DOI 10.26886/2414-634X.8(27)2018.4
UDC: 616.36-003.826:616.12-008.331.1-056.257

PARAMETERS OF LIPID METABOLISM AND SEVERITY OF LIVER STEATOSIS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE ON THE BACKGROUND OF HYPERTENSION DEPENDING ON THE STATUS OF CARBOHYDRATE METABOLISM

O. Babak, PhD of Medical Sciences, Professor
A. Bashkirova, PhD Student
Kharkiv National Medical University, Kharkiv, Ukraine

The aim of the study was to establish relationships between the parameters of lipid metabolism, the severity of liver steatosis and the concentration of endothelial lipase (EL) serum levels depending on the state of carbohydrate metabolism and the presence of type 2 diabetes .

60 patients with non-alcoholic fatty liver disease (NAFLD) on the background of hypertension and overweight have been examined. The distribution of the examined patients was carried out in the following groups: group 1 - patients with hypertension without an increase in NAFLD liver fat score normal weight (n = 8); Group 2 - with hypertension without increse in NAFLD liver fat score with overweight (n = 8); group 3 - with liver steatosis without type 2 diabetes (n = 10); group 4 - with liver steatosis and type 2 diabetes (n = 10); group 5 - with laboratory signs of steatohepatitis without type 2 diabetes (n = 16); group 6 - with laboratory signs of steatohepatitis and type 2 diabetes (n = 8). All patients were divided with accordance of age and sex. The control group consisted of 20 healthy individuals.

All patients with NAFLD on the background of hypertension and the presence of type 2 diabetes had significantly (p <0.001) higher hyperinsulinism (32.27 + 4.71 vs. 20.75 + 9.5 mkU/ml) and significantly (p

<0.001) increased values of insulin resistance index HOMA-IR (9.52 + 4.21 against 4.76 + 2.23 U), which testifies in favour of type 2 diabetes.

In all patients with NAFLD on the background of hypertension, there are proatherogenic changes in lipid status, the presence of which is exacerbated with obesity and the severity of steatosis. It is most evident in patients with steatohepatitis in combination with type 2 diabetes.

The level of EL is significantly higher in patients with steatosis, regardless of the presence of diabetes and with steatohepatitis without diabetes compared with controls and patients with hypertension and normal weight. Significantly high levels of endothelial lipase were found in patients with steatohepatitis and diabetes. Correlation analysis between the HbA1c and EL levels showed a reliable direct relationship between the parameters.

So the level of EL in patients with hypertension in combination with the severity of liver steatosis is significant relative to atherosclerotic vascular lesions and prognostic as the occurrence of cardiovascular complications.

Keywords: NAFLD, hypertension, type 2 diabetes, endothelial lipase, insulin resistance

Introduction. Non-alcoholic fatty liver disease (NAFLD) is one of the most actual problems of modern medicine. Every year its prevalence increases, requiring even more attention to this problem [1, p. 261-271]. NAFLD is found in 20-30% of the population of Western European countries and the United States and 15% of the population of Asia [2, p. 33-38]. According to G. Marchesini et al. (2001), 67% of patients with NAFLD suffer from overweight; 57% have disorders of glucose tolerance, 47% have hypertriglyceridemia, 27% have low alpha cholesterol, 17% have hypertension [3, p. 873-880].

A generalized model of the pathogenesis of NAFLD was previously recognized as the "theory of two strikes," according to which the "first strike"

is the increase in the intake of free fatty acids (FFA) in the liver. Accumulation of fat in hepatocytes is a consequence of increased intake of FFA from adipose tissue, reducing the rate of their oxidation in mitochondria, and excess synthesis of FFAs from acetylcoenzyme A. Increasing the flow of FFA and reducing the rate of their oxidation leads to esterification of FFA with excessive formation of triglycerides in hepatocytes and secretion of increased amounts of cholesterol of very low density lipoprotein (VLDL), which contribute to the enhancement of free radical lipid oxidation and the accumulation of products of their peroxidation ("second strike") [4].

