

# МЕДИЦИНСКИЕ НАУКИ

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## CLINICAL SIGNIFICANCE OF PENTRAXIN-3 AND C-REACTIVE PROTEIN IN THE DIFFERENTIATION OF STAGES OF NONALCOHOLIC FATTY LIVER DISEASE

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## КЛИНИЧЕСКАЯ ЗНАЧИМОСТЬ ПЕНТРАКСИНА-3 И С-РЕАКТИВНОГО БЕЛКА В ДИФФЕРЕНЦИРОВАНИИ СТАДИЙ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

**Summary.** The object of this research was to investigate clinical usefulness of Pentraxin-3 and C-reactive protein plasma levels in differentiation of stages of nonalcoholic fatty liver disease. It has been established that the level of pentraxin-3 and C-reactive protein in blood plasma is significantly increased in the group of patients with nonalcoholic steatohepatitis compared with group of patients with steatosis and control group.

**Аннотация.** Целью работы являлось изучение клинической значимости пентраксина-3 и С-реактивного белка сыворотки крови в дифференцировании стадий неалкогольной жировой болезни печени. Было установлено, что уровень пентраксина-3 и С-реактивного белка в плазме крови был значительно повышен в группе пациентов с неалкогольным стеатогепатитом в сравнении с группой пациентов в стадии стеатоза печени и группой контроля.

**Key words:** *nonalcoholic fatty liver disease, liver steatosis, non-alcoholic steatohepatitis, pentraxin-3, C-reactive protein*

**Ключевые слова:** *неалкогольная жировая болезнь печени, стеатоз печени, неалкогольный стеатогепатит, пентраксин-3, С-реактивный белок*

**Introduction.** Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, showing a variety of histopathological findings ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis [1]. Patients with NAFLD have the potential to develop fibrosis and cirrhosis leading to portal hypertension, liver decompensation, and even hepatocellular carcinoma [2,3].

NASH can be differentiated from simple steatosis by liver biopsy and is diagnosed when all of the following three criteria are met: macrovesicular fatty change of hepatocytes, inflammatory cell infiltration, and ballooning degeneration of hepatocytes [4]. Lipid accumulation in hepatocytes can lead to inflammation within them. Accordingly, significant fibrosis can cause cirrhosis over a period of 10-20 years, but the pathophysiology is not well understood yet [5]. However, liver biopsy is invasive, has drawbacks such as sampling error and cost, and it is not applicable for all patients [6].

Determining stage of NAFLD is essential for identifying prognosis and treatment decisions. Distinguishing pure steatosis from NASH is an important issue, as pure steatosis has benign prognosis while NASH can potentially lead to liver fibrosis [7]. A new composite model including metabolic syndrome, alanine aminotransferase and cytokeratin-18 for the diagnosis of NASH in morbidly obese patients. So, early diagnosis of NASH is of great value. Currently, percutaneous liver biopsy remains the gold standard in evaluating liver histology and diagnosis of NASH. However, there are some limitations regarding performing biopsy such as being invasive, expensive and carrying sampling errors [8].

In patients with NAFLD, the progression from simple steatosis to NASH and cirrhosis is characterized by cellular injury from oxidative stress and cytokine-driven intrahepatic inflammation [9]. There are studies suggesting that the intrahepatic inflammation associated with NAFLD may be linked to systemic elevations in inflammatory biomarkers, such as C-reactive protein (CRP) [10] and novel marker for

NASH - Pentraxin-3 [11]. The classical short pentraxins, CRP are acute-phase proteins that are manufactured in the liver under the guidance of inflammatory cytokines [12]. Despite similarities of action, Pentraxin-3 differs from CRP in many basic aspects, such as gene organization, chromosomal localization, cellular sources, inducing stimuli, and the recognized ligands [13]. The levels of plasma Pentraxin-3 are found higher than normal controls in various inflammatory conditions such as rheumatologic disorders [14], asthma [15], coronary artery diseases [16] and systemic inflammation and sepsis [17]. Because NASH is also an ongoing inflammatory condition, we hypothesized that plasma Pentraxin-3 levels increase in patients with NASH.

