Introduction

Non-alcoholic fatty liver disease (NAFLD) has various clinical forms - from steatosis of the liver and steatohepatitis to liver cirrhosis and hepatocellular carcinoma differing in severity, spectrum of complications, and disease prognosis. With the progression of NAFLD (the growth of the fibrosis stage), the risk of cardiovascular diseases, type 2 diabetes mellitus (DM-II) increases in parallel with the risk of progression of hepatic insufficiency. Today, NAFLD is regarded as a hepatic component of metabolic syndrome (MS). The treatment of patients suffering from NASH provides early diagnosis and treatment of concomitant metabolic diseases in order to prevent the progression of hepatic insufficiency and metabolic complications [1]. Undoubtedly, the first step in the treatment of patients with NAFLD should be considered a lifestyle modification. Pharmacotherapy should be given to patients with moderate and severe fibrosis (>F2). Early detection of patients with NASH with severe liver fibrosis is relevant for clinical practice. Given the lack of clinical indications for liver biopsy in this category of patients, it is necessary to develop and widely implement non-invasive methods for diagnosis of fibrosis and steatosis of the liver in NAFLD both for primary diagnosis and for evaluation of treatment outcomes. Treatment is also indicated for patients with...
less severe fibrosis stage, but with a high risk of its progression (with CD-II, MS, sustained increase in ALT and necroinflammatory reaction in liver tissue) [2].

Objective

To study the markers of inflammatory activity, insulin resistance, lipid spectrum and their contribution to the formation of fibrosis and steatosis of the liver; non-invasive evaluation of fibrosis and fibroscan stage (FibroScan 502 TOUCH with CAP software), and development of a noninvasive method for diagnosis of fibrosis and steatosis liver in patients with NAJBP for early diagnosis of the disease based on clinical and laboratory data, comparison with the results of serum fibrosis evaluation tests (GUCI, APRI, Fib4, Forns, MDA – selection.

Materials and Methods

In the study, 183 patients with a BMI> 25 kg / sq. M, steatosis of the liver according to ultrasound of the liver: Male 101, female 82, median age 44 (38-49) years. All patients underwent a clinical examination including a assessment of clinical syndromes and quality of life (SF-36 questionnaire), elimination of alcoholic liver damage according to the AUDIT questionnaire (score less than 8 points), lipid spectrum, carbohydrate metabolism, insulin resistance, inflammatory activity in the liver level of ALT, AST, CRP) and cholestasis syndrome. In addition, autoimmune, cholestatic liver diseases, drug-induced hepatitis and Wilson-Konovalov’s disease are excluded. The data obtained during the examination of patients allowed to assess the presence of liver fibrosis using the NAFLD fibrosis score. Evaluation of the stage of fibrosis and the degree of steatosis was carried out on the Fibroscan 502 TOUCH apparatus with an ultrasonic sensor for obese patients with the CAP software. The technique allows simultaneous non-invasive determination of the stage of fibrosis and steatosis at the point of the study. The sensitivity and specificity of the method is about 90% (compared with liver biopsy) [1]. Statistical analysis of the results was carried out using the software package for statistical analysis of IBM SPSS Statistics 19.

Results of the Study

The general characteristics of a group of patients are shown in Table 1. Patients who were included in the group, mostly men, middle-aged, had an excess of body weight or obesity - the median BMI was 30 kg / sq. M. Two-thirds of the patients had MS components in the first line of kinship, more than half of them reported eating less than 3 times a day (lack of breakfast, late supper) and inactivity. Violation of carbohydrate metabolism, dietary habits, and activity level in patients with MS was observed in 60% of patients. Two thirds of patients had hypertensive dyslipidemia (hypercholesterolemia, hypertriglyceridemia), pathology of the biliary tract (according to the US - cholelithiasis in 53% and CLS in 11% of cases). Two or more components of the metabolic syndrome had two-thirds of the patients. Fibroscanning of the liver was performed for all patients with a diagnostic purpose, in Further it defined or determined medical tactics-purpose or appointment of medicamental therapy in addition to recommendations on modification of a way of life. The average value of the elasticity of the liver was Me = 7.5 kPa, which corresponds to the 2 stages of liver fibrosis. The stage of steatosis - Me = 310 kPa - in this case corresponded to 2-3 stages.