NAFLD in the background of overweight or obesity suggests disorders of adipose tissue secretion of hormones adipokines, which reduces tissue sensitivity to insulin by reducing adiponectin levels and increasing levels of visfatin and resistin, as well as increasing the level of chemokines that activate macrophages and promote their accumulation in fatty tissue. Activated macrophages produce cytokines that negatively affect sensitivity to insulin [5].

According to most researchers, the clinical significance of NAFLD is associated with the genesis of atherosclerosis [6], which allows NAFLD to be considered as an independent risk factor for the development of cardiovascular disease (CVD) [16]. As triggers, associated with the development of NAFLD and metabolic disorders, oxidative stress, inflammation, dyslipidemia, IR, abdominal obesity, low adiponectin levels, endothelial dysfunction and postprandial dyslipidemia are reported [7, p. 8407-8415]. The relationship between NAFLD and CVD was first established in relation to patients with type 2 diabetes [8, p. 479-482].

Insulin resistance (IP) is a disturbed biological response of the peripheral tissues of an organism to the effect of endogenous or exogenous insulin, manifested in the regulation of the metabolism of carbohydrates,

proteins, fats, growth processes, tissue differentiation, DNA synthesis, gene transcription. Therefore, the modern concept of IP is not limited to parameters that characterize exclusively the exchange of glucose. The greatest clinical significance is the loss of sensitivity to insulin of fatty, liver and muscle tissue [9, p. 2701-2704]. IR of liver tissue is accompanied by a decrease in the synthesis of glycogen, the activation of its processes of dissociation to glucose, the synthesis of glucose from amino acids, lactate, pyruvate, glycerol. Changes in the metabolism of glucose and lipids in the adipose tissue are an important pathogenetic link that leads to increased lipolysis, increased release of free fatty acids (FFA), triglycerides (TG) entering the liver, which become the main source of formation of very low density atherogenic lipoprotein (VLDL) and increased sedimentation of adipose tissue in the liver itself [10]. It enhances hepatic insulin resistance. In the liver there is an increase in the utilization of FFA, which leads to compensatory hyperinsulinaemia and the beginning of a cascade of reactions for the transformation of lipids in the blood. So the development of fatty liver dystrophy is a result of increased intake, excess synthesis and a decrease in the rate of β-oxidation of FFA in mitochondria, increased formotion and secretion of VLDL [11].

Cardiovascular mortality in patients with diabetes is in 3-4 times higher than in people without diabetes [12]. There is clinical evidence that hyperinsulinemia is an independent risk factor for developing CVD in people without diabetes. Insulin is able to exert a direct atherogenic effect on the walls of the vessels, causing proliferation and migration of smooth muscle cells, lipid synthesis in them, proliferation of fibroblasts, activation of the blood coagulation system, and decreased activity of fibrinolysis. So hyperinsulinemia makes a significant contribution to the development and progression of cardiovascular risk [13].

It has now been proven that IR and endothelial dysfunction are the links of the same process and play an important role in the formation of metabolic disorders and, as a consequence, CVD. It is endothelial dysfunction that leads to the formation of atherosclerosis and predetermines the development of atherothrombosis [14].

Endothelial cells liner vessels from the inside and serve as a border between blood and tissues, which makes the endothelium vulnerable to various factors such as hypercholesterolemia, hyperglycemia, free radicals, high hydrostatic pressure, smoking, etc. Endothelial damage leads to a decrease in the release of endothelium-relaxing factors, which increases the formation of vasoconstrictive factors that forms endothelial dysfunction [15, p. 494–511].

Endothelial lipase (EL) is identified as a new member of the family of triglycerides and is very similar to lipoprotein lipase and hepatic lipase, but is a more sensitive marker of phospholipid hydrolysis. EL is the only lipase synthesized by endothelial cells. Data from laboratory studies have shown that EL can play a key role in modulating the metabolism of high density lipoproteins and contributes to the metabolism of atherogenic apoB-containing lipoproteins. An increase in the plasma concentration of EL is associated with an increase in triglycerides and the concentration of apolipoprotein B in plasma. These facts suggest that EL is one of the key regulatory lipid metabolism enzymes [16]. Numerous studies also show that EL is a new marker of cardiovascular risk, which is closely related to dyslipidemia and insulin resistance [17].

