ожирением и патологией билиарного тракта. Выявлены изменения показателей липидного-фосфолипидных фракций сыворотки крови до начала лечения во всех группах наблюдения, которые сопровождались снижением содержания фосфолипидов (ФЛ), фосфатидилхолина и сфингомиелина и значительным ростом лизоформ ФЛ – лизофосфатидилхолина и фосфатидилэтаноламина, триглицеридов, эфиров холестерола (от $p<0,05$ до $p<0,001$). Комбинированная терапия с включением в стандартное лечение препаратов урсодезоксихолиевой кислоты и аргинина глутамата при коморбидном течении НАСГ может рассматриваться как перспективное направление в лечении этой категории пациентов, которое позволяет улучшить показатели липидно-фосфолипидных фракций и стабилизировать мембрану гепатоцитов (от $p<0,05$ до $p<0,001$).*

Non-alcoholic fatty liver disease (NAFLD) is a chronic, progressive disease, sometimes is difficult to diagnose and now is considered as a part of multidisciplinary problems of medicine [6, 7]. Clinical manifestation of this disease occurs in the late stages of development, which significantly narrows the spectrum of therapeutic measures [6, 8]. NAFLD and obesity have a lot in common: from risk factors, social aspects to pathogenetic mechanisms, including energy imbalance, genetic and epigenetic factors, lipid metabolism disorders, oxidative stress, inflammation, dysbiosis [8, 9]. Great importance in the pathogenesis of non-alcoholic of steatohepatitis (NASH), as a progressive form of NAFLD, are disorders of lipid metabolism, especially membrane-stabilizing function, which is directly related to the processes of hepatocytes and hepatic parenchyma functioning [4]. In NAFLD, hepatocyte membranes are affected first as compared to other cellular structures, they meet with damaging agents and protect the internal structure of the cells from external influences [5]. Today, there are virtually no studies highlighting changes in the membrane-stabilizing function of hepatocytes and lipid-phospholipid disorders, their correction in NAFLD progression. Disorders of lipid metabolism are complex and diverse due to the heterogeneity of lipids [3, 10]. It is lipids and phospholipids that play an important role in cellular metabolism. There is limited information on the change of serum lipids in patients with NAFLD, mainly related to the study of individual lipid parameters, rather than the simultaneous study of lipid-phospholipid spectrum and their correction.

Treatment of NAFLD is not always effective enough, standard treatment regimens are absent, particularly in comorbid patients on the background of obesity and pathology of the biliary tract (BT). It is envisaged that the treatment of each disease individually will help to improve the course of concomitant one due to the impact on common pathogenic components and reduce the burden on metabolic processes as a whole [7]. The main approaches to the treatment of NASH should be complex, with a primary impact on metabolic processes, energy imbalance and membrane potential of

hepatocytes. Thus, the main purpose of NAFLD therapy is prevention of disease progression, which requires control of body weight, adherence to dietary guidelines, active lifestyle, abandon bad habits, control blood glucose levels, adjust lipid profile and intestinal microbiocenosis; in addition, adequate treatment of comorbidities will be required [6]. According to many researchers, dietary, physical and drug treatment of patients with NAFLD can be divided into two stages: the first is the treatment of liver steatosis, which involves drug-free gradual weight loss by the patient. The second stage is reduction of inflammatory response from the liver with drugs, normalization of its functional state and correction of metabolic disorders in patients with NASH [7]. When choosing a NASH treatment strategy for a comorbid patient, these sequential steps must be taken into account.

Today, it has been found that drug-free therapy helps to reduce NAFLD progression, which is reflected in a decrease in body mass index (BMI) and contributes to the recovery of many laboratory parameters in comorbid patients. That is why drug-free prophylactic agents are now considered the first-line therapy in the treatment of NAFLD.

