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Research Article

The Results of Serum Markers of Liver Fibrosis in Patients with Posthepatic Fibrosis and in Patients with Non-alcoholic Fatty Liver Disease Depending on Body Weight

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Abstract

Liver fibrosis is a significant medical and economic problem in many countries, particularly developed ones, with excess incidence of overweight and obesity, as well as in the countries with high incidence of viral hepatitis. Taking into account the significant progress in the molecular understanding of liver fibrosis, the problem of early diagnostics, disease course prediction and search for effective pathogenetically substantiated approaches to its treatment remains important. The presented article highlights the main methods of posthepatitis liver fibrosis diagnostics after elimination of viral hepatitis type C and in patients with non-alcoholic fatty liver disease affected by overweight and obesity by evaluating fibrosis serum markers. Authors highlighted connections with non-alcoholic fatty liver disease, posthepatitis liver fibrosis after elimination of viral hepatitis type C in patients with overweight and obesity, perspective directions for the use of these data are also formulated.

Keywords: Posthepatic Fibrosis; NAFLD; Overweight; FibroTest; FIB-4; TGF-β1

Abbreviations

NAFLD: Non-alcoholic Fatty Liver Disease (NAFLD); TGF-β1: Transforming Growth Factor β1; VHC: Viral Hepatitis Type C

Introduction

Chronic liver disease, which is the result of various injuries and has high prevalence rate in the world and limited treatment options is the global problem of modern medicine in many countries [1-3]. In terms of the physiology, fibrosis is the universal repairing and therapeutic reaction to liver injury characterized by hypernormal extracellular matrix protein deposition under the influence of various pathological factors. Under long-term damage or apoptosis of liver cells, their replacement by connective tissue results in the distortion of blood vessel architecture and dispragia [4,5].

Liver fibrosis is a significant medical and economic problem in many countries, particularly developed ones, with excess incidence of overweight and obesity, as well as in the countries with high incidence of viral hepatitis [1,6]. This leads to the spread of non-alcoholic fatty liver disease (NAFLD), where steatosis and steatohepatitis are involved in the development of liver cirrhosis and hepatocellular carcinoma and increased mortality from liver disease [7].

Taking into account the significant progress in the molecular understanding of liver fibrosis achieved during recent decades in a number of experimental investigations, the problem of early diagnostics, disease course prediction and search for effective pathogenetically substantiated approaches to its treatment remains impor-

tant [8,9]. In most cases, NAFLD and liver fibrosis in overweight and obese patients, as well as in patients after elimination of viral hepatitis type C (VHC), often remain undiagnosed and are not treated, and patients consult a doctor in the presence of cardiovascular and liver complications in advanced stages.

Purpose. Improvement of the diagnostics of posthepatitis liver fibrosis after HCV infection elimination and in patients with non-alcoholic fatty liver disease affected by overweight and obesity by evaluating fibrosis serum markers.

Materials and Methods

The investigation was carried out at the Department of Gastroenterology and Hepatology, of Ternopil University Hospital. We examined 115 patients with different body mass index. The first group included 56 patients with liver fibrosis without concomitant pathology and registered recovery from HCV infection. The second group included 59 patients with NAFLD. According to the classification of the WHO International Obesity Group (1997), all patients were divided into subgroups: 18.5-24.9 kg/m^2 - normal body weight; 25-29.9 kg/m^2 - overweight (pre-obesity); 30.0-34.9 kg/m^2 - obesity of the I degree. Beside biochemical analysis, the patients were examined for serum markers alpha2-macroglobulin, haptoglobulin, apoliproprotein A1 in order to determine FibroTest index for fibrosis stage verification. In addition, FIB-4 index was calculated.

In order to interpret FibroTest results and data translation into fibrosis stage, the most common scale of histological METAVIR indices was used.

FibroTest	METAVIR stage of fibrosis
0.75-1.00	F4
0.73-0.74	F3-F4
0.59-0.72	F3
0.49-0.58	F2
0.32-0.48	F1-F2
0.28-0.31	F1
0.22-0.27	F0-F1

Table a

FIB-4 <1.45 value indicated the absence of significant fibrosis (F0-F2 fibrosis), and FIB-4> 3.25 value indicated the presence of significant fibrosis (F3-F4 fibrosis).

Another predictor of liver fibrosis progression is serum transforming growth factor β1 (TGF-β1). For TGF-β1 quantitation in blood serum we used the Enzyme-linked Immunosorbent Assay (ELISA) analyses on automated enzyme-immunoassay analyzer "MultiskanFC-357" according to the instructions of the test system "Human TGF β1 Platinum ELISA (BMS249/4 BMS249/4TEN; eBioscience, Austria)".

