







Non-invasive fibrosis markers and elastography in diagnosis of fibrosis severity in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

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Objective: to evaluate the possibility of determining the stage of non-alcoholic fatty liver disease (NAFLD) with the help of indirect non-invasive markers of fibrosis and elastography.

Material and methods. The study involved 43 patients with type 2 diabetes mellitus (DM) and manifestation of NAFLD, including 26 (60.5 %) females and 17 (39.5 %) males. All the patients underwent an extensive ultrasound examination of the liver, namely determination of its size below the costal arch, a duplex examination to assess the distribution of hepatic vessels, determine possible blood flow trouble and its type.

B-mode liver ultrasound with real-time elastography on Hitachi Hi Vision Avius apparatus was also performed. The presence and stage of fibrosis were assessed using the Bonacini discriminant score, METAVIR and Ishak scoring systems. A correlation analysis between results of various methods of liver fibrosis stage assessment in patients with type 2 DM and NAFLD was also conducted.

Results. Generally, in patients with type 2 DM and NAFLD, mild fibrosis (F0–F2) was diagnosed. The assessment of liver fibrosis intensity according to sonoelastography and other non-invasive methods (Bonacini, Ishak and METAVIR scores) gave comparable results. The results of liver fibrosis stage assessment in patients with type 2 DM and NAFLD according to sonoelastography were strongly correlated with the results of Bonacini classification (discriminant) score. The results of the Ishak and METAVIR scores were moderately correlated with the sonoelastography data and strongly correlated precisely in advanced stages of hepatic fibrosis.

Conclusions. The results obtained show the importance of criteria for NAFLD assessment in patients with type 2 DM, the need to determine NAFLD and liver fibrosis stages. The combination of ultrasound diagnosis, serum biomarkers and use of diagnostic scales is more informative and appropriate for assessing the liver fibrosis presence in patients with NAFLD, compared with separate use of these methods allowing reducing the frequency of invasive traumatic methods using.

Ключові слова:

неінвазивні маркери фіброзу, еластографія, цукровий діабет 2 типу, неалкогольна жирова хвороба печінки.

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Неінвазивні маркери фіброзу та еластографія в діагностиці тяжкості фіброзу у хворих на цукровий діабет 2 типу та неалкогольну жирова хвороба печінки

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Мета роботи – оцінити можливість визначення стадій неалкогольної жирової хвороби печінки (НАЖХП) за допомогою непрямих неінвазивних маркерів фіброзу та еластографії.

Матеріали та методи. Обстежили 43 особи, які хворі на цукровий діабет (ЦД) 2 типу з проявами НАЖХП: 26 (60,5 %) жінок та 17 (39,5 %) чоловіків. Усім пацієнтам здійснили розширене ультразвукове обстеження печінки, що передбачало визначення її розміру нижче краю реберної дуги, дуплексне обстеження для оцінювання ходу судин печінки, визначення можливих перешкод кровотоку, встановлення його типу.

Виконали УЗД печінки у В-режимі з еластографією в режимі реального часу на апараті Hitachi Hi Vision Avius. Наявність і ступінь фіброзу оцінювали, використовуючи класифікаційну (дискримінантну) лічильну шкалу Bonacini, шкали METAVIR та Ishak. Також виконали кореляційний аналіз результатів різних методик оцінювання ступеня фіброзу печінки у хворих на ЦД 2 типу та НАЖХП.

Результати. У більшості хворих на ЦД 2 типу за наявності НАЖХП діагностували фіброз слабкого ступеня (F0–F2). Оцінювання інтенсивності фіброзу печінки за даними соноеластографії та іншими неінвазивними методами (шкали Bonacini, Ishak та METAVIR) дало можливість отримати зіставні результати. Результати оцінювання ступеня фіброзу печінки в обстежених хворих за даними соноеластографії найсильніше корелюють із результатами класифікаційної (дискримінантної) лічильної шкали Bonacini. Результати шкал Ishak і METAVIR мають кореляційні зв'язки середнього ступеня з даними соноеластографії, а сильні кореляційні зв'язки встановили саме для важчих ступенів фіброзу печінки.

Висновки. Результати, що одержали, показали важливість оцінювання критеріїв наявності або відсутності НАЖХП у хворих на ЦД 2 типу, необхідність діагностики стадій НАЖХП і визначення ступеня фіброзу печінки. Поєднання УЗД діагностики та сироваткових біомаркерів, застосування діагностичних шкал є значно інформативнішим і доцільнішим для оцінювання наявності фіброзу печінки в пацієнтів із НАЖХП порівняно із застосуванням цих методів поодиночі, що також дає змогу зменшити частоту використання інвазивних травматичних методів.

