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прогностических критериев перинатальных исходов у пациенток с тяжелой преэклампсией. С одной стороны, досрочное родоразрешение женщин с преэклампсиями увеличивает процент преждевременных родов и ухудшает показатели перинатальной заболеваемости и смертности. С другой стороны, несвоевременное родоразрешение может усугублять системные нарушения в организме матери с преэклампсией и, соответственно, состояние внутриутробного плода. Поэтому использование в практике достоверных критериев диагностики плацентарной недостаточности и прогнозирования перинатальных исходов позволит использовать дифференцированные подходы ведения женщин с ранними и поздними преэклампсиями.

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PREDICTORS OF ERLY DIAGNOSIS OF FIBROSIS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT
The article describes the predictors of early diagnosis of fibrosis in patients with non-alcoholic fatty liver disease. Used non-invasive techniques FibroMax and FibroScan, have shown that the structural and functional state of liver parenchyma in patients with nonalcoholic steatosis and nonalcoholic steatohepatitis is different. That helped to refine and supplement the diagnostic criteria of fibrosis in the liver.

Keywords: nonalcoholic fatty liver disease, fibrosis, nonalcoholic steatosis, nonalcoholic steatohepatitis, FibroMax, FibroScan.

Nonalcoholic fatty liver disease (NAFLD) is a significant problem in modern healthcare worldwide due to the prevalence of the disease and the severity of outcomes [5, 3, 7]. NAFLD represents a liver steatosis with inflammation and further maturation of fibrosis [4,

6]. Nonalcoholic steatosis (NAST) in 12-14% of cases leads to the development of non-alcoholic steatohepatitis (NASH), in 13% it is transformed into cirrhosis of the liver (LC), in 5-10% to severe fibrosis [1, 12, 9]. NASH is accompanied by inflammatory necrotic processes in the liver tissue and characterized by the presence of fibro-formation, in 40% development of LC and adenocarcinoma [2, 10].

Until recently, a liver biopsy was the gold standard in the diagnosis of liver fibrosis (LF), but the biopsy is said to be limited by the invasive nature of the procedure, the variability of the results and the risk of complications such as subcutaneous emphysema, internal bleeding, hematoma at the biopsy site, collaptoid state, reflex paresis of the intestine [6, 8, 13]. At the moment, there are no clear algorithms for early noninvasive diagnosis of LF, therefore their search is of considerable interest, since LF is a link between inflammation of the liver tissue and the formation of LC [11, 4].

The advantages of non-invasive diagnostic methods consist in the painless detection of biochemical and morphological changes in the liver [3, 6]. The FibroMax test is a comprehensive study aimed at determining the degree of liver fibrosis, steatosis and activity of these processes, the main advantage is that it practically does not require invasive interventions [10, 9, 13]. Fibroelastography by apparatus FibroScan completely excludes invasion, does not cause discomfort to the patient, the area under research is a hundred times lager than it is with biopsy, FibroScan has no contraindications. The results of these non-invasive diagnostic methods are calculated using patented algorithms [1, 8]. In this regard, early noninvasive diagnosis of LF in this category of patients is an important and urgent issue, has a number of diagnostic advantages that contribute to the proper selection and timely administration of therapy [11,10].

The purpose of research - improvement of early diagnosis of fibrosis in patients with NAFLD using a comprehensive assessment of metabolic and instrumental research methods.

Materials and methods. The research includes 76 patients (35 men and 41 women) with NAFLD. Patients are divided into 2 groups: 1st group - with NAST (n = 33) and 2nd group - with NASH (n = 43). The control group (n = 20) was maximally comparable in age and sex to the patients being examined. The average age of the patients was 52.5 ± 2.1 years. In addition to the standard methods of the research, were used the FibroMax test and fibroelastography by apparatus FibroScan. FibroMax consists of 5 calculation algorithms and is performed according to the results of mathematical processing of 5 biochemical parameters of blood serum: alpha 2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyltranspeptidase (GGTP), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose fasting (OCG), triglycerides (TG) and total cholesterol (TC) in the blood serum. The calculations were carried out using a patented algorithm (BioPredictive, France) [6, 7]. Fibroelastography was carried out by using the apparatus of FibroScan 502 TOUCH CAP (Echosens, France). FibroScan is based on proprietary technology: Vibration Controlled Transient Elastography (VCTE), which allows a painless and simultaneous measurement of two quantitative parameters: the density of the liver parenchyma (kPa) and the controlled attenuation parameter (dB / meter). Both parameters are evaluated in one part of the liver tissue - 3 cm^3, which in a 100 times lager than it is with biopsy [10, 6]. The stage of fibrosis and level of inflammatory activity in the liver was calculated based on the age and sex of the patient. The quantitative indicators were evaluated according to the METAVIR system.