Results and Discussion

The examined group I included 29 (25.22%) men and 27 (23.48%) women (mean age - (45.79 ± 2.00) and (53.41 ± 1.90) years). Group II, consisted of 28 (24.35%) men and 31 (26.95%) women with mean age (48.71 ± 2.37) and (51.1 ± 1.78) years. Both groups were representative by age and gender. While using FIB-4 index in patients with various BMI, we obtained a significant difference in index value in patients with normal body weight and pre-obesity ($p < 0.01$), normal body weight and obesity of the I degree ($p < 0.01$), pre-obesity and obesity of the I degree ($p < 0.01$) (Figure 1, Table 1). Correlation analyses by Spearman's rank definitely confirms the liver fibrosis progression, calculated by FIB-4 index, with increasing BMI ($r = 0.83$, $p < 0.05$).

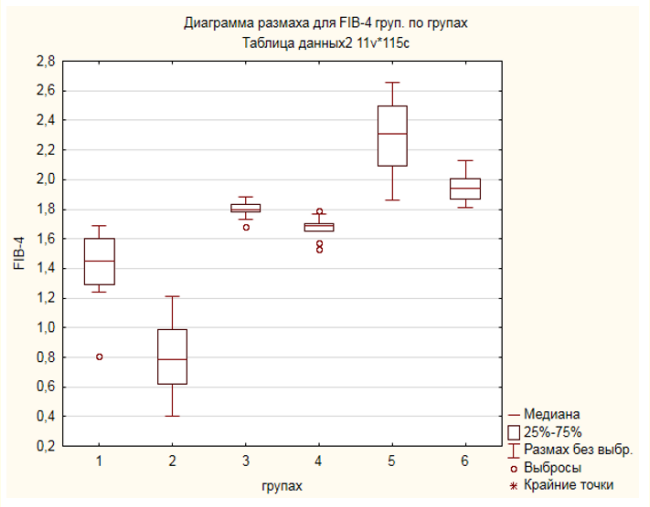

Figure 1: Comparative characteristics of FIB-4 index in subgroups.

While interpreting the given index results, we can confirm that moderate fibrosis was not observed in patients with normal body weight, since the calculated average values were less than 1.45. In

patients with pre-obesity and obesity of the I degree, the average values were less than 3.25, indicating the absence of significant fibrosis.

The dependence FIB-4 on the level of АлТ (r = 0.64, p < 0.05), АсТ (r = 0.67, p < 0.05), dyslipidaemia (r = 0.28, p < 0.05) platelets (r = -0.55, p < 0.05) was also found.

Group	FIB-4		
	Posthepatic fibrosis	NAFLD	p
BMI 18,5-24,9 kg/m^2	1,42 ± 0,05	0,80 ±0,05	< 0,01*
BMI 25-29,9 kg/m^2	1,80 ± 0,01	1,68 ± 0,01	< 0,01*
BMI 30-34,9 kg/m^2	2,26 ± 0,06	1,94 ± 0,02	< 0,01*
Note. significant difference was calculated by the Kraskel-Wallis criterion: * - p < 0,01.			

Table 1: Indicators of FIB-4 index in subgroups (M ± m).

FibroTest (Fibrotest) was used for differential diagnostics of liver fibrosis stages. In the application of minimally invasive method for FIB-4 liver fibrosis diagnosing, and Fibrotest use as well, we obtained a significant difference in test values in patients with normal body weight and pre-obesity (p < 0.01), normal body weight and obesity of the I degree (p < 0.01), pre-obesity and obesity of the I degree (p < 0.01). Comparative characteristics of FibroTest indicators by subgroups is given in figure 2.

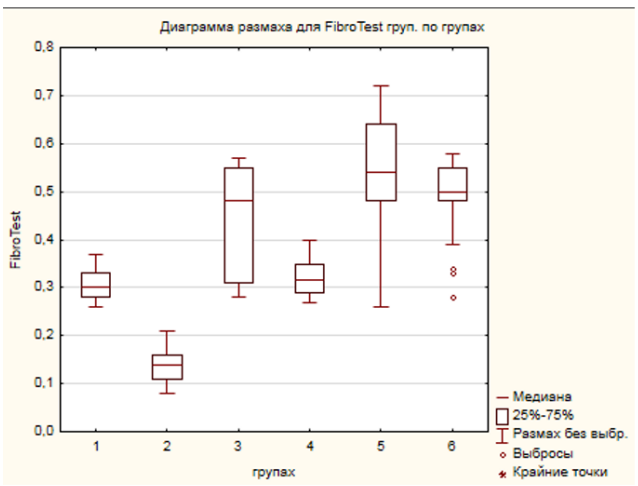

Figure 2: Comparative characteristics of FibroTest by subgroups.