Неинвазивные маркеры фиброза и эластография в диагностике тяжести фиброза у больных сахарным диабетом 2 типа и неалкогольной жировой болезнью печени

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Цель работы – оценить возможность определения стадии неалкогольной жировой болезни печени (НАЖБП) с помощью непрямых неинвазивных маркеров фиброза и эластографии.

Материал и методы. Обследованы 43 пациента с сахарным диабетом (СД) 2 типа с проявлениями НАЖБП: 26 (60,5 %) женщин и 17 (39,5 %) мужчин. Всем пациентам проводили расширенное ультразвуковое обследование печени, которое предусматривало определение ее размера ниже края реберной дуги, дуплексное обследование для оценки хода сосудов печени, определения возможных препятствий кровотоку, установление его типа. Также проводили УЗИ печени в В-режиме с эластографией в режиме реального времени на аппарате Hitachi Hi Vision Avius. Наличие и степень фиброза оценивали с использованием классификационной (дискриминантной) счетной шкалы Bonacini, а также шкал METAVIR и Ishak. Проведен корреляционный анализ результатов различных методик оценки степени фиброза печени у больных СД 2 типа при наличии НАЖБП.

Результаты. У большинства больных СД 2 типа при наличии НАЖБП диагностирован фиброз слабой степени (F0–F2). Оценка интенсивности фиброза печени по данным соноэластографии и других неинвазивных методов (шкалы Bonacini, Ishak и METAVIR) позволила получить сопоставимые результаты. Результаты оценки степени фиброза печени у обследованных больных по данным соноэластографии наиболее сильно коррелируют с результатами классификационной (дискриминантной) счетной шкалы Bonacini. Результаты шкал Ishak и METAVIR имеют корреляционные связи средней степени с данными соноэластографии, а сильные корреляционные связи отмечены именно для более тяжелых степеней фиброза печени.

Выводы. Полученные результаты показывают важность оценки критериев наличия или отсутствия НАЖБП у больных СД 2 типа, необходимость диагностики стадий НАЖБП и определения степени фиброза печени. Сочетание УЗИ диагностики и сывороточных биомаркеров, применение диагностических шкал является более информативным и целесообразным для оценки наличия фиброза печени у пациентов с НАЖБП по сравнению с применением этих методов порознь, что также позволяет снизить частоту применения инвазивных травматичных методов.

Ключевые слова:

фиброз, эластография, сахарный диабет 2 типа, неалкогольная жировая болезнь печени.

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Diabetes mellitus (DM) is the most serious threat for the population all over the world. According to the World Health Organization, it is ranked third among the leading risk factors for premature death after arterial hypertension and smoking. International Diabetes Federation reveals that approximately 4 million people aged between 20 and 79 years in the world died in 2017 due to DM. The prevalence of diagnosed diabetes is 425 million people or 8.8 % of adult population (20–79 years) in the world. 212.4 million people or 50.0 % of all people aged 20–79 years with DM are unaware of their disease [1].

Non-alcoholic fatty liver disease (NAFLD) is pathogenetically associated with DM, its prevalence reaches 88 % in diabetic patients, while its prevalence is no more than 30% in the general population [2–6].

At present, the pathogenesis of NAFLD is explained by the concept of “multiple impact”, which means the set of factors to be the reason of NAFLD development [7,8].

It is generally accepted that steatohepatitis has no tendency to progress, or it occurs very slowly. At the same time, the development of liver cirrhosis is relatively fast in patients with non-alcoholic steatohepatitis (NASH) [9–11]. Thus, it is critically important to determine the stage of the disease development and estimate the presence of liver fibrosis.

So far, there are many debatable questions regarding the use of non-invasive and minimally invasive methods for diagnosing various diseases, including NAFLD, using biomarkers. It is necessary to find the most informative non-invasive diagnostic methods and implement them into clinical practice for equivalent replacement of traumatic and potentially dangerous instrumental methods.

Objective

To evaluate the possibility of determining the stage of NAFLD with the help of indirect non-invasive markers of fibrosis and elastography.

