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## GENDER-DEPENDENT PECULIARITIES OF CERTAIN BIOCHEMICAL, LIPID, PRO- AND ANTIOXIDANT BLOOD PARAMETERS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Vasilie Prisyazhnyuk – PhD, as. prof.,

Department of Propaedeutics of Internal Diseases, Bukovinian State Medical University,  
Chernivtsi, Ukraine

E-mail: [surgery\\_OKL@bsmu.edu.ua](mailto:surgery_OKL@bsmu.edu.ua) Tel. (0372)51-47-41

**Summary. Gender-dependent peculiarities of certain biochemical, lipid, pro- and antioxidant blood parameters in patients with nonalcoholic fatty liver disease**

Gender-dependent peculiarities of certain biochemical, lipid, pro- and antioxidant blood parameters in patients with nonalcoholic fatty liver disease (NAFLD) were investigated. In male patients aspartateaminotransferase activity was found to increase by 45,4% ( $p = 0,0003$ ), alanineaminotransferase – by 57,0% ( $p < 0,0001$ ) and gamma-glutamyltransferase twice ( $p < 0,0001$ ) as compared with the appropriate parameters in females. Male patients with NAFLD were characterized by significantly lower at 10,6% ( $p = 0,03$ ) general cholesterol plasma level as compared with females. That was accompanied by decreased plasma concentration of cholesterol of high density lipoproteins and low density lipoproteins by 17,7% ( $p = 0,001$ ) and by 15,4% ( $p = 0,05$ ) respectively, as compared with female patients. No significant differences between NAFLD patients of different gender in parameters of pro- and antioxidant systems were found.

**Key words:** nonalcoholic fatty liver disease, aspartateaminotransferase, alanineaminotransferase, gamma-glutamyltransferase, cholesterol

**Rezumat. Particularitățile de gen a anumitor parametri biochimici, lipidici, pro și antioxidanți a sângelui la pacienții cu boli de ficat gras nealcoolizate**

Au fost investigate particularitățile de gen a unor anumiți parametri biochimici, lipidici, pro și antioxidanți a sângelui la pacienții cu boli de ficat gras nealcoolizate (BFGNA). S-a constatat că la pacienții de sex masculin activitatea aspartataminotransferazei a crescut cu 45,4 % ( $p = 0,0003$ ), alaninaminotransferazei – cu 57,0 % ( $p < 0,0001$ ) și gamma-glutamilttransferazei - de două ori ( $p < 0,0001$ ), în comparație cu parametrii coresponzatori la femei. La pacienții de gen masculin cu BFGNA se caracterizează cu un nivel general inferior cu 10,6 % ( $p = 0,03$ ) în comparație cu acești parametri la femei. Aceasta era însoțită de scăderea concentrării colesterolului lipoproteinei cu densitate mare și lipoproteinei cu densitate scăzută în plasmă cu 17,7 % ( $p = 0,001$ ) și 15,4 % ( $p = 0,05$ ), respectiv în comparație cu pacientele. Diferențe esențiale a parametrilor sistemelor pro și antioxidante la pacienți cu BFGNA de diferite sexe n-au fost descoperite.

**Cuvinte-cheie:** boală de ficat gras nealcoolizat, aspartataminotransferaza, alaninaminotransferaza, gammaglutamilttransferaza, colesterol

**Резюме. Гендерные особенности отдельных биохимических, липидных, про- и антиоксидантных параметров крови у больных неалкогольной жировой болезнью печени**

Исследованы гендерные особенности некоторых биохимических, липидных, про- и антиоксидантных параметров крови у больных неалкогольной жировой болезнью печени (НАЖБП). Установлено, что у пациентов мужского пола активность аспартатаминотрансферазы возрастает на 45,4% ( $p = 0,0003$ ), аланинаминотрансферазы – на 57,0% ( $p < 0,0001$ ) и гамма-глутамилтрансферазы – в два раза ( $p < 0,0001$ ), по сравнению с соответствующими параметрами у женщин. Мужской пол у пациентов с НАЖБП характеризуется низшим на 10,6% ( $p = 0,03$ ) общим уровнем холестерина в плазме, по сравнению с женским. Это сопровождалось снижением концентрации холестерина липопротеинов высокой плотности и липопротеинов низкой плотности в плазме на 17,7% ( $p = 0,001$ ) и на 15,4% ( $p = 0,05$ ) соответственно, по сравнению с пациентками. Существенных различий параметров про- и антиоксидантной систем между пациентами с НАЖБП разного пола не найдено.