The significance of difference between FibroTest values in the subgroups relatively to BMI and the disease etiology are given in table 2. Similar difference between the above-mentioned groups was observed in the analysis of 5 separate indicators used to calculate the fibrotest, namely in analysis of alpha-2-macroglobulin, haptoglobulin, apolipoprotein A1, total bilirubin, GGTP.

Group	Fibrotest		
	Posthepatic fibrosis	NAFLD	p
BMI 18,5-24,9 kg/m^2	0,31 ± 0,01	0,14 ± 0,01	< 0,01*
BMI 25-29,9 kg/m^2	0,43 ± 0,03	0,33 ± 0,01	< 0,02*
BMI 30-34,9 kg/m^2	0,52 ± 0,03	0,49 ± 0,02	0,22
Note. significant difference was calculated by the Kraskel-Wallis criterion: * - p < 0,01.			

Table 2: Fibrotest index indicators in subgroups (M ± m).

No differences were found While analyzing the total bilirubin concentration between groups with different body weight. While determining GGTP level in blood, a significant difference was found only between patients with normal body weight and obesity of the I degree (p < 0.01).

Correlation analysis showed a significant connection between Fibrotest and FIB-4 index (r = 0.86, p < 0.05). Thus, it is recommended to carry out both methods for case follow-up of patients with liver fibrosis, as they complement each other.

The content of TGF-β1 in blood significantly increased with increasing fibrosis stage and BMI with maximum values in the group of patients with NAFLD and BMI 30-34.9 kg/m^2 (p < 0.05). With liver fibrosis progression, the concentration of TGF-β1 in blood increases (r = 0.78, p < 0.05), confirming the role of TGF-β1 in activating hepatic stellate cells and stimulating the synthesis of collagen and other BMA components and is the probable marker of NAFLD progression (Table 3).

During the anthropometric data analysis, direct correlations between BMI and TFG - β1 (r = 0.74, p < 0.05) were determined. A significant relationship between the level of direct (TFG-β1) and

Group	TGF-β1, пг/мл		
	posthepatic fibrosis	NAFLD	p
BMI 18,5-24,9 kg/m^2	12020,76 ± 973,9	8023,33 ± 945,5	0,016*
BMI 25-29,9 kg/m^2	14910,70 ± 600,1	12492,83 ± 376,9	0,006*
BMI 30-34,9 kg/m^2	20529,60 ± 948,7	18794,40 ± 438,8	0,130
Note. significant difference was calculated by the Kraskel-Wallis criterion: * - p < 0,01.			

Table 3: Comparative characteristics of TGF-β1 (M ± m).

indirect (ALT and AST) markers of fibrosis was revealed. Respectively, TFG - β1 with the level of ALT (r = 0.59, p < 0.05) and with the level of AST (r = 0.62 p < 0.05).

We found direct correlations of TFG-β with liver fibrosis stage according to the fibrotest (r = 0.86, p < 0.05) with FIB-4 index (r = 0.77, p < 0.05). In detailed correlation analysis with fibrotest parameters, direct relationship between TFG-β and alpha-2-macroglobulin (r = 0.66, p < 0.05) and apolipoprotein A1 (r = 0.37, p < 0.05), and feedback with haptoglobulin (r = -0.57, p < 0.05) were obtained.

The presence of direct correlations between liver density, TFG - β in patients with posthepatic fibrosis and patients with NAFLD in combination with increased body mass index indicates mutually precipitating effect of these diseases, which generally contributes to the activation of fibrosis in the liver and is confirmed by literature data [10].

Conclusion

Thus, while verifying liver fibrosis with FIB-4, Fibrotest it was found that overweight and obesity significantly affect the fibrosis stage regardless of its etiology (p < 0.01), but the indices in patients with posthepatic fibrosis after HCV- infection elimination were significantly higher than in patients with NAFLD and BMI 18.5-24.9 kg/m^2 and BMI = 25-29.9 (p < 0.01). Analyzing the indicators of serum markers for fibrosis diagnostics, such as FIB-4, FibroTest (Fibrotest) we can state that they correlate with each other and with biochemical parameters of blood and generally complement the dependence of overweight and obesity on the liver fibrosis degree and are confirmed by many authors.

The content of TGF-β in blood significantly increases with the growth of fibrosis stage and BMI with maximum values in the group of patients with NAFLD and BMI 30-34.9 kg/m^2 (p < 0.05). With the liver fibrosis progression, the concentration of TGF-β1 in blood increases (r = 0.78, p < 0.05), confirming the role of TGF-β1 in the activation of hepatic stellate cells and stimulation of the synthesis of collagen and other extracellular matrix components and is a probable marker of NAFLD progression.

Conflict of Interest

The authors declare that there is no conflict of interest.

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