Regarding NAFLD therapy with drugs, it is possible to distinguish the main approach, which is normalization of the structural damage of the hepatocyte membrane and reduction of the degree of damage to the liver parenchyma [7, 11]. Nowadays there exists a big pool of drugs that can affect the hepatocyte membrane and metabolic processes. So, ursodeoxycholic acid (UDCA) preparations, which have shown great effecacy in NAFLD therapy are well known and have long been successfully used [11]. UDCA provides a long-lasting clinical-biochemical response in NAFLD therapy in many studies, meets the criteria of efficacy and safety, and has many pleiotropic effects, a cytoprotective effect without which none of the hepatoprotectors have a future today [11]. With regard to arginine glutamate, this active ingredient stabilizes disorders in lipid metabolism and has hepatoprotective properties in the comorbid course of many chronic diffuse liver diseases [2].

Therefore, the treatment of a patient with comorbid pathology remains a difficult issue for the clinician, and the search for new aids for complex therapy of NAFLD is relevant, as our study is dedicated.

The purpose of the study is to evaluate the impact of different treatment regimens on the lipid-phospholipid fraction in patients with NASH in combination with obesity and BT pathology according to a 6-month dynamic follow-up.

MATERIALS AND METHODS OF RESEARCH

We examined 52 patients with NASH combined with obesity and BT pathology, undergoing inpatient treatment at the Clinic of SI "Institute of Gastroenterology of NAMS of Ukraine". During sonographic or morphological study of liver biopsy of patients there were revealed signs of liver steatosis and steato-hepatitis. There were 21 male patients and 31 female patients. The mean age of the patients was 52.2±1.1 years. The control group consisted of 20 practically healthy subjects (PHS) compared by age (mean age – 46.5±2.3 years) and gender (9 men, 11 women) with patients in the main group ($p>0.05$).

Diagnosis of NAFLD and BT pathology (chronic cholelithiasis, chronic calculous cholecystitis, post-cholecystectomy syndrome) was established according to standardized protocols for the diagnosis and treatment of digestive diseases according to the recommendations of the Ministry of Health of Ukraine from 06.11. 2014 No. 826 "On approval and introduction of documents on standardization of medical care in chronic non-communicable hepatitis", as well as practical recommendations of the American Association for the Study of Liver Diseases, American College of Gastroenterologists and the American Gastroenterology Association [7].

Patients enrolled in the study did not abuse alcohol (consumption <50 g ethanol/week for men, <30 g ethanol/week for women during the last year). Serum markers of viral hepatitis B and C, autoimmune and hereditary diseases of the liver were not detected in the examined.

In order to detect excessive body weight and obesity all patients underwent in-depth anthropometric examination: weighing on an empty stomach, height measurement, waist measurement, hip width. BMI was determined by the Kettle formula.

The qualitative composition and quantitative content of lipids and phospholipids (PL) were studied by thin layer chromatography (TLC), which allows them to be divided into separate components [1]. Separation of lipid components was performed after extraction of lipids by Folch and TLC on Silufol plates, which made possible to reveal the following lipid components: PL, free cholesterol (FCS), non-esterified fatty acids (NEFA), TG, cholesterol esters (CE). PLs were divided into the following fractions: lysophosphatidylcholine (LPTC), phosphatidylcholine (PTC), sphingomyelin (SM), phosphatidylethanolamine (PTEA).

To evaluate the efficacy of different NAFLD treatment regimens, all patients were divided into 3 groups by adaptive randomization (distribution of patients into groups at first evenly, then into a

smaller group or evenly). All groups were statistically comparable by age and gender, degree of NASH activity, degree of obesity by BMI, concomitant BT pathology ($p>0.05$ at all comparisons between groups). Patients of all groups, irrespective of the treatment regimen, were administered a 6-month lifestyle adjustment, namely diet, physical activity, work, and rest.

Patients in group 1 (n=16) received drug-free treatment with a 200 kcal reduction in calorie intake every 2 weeks at the expense of limitation of simple carbohydrates and animal fats and adding seasonal fresh vegetables and fruits to the diet. Aerobic exercise – 150 minutes or more per week, taking into account physical condition and wishes of patients. Drug treatment: standard therapy according to protocols of health care delivery in case of NASH and chronic cholecystitis (evidence based metabolites – L-carnitine, B-group vitamins, myotropic antispasmodics – mebeverine hydrochloride or properinetics – domperidone) during 30 days.