**The aim of the study** was to investigate clinical usefulness of CRP and Pentraxin-3 plasma levels in differentiation of stages of NAFLD.

**Materials and methods.** The study was conducted on the Department of Gastroenterology of the State Institution "National Institute of Therapy named after L.T. Malaya of Ukraine", and on the therapeutic department of the Municipal Health Institution "Lozovsky Territorial Medical Association, Ukraine". This study was approved by the ethics commission of Kharkov National Medical University, Ukraine, in accordance with the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as the object of study" in 1964 (revision in 2008). Patients included in the study signed an informed consent to participate in the study. The study was conducted as part of research work of the Department of Internal Medicine №1 Kharkov National Medical University "Clinical significance of markers of inflammation and metabolic disorders in patients with nonalcoholic fatty liver disease » registration № 015U000236.

40 patients with NAFLD were examined. They were divided into 2 groups: group 1 included 15 patients with hepatic steatosis (8 men and 7 women, average age of  $41 \pm 4.6$  years), and group 2 included 25 patients with NASH (13 men and 12 women, average age of  $42 \pm 3.2$  years). Control group (group 3) was formed of 20 apparently healthy people (9 men and 6 women, average age of  $40 \pm 2.9$  years).

Inclusion criteria were the following: persistently (at least 6 months) elevated aminotransferases, presence of ultrasonography brightness in liver without any other liver or biliary tract disease.

Exclusion criteria were the following: consume more than 20 g of ethanol daily, serologically

confirmed liver infectious diseases (including viral hepatitis A, B and chronic hepatitis C), primary biliary cirrhosis, sclerosing cholangitis, chronic inflammatory diseases, chronic cardiac insufficiency, autoimmune rheumatologic diseases (that may also increase pentraxin-3 level in blood), thyroid disorders, oncology diseases, renal insufficiency. Pregnant women, as well as aged over 55 years were also excluded from the research.

The Ethics Committee of the Kharkov National Medical University approved the study and all participants gave their consent to the study, which was conducted according to the Helsinki Declaration Biological measurements.

NAFLD was diagnosed in accordance with the criteria of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO).

The level of Pentraxin-3 was determined according to the enzyme multiplied immunoassay method using Human Pentraxin-3 ELISA KIT produced by Multisciences (Lianke) Biotech Co. (China) with Immunochem-2100 immunoenzymometric analyzer (USA).

CRP level was determined by the photometric turbidimetric method by utilizing Beckman Coulter AU480 biochemical analyzer (USA).

The results statistical processing was performed with Microsoft Office Excel 2013 and Statistica 13.1 computer programs on a personal computer with the use of parametric (Student's t-test) and non-parametric (Mann-Whitney U-test) statistical methods. The relationship between variables was analyzed using Spearman's correlations. A p-value of less than 0.05 was considered statistically significant.

**Results and their discussion.** The main clinical and biochemical characteristics of the NAFLD patients and control subjects are shown in Table 1. It was found that the average level of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with NASH was slightly higher in comparison with the group of patients with hepatic steatosis, and significantly higher in comparison with the control group.

Thus, the SBP level was ( $128 \pm 7.4$ ) Mmhg in group 1, ( $138 \pm 10.5$ ) Mmhg in group 2, and ( $115 \pm 9.1$ ) Mmhg in the control group ( $p < 0.05$ ). The DBP level was, respectively: ( $88 \pm 7.5$ ) Mmhg in group 1, ( $96 \pm 8.1$ ) Mmhg in group 2, and ( $77 \pm 8.4$ ) Mmhg in the control group ( $p < 0.05$ ).

Table 1

**The studied patient groups anthropometric characteristics**

Patient groups Parameters	Group NAFLD with steatosis (n = 15)	Group NAFLD with NASH (n=25)	Control group (n = 15)	p*
Sex m/f, %	53.3/46.7	52/48	45/55	>0.05
Age	41±4.0	42±4.8	41±5.0	>0.05
BMI, kg/m <sup>2</sup>	26.1±1.2	28.3±1.7	24.1±1.7	< 0.05
Waist circumference, cm	101±7.2	106±6.1	84.2±8.3	< 0.05
Hip circumference, cm	0.95±0.2	1.05±0.1	0.7±0.2	< 0.05
SBP, MmHg	128±7.4	138 ±10.5	115±9.1	< 0.05
DBP, MmHg	88±7.5	96±8.1	77±8.4	< 0.05

**\*Note:**

The difference from the control group parameters is statistically significant (p < 0.05).

