Клинические аспекты медицины транспорта | **Clinical Aspects of Transport Medicine**

УДК 615.244+615.272]: 616.36-003.826+616.61-036.12]-056.527
DOI http://dx.doi.org/10.5281/zenodo.2611238

THE INTENSITY OF LIPID DISTRESS SYNDROME IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE ON THE BACKGROUND OF OBESITY AND CHRONIC KIDNEY DISEASE (CHRONIC PYELONEPHRITIS)

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ИНТЕНСИВНОСТЬ ЛИПИДНОГО ДИСТРЕСС-СИНДРОМА У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ НА ФОНЕ ОЖИРЕНИЯ И ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК (ХРОНИЧЕСКИЙ ПИЕЛОНЕФРИТ)

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ІНТЕНСИВНІСТЬ ЛІПІДНОГО ДИСТРЕС-СИНДРОМУ У ПАЦІЄНТІВ З НЕАЛКОГОЛЬНОЮ ЖИРОВОЇ ХВОРОБОЮ ПЕЧІНКИ НА ТЛІ ОЖИРІННЯ І ХРОНІЧНОЇ ХВОРОБИ НИРОК (ХРОНІЧНИЙ ПИЕЛОНЕФРИТ)

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Summary / Резюме

Introduction. The comorbid flow of non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) on the background of obesity is often recently drawn to the attention of both practitioners and researchers.

The aim of the study was to find out the likely interaction of the blood lipid profile on the clinical course of NAFLD on the background of obesity, depending on its form and the presence of comorbid chronic kidney disease.

The object and methods of research. 384 patients with NAFLD were examined: 84 of them were NAFLD with obesity 1st degree (1 group), which contained 2 subgroups: 32 patients with non-alcoholic steatosis (NAS) and 52 patients with non-alcoholic steatohepatitis (NASH); 270 patients with NAFLD with comorbid obesity of the I degree and CKD I-III stage (group 2), including 110 patients with NAS and 160 patients with NASH. The control group consisted of 90 patients with CKD of the I-III stage with normal body weight (group 3). To determine the dependence of the NAFLD course on the form and stage of CKD, the group of patients was randomized according to age, sex, degree of obesity, and activity of NASH.

Results of the research and their discussion. Significant metabolic prerequisites for the development of NASH against the background of obesity and CKD are likely postprandial hyperglycemia, hyperinsulinemia, increase in the degree of glycosylation of hemoglobin, the primary tissue insulin resistance. The reason for the progression of the metabolic syndrome on the background of NASH and CKD is lipid distress syndrome with an increase in blood total cholesterol, proatherogenic LDL, HDL antiatherogenic deficiency. The leading role in the development and progression of steatohepatitis is the disorders of the hepatic circulation that results in an TG increase in blood.

*Conclusion.*Thus, the development of NASH in patients with CKD and obesity is accompanied by a significant disorder of hyperlipidemia with the highest among the groups compared with the increase in the content of cholesterol and low density proatherogenic lipoproteins, the probable decrease in anti-atherogenic high-density lipoproteins and the increase in the atherogenicity index.

***Key words**: nonalcoholic fatty liver disease, obesity, chronic kidney disease, lipid blood spectrum.*

У статті наведено теоретичне узагальнення результатів дослідження інтенсивності ліпідного дестрес-синдрому у хварих на неалкогольну жирову хворобу печінки за коморбідності з ожирінням та хронічною хворобою нирок (хронічний пієлонефрит), який супроводжується суттєвою дис- та гіперліпідемією із максимальним серед груп порівняння, зростанням вмісту в крові холестеролу та проатерогенних ліпопротеїнів низької щільності, вірогідним зниженням протиатерогенних ліпопротеїнів високої щільності та зростанням індексу атерогенності. Провідну роль у розвитку та прогресуванні неалкогольного стеатогепатиту, розладів печінкового кровообігу грає зростання вмісту тригліцеридів в крові.