Materials and methods

The study involved 43 patients with type 2 DM and NAFLD, including 26 females (60.5 %) and 17 males (39.5 %). The average age of patients was 55.9 ± 1.3 years. All patients were examined and treated in the SI “V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine”, Kharkiv.

The following inclusion criteria were applied: a written informed consent obtained from each patient to participate in the study, verified diagnosis of type 2 DM, verified diagnosis of NAFLD. Exclusion criteria were a diagnosis of type 1 DM, alcoholic liver disease, hepatitis C infection.

All patients underwent an extensive ultrasound examination of the liver, namely determination of its size below the costal arch, a duplex examination to assess the location of hepatic vessels, determine possible blood flow trouble and its type, etc. B-mode liver ultrasound with real-time elastography on Hitachi Hi Vision Avius apparatus was also performed.

The assessment of fibrosis presence and its stage was performed using the Bonacini discriminant score [23]. For evaluating the index of fibrosis according to this scoring system, the INR, AIAT/AsAT ratio and platelet count were determined. Based on the fibrosis index values, we assessed the intensity of fibrosis and correspondence between the stage of fibrosis and the results of histological evaluation by METAVIR and Ishak scores [17,18].

A correlation analysis between the results of various methods for assessing the stage of liver fibrosis in patients with type 2 DM in the presence of NAFLD was done.

The principles of bioethics were taken into account in the study: the general principles of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the GCP (1996), the ethical principles of medical research involving human subjects of the World

Table 1. Indexes of liver ultrasound examination in patients with type 2 DM and NAFLD, M ± m

Indexes	Males, n = 19	Females, n = 28	P
Hepatomegaly, cm	2.34 ± 0.37	1.59 ± 0.34	>0.05
Diameter of total bile duct, mm	6.11 ± 0.02	6.22 ± 0.05	>0.05
Diameter of spleen vein, mm	6.79 ± 0.10	6.48 ± 0.13	>0.05
Diameter of the portal vein, mm	11.61 ± 0.17	11.59 ± 0.20	>0.05
Velocity of blood flow in the portal vein, cm/sec	13.82 ± 0.19	13.87 ± 0.16	>0.05
Index of liver density according to sonoelastography Me [Q1;Q3]	2.00 [1.00; 2.25]	2.0 [1.0; 2.0]	>0.05

Table 2. Comparative analysis of fibrosis stage by the results of elastography and other non-invasive methods, M ± m

Staging of liver fibrosis, points	Males	Females	P
Index of liver density according to sonoelastography	2.63 ± 0.05	2.49 ± 0.06	0.05
Bonacini discriminant score	2.29 ± 0.32	2.45 ± 0.25	>0.05
Fibrosis stage by Ishak score			
min	0.64 ± 0.34	0.63 ± 0.29	>0.05
max	2.5 ± 0.39	2.53 ± 0.32	>0.05
Fibrosis stage by METAVIR score			
min	0.43 ± 0.23	0.38 ± 0.18	>0.05
max	1.36 ± 0.25	1.33 ± 0.19	>0.05

Table 3. Results of comparative analysis of liver fibrosis stage in patients with type 2 DM and NAFLD by various non-invasive methods, n (%)

Method for determining liver fibrosis	Intensity of liver fibrosis	Males, n = 17	Females, n = 26	χ ²
Elastography	Mild fibrosis	12 (70.6 %)	15 (57.7 %)	0.05
	Moderate fibrosis	5 (29.4 %)	11 (42.3 %)	
METAVIR score	Mild fibrosis	11 (64.7 %)	17 (65.4 %)	0.88
	Moderate fibrosis	6 (35.3 %)	9 (34.6 %)	
Ishak score	Mild fibrosis	11 (64.7 %)	15 (57.7 %)	0.65
	Moderate fibrosis	6 (35.3 %)	11 (42.3 %)	

Table 4. Correlation analysis of the liver fibrosis staging results detected in patients with type 2 DM and NAFLD based on sonoelastography and other non-invasive methods (rxy ± mrx)

Correlation pairs	Results of elastography		
	All patients	Males	Females
Density index	0.77 ± 0.17, P < 0.001	0.77 ± 0.27, P < 0.01	0.76 ± 0.26, P < 0.05
Bonacini	0.68 ± 0.13, P < 0.001	0.61 ± 0.23, P < 0.05	0.73 ± 0.16, P < 0.001
Ishak min	0.36 ± 0.17, P < 0.05	0.20 ± 0.28	0.47 ± 0.21, P < 0.05
Ishak max	0.50 ± 0.16, P < 0.01	0.37 ± 0.27	0.59 ± 0.20, P < 0.01
METAVIR min	0.37 ± 0.16, P < 0.05	0.20 ± 0.28	0.48 ± 0.20, P < 0.05
METAVIR max	0.47 ± 0.15, P < 0.01	0.34 ± 0.27	0.57 ± 0.19, P < 0.01

Medical Association Declaration of Helsinki (1964–2000) and the Health Ministry of Ukraine Order No 281 dated 01.11.2000.

