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Non-alcoholic fatty liver disease: new additional non-invasive diagnostic markers and risks of comorbid diseases

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Abstract. ***Background.*** *Non-alcoholic fatty liver disease (NAFLD) is a pressing issue in modern society. While excess circulating glucose and insulin resistance contribute to its pathogenesis, the diagnosis poses particular challenges. The purpose of the study was to identify new additional non-invasive diagnostic markers of NAFLD and the risk of developing comorbid diseases in these patients.* ***Materials and methods.*** *The study involved 64 men aged 39 to 62 years: 35 patients were diagnosed with non-alcoholic fatty liver disease according to EASL-EASD-EASO guidelines, 29 patients comprised the control group. The results of complete blood count, biochemical blood tests, and abdominal ultrasound were evaluated in both groups.* ***Results.*** *Patients with NAFLD had significantly higher body weight and body mass index, higher glucose, HOMA-IR, total cholesterol, triglycerides, low-density lipoproteins, atherogenic index, alkaline phosphatase, gamma-glutamyl transferase, alanine aminotransferase, and aspartate aminotransferase. Additional non-invasive markers of NAFLD were high body mass index, HOMA-IR, total cholesterol, triglycerides, low-density lipoproteins, atherogenic index, and alanine aminotransferase, which may also indicate future risks of type 2 diabetes and hypertension.* ***Conclusions.*** *Among patients with NAFLD within three years, hypertension occurred in 22.2 % of cases and type 2 diabetes in 20.0 %, which is higher than in patients without NAFLD (8.7 and 4.3 %, respectively). We found that at the time of initial examination, patients with NAFLD had higher body weight and body mass index, as well as higher glucose, HOMA-IR, total cholesterol, triglycerides, low-density lipoproteins, atherogenic index, alkaline phosphatase, gamma-glutamyl transferase, alanine aminotransferase, and aspartate aminotransferase. From these metrics, we identified high body mass index, HOMA-IR, total cholesterol, triglycerides, low-density lipoproteins, atherogenic index, alkaline phosphatase as potential non-invasive risk markers for NAFLD. This highlights the importance of studying them for the early diagnosis of type 2 diabetes and hypertension, which could improve the treatment of this cohort of patients in the future.*

Keywords: *non-alcoholic fatty liver disease; type 2 diabetes; hypertension; obesity; non-invasive diagnostic markers*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a growing concern in modern society due to its high prevalence, which poses a threat to the health of millions of people [1]. This chronic condition encompasses a diverse spectrum of pathologies, from asymptomatic hepatic steatosis to necroinflammation, with or without centrilobular fibrosis, which can result in cirrhosis and other serious complications [2].

One of the pathogenetic links in the development of the condition, as mentioned above, is an excess of circulating glucose, which, due to the resistance of skeletal muscles to insulin, can be absorbed by the liver and serve as a source for new lipogenesis, particularly saturated long-chain fatty acids, resulting in the further deposition of lipids in the liver and the secretion of very low-density lipoprotein particles. This theory, namely that aging hepatocytes and adipocytes may contribute to the development of metabolic diseases, has been confirmed in recent studies [3]. The disorder most often occurs with obesity, insulin resistance, type 2 diabetes (T2D), dyslipidemia, hypertension, and metabolic syndrome [4]. At the same time, it has been shown that concomitant NAFLD significantly increases the risk of complications compared to the presence of T2D alone. Patients with chronic liver diseases and diabetes demonstrate higher mortality rates, in-

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cluding all-cause mortality, cardiovascular mortality, as well as mortality due to non-hepatic oncology [5]. The link between insulin resistance and hypothyroidism, which most often develops against the background of autoimmune thyroiditis, has been studied for a long time. Pathogenetic components of dysbacteriosis and various autoimmune disorders are frequently described, and it is believed that intestinal dysbacteriosis can trigger autoimmune thyroid diseases [6]. Wong et al. [8] described that patients suffering from non-alcoholic steatohepatosis have fecal dysbiosis with lower amounts of *Faecalibacterium* and *Anaerosporobacter* and higher amounts of *Parabacteroides* and *Allisonella*. Positive changes in intestinal microbiota, such as an increase in *Bacteroidetes* and a decrease in *Firmicutes*, correlate with improvement in patients with liver steatosis [8]. It was found that in case of fatty liver disease, already at the stage of steatosis, there is a shift in the composition of the intestinal microbiome with an increase in the total bacterial mass, a lower number of obligate strains, as well as an increase in opportunistic strains, which in turn, due to active participation in metabolic processes, can cause the progression of liver disease [9].