**Ключевые слова:** неалкогольная жировая болезнь печени, аспартатаминотрансфераза, аланинаминотрансфераза, гамма-глутамилтрансфераза, холестерин

### Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common nosology among liver diseases [1]. Its prevalence is 20% – 30% of adults in Western Europe and North America and 15% of adult population of Asia [4]. Increased incidence of NAFLD is observed against the background of a growing number of people

with obesity, metabolic syndrome and diabetes [3]. NAFLD is predicted to become a leading indication for liver transplantation in the USA over the next 20 years, surpassing in this respect chronic hepatitis associated with hepatitis C virus [8]. In particular, in the USA NAFLD is diagnosed in 34% of the adult population [5], and in 3-10% of children [9]. Among

various nationalities NAFLD more often occurs in Latin American population and rarer this disease is detected among African Americans [10]. In Z.W. Chen et al. investigation, which included more than 26,000 patients, the signs of NAFLD was found in 31% males and 16% females [6]. Some authors revealed, that male gender is associated with increased aminotransferase activity, more frequent development of liver fibrosis and higher total mortality among NAFLD patients [10]. Considering all of the above, an important medical problem is investigation of the gender-specific peculiarities of NAFLD.

The **objective** of the study was to investigate the gender-dependent peculiarities of certain biochemical, lipid, pro- and antioxidant blood parameters in patients with nonalcoholic fatty liver disease.

**Materials and methods.** The study involved 139 patients with nonalcoholic fatty liver disease, which were divided into two groups according to their gender. The first group consisted of females with the average age  $53,15 \pm 11,4$  years. The second group included males (average age  $49,5 \pm 12,2$  years). NAFLD duration since the disease onset ranged from one to five years. The control group consisted of 20 practically healthy individuals correlative by their age and gender to the groups examined. Blood samples were obtained in the morning before taking meal from antecubital vein until the administration of treatment. 5% solution of disodium salt of ethylene diamine tetraacetate was used as an anticoagulant. The study protocol was in accordance with the revised Helsinki Declaration (2008) and was approved by the local medical ethics committee. Written informed consent was obtained from all the participants.

All of the patients and healthy volunteers underwent general complex clinical, laboratory and instrumental diagnostic investigations. The range of indicators of biochemical blood analysis included: total bilirubin and its fractions, total protein and albumin, urea, creatinine, plasma enzyme activity (aspartate-aminotransferase (AST), alanineaminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP)).

Lipid profile investigation included measuring the content of cholesterol, triacylglycerols, cholesterol of high density lipoproteins (HDL), cholesterol of low density lipoproteins (LDL), cholesterol of very low density lipoproteins (VLDL) in plasma. For each patient or practically healthy individual atherogenic index was calculated. Biochemical studies were performed on the blood biochemical analyzer «Accent-200» («Cormay SA», Poland).

Key processes of free radical oxidation were

determined by means of spectrophotometric method containing reactive products of tiobarbituric acid (TBA-reactive products) in the blood. Antioxidant systems were studied by measuring content of reduced glutathione, activities of catalase, glutathione-S-transferase (GST) and glutathione peroxidase (GP).

Statistical processing of the data was performed by the computer program PAST Version 2.05 [7]. To determine the type of data distribution, comparing the arithmetic mean, median and mode, Wilcoxon-Shapiro test was used. To determine statistical differences between two independent groups Mann-Whitney test was applied.

**Results and their discussion.** Male patients with NAFLD have a significantly higher direct bilirubin plasma level, which by 30,0% ( $p = 0,01$ ) prevailed the appropriate level in females (**tab. 1**). But neither in males nor in females it wasn't higher than the parameters of common normal values. Males also showed evaluated creatinine plasma concentration, which was by 13,0% ( $p < 0,0001$ ) higher as compared with female patients.