The study results were processed using Microsoft Excel 2010 and StatPlus Pro 5 (6.7.1.0). The adequacy of the parameters to normal distribution was tested using the Shapiro–Wilks and Kolmogorov–Smirnov tests. Descriptive statistics parameters for continuous variables were presented as the arithmetic mean and standard deviation. Results, which did not follow normal distribution, were expressed as median and interquartile range. The significance of differences was evaluated using Student's

t-criterion for independent samples in a normal distribution or the Mann-Whitney U-test for independent samples in a distribution different from normal. The relationship between two variables was measured by using Spearman correlation coefficient. A P value <0.05 was considered statistically significant.

Results

An assessment of the liver morphological state was performed and the stages of fibrosis were determined in patients with type 2 DM and NAFLD (Table 1). The degree of liver enlargement, its structure, the size of the total bile duct, splenic and portal veins, the velocity of blood flow in the portal vein, as well as the liver density index according to the sonoelastography, were evaluated.

This data demonstrates a liver enlargement of 1 cm to 6 cm, mainly of the right lobe. On average, it was 2.34 ± 0.37 cm in males and 1.59 ± 0.34 cm in females. There was no significant difference between men and women according to this indicator.

In the examined patients, the liver predominantly had a hyperechoic, coarse-grained structure that was diagnosed in 13 males (68.4 %) and 19 females (67.9 %). A hypoechoic liver structure was detected in 6 men (31.6 %) and 9 women (32.1 %). Such data testifies the development of fibrotic changes in the liver of patients with type 2 DM, which are typical for NAFLD.

The diameter of the total bile duct in men was on average 6.11 ± 0.02 mm, it was higher than that in women (6.22 ± 0.05). The mean diameters of the splenic vein in men and women were 6.79 ± 0.10 and 6.48 ± 0.13 mm, respectively. The portal vein diameter in the examined patients was 11.61 ± 0.17 for men and 11.59 ± 0.20 for women on average. The portal vein blood flow velocity in the examined patients was 13.82 ± 0.19 cm/sec in men and 13.87 ± 0.16 cm/sec in women on average. The liver density index according to the sonoelastography data in the examined men was 2.0 [1.00; 2.25] points, and in women this figure was 2.0 [1.0; 2.0] points as well.

A comparative analysis of the elastography results and detection of the liver fibrosis stage based on the Bonacini, Ishak and METAVIR scores was performed (Table 2).

The data given demonstrate that the liver density index by sonoelastography and results of other methods did not differ significantly in men and women. Thus, the stages of fibrosis according to the Bonacini discriminant score were 2.29 ± 0.32 points in males and 2.45 ± 0.25 in women. The detection of fibrosis stage according to the Ishak scores in the examined men and women was 0.64 ± 0.34 and 0.63 ± 0.29 points (minimum values) and 2.50 ± 0.39 and 2.53 ± 0.32 points (maximum values), respectively. The severity of fibrosis manifestations by the METAVIR score was estimated, on average, as 0.43 ± 0.23 points in males and 0.38 ± 0.18 points in women (minimum values) and 1.36 ± 0.25 points in males and 1.33 ± 0.19 points in women (maximum values).

The number of patients with mild and moderate liver fibrosis diagnosed according to various non-invasive techniques is presented in Table 3.

We can see that in the predominant number of examined patients with type 2 DM and NAFLD, a mild degree

fibrosis was diagnosed. According to the results of elastography, the proportion of such patients was 70.6 % of men and 57.7 % of women; by the METAVIR score – 64.7 % and 65.4 %, respectively; by the Ishak score – 64.7 % and 57.7 %, respectively. Thus, estimating the grade of liver fibrosis according to sonoelastography and other non-invasive methods allowed us to obtain similar results.

We also carried out a correlation analysis of the results of various methods for assessing the liver fibrosis stage in patients with type 2 DM and NAFLD (*Table 4*).