Diagnosing NAFLD is still a challenge. While liver ultrasound is the primary diagnostic method according to the latest guidelines, it has some drawbacks, such as subjective evaluation by the diagnostician, as well as low informativeness in the presence of a high degree of fibrosis or obesity with a body mass index (BMI) of more than 40.0 kg/m^2 [10–13]. Liver biopsy remains the gold standard. However, it is rarely performed for the NAFLD diagnosis as it is an expensive and invasive method and carries risks of sampling errors and serious complications [10, 13]. Considering the above, several non-invasive indices have been introduced in recent years. For their calculation, it is necessary to obtain anthropometric (BMI, waist circumference, etc.) and laboratory indicators (platelets, triglycerides, gamma-glutamine transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, etc.) [14–17], which, unfortunately, are not always simultaneously available to the physician.

The purpose of the study was to identify new additional non-invasive diagnostic markers of NAFLD and the risk of developing comorbid diseases in these patients.

Materials and methods

Following written informed consent to conduct a randomized comprehensive examination, 64 men aged 39 to 62 years (mean of 46.9 (45.0; 49.8) years) were enrolled. They were referred for a preventive annual check-up in 2020–2021 at the Communal Non-Commercial Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital" and Lviv Regional State Clinical Medical and Diagnostic Endocrinological Center. The non-inclusion criteria were the presence of alcoholic, medicinal, viral, autoimmune liver damage, and storage diseases.

All patients underwent a thorough examination for NAFLD following EASL-EASD-EASO (European Association for the Study of the Liver — European Association for the Study of Diabetes — European Association for the Study of Obesity) Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease [10] using liver ultrasound in the absence of apparent reasons for the secondary build-up of fats in the liver (alcohol abuse, use of hepatotoxic drugs, infection with viral hepatitis, autoimmune and hereditary diseases).

All patients underwent a standard abdominal ultrasound on a Siemens Acuson device (Siemens AG, Germany) with a 2–5 MHz convex probe under standard conditions (in the morning, on an empty stomach, in a horizontal position lying on the back) to detect functional and structural changes in the internal organs, evaluate the size of the liver, its outlines, structure, and echogenicity. Considering that the detection of liver steatosis using ultrasound is subjective due to the assessment of the intensity and specific patterns of echo signals by a doctor [18], we additionally calculated the recommended EASL-EASD-EASO indices of liver steatosis: fatty liver index [14], non-alcoholic fatty liver disease liver fat score [15], hepatic steatosis index for all patients [16].

The exclusion of alcoholic liver damage was based on reports of daily alcohol consumption at a minimum dose of 50.0 g of pure ethanol for a period of 2–5 years and screening for alcohol abuse (CAGE questionnaire — Cut down, Annoyed, Guilty, Eye-opener). Hepatitis B viral etiology was identified by analyzing serological markers of hepatitis B virus (HBsAg) and hepatitis C virus using serological markers of hepatitis C virus (anti-HCV). Additionally, the history of acute viral hepatitis was taken into consideration. Autoimmune reactions were evaluated based on the study of serological markers of autoimmune liver damage.

Thus, two groups of patients were formed: 35 patients with confirmed NAFLD using ultrasound and calculated indices of NAFLD (study group, SG) and 29 patients without confirmed NAFLD (control group, CG).

The following demographic and anthropometric data were considered for the study: patients' age, height, and body weight at the time of examination. BMI was calculated according to the A. Quetelet formula:

$$BMI = \frac{mass\ (kg)}{height^2\ (m^2)}.$$

A complete blood count was done using a Sysmex XN-530 analyzer (Sysmex Corporation, Japan) to evaluate the hemoglobin level, the number of red blood cells, and platelets. Biochemical blood serum parameters were analyzed with an automatic analyzer Beckman Coulter AU680 (USA). The levels of total protein, total bilirubin, creatinine, urea, uric acid, glucose, total cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), alkaline phosphatase, GGT, ALT, and AST were determined. Moreover, all patients were examined using the homeostasis model assessment (HOMA). Variants of the HOMA are calculated differently [20]; our study used HOMA of insulin resistance (HOMA-IR).

It is calculated according to the formula:

$$HOMA\text{-}IR = \frac{fasting\ glycemia\ (mmol/L) \times \times\ fasting\ insulin\ (\mu U/mL)}{22.5},$$

where the constant 22.5 as a normalizing factor is formed from the product of the average fasting insulin content, which is 5 μU/ml, and fasting glucose with a level of 4.5 mmol/L.