***Ключові слова**: неалкогольна жирова хвороба печінки, ожиріння, хронічна хвороба нирок, ліпідний спектр крові.*

В статье приведено теоретическое обобщение результатов исследования интенсивности липидного дестрес-синдрома у пациентов с неалкогольной жировой болезнью печени в коморбидности с ожирением и хронической болезнью почек (хронический пиелонефрит), что сопровождается существенной дис- и гиперлипидемией с максимальным среди групп сравнения ростом содержания в крови холестерина и проатерогенных липопротеинов низкой плотности, вероятным снижением противоатерогенных липопротеинов высокой плотности и ростом индекса атерогенности. Ведущую роль в развитии и прогрессировании неалкогольного стеатогепатита, расстройств печеночного кровообращения оказывает рост содержания триглицеридов в крови.

***Ключевые слова**: неалкогольная жировая болезнь печени, ожирение, хроническая болезнь почек, липидный спектр крови.*

Introduction

The comorbid flow of non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) on the background of obesity is often recently drawn to the attention of both practitioners and researchers [4, 9]. Without correction of clinical and biochemical syndromes of

liver damage by interrupting the cascade of interactions, the cessation of the progression of their inflammation and the fibrosis of these organs, the restoration of their functional state cannot be achieved [1, 7, 8]. The dominant place in the pathogenesis of both diseases is the disturbance of carbohydrate and lipid metabolism, which promote the acceleration of apoptosis of hepatocytes, endothelium, and further their cytolysis with the activation of autoimmune cytokine mechanisms of inflammation progression and fibrosing reactions which leads to progressive functional insufficiency of organs [9, 10].

The aim of the study was to find out the likely interaction of the blood lipid profile on the clinical course of NAFLD on the background of obesity, depending on its form and the presence of comorbid chronic kidney disease.

The object and methods of research

384 patients with NAFLD were examined: 84 of them were NAFLD with obesity 1st degree (1 group), which contained 2 subgroups: 32 patients with non-alcoholic steatosis (NAS) and 52 patients with non-alcoholic steatohepatitis (NASH); 270 patients with NAFLD with comorbid obesity of the I degree and CKD I-III stage (group 2), including 110 patients with NAS and 160 patients with NASH. The control group consisted of 90 patients with CKD of the I-III stage with normal body weight (group 3). To determine the dependence of the NAFLD course on the form and stage of CKD, the group of patients was randomized according to age, sex, degree of obesity, and activity of NASH. The average age of patients was (45.8 ± 3.81) years. The lipid blood spectrum was studied in terms of the content of common lipids, total cholesterol, TG, LDL, and HDL in blood, using standard diagnostic sets of Danush Ltd (Lviv). The level of LDL in the blood was calculated using the mathematical formula: the content of TG/2.2. The index of atherogenicity (IA) was also calculated based on the ratio of the content of total Cholesterol/HDL. The degree of carbohydrate metabolism compensation was determined by the level of glycemia in the onset and two hours after glucose loading (glucose tolerance test) by glucose oxidase method, blood intake of insulin onset (DRG System) — by ELISA, glycated hemoglobin (HbA1c) in the blood by using standard reagent kits Danush Ltd» (Lviv). The statistical analysis of the results was carried out in accordance with the type of research carried out and the types of numerical data that were obtained. Distribution normality was verified using Liliefors, Shapiro-Uilka tests and the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented 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 surveyed). For comparisons of data that had a normal distribution pattern, parametric tests were used to estimate the Student's t-criterion, Fisher's F-criterion. In the case of abnormal distribution, the median test, Mann-Whitney Rank U-Score, and Wilcox's T-criterion (in the case of dependent groups) were used for multiple comparison. Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results of the research and their discussion

A study of the lipid profile of the blood in patients with NAS showed a number of similar changes (Table 1), however, differing in degree of probability depending on the presence of the accompanying CKD. Thus, according to

the concentration of total lipids in the blood of general lipids in patients with NAS and obesity, a significant excess of the norm of common lipids and total blood cholesterol was detected — 1.3 times ($p < 0.05$), and in the group of patients with NAS with CKD — respectively 1.4 times ($p < 0.05$) with the probable statistical difference between the groups ($p < 0.05$). TG blood levels also indicate their probable growth in patients with NAS — 1.5 times, in patients with NAS with CKN — significantly (2.0 times, $p < 0.05$) compared with practically healthy person (PHP). That is, the content of TG in the comorbidity of NAS with CKD was significantly higher than in patients with NAS without CKN. The study of the proatherogenic fractions of lipoproteins concentrations in blood indicates a number of possible changes: LDL concentrations in patients with NAS were significantly higher than the concentrations in the control group in 1.3 times ($p < 0.05$), and in patients with NAS and CKD, a statistically significant increase in LDL cholesterol in 1,7 times ($p < 0,05$) with the presence of a probable statistical difference between the groups ($p < 0,05$).