Aims and methods. The aim of the study was to establish a relationship between the parameters of lipid metabolism, the severity of liver steatosis and the concentration of blood serum EL levels, depending on the state of carbohydrate metabolism and the presence of type 2 diabetes.

The work has been performed on the basis of the National Institute of Therapy named by L.T. Malaya of National Academy of Medical Sciences of Ukraine within the department's research work of the department of internal medicine №1 of Kharkiv National Medical University "Clinical significance of markers of inflammation and metabolic disorders in patients with NAFLD taking into account comorbidity".

The research was approved by the Ethics Commission of the Kharkiv National Medical University and conducted in accordance with the principles of the Helsinki Declaration. All patients signed an informed consent to participate in the study.

60 patients with NAFLD on the backdrop of hypertension and overweight have been examined. The NAFLD diagnosis was established in accordance with the Protocol of the Ministry of Health of Ukraine dated November 6, 2014, based on the criteria of the American Association for the Study of Liver Diseases [18, p. 2005-2023] and European Recommendations for the Diagnosis and Treatment of NAFLD [19, p. 65-90]. The diagnosis of hypertension is in accordance with the Protocol No. 384 of the Ministry of Health of Ukraine dated May 24, 2012, determining the stage and degree of hypertension is according to the clinical guidelines for arterial hypertension (2013) of the European Society for Hypertension (ESH) and the European Society of Cardiology (ESC) [20, p. 193-278]. The diagnosis of steatohepatitis was established in the presence of ultrasound data, elevated liver transaminases and the NAFLD liver fat score.

The analysis of carbohydrate metabolism parameters in patients with NAFLD on the backdrop of hypertension and overweight found 18 patients with signs of type 2 diabetes with glycated haemoglobin level higher than 6.5 mmol/l and / or hyperglycemia higher than 6.1 mmol/l. Given the fact that the presence of diabetes mellitus plays a pathogenic role in the

formation of liver steatosis [21, p. 479-482.], we conducted the distribution of the examined patients into the following groups:

- Group 1 - with hypertension without increasing NAFLD liver fat score with normal weight (n = 8)
- Group 2 - with hypertension without increased NAFLD liver fat score with overweight (n = 8)
- Group 3 - with liver steatosis without type 2 diabetes (n = 10)
- Group 4 - with liver steatosis and type 2 diabetes (n = 10)
- Group 5 - with laboratory signs of steatohepatitis without type 2 diabetes (n = 16)
- Group 6 - with laboratory signs of steatohepatitis and type 2 diabetes (n = 8)

The control group consisted of 20 practically healthy individuals. All patients were divided with accordance of age and sex.

The exclusion criteria were: acute and chronic inflammatory processes in the period of exacerbation of any localization; age over 60 and under 45 (excluding the non-informative age for comorbidity of these pathologies [14]); obesity of the third degree and above; diffuse connective tissue diseases; oncological diseases; symptomatic hypertension; viral (HBV-, HCV-, HDV), toxic and medicated hepatitis; alcohol abuse (more than 30g of ethanol or 3.75 alcohol units per day for men and 20g or 2.5 alcoholic units for women); diabetes mellitus type I; hypertension of III stage and above; anamnesis data for Wilson-Konovalov's disease, idiopathic hemochromatosis and congenital failure of α1-antitrypsin; coronary heart disease with postinfarction cardiosclerosis; heart failure of stage III; hypothyroidism and hyperthyroidism; refusal of the patient at any stage of the study.

The body mass index (BMI) and measured the waist circumference (WC) have been accessed for all patients. Measurement of blood pressure

(BP) was performed according to the standard auscultatory method by N.S. Korotkov (office measurement) using a sphygmomanometer No. 31304500 (Erka, Chemnitz, Germany).