For the patients of the second group increased activity of transaminases as compared with patients of the first group was typical. In particular, in males AST increased by 45,4% ( $p = 0,0003$ ) and ALT – by 57,0% ( $p < 0,0001$ ) respectively as compared with females (**tab. 1**). Our results are coincide with the data of other investigators [10], which revealed that male gender is associated with increased aminotransferase activity and more frequent development of liver fibrosis.

Moreover, increased GGT activity was inherent for the observed male patients with NAFLD. Activity of this enzyme in patients of the second group was more than twice higher ( $p < 0,0001$ ) as compared with the appropriate parameters in patients of the first group (**tab. 1**). GGT plays an important role in metabolism of aminoacids and is a marker of intoxication, including dysmetabolic one. Also, GGT is believed to bind molecules of substances that should be excreted, thus increasing of its activity may be indicative of augmentation of toxical load and serve as an indicator of increased cholestasis [2]. That's why we can conclude, that increased activity of GGT in male patients with NAFLD probably reflect augmented intoxication syndrome as compared with female patients.

Male patients with NAFLD were characterized by significantly lower at 10,6% ( $p=0,03$ ) general cholesterol plasma level as compared with females (**tab. 2**).

That was accompanied by decreased plasma concentration of cholesterol of HDL and LDL by 17,7% ( $p=0,001$ ) and by 15,4% ( $p=0,05$ ) respectively,

Table 1

**Biochemical blood parameters in patients with nonalcoholic fatty liver disease according to their gender**

Plasma level	Healthy volunteers, n = 20	Patients with NAFLD, n = 139	
		Females, n = 68	Males, n = 71
Glucose, mmol/L (N= 3,9-6,0 mmol/L)	4,8 ± 0,19	6,5 ± 0,27 p <sub>1</sub> < 0,0001	6,5 ± 0,35 p <sub>1</sub> < 0,0001
Total bilirubin, mkmol/L (N=5,0-20,5)	10,3 ± 0,76	11,8 ± 0,70	13,3 ± 0,81
Direct bilirubin, mkmol/L (N=0,5-5,0)	2,6 ± 0,29	3,0 ± 0,34	3,9 ± 0,36 p <sub>1</sub> = 0,03, p <sub>2</sub> = 0,01
Albumin, g/L (N=35-50)	46,3 ± 0,53	44,0 ± 0,40 p <sub>1</sub> = 0,002	45,4 ± 0,62
Total protein, g/L (N=65-85)	70,8 ± 0,93	71,0 ± 0,64	72,6 ± 0,77 p <sub>2</sub> = 0,05
Urea, mmol/L (N=2,4-8,3)	4,3 ± 0,39	5,4 ± 0,32	5,3 ± 0,26 p <sub>1</sub> = 0,04
Creatinine, mkmol/L (N=40-110)	80,6 ± 2,99	82,1 ± 1,92	92,8 ± 2,67 p <sub>1</sub> = 0,005, p <sub>2</sub> < 0,0001
Aspartate aminotransferase, units of action/L (N<37)	24,9 ± 2,50	24,0 ± 1,38	34,9 ± 2,48 p <sub>1</sub> = 0,05, p <sub>2</sub> = 0,0003
Alanine aminotransferase, units of action/l (N<32)	22,1 ± 3,01	27,2 ± 2,10 p <sub>1</sub> = 0,03	42,7 ± 3,71 p <sub>1</sub> = 0,0008, p <sub>2</sub> < 0,0001
Lactate dehydrogenase, units of action/L (N=210-420)	385,1 ± 21,15	493,3 ± 17,94 p <sub>1</sub> = 0,001	457,4 ± 18,64 p <sub>1</sub> = 0,04
Alkaline phosphatase, units of action/L (N=42-141)	84,7 ± 5,40	90,9 ± 2,64 p <sub>1</sub> = 0,04	88,6 ± 3,53
Gamma-glutamyl transferase, units of action/L (N=10-50)	25,3 ± 2,85	35,8 ± 3,40 p <sub>1</sub> < 0,0001	72,7 ± 8,59 p <sub>1</sub> = 0,04, p <sub>2</sub> < 0,0001

p<sub>1</sub> – significance of differences compared with the indicators in the group of healthy people; p<sub>2</sub> – significance of differences compared with rates in NAFLD patients of female gender.