As can be seen from the results of the study, the maximum suppression of the synthesis of HDL cholesterol was observed in patients with NAS and CKD, indicating a minimum level of protection of endothelial vessels from free radicals' aggression and atherogenic fractions of blood lipoproteins. The result of these changes was a significant increase in the atherogenicity index in patients of both observation groups: 2.1 times and 2.6 times, respectively ($p < 0.05$) (Table 1) with the maximum changes in the index in patients with NAS, CKD and obesity, indicating that there are significant risk factors for the progression of atherosclerosis against the background of hyperthyroidism and dyslipidemia in the CKD on the background of obesity, and on the other hand, on the favorable pathogenetic situation with regard to the progression of NAS. In essence, with NAS we have established a lipid distress syndrome, which significantly progresses in comorbidity with CKD.

The analysis of blood lipid profile in NAS patients which presented in Table 1, indicates a higher lipid distress syndrome compared to previous patient groups, especially with the presence of comorbid CKD. Thus, the content in the blood of common lipids in patients with NAS and obesity and total blood CH exceeded the reference values in 1.4 times ($p < 0.05$), and in the group of patients with NAS with CKD — respectively, 1.5 times ($p < 0,05$) with the presence of a probable statistical difference between

Table 1

Indicators of the lipid profile of blood in patients with non-alcoholic steatosis and steatohepatitis, obesity depending on the presence of comorbid chronic kidney disease and the isolated flow of CKD (M ± m)

Indicators, measurement units	PHP, *n* = 30	Groups of examined patients				
		NAS, *n* = 32	NAS, CKD, *n* = 110	NASH, *n* = 52	NASH, CKD, *n* = 160	CKD, *n* = 90
Total lipids mmol/l	5,85 ± 0,11	7,45 ± 0,14 *	8,13 ± 0,12 */**	7,97 ± 0,11 */**	8,89 ± 0,10 */***/#	6,59 ± 0,20 */***/##
Total Cholesterol, mmol/l	4,72 ± 0,10	6,08 ± 0,11 *	6,61 ± 0,09 */**	6,37 ± 0,11 */**	6,93 ± 0,14 */***/#	5,48 ± 0,12 */***/##
TG, mmol/l	1,47 ± 0,03	2,27 ± 0,01 *	2,94 ± 0,01 */**	2,73 ± 0,03 */**	3,19 ± 0,02 */***/#	1,96 ± 0,03 */***/##
LDL, mmol / l	2,59 ± 0,02	3,35 ± 0,03 *	4,29 ± 0,02 */**	3,68 ± 0,05 */**	4,57 ± 0,02 */***/#	2,97 ± 0,03 */***/##
HDL, mmol / l	1,29 ± 0,04	0,93 ± 0,01 *	0,85 ± 0,01 */**	0,79 ± 0,01 */**	0,72 ± 0,01 */***/#	1,03 ± 0,02 */***/##
IA	2,65 ± 0,02	5,54 ± 0,03*	6,78 ± 0,04 */**	7,06 ± 0,05 */**	8,63 ± 0,03 */***/#	4,32 ± 0,03 */***/##

Notes: * — the difference is probable compared to the index in the PHP ($p < 0,05$);
** — the difference is probable in comparison with the indicator in patients with NAS ($p < 0,05$);
*** — the difference is probable compared to the index in patients with NASH ($p < 0,05$);
# — the difference is likely in comparison with the index for patients with NAS with CKD ($p < 0,05$);
— the difference is probable compared with the index in patients with NASH with CKD ($p < 0,05$).

the groups ($p < 0,05$). The content of general CH and TG in blood also indicates their probable growth in patients with NAS — 1.4 and 1.9 times, respectively, in patients with NAS with CKD — significantly (1.5 and 2.2 times, $p < 0.05$) in comparison with PHP.