Patients in group 2 (n=17) received drug-free treatment with a 400 kcal reduction in calorie intake every 2 weeks at the expense of reducing consumption of simple carbohydrates and animal fats with adding seasonal vegetables and fruits at least 3 servings per day. Aerobic exercise – 200 minutes or more per week. Drug treatment: standard therapy in combination with UDCA for 30 days at a dose of 15 mg • kg-1 • d-1.

Patients in group 3 (n=19) received drug-free treatment with a 600 kcal reduction in calorie intake every 2 weeks, achieved by reducing the amount of carbohydrates and fats consumed, with mandatory adding seasonal vegetables and fruits at least 5 servings per day. Aerobic exercise – 250 minutes or more per week. Drug treatment: standard therapy and UDCA were combined with arginine glutamate (5 days – IV infusion 5 ml of 40% solution with 200 ml of saline solution twice daily, the next 20 days – arginine glutamate tablets 0.75 g three times a day).

Dynamic monitoring of serum lipid-phospholipid fractions was performed in 52 patients 30 days after treatment and in 30 patients 6 months after treatment.

Primary data were processed using the Microsoft Office Excel-2003® software package (No. 74017-641-9475201-57075) (Microsoft Corporation, USA) and the STATISTICA v.6.1 licensing program (No. AGAR909E415822FA). Taking into account the distribution law (Kolmogorov-Smirnov criterion with Liliefors' correction), the quantitative indicators are given as mean and standard error of mean (M±m). To compare the means between the groups and in the dynamics, we used the Student's t test (t) and Mann-Whitney (U) for the unrelated samples, for the related ones the Student's t test (T) and Wilcoxon (W) with the Bonferon correction for multiple comparison.

RESULTS AND DISCUSSION

Analyzing findings of serum lipid fractions in patients with a comorbid course of NASH prior to treatment, it was found (Table 1) that disorders of lipid fractional composition occurred in all groups (from $p<0.05$ to $p<0.001$). Changes of PL with a significant decrease in all observation groups with respect to PHS ($p<0.001$) were the most significant, together with an increase in the percentage of FCS, TG, CE (from $p<0.05$ to $p<0.001$), indicating qualitative changes of neutral lipids spectrum in comorbid patients with advanced NAFLD.

Carried out study of serum lipid fractions in dynamics made it possible to establish (Table 1) that at the end of treatment on day 30 in group 3, the level of PL increased by1.6 times and reached normal values 6 months after treatment with an increase by 1.9 times relative to pre-treatment rates ($p<0.001$), while at the same time in group 1 decreased PF level persisted, relative to patients in group 2 ($p<0.05$) and group 3 ($p<0.01$). Complete normalization of FCS level was observed only in group 3 with a 1.5-fold increase 6 months after treatment, this statistically differentiated these patients from those ones in group 1 ($p<0.05$). The level of NEFA in all observation groups was not statistically different from PHS values. Statistically significant direction in TG changes was noted as early as 30 days after treatment, with a 1.4-fold decrease after 6 months in group 2 and group 3 relative to pre-treatment indicators (from $p<0.01$ to $p<0.001$). Complete normalization of CE was recorded only in group 3 with a decrease by 1.2 times ($p<0.001$) 6 months after treatment, this statistically differentiated these patients from those ones in group 1 ($p<0.05$).

The results of the study of serum phospholipid fractions in patients with NASH are presented in table 2. In comorbid patients with NASH in all observation groups the content of lysoforms of phospholipids in serum – LPTC significantly increased compared with the control group ($p<0.001$). A similar increase with respect to the control values was observed in such PTEA fractions ($p<0.001$) against the background of the decrease in the percentage of SM, PTC in all groups (from $p<0.05$ to $p<0.001$).

When analyzing the data of phospholipid fractions of serum after treatment (Table 2), it was found that normalization of the level of LPTC was observed only

in patients of group 3 with a decrease by 1.7 times 6 months after treatment (p<0.001), which was also probable for patients of group 1 and 2 (p<0.001).

An increase in the level of SM by 1.2 times 30 days after treatment and its normalization with an increase by 1.3 times in further analysis was also achieved only in patients of group 3, which statistically differentiated these patients from similar values of group 1 (p<0.05 at all comparisons).