Table 2

**Lipid profile parameters in patients with nonalcoholic fatty liver disease according to their gender**

Plasma level	Healthy volunteers, n = 20	Patients with NAFLD, n = 139	
		Females, n = 68	Males, n = 71
Cholesterol, mmol/l	4,72 ± 0,24	5,95 ± 0,18 p <sub>1</sub> = 0,0005	5,38 ± 0,18 p <sub>1</sub> = 0,02, p <sub>2</sub> = 0,03
Triacylglycerols, mmol/l	1,26 ± 0,13	1,94 ± 0,10 p <sub>1</sub> = 0,0001	2,17 ± 0,18 p <sub>1</sub> = 0,001
Cholesterol HDL, mmol/l	1,50 ± 0,06	1,46 ± 0,04	1,24 ± 0,04 p <sub>1</sub> = 0,001, p <sub>2</sub> < 0,0001
Cholesterol LDL, mmol/l	3,03 ± 0,23	3,60 ± 0,16 p <sub>1</sub> = 0,03	3,12 ± 0,15 p <sub>2</sub> = 0,05
Cholesterol VLDL, mmol/l	0,62 ± 0,07	0,89 ± 0,05 p <sub>1</sub> = 0,008	1,02 ± 0,09 p <sub>1</sub> = 0,02
Atherogenic index	2,44 ± 0,21	3,15 ± 0,12 p <sub>1</sub> = 0,01	3,41 ± 0,13 p <sub>1</sub> = 0,002

p<sub>1</sub> – significance of differences compared with the indicators in the group of healthy people; p<sub>2</sub> – significance of differences compared with rates in NAFLD patients of female gender.

Table 3

**Pro- and antioxidant indicators in patients with nonalcoholic fatty liver disease according to their gender**

Plasma level	Healthy volunteers, n = 20	Patients with NAFLD, n = 139	
		Females, n = 68	Males, n = 71
Reduced glutathione, mmol/l	1,15 ± 0,04	0,81 ± 0,03 p <sub>1</sub> < 0,0001	0,84 ± 0,04 p <sub>1</sub> < 0,0001
Glutathione peroxidase, nmol/min*mg of hemoglobin	107,63 ± 6,25	146,23 ± 3,06 p <sub>1</sub> < 0,0001	148,14 ± 4,05 p <sub>1</sub> < 0,0001
Glutathione-S-transferase, nmol/min*mg of protein	16,88 ± 1,11	23,90 ± 1,16 p <sub>1</sub> < 0,0001	21,34 ± 1,88 p <sub>1</sub> = 0,03
Catalase, mkmol/min*1	15,02 ± 0,89	12,21 ± 0,43 p <sub>1</sub> = 0,04	12,89 ± 0,86
Reactive products of tiobarbituric acid, mkmol/l	14,05 ± 0,56	17,95 ± 0,54 p <sub>1</sub> < 0,0001	16,83 ± 0,76 p <sub>1</sub> = 0,02

p<sub>1</sub> – significance of differences compared with the indicators in the group of healthy people; p<sub>2</sub> – significance of differences compared with rates in NAFLD patients of female gender.

as compared with female patients. Atherogenic index was higher in patients of both groups as compared with healthy volunteers. In patients of the first group this indicator was higher by 29,1% (p = 0,01) and in patients of the second group – by 39,8% (p = 0,002) in comparison with the appropriate control parameter. Significant differences in atherogenic index between patients of both studied groups were not found.

Increased contents of glutathione peroxidase and glutathione-S-transferase activity, elevated TBA-reactive products in plasma, decreased level of reduced glutathione in the blood of NAFLD patients of both studied groups, in comparison with similar indicators in practically healthy individuals were detected (tab. 3).

In female patients with NAFLD a significant decrease of catalase plasma activity was observed, male patients showed a tendency to such decrease. No significant differences between NAFLD patients of different genders in parameters of pro- and antioxidant systems were found.

**Conclusions.** Male gender among NAFLD patients is associated with increased activity of aspartateaminotransferase, alanineaminotransferase and gamma-glutamyltransferase plasma activities. Female patients with NAFLD were characterized by significantly higher general cholesterol plasma level together with elevated cholesterol of high density lipoproteins and low density lipoproteins concentrations as compared with males. There were no significant differences between NAFLD patients of different genders in parameters of pro- and antioxidant systems.

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