Table 1: General characteristics of a group of patients (n =183).

| Parameter                          | Absolute quantity /% |
|------------------------------------|-----------------------|
| Men 101 (55%)                      | Men 101 (55%)         |
| Women 82 (45%)                     | Women 82 (45%)        |
| Age (years) (Me (25 - 75 P)        | 44 (38-49)            |
| BMI kg / sq. M (Me (25 - 75 P)      | 30 (28-34)            |
| Waist circumference, cm (Me (25 - 75 P) | 97 (92-104)        |
| Components of the metabolic syndrome in the first line of kinship | 112 (61%) |
| Hypodinamy                         | 142 (77%)             |
| Eating less than 3 times a day (no breakfast) | 118 (64%)  |
| Diabetes                           | 18 (14%)              |
| Impaired fasting glycemia (NGN)    | 54 (42%)              |
| Hypertonic disease                 | 118 (64%)             |
| Dyslipidaemia                      | 116 (63%)             |
| Cholecystitis (according to ultrasound) | 98 (53%)        |
| LCM (according to ultrasound)      | 20 (11%)              |
| ALT, the norm is up to 40 units / liter (Me (25 - 75 P) | 69 (62-77) |
| AST, the norm is up to 40 units / liter (Me (25 - 75 P) | 73 (68-79) |
| GGT, the norm is up to 50 units / liter (Me (25 - 75 P) | 76 (41%)  |
| CRP, the norm is up to 3 units (Me (25 - 75 P) | 4,6 (4,1-5,0) |
| Glycemia, the norm to 6 mmol / l / (Me (25 - 75 P) | 6,0 (5,6-6,4) |
| HOMA-index, norm up to 2,7         | 3,7 (3,4-4,2)         |
| Cholesterol, mmol / l (Me (25 - 75 P) | 6,3 (5,8-6,7) |
| Triglycerides mmol / l (Me (25 - 75 P) | 2,1 (1,8-2,4) |
| LDL, mmol / l, (Me (25 - 75 P)      | 3,8 (3,4-4,2)         |
| HDL mmol / l, (Me (25 - 75 P)       | 1,2 (0,8-1,4)         |
| The coefficient of atherogenicity   | 3,9 (3,5-4,3)         |
| Fibro scanning of the liver:       |                       |
| Elasticity-liver fibrosis-normal up to 5.8 kPa | 7,5 (7,1-7,9) |
| Steatosis of the liver, norm up to 200 dB | 310 (286-342) |

Given that liver biopsy in NAJBP is rarely performed in a wide clinical practice due to the lack of medical indications, and Fibroscan 502 TOUCH with the CAA software remains inaccessible, it is interesting to develop a noninvasive method for diagnosing both fibrosis and steatosis of the liver based on clinical and laboratory data, replacing liver fibroscans. To determine the significance of the studied parameters in the formation of fibrosis and steatosis.