The HOMA-IR < 2.5 indicates the absence of insulin resistance.

Additionally, the atherogenic index (AI) was calculated according to the formula:

$$AI = \frac{total\ cholesterol\ (mmol/L) - HDL\ (mmol/L)}{HDL\ (mmol/L)}.$$

AI above 3 is considered to be elevated.

The study was conducted in three steps. In the first step, we analyzed patient data obtained 3 years following the first detected NAFLD regarding the manifestation of type 2 diabetes and hypertension. In the second step, some anthropometric and laboratory indicators, and their peculiarities in patients with and without NAFLD were analyzed retrospectively, and in the third step, new additional non-invasive diagnostic markers of NAFLD were discovered.

The data was processed on a personal computer in Microsoft Excel using descriptive statistics and Student's t-test. The statistical reliability of the markers was evaluated using the SPSS software based on contingency tables with the calculation of indicators of diagnostic value. The correlation between steatosis and the indicator studied was considered confirmed by a module if the association coefficient exceeded 0.5 (or 0.3 for the contingency coefficient). The obtained results were presented as M (p_1; p_2), where M is the arithmetic mean, p_1 is the lower limit of the 95% confidence interval of the arithmetic mean, p_2 is the upper limit of the 95% confidence interval of the arithmetic mean. The difference was considered statistically significant if $p < 0.05$.

Results

During the follow-up of patients of both groups after 3 years, we found that hypertension occurred in 2 patients of the CG (8.7 %) and 10 patients of the SG (22.2 %). Type 2 diabetes manifested in 1 patient of the CG (4.3 %) and 9 patients of the SG (20.0 %).

Table 1 represents the results of the assessment of anthropometric and some laboratory characteristics in patients with NAFLD at the time of the initial examination.

As can be seen from Table 1, there was a statistically significant difference between body mass (86.9 (82.2; 91.5) kg vs. 65.8 (61.4; 67.8) kg) and, accordingly, the indicator derived from it, BMI (28.8 (27.7; 29.8) kg/m^2 versus 22.0 (21.2; 22.9) kg/m^2). Additionally, we found a statistically significant difference between the following laboratory indicators: glucose (4.95 (4.7; 5.2) mmol/L vs. 4.4 (4.1; 4.7) mmol/L), the HOMA-IR (6.2 (4.9; 7.4) units vs. 1.8 (1.5; 2.1) units), total cholesterol (5.8 (5.4; 6.2) mmol/L vs. 4.1 (3.7; 4.5) mmol/L), triglycerides (2.1 (1.8; 2.4) mmol/L vs. 1.1 (1.0; 1.3) mmol/L), LDL (4.1 (3.7; 4.5) mmol/L vs. 2.8 (2.6; 3.1) mmol/L), AI (4.9 (4.2; 5.5) units vs. 2.4 (2.0; 2.8) units), alkaline phosphatase (101.7 (87.4; 116.0) U/L vs. 81.2 (74.3; 88.0) U/L), GGT (45.4 (29.1; 61.8) U/L vs. 16.8 (11.3; 22.2) U/L), ALT (71.6 (40.1; 103.1) U/L vs. 18.0 (14.4; 21.6) U/L) and AST (45.2 (31.8; 58.6) U/L vs. 27.1 (20.9; 33.4) U/L). However, we did not find significant differences between the two groups for other laboratory parameters, such as hemoglobin, red blood cells, platelets, total protein, total bilirubin, creatinine, urea, uric acid, and HDL.

The next step of the study is a statistical analysis by calculating the chances of making a correct diagnosis of NAFLD using a separate indicator — a marker. The reliable probability of diagnosis was determined using indicators of diagnostic value: sensitivity, specificity, and accuracy. Based on them, the odds ratio is defined — a number that shows how much the absence or presence of a specific outcome is associated with the presence or absence of a particular disease in a statistical group, and the coefficient of association (or contingency), which characterizes how close the stochastic relationship between qualitative traits — alternative random variables is. The results of the study of sensitivity, specificity, accuracy, and coefficient of association (or con-

Table 1. Anthropometric and laboratory characteristics of patients with NAFLD at the time of initial examination

