FEATURES OF THE COURSE OF NON-ALCOHOLIC FATTY LIVER DISEASE INTYPE 2 DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

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Abstract

Background. Non-alcoholic fatty liver disease and type 2 diabetes mellitus or impaired glucose tolerance are common diseases with a high risk of developing cardiovascular diseases, the leading cause of disability and death. Our aim is to develop new methods for screening, prevention, and treatment of cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes mellitus, and impaired glucose tolerance.

Methods and methods. This study is single-center, open-label, uncontrolled, diagnostic study. Between 2023 and February 2024, 216 patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance were selected at Heart Center "University Medical Center" Corporate Fund.

Results. All examined patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease showed increased liver enzyme activity. Blood lipid profile indicators were significantly higher than optimal levels for patients with cardiovascular diseases. There was also a significant increase in liver enzymes, C-reactive protein, triglycerides, and lipoproteins in patients with cardiovascular diseases and non-alcoholic fatty liver disease combined with type 2 diabetes and impaired glucose tolerance.

Conclusion. Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis showed significant increases in these indicators in patients with cardiovascular diseases and non-alcoholic fatty liver disease, especially in the presence of type 2 diabetes and impaired glucose tolerance. All examined patients showed increased liver enzyme activity and lipid levels, indicating the impact of these diseases on the liver and metabolism.

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The authors declare no potential conflict of interest requiring disclosure in this article.

Key words:
Non-Alcoholic Fatty Liver Disease, Type 2 Diabetes, Glucose Tolerance, Cardiovascular Diseases, Metabolic Syndrome.

Бауырдың алкогольсіз майлы ауруларының үдерістерінің ерекшеліктері 2 типті қант диабеті және глюкозаға төзімділіктің бұзылуы

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Тұжырым

Өзектілігі. Бауырдың алкогольсіз майлы ауруы және 2 типті қант диабеті немесе глюкозаға төзімділіктің бұзылуы -бұл жүрек-қан тамырларыауруларының даму

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Түйін сөздер:
Бауырдың алкогольсіз майлы ауруы, 2 Типті қант диабеті, Глюкозаға төзімділігі, Жүрек-Қан тамырлары аурулары, метаболикалық синдром.

қаупі жоғары жалпы аурулар, мүгедектік пен өлімніңнегізгі себебі. Біздің мақсатымыз-жоғарыда аталған аурула диагнозы қойылған бар науқастарда жүрек қан тамыр ауруларының скринингінің, алдын алудың және емдеудің жаңа әдістерін әзірлеу.

Методология және әдістеме. Бұл зерттеу бір орталықты, ашық, бақыланбайтын, диагностикалық болып табылады. 2023-2024 жылғы ақпан аралығында "University Medical Center" корпоративтік қорының жүрек орталығында жүрек-қан тамырлары аурулары және бауырдың алкогольсіз майлы ауруы, 2 типті қант диабеті және глюкозаға төзімділік бұзылыстары бар 216 пациент іріктелді.

Нәтиже. Жүрек-қан тамырлары аурулары және бауырдың алкогольсіз майлы аурулары бар барлық тексерілген науқастарда бауыр ферменттерінің белсенділігі жоғарылаған. Қандағы липидті профиль көрсеткіштері жүрек-қан тамырлары аурулары бар науқастар үшін оңтайлы деңгейден едәуір жоғары болды. Сондай-ақ, 2 типті қант диабетімен және глюкозаға төзімділіктің бұзылуымен бірге жүрек-қан тамырлары аурулары мен алкогольсіз майлы бауыр аурулары бар науқастарда бауыр ферменттерінің, С-реактивті ақуыздың, триглицеридтердің және кіші липопротеин деңгейінің айтарлықтай жоғарылауы байқалды.

Қортынды. Зерттеу көрсеткендей, алкогольсіз майлы бауыр ауруы, 2 типті қант диабеті және глюкозаға төзімділігі бұзылған науқастарда стеатогепатит пен фиброздың жоғарылауы байқалады, бұл ерлерде де, әйелдерде де жүрек-қан тамырлары асқынуларының дамуын болжауы мүмкін. Бауыр ферменттерінің белсенділігі, С-реактивті ақуыз, глюкоза және липидті профильді талдау жүрек-қан тамырлары аурулары және алкогольсіз майлы бауыр аурулары бар емделушілерде, әсіресе 2 типті қант диабеті және глюкозаға төзімділіктің бұзылуы кезінде бұл көрсеткіштердің айтарлықтай жоғарылағанын көрсетті.. Барлық тексерілген емделушілерде бауыр ферменттерінің белсенділігі мен липидтер деңгейінің жоғарылауы байқалды, бұл осы аурулардың бауыр мен метаболизмге әсерін көрсетеді.

Особенности течения неалкогольной жировой болезни печени при сахарном диабете 2 типа и нарушении толерантности к глюкозе

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Анотация

Фон. Неалкогольная жировая болезнь печени и сахарный диабет 2 типа или нарушение толерантности к глюкозе являются распространёнными заболеваниями с высоким риском развития сердечно-сосудистых заболеваний, основной причиной инвалидности и смерти. Наша цель - разработать новые методы скрининга, профилактики и лечения сердечно-сосудистых заболеваний у пациентов с вышеуказанными заболеваниями.

Методы и методология. Данное исследование является одно-центровым, открытым, неконтролируемым, диагностическим. В период с 2023 по февраль 2024 года в Кардиологическом центре «Университетский медицинский центр» Корпоративного фонда отобрано 216 пациентов с сердечно-сосудистыми заболеваниями и сопутствующей неалкогольной жировой болезнью печени, сахарным диабетом 2 типа и нарушением толерантности к глюкозе.