In order to monitor the implementation of dietary recommendations, a questionnaire was used in which patients, in which patients were questioned about the use of 15 main "forbidden" foods. The suggested answers included options of frequency of intake of products - every day; several times a week; several times a month; several times a year; never - that had a gradation of points from 4 to 0, respectively. The sum of points was evaluated as: 0-15 - coefficient 0: dietary recommendations were observed almost without breaks; 15-30 - coefficient 1: dietary recommendations were followed by rare breaks; 30-45 - coefficient 2: dietary recommendations were followed by frequent breaks; 45-60 - coefficient 3: dietary recommendations were practically not respected.

The ultrasound of the abdominal cavity was performed by using ultrasound diagnostic systems with Doppler LOGIQ 5 (No. 1822SU6, 2003) and Vivid 3 (metrology No. 6009, 2004).

With the purpose of excluding of an alcoholic genesis of NAFLD all patients underwent questioning for definition of alcohol units by the formula:

Alcohol units = amount (liters) × alcoholic strength (%) × 0.789

Alcohol abuse was excluded in cases if use of alcohol was less than 30g of ethanol or 3.75 alcohol units per day for men (or 14 units per week) and 20g or 2.5 alcohol units for women (or 8 units per week).

Glucose concentration in venous blood was determined by photometric method using an automatic biochemical analyzer - general purpose photometer "Humalyzer 2000", (metrology No. 18300 - 5397, Germany). To assess long-term carbohydrate metabolism compensation, the concentration of glycated haemoglobin (HbA1c) was determined using the kit "Reagent" (Ukraine) by reaction with thiobarbituric acid. The

concentration of insulin was determined by ELISA using the DRG reagent kit (USA).

For the quantitative assessment of the severity of insulin resistance, the mathematical model HOMA-IR was used:

HOMA-IR = (fasting insulin (U / mL) x fasting glucose (mmol / L))/22.5.

If HOMA-IR was ≥ 2.77 it was considered as the presence of insulin resistance.

For the liver steatosis identification, the NAFLD liver fat score was used according to the formula:

NAFLD liver fat score= - 2.89+1.18×metabolic syndrome (yes=1/no=0)+ 0.45×type 2 diabetes (yes=2/no=0)+0.15× fasting serum Insulin (mU/L)+ 0.04 × fasting serum AST(U/L) – 0.94 × AST/ALT.

The concentration of EL serum was determined by ELISA using kits of reagents "Aviscera Bioscience INC" (USA).

Statistical processing of the results of the study was conducted using Microsoft Exel and Statistica 7.0 programs using standard methods of virological statistics.

Results of study. In all patients with NAFLD on the background of hypertension and type 2 diabetes, significantly ($p < 0.001$) higher hyperinsulinism (32.27 + 4,71 versus 20.75 + 9.5 mkU/ml) and significantly ($p < 0.001$) increased index of insulin resistance of HOMA-IR (9.52 + 4.21 versus 4.76 + 2.23 USD) was detected. This fact proves the presence of the type 2 of diabetes. It should be noted that patients with type 2 diabetes in the hypertension group without increasing NAFLD liver fat score were not observed at all, 10 people with type 2 diabetes have liver steatosis and 8 ones have laboratory signs of steatohepatitis.

The level of systolic and diastolic blood pressure in all study groups was higher than one in the control group. It confirms the presence of hypertension in all patients in the main groups (tab. 1).

Table 1

Anthropometric parameters of patients with hypertension according to the severity of liver steatosis and the presence of type 2 diabetes