Parameter	SG	CG
Body mass, kg	86.9 (82.2; 91.5)*	65.8 (61.4; 67.8)
Height, cm	179.1 (176.6; 181.6)	178.3 (176.0; 183.9)
BMI, kg/m^2	28.8 (27.7; 29.8)*	22.0 (21.2; 22.9)
Glucose, mmol/L	4.95 (4.7; 5.2)*	4.4 (4.1; 4.7)
HOMA-IR, units	6.2 (4.9; 7.4)*	1.8 (1.5; 2.1)
Total cholesterol, mmol/L	5.8 (5.4; 6.2)*	4.1 (3.7; 4.5)
Triglycerides, mmol/L	2.1 (1.8; 2.4)*	1.1 (1.0; 1.3)
LDL, mmol/L	4.1 (3.7; 4.5)*	2.8 (2.6; 3.1)
AI, units	4.9 (4.2; 5.5)*	2.4 (2.0; 2.8)
Alkaline phosphatase, U/L	101.7 (87.4; 116.0)*	81.2 (74.3; 88.0)
GGT, U/L	45.4 (29.1; 61.8)*	16.8 (11.3; 22.2)
ALT, U/L	71.6 (40.1; 103.1)*	18.0 (14.4; 21.6)
AST, U/L	45.2 (31.8; 58.6)*	27.1 (20.9; 33.4)

Note: * — p < 0.05 according to Student's t-test, compared to CG values.

Table 2. New additional non-invasive diagnostic markers of NAFLD

Parameter	Sensitivity, %	Specificity, %	Accuracy, %	Association (contingency) coefficient
BMI	88.9	95.5	91.0	0.98*
Glucose	16.7	100.0	37.5	0.21
HOMA-IR	80.0	85.7	81.6	0.92*
Total cholesterol	75.0	86.7	79.1	0.90*
Triglycerides	60.7	66.7	62.8	0.51*
LDL	22.2	100.0	50.0	0.30*
AI	88.9	80.0	85.7	0.93*
Alkaline phosphatase	23.1	100.0	46.4	0.29
GGT	23.1	100.0	48.3	0.29
ALT	51.1	95.7	66.2	0.92*
AST	31.1	82.6	48.5	0.36

Note: * — statistically confirmed correlation between the marker and the risk of NAFLD.

tingency) of anthropometric and laboratory parameters, which differ significantly in the groups, — markers, are given in Table 2.

Based on the data collected, it has been found that only BMI and some laboratory parameters can be considered additional non-invasive risk markers for the presence of NAFLD. BMI equal to or greater than 25.0 kg/m^2 with a sensitivity of 88.9 %, specificity of 95.5 %, and accuracy of 91.0 % suggests the presence of NAFLD. HOMA-IR above 2.5 units, with a sensitivity of 80.0 %, specificity of 85.7 %, and accuracy of 81.6 % suggests the diagnosis of NAFLD. Moreover, some blood lipids, such as total cholesterol, triglycerides, and LDL, have a diagnostic value. Hypercholesterolemia with a sensitivity of 75.0 %, specificity of 86.7 %, and accuracy of 79.1 % indicates the risk of NAFLD. Similarly, an increased level of triglycerides with a sensitivity of 60.7 %, specificity of 66.7 %, and accuracy of 62.8 %, and high LDL with a sensitivity of 22.2 %, specificity of 100.0 % and accuracy of 50.0 % suggest the presence of the studied disease. Accordingly, increased AI confirms NAFLD with a sensitivity of 88.9 %, specificity of 80.0 %, and accuracy of 85.7 %. Among cytolysis markers, only ALT with a sensitivity of 51.1 %, specificity of 95.7 %, and accuracy of 66.2 % indicates the presence of NAFLD.

Discussion

It has been reported that NAFLD poses a significant threat to the health of millions [1]. The association of the disease with obesity, insulin resistance, hypertension, and dyslipidemia has also been described [1, 10–13, 19], which we were able to confirm. Our research group reported a clear causal association between NAFLD and hypertension, as well as type 2 diabetes. Throughout a three-year follow-up observation, we have recorded the occurrence of these diseases in patients with NAFLD.

However, the problem of NAFLD is urgent not only because it is associated with severe diseases and diagnosing it can be difficult. While liver ultrasound is recognized as a first-line method for diagnosing NAFLD, it can sometimes be subjective and insufficiently informative [10]. Significant advances in diagnosing NAFLD were made by introducing non-invasive indices that consider anthropometric and laboratory parameters [14–17] in the diagnostic process. However, this process is imperfect and often requires a comprehensive list of variables. Considering that and given the impact of NAFLD on a patient's quality of life and life expectancy, we have suggested additional markers that can independently indicate the risk of NAFLD in a patient. They can prompt doctors to examine the patients additionally and more thoroughly.