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of the liver, a correlation analysis was performed (Table 2). As can be seen from the data of the table, the stage of fibrosis and steatosis of the liver in NAJBP correlates with the stigmata of the disease activity, insulin resistance, dyslipidemia, the presence of metabolic syndrome components. Models of diagnostics of fibrosis and steatosis of the liver are presented in the form of discriminant analysis (Table 3) and 4. The equations of the discriminant functions (Figures 1 & 2) with high sensitivity and specificity can diagnose fibrosis and steatosis of the liver of the second and more stages (Fibrosteatotest ©) standard methods of research available in a wide clinical practice. For the standard of diagnosis of the stage of fibrosis and steatosis of the liver, the results of fibroscanization of the liver of the device Fibroscan 502 with the software of the CAPS were taken. The created method of non-invasive diagnostics of liver steatosis can, therefore, with a diagnostic accuracy of more than 80%, replace the diagnosis of fibrosis and steatosis of the liver with this fibroscan model. The diagnostic model for fibrosis Fibrosteatotest © is characterized by less sensitivity and specificity, as for a more accurate diagnosis of fibrosis, direct serum markers are required. The use of these reagents is often not available, so Fibrosteatotest © can be used to screen the stage of the disease requiring medical therapy (stage 2 or more of fibrosis and steatosis of the liver). The determination of the stage of fibrosis and steatosis of the second and more stages determines the group of patients of NAPP, for which drug therapy should be performed in connection with a greater likelihood of progressing fibrosis. To assess the information content of the model created, a comparative analysis was carried out with GUCL, APRI, FIB4, Forns, MDA. The results of the AUROC analysis are presented in Figure 3. Available for comparative analysis of models of steatosis of the liver was not found.

![Figure 1: Discriminant equation for the diagnosis of hepatic steatosis of the second and more stage.](image1)

![Figure 2: A discriminatory equation for the diagnosis of liver fibrosis of the second and more stage.](image2)
Changes in diet and lifestyle (hypodynamia), increased consumption of carbohydrates and fats, alcohol, led to a wide spread of NAZHBP. It is generally accepted that early diagnosis and treatment can prevent the progression of chronic liver disease. Fibrosis and steatosis of the liver stages or more is an indication to the beginning of drug therapy. In our study, we presented the possibilities of noninvasive diagnosis of fibrosis and steatosis of the liver on a Fibro scan Fibro Scan 502 TOUCH apparatus with an ultrasound transducer for obese patients with CAP software. The technique is highly informative, safe in any age and state of the patient, but is inaccessible. Creation of accessible non-invasive methods for diagnosis of the stage of fibrosis and steatosis of the liver in NAZHBP is in demand by clinical practice. Given the high diagnostic accuracy of diagnosis of fibrosis and fibroscans in fibroscan (more than 90%) compared to liver biopsy, it is justified to create mathematical models for diagnosis of fibrosis and steatosis of the liver using its data as a standard instead of liver biopsy. To create models for the diagnosis of steatosis and fibrosis in stages, more patients are needed. For practice, it remains urgent to identify the group of patients who need to start therapy (fibrosis and steatosis more than 2 stages - the Fibrosteatotest © test solves this problem), since it has a high risk of progression not only to liver disease, but also the realization of cardiovascular risks and development diabetes mellitus. As can be seen from the formula of the created model, in the progression of the disease, the growth of the stage of fibrosis and steatosis, the weight of the patient, the growth of the stigma of insulin resistance, and the activity of inflammation are important.

An important point in the treatment of NAJBP is the identification of patients who have advanced stages of fibrosis and steatosis of the liver with a risk not only of liver failure, but also of metabolic disorders. Timely and high-quality therapy of NAJBP in this category of patients with mandatory monitoring of the stage of fibrosis and steatosis of the liver is important for prognosis. Therefore, the development and application of available non-invasive methods for the diagnosis of fibrosis and steatosis of the liver remains one of the priority areas in hepatology. The proposed diagnosis model Fibrosteatotest © is a simple and affordable method for the clinician.

References

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The Discussion of the Results

Changes in diet and lifestyle (hypodynamia), increased consumption of carbohydrates and fats, alcohol, led to a wide spread of NAZHBP. It is generally accepted that early diagnosis and treatment can prevent the progression of chronic liver disease.
Pirogova I Yu, et al. New Possibilities of Diagnostics of Non-Alcoholic Fatty Liver Disease. Curr Tr Gastroenterol 1(3)-2018. CTGH.MS.ID.000111. DOI: 10.32474/CTGH.2018.01.000111.