Parameter		Control group (n=20)	group 1 (n=8)	group 2 (n=8)	group 3 (n=10)	group 4 (n=10)	group 5 (n=16)	group 6 (n=8)
SBP, mmHg	Mean	116	156,43*	165,56*	166,67*	161,11*	165,94*	175,63*
	SD	4,16	12,86	12,61	18,02	17,63	17,05	15,41
	SE	0,93	4,64	4,21	6,01	5,87	4,26	5,75
DBP, mmHg	Mean	73,5	98,57*	103,88*	101,11*	104,44*	101,56*	101,25*
	SD	5,15	6,26	7,81	3,33	11,3	10,28	9,91
	SE	1,15	2,36	2,61	1,11	3,76	2,57	3,51
BMI, kg/m^2	Mean	21,43	23,12	28,07*	30,43*	29,57*	28,1*	30,91*
	SD	1,56	2,85	1,91	2,81	2,85	4,24	7,25
	SE	0,35	1,08	0,63	0,88	0,9	1,06	2,56
WC, cm	Mean	75,5	74,57	83*	95,2*	100,95*	103,53*	105,25*
	SD	6,83	6,92	8,18	9,51	11,19	8,41	9,66
	SE	1,52	2,61	2,72	3	3,54	2,1	3,41
WC/ height, units.	Mean	0,44	0,44	0,5*	0,55*	0,57*	0,59*	0,61*
	SD	0,033	0,042	0,026	0,045	0,042	0,035	0,031
	SE	0,007	0,016	0,009	0,014	0,011	0,008	0,006

Note * The difference in parameters is statistically significant ($p < 0,05$)

However, there is no significant difference between the study groups, which reduces the difference between the groups in parameters of hypertension. The only investigated subgroup, which differs from other by significantly higher values of SBP is a group of patients with laboratory

signs of steatohepatitis and diabetes mellitus. At the same time, DBP in this group is not significantly different from other groups.

The analysis of anthropometric parameters showed that the overweight is significantly more evident in all patients from the studied groups compared to the control. BMI is also significantly lower in group of patients with hypertension without overweight. BMI of patients of other groups was not significantly different. Therefore, the subgroup of patients with hypertension and overweight has the right to exist as a separate subgroup

There is a significant fact that patients from 2-6 subgroups have an equivalent degree of overweight, which in average values corresponds to 1st degree of obesity.

The waist circumference and waist circumference ratio to height did not differ between controls and group of hypertension without overweight. However, patients with steatosis and steatohepatitis on the background of hypertension had an abdominal type of fat distribution, the degree of which was higher than that of patients who had overweight and hypertension. The expressiveness of abdominal fat distribution (by the ratio of the waist circumference to height that had no gender difference) was most evident in patients of group 6 (with NAFLD, diabetes, overweight and hypertension).

Levels of liver transaminases and alkaline phosphatase (AP) were not significantly different in patients with steatosis on the background of hypertension and in patients with hypertension without increased NAFLD liver fat score, but in patients with laboratory evidence of steatohepatitis there is a significant increase in these parameters. Moreover, attention is paid to the significant increase in the ALT/AST ratio in patients with steatohepatitis with type 2 diabetes (Tab. 2).

The nutrition style in the groups is approximately the same and does not differ significantly from the control group. It shoul be noted that the consumption of alcohol in patients in the control group and in the

hypertension group without increasing NAFLD liver fat score is not significantly different from each other. In patients with steatosis of the liver and steatohepatitis alcohol use was significantly more in amount regardless of the presence of type 2 diabetes.

A detailed analysis of the parameters of carbohydrate metabolism of patients with hypertension in relation to the severity of liver steatosis and the presence of type 2 diabetes is presented in Table. 3. It is evident that fasting glucose levels have normal values in patients with normal weight and hypertension, but they are significantly higher in patients with overweight and hypertension (but does not differ from the reference values).

Table 2

Transaminases, alkaline phosphatase, dietary and alcohol regimens, depending on the severity of liver steatosis and the presence of diabetes mellitus

Parameter		Control group (n=20)	group 1 (n=8)	group 2 (n=8)	group 3 (n=10)	group 4 (n=10)	group 5 (n=16)
AP, mmol/l	Mean	1637,5	1279,17*	1338,33	1536,33*	2083,54*	2376,66*
	SD	252,37	254,58	328,67	416,27	279,38	324,55
	SE	126,18	103,93	134,18	138,75	126,95	132,49
ALT, U/l	Mean	21*	23,55*	25,91*	23,4*	64,06*	59,51*
	SD	6,35	6,38	8,97	5,01	19,24	15,9
	SE	2,4	2,12	2,83	1,58	12,31	5,62
AST, U/l	Mean	23,28*	25,55*	23,1*	22,7*	44,06*	28,11
	SD	4,23	9,96	6,08	13,48	13,14	7,94
	SE	1,59	3,32	1,92	4,26	4,78	2,81
ALT/ AST, units.	Mean	0,897*	0,999*	1,151*	1,237*	1,469*	2,301*
	SD	0,176	0,307	0,311	0,541	0,454	1
	SE	0,066	0,102	0,098	0,171	0,113	0,354
Diet	Mean	2,666	2,5*	2,857*	2,428	2,125*	2, 41
	SD	0,577	0,577	1,463	0,786	0,834	0,94
	SE	0,333	0,288	0,553	0,297	0,295	0,447