It should be noted separately that the results obtained in our study are in line with the newly proposed diagnostic criteria of metabolic-associated fatty liver disease. This new nosology is being suggested as a replacement for NAFLD. The scientific community is actively discussing the introduction of a new term and its criteria — metabolic-associated fatty liver disease. At this point, a consensus among experts is yet to be reached. Introducing or excluding a new term requires additional cohort-controlled studies in compliance with the principles of evidence-based medicine [20].

According to our retrospective review and statistical analysis, patients with NAFLD typically have higher body weight and BMI, as well as elevated levels of glucose, HOMA-IR, total cholesterol, triglycerides, LDL, AI, alkaline phosphatase, GGT, ALT, and AST. Accordingly, we can suggest that parameters, which differed reliably in both groups, can be used as risk markers for the development of NAFLD. While these indicators are closely related to liver steatosis, their cause-and-effect relationship with NAFLD remains open.

The results of our statistical analysis confirm the significance of the chosen approach and indicate the possibility of improving the process of NAFLD diagnosis. An important stage of further research can be the development of even more accurate and affordable methods for determining the characteristics of this disease, which will aid in improving early diagnosis and the effectiveness of NAFLD treatment.

Conclusions

We have found that patients with NAFLD have higher body weight and BMI, as well as higher levels of glucose, HOMA-IR, total cholesterol, triglycerides, LDL, AI, alkaline phosphatase, GGT, ALT, and AST. Among these parameters, additional non-invasive markers of NAFLD include high BMI, HOMA-IR, total cholesterol, triglycerides, LDL, AI, and ALT, which may also indicate the risk of T2D and hypertension development in this cohort of patients.

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Неалкогольна жирова хвороба печінки: нові додаткові неінвазивні діагностичні маркери та ризики розвитку коморбідних захворювань

Резюме. ***Актуальність.*** Неалкогольна жирова хвороба печінки (НАЖХП) є актуальною проблемою сучасного суспільства, у патогенезі якої особливу роль відіграють надлишок циркулюючої глюкози та інсулінорезистентність, а її діагностування викликає певні труднощі. ***Мета:*** виявити нові додаткові неінвазійні діагностичні маркери в пацієнтів із НАЖХП та ризик розвитку в них коморбідних захворювань. ***Матеріали та методи.*** У дослідження залучено 64 чоловіки віком від 39 до 62 років: у 35 встановлено діагноз неалкогольної жирової хвороби печінки згідно з рекомендаціями EASL-EASD-EASO, 29 осіб увійшли в контрольну групу. В обох групах оцінювали результати загального, біохімічного аналізів крові та ультразвукового обстеження органів черевної порожнини. ***Результати.*** У пацієнтів із НАЖХП були вірогідно вищими маса тіла та індекс маси тіла, вищими — індекс HOMA, рівні глюкози, загального холестерину, тригліцеридів, ліпопротеїнів низької щільності, лужної фосфатази, гамма-глутамінтрансферази, аланінамінотрасферази, аспартатамінотрансферази й коефіцієнт атерогенності. Усі інші лабораторні показники вірогідно не відрізнялися в обох групах. Додатковими неінвазивними маркерами НАЖХП були високі індекс маси тіла, індекс HOMA, рівні загального холестерину, тригліцеридів, ліпопротеїнів низької щільності, аланінамінотрансферази й коефіцієнт атерогенності, що також може вказувати на ризики розвитку в майбутньому цукрового діабету 2-го типу та артеріальної гіпертензії. ***Висновки.*** Серед пацієнтів із НАЖХП протягом трьох років артеріальна гіпертензія виникала в 22,2 % випадків, а ЦД 2-го типу — у 20,0 %, що вище, ніж в осіб без НАЖХП (8,7 і 4,3 % відповідно). Виявлено, що на момент першого обстеження пацієнти з НАЖХП мали наступні вищі параметри: маса тіла та індекс маси тіла, рівні глюкози, HOMA-IR, загального холестерину, тригліцеридів, ліпопротеїнів низької щільності, лужної фосфатази, гамма-глутамілтрансферази, аланінамінотрансферази, аспартатамінотрансферази та індекс атерогенності. З цих показників високий індекс маси тіла, HOMA-IR, загальний холестерин, тригліцериди, ліпопротеїни низької щільності, індекс атерогенності й лужна фосфатаза є потенційними неінвазивними маркерами ризику НАЖХП. Це підкреслює важливість їх вивчення для ранньої діагностики ЦД 2-го типу та артеріальної гіпертензії, що може покращити лікування цієї когорти пацієнтів у майбутньому.

Ключові слова: неалкогольна жирова хвороба печінки; цукровий діабет 2-го типу; артеріальна гіпертензія; ожиріння; неінвазивні діагностичні маркери