Table 1

Findings of serum lipid fractions in patients with NASH with concomitant obesity and BT pathology in dynamics of treatment (M±m)

Finding	PHS, n=20	Group	Before treatment	30 days after	Group	6 months after
PL, %	25,56 ±0,82	1 (n=16)	15,45±1,75###	17,75±1,38###	1 (n=10)	18,04±1,63###
		2 (n=17)	15,07±1,86###	21,09±0,55**###″	2 (n=9)	23,24±1,53**″
		3 (n=19)	13,70±1,45###	21,32±0,86***###″	3 (n=11)	25,40±1,53***″″
FCS, %	14,06 ±0,26	1 (n=16)	20,76±1,35###	18,38±1,22##	1 (n=10)	17,25±1,02*#
		2 (n=17)	22,45±1,60###	16,54±0,99**#	2 (n=9)	15,52±1,17**
		3 (n=19)	21,52±1,49###	16,07±0,79**#	3 (n=11)	14,30±1,06***″
NEFA, %	8,42 ±0,35	1 (n=16)	8,96±1,24	8,70±0,79	1 (n=10)	8,50±0,91
		2 (n=17)	8,39±0,84	8,15±0,29	2 (n=9)	7,63±0,36
		3 (n=19)	8,34±0,91	8,04±0,30	3 (n=11)	7,32±0,42
TG, %	16,11 ±0,22	1 (n=16)	22,13±1,94##	18,68±1,27#	1 (n=10)	17,81±1,65
		2 (n=17)	22,38±1,56###	17,44±0,84**	2 (n=9)	15,94±0,57***
		3 (n=19)	21,17±0,97###	16,02±0,65***	3 (n=11)	15,21±0,87***
CE, %	32,72 ±0,40	1 (n=16)	37,49±1,99 #	36,17±1,83#	1 (n=10)	35,26±1,11#
		2 (n=17)	39,65±1,91##	35,22±1,08*#	2 (n=9)	34,12±1,51*
		3 (n=19)	38,49±1,31###	34,04±1,08**	3 (n=11)	32,09±1,14***″

Notes: * – p<0.05; ** – p<0.01; *** – p<0.001 compared to pre-treatment level; # – p<0.05; ## – p<0.01; ### – p<0.001 vs. PHS; ″ – p<0.05; ″″ – p<0.01 compared with 1 group of patients.

A similar pattern was observed for PTC findings, which also increased by 1.2 and 1.3 times respectively in 30 days (p<0.05) and reached normal values 6 months after treatment in patients of group 3 only (p<0.001), which statistically differentiated these patients from group 1 (p<0.05). In the analysis of the obtained data as for PTEA findings, the probable values were obtained in patients of group 2 and 3 (p<0.001). Normalization of PTEA with a 2.2-fold increase in 6 months after treatment as for baseline findings (p<0.001) and those ones in group 1 (p<0.01) were recorded in group 3.

Based on the results of the studies, it was concluded that the comorbid course of NASH is accompanied by disturbances in the structural and functional state of hepatocyte membranes due to the imbalance of lipid-phospholipid interactions. They are based on changes in the membrane lipid matrix, which can also be reflected in the physicochemical properties of membrane proteins [3]. Thus, the structure and function of hepatocyte membranes are directly dependent on the level of lipids and phospholipids, which has also been reflected in the works of other researchers [3, 4, 5], so the study of

lipid-phospholipid balance is of both scientific and practical interest. High levels of LPTC and PTEA with a significant decrease in PL may be a diagnostic criterion for impaired hepatocyte membrane permeability in patients with NASH in combination with obesity and BT pathology.