BMI — body mass index;

SBP — systolic blood pressure;

DBP — diastolic blood pressure.

The studied patient's main clinical and biochemical characteristics are shown in Table 2.

Table 2

**The studied patient's main clinical and biochemical characteristics**

Parameters	Group NAFLD with steatosis (n = 15)	Group NAFLD with NASH (n=25)	Control group (n = 15)
Glucose, umol/l	5.6 ±1.1 p <sup>1</sup> < 0.01	5.8 ±1.3 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	4.1 ±1.6
Insulin, m/mL	23.4 ±3.3 p <sup>1</sup> < 0.01	24.2 ±2.1 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	15.4±3.7
HOMA-IR	5.8 ±0.6 p <sup>1</sup> < 0.01	6.2 ±0.5 p <sup>1</sup> < 0.05 p <sup>2</sup> < 0.05	2.8 ±0.6
AST, U/L	43.1 ±10.2 p <sup>1</sup> < 0.01	56.3 ±12.6 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	22.1 ±11.4
ALT, U/L	65±21.3 p <sup>1</sup> < 0.01	82.3±20.4 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	21.3±12.3
Total cholesterol, mg/dL	5.0±0.8 p <sup>1</sup> < 0.01	6.1±0.7 p <sup>1</sup> < 0.05 p <sup>2</sup> < 0.05	4.8±0.9
LDL-C, mg/dL	5.9±1.9 p <sup>1</sup> < 0.01	6.4±2.3 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	4.1±1.5
HDL-C, mg/dL	1,5±2,5 p <sup>1</sup> < 0.01	1,1±2,3 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	2,6±1,3
TG, mg/dL	5.4±1.7 p <sup>1</sup> < 0.01	6.3±1.5 p <sup>1</sup> < 0.05 p <sup>2</sup> < 0.05	1.6±0.7
CRP, mg/L	3.8±3.1 p <sup>1</sup> < 0.01	4.3±2.9 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	0.4±0.58
Pentraxin-3 ng/mL	254.35±44.4 p <sup>1</sup> < 0.01	453.9±35.86 p <sup>1</sup> < 0.01 p <sup>2</sup> < 0.05	53.2±14.3

**Note:**

p<sup>1</sup> - the probability of changes compared to the control group;

p<sup>2</sup> - the probability of changes in the group NAFLD with steatosis compared to the group NAFLD with NASH;

HOMA-IR, homeostasis model assessment of insulin resistance;  
 ALT - alanine aminotransferase;  
 AST - aspartate aminotransferase;  
 LDL-C - Low-density lipoprotein cholesterol;  
 HDL-C - High-density lipoprotein cholesterol;  
 TG - triglyceride;  
 CRP- C-reactive protein;

Analyzing the state of studied patient's carbohydrate metabolism, it was found that the level of insulin resistance (IR) was significantly higher in the group of patients with NASH compared to the control group, and slightly higher in comparison with the group of hepatic steatosis. Thus, the average values of the HOMA-IR were ( $5.8 \pm 0.6$ ) in group 1, ( $6.2 \pm 0.5$ ) in group 2, and ( $2.8 \pm 0.6$ ) in the control group. ( $p < 0.05$ ).

Analysis of liver enzymatic activity showed the difference between alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Thus, the ALT level was ( $65 \pm 21.3$ ) in the liver steatosis group, ( $82.3 \pm 20.4$ ) in the group of patients with NASH and ( $21.3 \pm 12.3$ ) in the control group. The AST levels and were ( $43.1 \pm 10.2$ ) in group 1, ( $56.3 \pm 12.6$ ) in group 2, and ( $22.1 \pm 11.4$ ) in the control group.

A study of the severity of changes in lipid metabolism in patients with NAFLD was carried out. In the group of patients with NASH, a significant increase in all lipid parameters was found, while in patients with steatosis, such differences were found only when comparing the levels of low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). Such changes in the lipid profile are probably associated with the presence of overweight among the population of the studied patients.