Alcohol units	Mean	3,628*	4,8*	6,39*	6,39*	7,281*	6,87*
	SD	1,127	2,135	3,725	2,22	2,738	2,565
	SE	0,426	0,711	1,178	0,702	0,684	0,89

Note * The difference in parameters between groups is statistically significant ($p < 0,05$)

In patients with steatosis and with laboratory evidence of steatohepatitis without diabetes fasting glucose is significantly lower than in diabetics. The levels of glucose in patients with steatosis and steatohepatitis are not higher than average values, but have a significant tendency to increase in steatohepatitis ($p < 0.01$). At the same time, glycemia does not differ significantly in patients with steatosis and steatohepatitis with diabetes mellitus ($p = 0.47$).

Table 3

Carbohydrate parameters of patients with hypertension in accordance to the severity of liver steatosis and the presence of diabetes

Parameter		**group 1 (n=8)**	**group 2 (n=8)**	**group 3 (n=10)**	**group 4 (n=10)**	**group 5 (n=16)**	**group 6 (n=8)**
Fasting glucose, mmol/l	Mean	4,82*	5,17*	5,27*	7,35*	5,38*	6,39*
	SD	0,33	0,74	0,33	1,97	0,58	1,07
	SE	0,12	0,26	0,11	0,62	0,15	0,38
Fasting Insulin, mkU/l	Mean	13,27*	20,97*	18,64*	30,37*	32,82*	34,18*
	SD	3,21	6,7	9,75	11,58	20,51	19,68
	SE	1,66	2,53	3,08	3,61	5,12	6,96
HOMA-IR, units	Mean	2,336*	4,484*	4,338*	9,691*	7,918*	9,211*
	SD	1,604	1,477	2,337	5,143	5,652	4,577
	SE	0,301	0,558	0,739	1,626	1,413	1,618
HbA1C, %	Mean	5,211*	5,54*	5,336*	7,947*	5,235*	7,893*
	SD	0,591	0,661	0,581	1,555	0,438	0,41
	SE	0,223	0,22	0,183	0,492	0,109	0,144

Note * The difference between the groups is statistically significant (p < 0,05)

The concentration of insulin in patients with liver steatosis is higher in the presence of diabetes (p = 0.024). However, in patients with steatohepatitis, the level of insulin is high, but does not differ significantly in groups regarding the presence of diabetes. An analysis of the concentration of insulin in hypertensive patients without overweight is significant (p <0.01) lower than in patients with overweight.

Accordingly, the HOMA-IR index does not significantly differ in patients with hypertension and overweight and in patients with liver steatosis without diabetes (p = 0.87). However, values in patients with steatosis without diabetes are significantly lower than ones in patients with steatosis and diabetes and lower than ones of both subgroups with steatohepatitis (p <0.01). Also, the HOMA-IR index is in the range of normal values in hypertensive patients without overweight and is significantly higher in hypertensive patients with overweight (p <0.01).

In patients with hypertension and with and without overweight, as well as in patients with steatosis or steatohepatitis without diabetes is not significantly different and is within the range of normal values. In patients with diabetes mellitus, HbA1c is higher than in ones without diabetes, regardless of whether there is steatosis or steatohepatitis, since no significant difference is found among these subgroups (p = 0.97).