Table 2

Findings of serum phospholipid fractions in patients with NASH with concomitant obesity and BT pathology in the dynamics of treatment (M±m)

Finding	PHS, n=20	Group	Before treatment	30 days after	Group	6 months after
LPTC, %	6,46±0,20	1 (n=16)	10,76±1,04###	9,23±0,80##	1 (n=10)	8,61±0,82#
		2 (n=17)	10,01±0,68###	7,95±0,58*#	2 (n=9)	7,20±0,13***#
		3 (n=19)	10,34±0,90###	7,44±0,42 **#″	3 (n=11)	5,94±0,29***″″¶
SM, %	17,46±0,32	1 (n=16)	12,88±1,25##	13,70±0,99##	1 (n=10)	14,68±0,93#
		2 (n=17)	14,66±1,08#	15,56±0,78#	2 (n=9)	15,99±0,87
		3 (n=19)	13,49±1,30##	16,12±0,61*″	3 (n=11)	17,49±1,06*″
PTC, %	65,5±0,56	1 (n=16)	54,9±1,12###	55,2±1,39###	1 (n=10)	56,7±2,89#
		2 (n=17)	52,2±1,61###	56,1±2,72##	2 (n=9)	61,0±3,80*
		3 (n=19)	52,4±1,75###	60,4±2,70*	3 (n=11)	65,3±3,13***″
PTEA, %	10,46±0,33	1 (n=16)	22,7±1,97###	19,1±1,46###	1 (n=10)	18,3±1,79##
		2 (n=17)	24,5±2,52###	14,3±1,27***##″	2 (n=9)	12,0±1,43***″
		3 (n=19)	23,1±1,67###	13,7±0,89***##″″	3 (n=11)	10,5±0,57***″″

Notes: * – p<0.05; ** – p<0.01; *** – p<0.001 compared to pre-treatment level; # – p<0.05; ## – p<0.01; ### – p<0.001 compared to PHS; ″ – p<0.05; ″″ – p<0.01 compared to group 1; ¶ – p<0.01 compared with group 2.

Conducting dynamic monitoring for 6 months allowed us to establish that the most effective of the differentiated treatment options studied is the adding UDCA and arginine glutamate to standard therapy in patients of group 3, which provides the restoration of lipid-phospholipid fractions with further elimination of the imbalance in the system lipid-phospholipid interactions by the level of PTEA, PTC, SM, as well as a probable decrease in the percentage of LPTC (p<0.01) in relation to patients of the 2 groups who received only UDCA preparations against the background of standard treatment. In addition, it should be noted the absence of side effects of complex therapy throughout the treatment period. The adding UDCA only to standard treatment in patients in group 2 also contributed to the recovery of lipid-phospholipid fractions compared with patients in group 1 (from p<0.05 to p<0.01). Conducting standard therapy was less effective because the positive changes in lipid-phospholipid findings were insufficiently expressed and likely only in relation to PHS and laboratory data before treatment (from p<0.05 to p<0.001). These patients maintained a condition of moderate exacerbation of the chronic pathology of the hepatobiliary system.

Thus, studying the patterns of mechanisms of inhibition of membrane-destructive processes allows to expand the possibilities of therapeutic measures on the basis of the introduction of replacement drugs that restore the structure of cell membranes of hepatocytes in patients with NASH against the background of obesity and BT pathology.

CONCLUSIONS

1. In patients with NASH, the combined course of the disease is accompanied by changes in serum lipid fractions with a significant decrease in PL with respect to PHS (p<0.001) in all groups, along with

an increase in the percentage of FCS, TG, CE (from $p<0.05$ to $p<0.001$), which contributes to the maintenance of structural changes in hepatocyte membrane and in the hepatobiliary system.

2. In comorbid patients with NASH an increased content of serum phospholipid lysforms – LPTC and PTEA was observed with a decrease in the percentage of SM, PTC in all groups (from $p<0.05$ to $p<0.001$), which may be a diagnostic criterion for impaired permeability of hepatocyte membranes.

3. Complex therapy of patients with a comorbid course of NASH can significantly improve the parameters of lipid-phospholipid fractions, which can contribute to the recovery of hepatocyte membranes and reduce the risk of disease progression. The results of the study indicate that combination therapy with the inclusion in standard treatment of UDCA and arginine glutamate in the comorbid course of NASH can be considered as a promising direction in the treatment of this category of patients, which allows to achieve the recovery of the main findings of lipid-phospholipid fractions $p<0.001$).

Prospects for further studies are to study the indicators of endogenous intoxication in the dynamics of treatment in patients with comorbid course of NASH.

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