Analysis the level of Pentraxin-3 in blood serum showed it's significant increase in the group of patients with NASH compared to the group of patients with hepatic steatosis and to the control group ( $p < 0.05$ ).

Significant increase of CRP level was observed in the group of patients with NASH compared to the control group ( $p < 0.05$ ). However, there were no significant differences in this indicator between the groups of patients with NASH and patients with hepatic steatosis ( $p > 0.05$ ).

This study has some limitations. Firstly, because of the small sample size and the strict inclusion criteria, the findings obtained are not representative for all subjects with NAFLD. Secondly, further prospective studies should be arranged to clarify the cause-and-effect relationship and test whether quantification of pentraxin-3 levels could provide additional information beyond the currently recognized risk factors to predict future cardiovascular events in subjects with NAFLD.

**Conclusions.** The present study demonstrated higher plasma Pentraxin-3 and CRP levels in patients with NASH than in patients with steatosis and control group. Pentraxin-3 and CRP may be promising biomarkers for the presence of NASH. Further evaluation of plasma Pentraxin-3 levels in larger numbers of NAFLD patients is recommended to assess any possible clinical usefulness for the noninvasive differentiation of stages of NAFLD.

**Author Disclosure Statement.** No competing financial interests exist.

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### ДИНАМІКА РОЗВИТКУ МЕРЕЖІ СПЕЦІАЛІЗОВАНИХ ЛІКАРЕНЬ, ЯК СУБ'ЄКТІВ РИНКУ МЕДИЧНИХ ПОСЛУГ

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### DYNAMICS OF DEVELOPMENT OF THE NETWORK OF SPECIALIZED HOSPITALS AS SUBJECTS OF THE MEDICAL SERVICES MARKET

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### ДИНАМИКА РАЗВИТИЯ СЕТИ СПЕЦИАЛИЗИРОВАННЫХ БОЛЬНИЦ, КАК СУБЪЕКТОВ РЫНКА МЕДИЦИНСКИХ УСЛУГ

**Анотація.** У статті виявлено, що держава здійснює безпосередній вплив на забезпечення якісними медичними послугами населення країни. Крім цього, органи державної влади за допомогою нормативно-правової бази створюють належні юридичні умови для ефективного функціонування лікарень, медичних установ та інших закладів охорони здоров'я. Проаналізовано нормативно-законодавчу базу, яка врегульовує питання забезпечення населення медичними послугами. Надано визначення поняттю “спеціалізована лікарня”, а також досліджені думки вчених, щодо виокремлення дефініції даному поняттю. Наведено аналітичні показники наявного стану та розвитку сучасної системи охорони здоров'я в Україні, також проаналізована оцінка рівня вторинної медицини в Україні за регіонами. Виокремлено та проаналізовано оплату надавачам спеціалізованої медичної допомоги за програмою медичних гарантій у 2020 році. Виявлено проблеми та особливості, які виникають в процесі реформування системи охорони здоров'я, враховано можливість розвитку та розгалуження мережі спеціалізованих лікарень, а також запропоновано шляхи вирішення наявних проблем в питаннях розвитку та функціонування спеціалізованих лікарень, покращення надання медичних послуг та реформування системи охорони здоров'я загалом.

**Аннотация.** В статье выявлено, что государство осуществляет непосредственное влияние на обеспечение качественными медицинскими услугами населения страны. Кроме этого, органы государственной власти с помощью нормативно-правовой базы создают надлежащие юридические условия для эффективного функционирования больниц, медицинских учреждений и других учреждений здравоохранения. Проанализированы нормативно-законодательную базу, которая регулирует вопросы обеспечения населения медицинскими услугами. Дано определение понятию "специализированная больница", а также исследованы мнения ученых относительно выделения дефиниции данному понятию. Приведены аналитические показатели существующего положения и развития современной системы здравоохранения в Украине, также проанализирована оценка уровня вторичной медицины в Украине по регионам. Выделены и проанализированы оплату поставщикам специализированной медицинской помощи по программе медицинских гарантий в 2020 году. Выявлены проблемы и особенности, которые возникают в процессе реформирования системы здравоохранения, учтена