Investigation of blood contents of proatherogenic lipoprotein fractions indicates an increase in the content of LDL cholesterol in patients with NASH in 1.4 times ($p < 0.05$), and in patients with NASH with CKD 1.8 times ($p < 0.05$) with a probable statistical difference between the groups ($p < 0,05$). Concentration in blood HDL cholesterol in patients of both groups was significantly lower in comparison with control (Table 1): in patients with NASH — 1.6 times ($p < 0.05$), patients with NASH with CKD in 1, 8 times ($p < 0,05$), that is, the maximum. As a result, a significant increase in the atherogenicity index was recorded in patients with both observation groups: 2.7 and 3.3 times respectively ($p < 0.05$) (Table 1) with the highest increase in the index in patients with NASH, CKD and obesity.

In patients with NASH and obesity with CKD, disorders of cholesterol homeostasis and lipoproteins in a weak interdependence are correlated with markers of cytolysis, mesenchymal inflammation and manifestations of polycystic kidney (Table 2).

Patients with non-alcoholic steatohepatitis and obesity without accompanying CKD are characterized by the following changes in the blood lipid profile: the maximum increase in the content of triacylglycerol in the blood (2.1 times, $p < 0.05$), the likely increase in the total cholesterol content (1.4 times, $p < 0,05$) and low-density proatherogenic lipoproteins (1,6 times, $p < 0,05$), the probable reduction of high-density anti-atherogenic lipoproteins (1,6 times, $p < 0,05$), which, with the addition of a comorbid CKD, is likely deepen (within 1.5-1.8 times, $p < 0.05$), except for the indicator of hypertriacylglycerolemia. The TG blood indexes and the index of hepatocyte steatosis in patients with NASH in the context of obesity are believed to be higher (1.3 times ($p < 0.05$)) (according to the steato test: within S1-S2) from the indicators in patients with a comorbid flow of NASH, obesity and CKD. For the comorbid flow of NASH and CKD, the maximum growth of the atherogeny index (2.7 times against 2.2 times the isolated flow of NASH, $p < 0.05$) was established.

Table 2

Matrix of correlations of morpho-functional parameters of the liver and kidneys with indicators of lipid homeostasis and adipokines content in blood in patients with NAS and CKD, obesity (*r, p*)

Indicator	CH	LDL	HDL	TG	IA	IMT
Billirubin	0,28	0,25	-0,12	0,39*	0,37*	0,31*
ALT	0,24	0,29	-0,15	0,37*	0,41*	0,33*
AST	0,23	0,23	-0,21	0,34*	0,43*	0,29
GTT	0,46*	0,39*	-0,43*	0,61*	0,72*	0,37*
Alkaline phos-phatase	0,44*	0,47*	-0,31*	0,65*	0,61*	0,35*
Thymol test	0,23	0,25	-0,11	0,28	0,31*	0,37*
Fibrinogen	-0,34*	-0,39*	0,10	-0,27	-0,40*	-0,39*
Albumin	-0,35*	-0,38*	0,29	-0,30*	-0,42*	-0,31*
Creatinine of blood	0,45*	0,49*	-0,31*	0,52*	0,53*	0,38*
GFR	-0,53*	-0,57*	0,42*	-0,58*	-0,61*	-0,33*
Steato-test	0,73*	0,77*	-0,72*	0,79*	0,75*	0,72*
Hepatorenal index	0,71*	0,70*	-0,67*	0,75*	0,73*	0,70*

Conclusion

Consequently, significant metabolic prerequisites for the development of NASH against the background of obesity and CKD are likely postprandial hyperglycemia, hyperinsulinemia, increase in the degree of glycosylation of hemoglobin, the primary tissue insulin resistance. The

reason for the progression of the metabolic syndrome on the background of NASH and CKD is lipid distress syndrome with an increase in blood total cholesterol, proatherogenic LDL, HDL antiatherogenic deficiency. The leading role in the development and progression of steatohepatitis is the disorders of the hepatic circulation that results in an TG increase in blood. Thus, the development of NASH in patients with CKD and obesity is accompanied by a significant disorder of hyperlipidemia with the highest among the groups compared with the increase in the content of cholesterol and low density proatherogenic lipoproteins, the probable decrease in anti-atherogenic high-density lipoproteins and the increase in the atherogenicity index.

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Впервые поступила в редакцию 12.01.2019 г.
Рекомендована к печати на заседании редакционной коллегии после рецензирования