The results of liver fibrosis stage assessment in patients with type 2 DM and NAFLD according to sonoelastography were most strongly correlated with the results of the Bonacini classification (discriminant) score. The results of the Ishak and METAVIR scores had a moderate correlation with the sonoelastography data. It should also be noted that these scores determined the degree of fibrosis as a range from less to greater, but stronger correlation with the results of sonoelastography was found in patients with severe liver fibrosis.

Discussion

The real prevalence of NASH and fibrosis remains uncertain, as the diagnosis requires a liver morphological examination. The gold diagnostic standard for NAFLD is liver biopsy, which allows assessing the stage of fibrosis and determining the presence of steatosis or NASH [12, 13]. Methods of histological analysis include evaluation the fibrosis stage by Brunt [14], NASH CRN [15], HAI-Knodel score [16], Ishak [17], METAVIR [18] and others. Histological, histochemical and immunohistochemical methods of liver tissue study may provide important information about the liver fibrosis stage.

At the same time, the biopsy has significant disadvantages, which limit its use and cause patient refusal of it, therefore in recent years, more and more attention has been paid to the use of clinical non-invasive markers for assessing the liver fibrosis stage [19–21]. According to the Practical Recommendations of the European Association for the study of liver diseases and the EASL-EASD-EASO Clinical Recommendations for the diagnosis and treatment of NAFLD, biomarkers and liver fibrosis scores as well as ultrasound elastography are acceptable non-invasive methods for identifying cases with a low risk of severe liver fibrosis [22]. Thus, determination of the biomarkers level and use of ultrasound elastography can improve the accuracy of the diagnosis and avoid a number of liver biopsy.

There were many attempts to estimate the grade of liver fibrosis in patients with NAFLD. Liver biopsy is still used for its diagnosis, though this method has some disadvantages. None of known non-invasive methods can guarantee the most accurate diagnosis of NAFLD. That is why it is important to understand an ability of complex examination of patients using sonoelastography. The need for such an approach is emphasized by other authors [22].

The results of our study indicate that generally examined patients with type 2 DM and NAFLD had mild fibrosis (F0–F2). The evaluation of the liver fibrosis grade according to sonoelastography and other non-invasive methods (Bonacini, Ishak and METAVIR scores) allowed us to get comparable results. The results of assessing the liver

fibrosis stage in patients with type 2 DM and NAFLD by sonoelastography were most closely correlated with the results of the Bonacini classification (discriminant) score. The results of the Ishak and METAVIR scores were moderately correlated with the sonoelastography data. Strong correlations were detected for more severe hepatic fibrosis. That is why such methods have some limitations in the cases of mild liver fibrosis in patients with type 2 DM and NAFLD.

The results obtained indicate the importance of evaluating the criteria for the presence or absence of NAFLD in patients with type 2 DM, the need to determine the stages of NAFLD and the presence of liver fibrosis and its grade. The combination of ultrasound diagnosis, serum biomarkers and use of diagnostic scales is more informative and appropriate for assessing the liver fibrosis presence in patients with NAFLD, compared with separate use of these methods allowing reducing the frequency of invasive traumatic methods using. In the vast majority of examined patients with type 2 DM and NAFLD, mild fibrosis was diagnosed. The estimation of the liver fibrosis grade according to sonoelastography and other non-invasive methods allowed obtaining comparable results.

In order to estimate the stage of fibrosis in patients with NAFLD, it is advisable to use sonoelastography and the Bonacini discriminant score, which have similar significance complementing each other and contribute greatly to detecting the very early manifestations of liver fibrosis in patients with type 2 DM and NAFLD.

Conclusions

1. Generally, in the examined patients with type 2 DM and NAFLD, mild fibrosis (F0–F2) was diagnosed. The estimation of the liver fibrosis grade according to sonoelastography and other non-invasive methods (Bonacini, Ishak and METAVIR scores) allowed to get comparable results.

2. The results of liver fibrosis stage assessment in patients with type 2 DM in the presence of NAFLD according to sonoelastography were most strongly correlated with the results of the Bonacini classification (discriminant) score. The results of the Ishak and METAVIR scores had a moderate correlation with the sonoelastography data and strong correlations were detected in advanced stages of hepatic fibrosis.

Prospects for further research. It is planned to continue the study of various fibrosis markers and results of liver puncture biopsy.

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