The level of total cholesterol is elevated relative to normal values in patients with hypertension, regardless of the degree of overweight. It also grows due to the severity of steatosis. The most notable difference is the difference between groups with and without type 2 diabetes. There are higher levels of total cholesterol in groups with steatosis and steatohepatitis in patients with type 2 diabetes (tab.4).

The concentration of triglycerides increases from group to group. It also should be noted that there is difference between the groups with steatosis and steatohepatitis, and between groups with and without diabetes.

LDL concentrations are too high in patients with hypertension, regardless of the degree of overweight, but are also greater in the respective groups depending on presence of type 2 diabetes. There is a tendency to decrease in parameter HDL from group to group, but the smallest values are present in patients with steatohepatitis suffering from type 2 diabetes. And the level of HDL no longer reaches the protective values in patients with hypertension without increasing the NAFLD liver fat score, regardless of overweight.

Table. 4.

Parameters of lipid metabolism depending on the severity of liver steatosis and the presence of type 2 diabetes

Parameter		Control group (n=20)	group 1 (n=8)	group 2 (n=8)	group 3 (n=10)	group 4 (n=10)	group 5 (n=16)	Parameter
Total cholesterol, mmol/l	Mean	3,85	5,541	5,02*	5,23*	6,07*	5,581*	6,242*
	SD	0,77	0,81	1,845	0,909	0,677	1,265	1,692
	SE	0,291	0,306	0,615	0,303	0,225	0,316	0,598
Triglycerides, mmol/l	Mean	0,92	1,251*	1,04*	1,575*	1,824*	1,785*	2,297*
	SD	0,16	0,462	0,308	0,632	1,007	1,217	1,051
	SE	0,06	0,174	0,163	0,21	0,335	0,304	0,371
HDL, mmol/l	Mean	1,77	1,44	1,49*	1,47	1,33	1,22	1,15*
	SD	0,28	0,31	0,22	0,33	0,24	0,28	0,24
	SE	0,11	0,13	0,17	0,11	0,11	0,07	0,11
LDL, mmol/l	Mean	2,36	3,698*	3,298	3,216*	3,753*	3,558*	4,253*
	SD	0,46	0,826	1,717	0,776	0,535	1,201	1,359
	SE	0,18	0,369	0,607	0,258	0,218	0,3	0,555
Endothelial lipase, ng / ml	Mean	8,231	9,56	11,299*	11,714*	11,709*	11,84*	15,51*
	SD	2,474	2,157	2,925	3,22	3,22	3,801	3,09
	SE	0,553	0,815	0,975	1,087	1,019	1,326	1,024

Note * The difference in parameters compared to the control group is statistically significant ($p < 0,05$)

The concentration of endothelial lipase is not significantly different in the control group and in the group of patients with hypertension without increasing the NAFLD liver fat score. Its level is significantly higher in patients with steatosis, regardless of the presence of diabetes and steatohepatitis without diabetes compared with controls and patients with hypertension and normal weight. The highest level of endothelial lipase is in patients with steatohepatitis suffering from type 2 diabetes. Since the integral diagnostic criterion and compensation marker of diabetes is glycated hemoglobin, we have correlated between the level of HbA1C and endothelial lipase. This analysis showed a significant direct correlation between the parameters (Spearman $R = 0.386$, $p < 0.05$).

Conclusions. All NAFLD patients with hypertension have proatherogenic lipid status changes that increase with obesity and severity of steatosis and are most evident in steatohepatitis in combination with type 2 diabetes.

The level of hepatic transaminases and alkaline phosphatase in patients with laboratory evidence of steatohepatitis is significantly increased. Moreover, attention is paid to the significant increase in the ALT/AST ratio in patients with steatohepatitis and type 2 diabetes.

Patients with liver steatosis and steatohepatitis drink alcohol significantly more than the control group and the group with hypertension without increasing the NAFLD liver fat score, regardless of the presence of type 2 diabetes.

Correlation analysis between the level of HbA1C and endothelial lipase showed a significant direct correlation between the parameters. Therefore, the process of glycation of proteins at type 2 diabetes, which is associated with the formation of microangiopathy, is related to the activation of endothelial lipase, which can be considered as an additional factor of vascular damage. Taking into account the fact that in patients with

laboratory characteristics of steatohepatitis and type 2 diabetes that the highest levels of SBP are detected, the elevated levels of endothelial lipase should be considered as an additional risk factor.