The statistical analysis for the result of the research were achieved by applying the software package Statistica - 8.0 using Student's t-criterion.

Results and discussions. Analysis of the functional state of the liver and lipid spectrum in patients with NAST and NASH established significant differences in cytolysis activity (Table 1).

Patients of the 2 nd group noted a significant increase in ALT 2.5 times in 63.2% of patients and AST 2.3 times in 47.3% ($p < 0.05$), whereas the figures for patients with NAST were increased 1.8 fold in 37.5% and 1.6 times at 28.1%, respectively ($p < 0,05$). GGTP was an increase of 1.2 times in 25.2% of patients with NASH. Hyperbilirubinemia 1.2 times, ($p < 0,05$) was determined in 11.5% of patients. Disorders lipid profile characterized by growth in serum TC level by 1.4 fold in 46.8% of patients with NASH ($p < 0.05$), while in patients with hypertriglyceridemia NAST prevailed, the TG levels increased 2.1-fold in 61.9% of patients ($p < 0.05$).

Table 1

Characteristics of the functional state of the liver and lipid spectrum in the examined patients

Indexes	Control group (n=20)	NAST (n =21)	NASH (n =24)	P
	1	2	3	
ALT, mmol/g·l	0,28 ±0,13	0,73 ±0,18	1,025 ±0,21	p_{1-2} =0,004 p_{1-3} =0,22 p_{2-3} =0,31
AST, mmol/g·l	0,26 ±0,14	0,61±0,28	0,86 ±0,35	p_{1-2} =0,007 p_{1-3} =0,002 p_{2-3} =0,004
GGTP (un/l)	12,2±6,4	36,8 ±23,4	62,3 ±18,6	p_{1-2} =0,53 p_{1-3} =0,51 p_{2-3} =0,82
TC mmol/l	5,2±2,3	5,7±2,7	7,9±2,9	p_{1-2} =0,52 p_{1-3} =0,27 p_{2-3} =0,49
TG, mmol/l	1,7 ±0,9	4,6±0,1	2,2 ±1,3	p_{1-2} =0,02 p_{1-3} =0,05 p_{2-3} =0,42

Notes: K) -p <0,05-difference is reliable in comparison with the parameters of the control group, 1-2) -p <0,05 the difference is reliable in comparison with the indices of patients of both groups

The regular effect on the progression of fatty liver infiltration was disturbed by the serum lipid spectrum, which was significantly more frequent in patients with NASH ($p < 0.05$). The level of TG in the serum in patients with NAST was in 2.1 times higher than in the control group and 1.5 times higher than the results of group number 2 ($p < 0.05$), which is due to the peculiarities of the fatty liver to synthesize triglycerides intensively [6, 7].

The research of the FibroMax test scores in patients with NAST and NASH established significant differences in the activity of the necroinflammatory process and fibrosis (Table 2).

In assessing the results of the tests, the average fibrosis indices in the 1-st group of patients were 0.19 ± 0.02, the activity index of the necroinflammatory process was 0.16 ± 0.03, which corresponded to the parameters of the control group - the absence of fibrosis (F0) and histological activity (A0). In 26% of patients in 2-nd group, the fibrotic indices were within 0.32 ± 0.05, which corresponded to (F1) portal fibrosis without septum formation and minimal histological activity (A1) 0.34 ± 0.04; In 17% - the portal fibrosis with the presence of single septs were within 0.58 ± 0.07 (F2) and moderate activity 0.54 ± 0.04 (A2) and 8.1% of patients 0.69 ± 0.07 (F3) fibrosis of multiple portocentral septum without cirrhosis and high histological activity (A3) 0.82 ± 0.09, which indicates the consequences of high levels of fibrosis and necroinflammatory activity in the hepatic tissue in patients with NASH.