Therefore, the level of EL in patients with hypertension in combination with the severity of steatosis is significant for atherosclerotic vascular damage and prognostic as cardiovascular complications. At the same time, the prognosis is deteriorating with the presence of additional independent risk factors such as the presence of type 2 diabetes and increased alcohol use, which directly correlates with the severity of liver steatosis.

References:

1. Cheah, M.C. (2017). Current Modalities of Fibrosis Assessment in Non-alcoholic Fatty Liver Disease. *J Clin Transl Hepatol, 5(3),* 261-271.

2. Barritt, A.S. 4th. (2017). Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: The TARGET-NASH study. *Contemp Clin Trials, no. 61,* 33-38.

3. Karim, M.F. (2015). Non-alcoholic Fatty Liver Disease (NAFLD)--A Review. *Mymensingh Med J, 24(4),* 873-880.

4. Marino, L. (2015). Endocrine causes of nonalcoholic fatty liver disease. *World J Gastroenterol, 21(39),* 76-77.

5. Rau, M. (2015). Non-alcoholic fatty liver disease (NAFLD). *Dtsch Med Wochenschr, 140(14),* 5-6.

6. Ogunsina, K. (2018). Association between life-course socio-economic status and prevalence of cardio-metabolic risk ractors in five middle-income countries. *J Glob Health, 8(2),* 102-123.

7. Liu, H. (2014). Nonalcoholic fatty liver disease and cardiovascular disease. *World J Gastroenterol, 20(26),* 8407-8415.

8. Vanjiappan, S. (2018). Nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and its association with cardiovascular disease. *Diabetes Metab Syndr, 12(4),* 479-482.

9. Gastaldelli, A. (2017). Insulin resistance and reduced metabolic flexibility: cause or consequence of NAFLD. *Clin Sci (Lond), 131(22),* 2701-2704.

10. Chen, Z. (2017). A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. *Lipids Health Dis, 16(1),* 203-204.

11. Karajamaki, A.J. (2017). Non-alcoholic fatty liver disease with and without metabolic syndrome: Different long-term outcomes. *Metabolism, no. 66,* 55-63.

12. Gummesson, A. (2018). Non-alcoholic fatty liver disease is a strong predictor of coronary artery calcification in metabolically healthy subjects: A cross-sectional, population-based study in middle-aged subjects. *PLoS One, 13(8),* 202-206.

13. Golabi, P. (2018). Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). *Medicine (Baltimore), 97(13),* 214-216.

14. Madan, S.A. (2017). Nonalcoholic fatty liver disease and carotid artery atherosclerosis in children and adults: meta-analysis. *Eur J Gastroenterol Hepatol, 27(11),* 1237-1248.

15. DiMarco, D.M. (2015). The regulation of reverse cholesterol transport and cellular cholesterol homeostasis by MicroRNAs. *Biology, 4(3),* 494–511.

16. Schilcher, I. (2017). Impact of Endothelial Lipase on Cholesterol Efflux Capacity of Serum and High-density Lipoprotein. *Sci Rep, 7(1),* 12485.

17. Takiguchi, S. (2018). Hepatic Overexpression of Endothelial Lipase Lowers High-Density Lipoprotein but Maintains Reverse Cholesterol Transport in Mice: Role of Scavenger Receptor Class B Type I/ATP-Binding Cassette Transporter A1-Dependent Pathways. *Arterioscler Thromb Vasc Biol, 38(7),* 1454-1467.

18. Chalasani, N. (2016). The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology, no. 55,* 2005-2023.
19. European Association for the Study of the Liver. (2016). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Obesity facts, 9(2),* 65-90.
20. Mancia, G. (2013). ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood pressure, 22(4),* 193-278.
21. Vanjiappan, S. (2018). Nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and its association with cardiovascular disease. *Diabetes Metab Syndr, 12(4),* 479-482.