Table 2

Characteristics of FibroMax test scores in the examined patients

Indexes	Control group (n=20)	NAST (n =21)	NASH (n =24)	P
	1	2	3	
Necroinflammatory activity	0,14±0,02	0,16±0,03	26% - ,34±0,04 17% - ,54±0,04 8,1% - ,82±0,09	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$
Fibrosis formation	0,17±0,03	0,19±0,02	26% - 0,32 ± 0,05 17% -0,58 ± 0,07 8,1% - 0,69±0,07	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$
METAVIR	F0, A0	F0, A0	26% -F1, A1 17% -F2, A2 8,1% -F3, A3	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$

The results of the research indicate that an increase in the indices of activity of the necroinflammatory process and fibrosis formation in NASH and their normal values at NAST and in the control group are predictors of the development and progression of LF [3, 2, 5]. The established direct correlation between the level of activity of the necroinflammatory process and the index of fibrosis formation ($r = 0.56$, $p < 0.05$), which corresponds to the latest studies of Day Ch. P. and co-authors in the diagnosis of fibro-formation in the liver [13].

Analysis of fibroelastography in patients with NAST and NASH established significant differences in the parameters of the density of liver parenchyma and fibrosis activity (Table 3).

Table 3

Characteristics of fibroelastography by apparatus FibroScan in the examined patients

Indexes	Control group (n=20)	NAST (n =21)	NASH (n =24)	p
	1	2	3	
Density of the liver parenchyma (kPa)	4,9±0,5	5,2±0,6	26% -5,9±1,3 17% -7,3±2,2 8,1% - 9,6±2,9	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$
METAVIR	F0, A0	F0, A0	26% -F1, A1 17% -F2, A2 8,1% -F3, A3	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$
Indexes	Control group (n=20)	NAST (n =21)	NASH (n =24)	p
	1	2	3	
Density of the liver parenchyma (kPa)	4,9±0,5	5,2±0,6	26% -5,9±1,3 17% -7,3±2,2 8,1% - 9,6±2,9	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$
METAVIR	F0, A0	F0, A0	26% -F1, A1 17% -F2, A2 8,1% -F3, A3	$p_{1-2}<0,05$ $p_{1-3}<0,05$ $p_{2-3}<0,05$

During the fibroelastography in the patients of the 1-st group and the control group, the density of the liver

parenchyma corresponded to the indices, which indicate the absence of fibrosis (F0) and histological activity (A0). In 2-nd group the density of the liver parenchyma in 26% patients was 5.9 ± 1.3 kPa (F1) - portal fibrosis without septum with minimal histological activity (A1), in 17% 7.3 ± 2.2 kPa (F2) - portal fibrosis with single septa, moderate activity (A2) and 8.1% 9.6 ± 2.9 kPa (F3) - fibrosis of multiple portocentral septum without cirrhosis with high histological activity (A3) [8, 9]. A correlation relationship was established between the density of the liver parenchyma and the severity of fibrosis ($r = 0.54$, $p < 0.05$). The prevalence of LF in patients with NASH and the absence of its progression in patients of the 1-st and control groups testify to the severity of the course and the disturbance of the morphology and liver functions in NASH, which correlates with the studies of Ratziu V. and Bellentani S. [12], in which described fibrotic changes of the liver parenchyma in patients with NASH when used FibroScan in diagnosis of fibrosis.

Conclusions. The use of tests FibroMax and FibroScan for the diagnosis of the degree of fibrosis by noninvasive techniques has shown that the structural and functional state of the liver parenchyma in patients with NAST and NASH is different. Patients with NASH were characterized by more pronounced fibrotic changes of the liver parenchyma. In this way the use of modern methods such as FibroMax and fibroelastography in patients with NAFLD contributes to clarifying and supplementing the diagnostic criteria of fibrosis in the liver.

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СОСТОЯНИЕ ЭЛЕКТРОЛИТНОГО ОБМЕНА У ШКОЛЬНИКОВ И ВЗАИМОСВЯЗЬ ЕГО С ФУНКЦИЕЙ МИТОХОНДРИЙ

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