Результаты. У всех обследованных больных с сердечно-сосудистыми заболеваниями и сопутствующей неалкогольной жировой болезнью печени выявлено повышение активности печеночных ферментов. Показатели липидного профиля крови достоверно превышали оптимальные уровни для пациентов с сердечно-сосудистыми заболеваниями. Также отмечено достоверное увеличение ферментов печени, С-реактивного белка, триглицеридов и малого липопротеина у пациентов с сердечно-сосудистыми заболеваниями и неалкогольной жировой болезнью печени в сочетании с сахарным диабетом 2 типа и нарушением толерантности к глюкозе.

Выводы. Анализ активности ферментов печени, С-реактивного белка, глюкозы и липидограммы показал достоверное увеличение этих показателей у пациентов с сердечно-сосудистыми заболеваниями и неалкогольной жировой болезнью печени, особенно при наличии сахарного диабета 2 типа и нарушения толерантности к глюкозе. У всех обследованных больных наблюдалось повышение активности ферментов печени и уровня липидов, что свидетельствует о влиянии этих заболеваний на печень и обмен веществ.

Introduction

Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT) are widespread diseases, each of which increases the risk of developing and progressing cardiovascular diseases (CVD), the main cause of premature disability and death in industrialized countries. Given the long asymptomatic course of both diseases and their impact on the patients' quality and longevity of life, screening for timely diagnosis and necessary therapy is essential.

Diabetes mellitus is one of the most pressing issues in modern medicine. According to the World Health Organization (WHO), this disease will rank 7th among all causes of mortality by 2030. In the absence of timely treatment, diabetes leads to damage to almost all organs and systems, with the development of macro- and micro vascular complications, causing disability and premature death.

Non-alcoholic fatty liver disease is recognized as a major component of metabolic syndrome and a primary risk factor for cardiovascular diseases, and in some studies, it even determines their outcome. The combination of type 2 diabetes mellitus and non-alcoholic fatty liver disease in a patient increases the risk of developing cardiovascular diseases by 53% and cirrhosis and hepatocellular carcinoma by 2–2.5 times.[1,2] Among patients with type 2 diabetes mellitus, the frequency of cardio- and cerebrovascular diseases, peripheral vascular lesions, as well as nephro- and retinopathy, is significantly higher when combined with non-alcoholic fatty liver disease.[3]

The goal of our study was to develop new methods for screening, prevention, and treatment of cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance.

Materials and Methods

This study is single-center, open-label, uncontrolled, diagnostic study.Between 2023 and February 2024, 216 patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance were selected at Heart Center "University Medical Center" Corporate Fund.

Inclusion criteria: patients from 18 to 65 years old, diagnosed with type 2 diabetes mellitus, impaired glucose tolerance, NAFLD and liver fibrosis.

Exclusion criteria: patients who did not sign informed consent, children and pregnant women.

Ethical approval This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Before commencing the research, approval was obtained from the Local Bioethics Committee of the Corporate Fund "University Medical Center" 2023/01-008 of 05.07.2023.

Statistical analysis Data were analyzed using IBM SPSS Statistics software (IBM SPSS Inc.). Numerical vari-

ables were expressed as mean ± SD and categorical variables as numbers and percentages. Nonparametric statistics were performed for dataset analysis. Between-group comparisons were assessed for numerical variables, and the Chi-square test was used for categorical variables and the corresponding causal relationship was evaluated by calculating the odds ratio (OR). P value ⩽0.05 was considered statistically significant.

Results

Study participants and diagnostic groups were divided according to Table 1.

Table 1.
Characteristics of patients with non-alcoholic fatty liver disease

Characteristics	Men (n=90)	Women (n=126)	Chi-squared	P value
Type 2 Diabetes	24 (11.1%)	14 (6.5%)	0,214	0,643
Impaired Glucose Tolerance	19 (8.8%)	7 (3.2%)	0.228	0.632
Non-alcoholic Fatty Liver Disease	110 (50.9%)	76 (35,2%)	4.462*	0.035*
Liver Fibrosis	99 (45,8%)	75 (34.7%)	2.161	0.142
*Chi-squared -test statistical significance; P⩽0.05 was considered statistically significant				

The definition of non-alcoholic fatty liver disease was adapted based on AASLD recommendations. We defined non-alcoholic fatty liver disease as the presence of steatosis - the absence of significant alcohol consumption (⩾2 portions per day for men, ⩾3 portions per day for women). The presence of steatosis in non-alcoholic fatty liver disease was quantified using either the Fatty Liver Index (FLI) or the US Fatty Liver Index (US-FLI) with threshold values ⩾60 and ⩾30,[4] respectively. Diabetes was defined as hemoglobin A1c (HbA1c) ⩾6.5%, fasting plasma glucose ⩾7 mmol/L, self-assessment of diabetes, or use of antidiabetic drugs. Impaired glucose tolerance was defined as HbA1c in the range of 5.7–6.5% or fasting plasma glucose in the range of 5.6–7 mmol/L. Non-invasive tests (NITs) for fibrosis included the Aspartate Aminotransferase to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) index, and NAFLD fibrosis score. These tests have an area under the curve (AUC) accuracy of 0.74 - 0.80 and 0.75–0.82, respectively, for diagnosing advanced fibrosis.[5,6,7] Lean patients were defined as having a body mass index (BMI) <23 kg/m^{2}for Asians and BMI <25 kg/m^2 for other races. Patients were considered overweight if their BMI was in the range of 23–27.5 kg/m^2 for Asians and 25–30 kg/m^2 for other races. Obese patients were defined as BMI >27.5 kg/m^2 for Asians and BMI >30 kg/m^2 for other races.[8,9]

Table 2.
Liver stiffness and fibrosis assessment

NAFLD / NASH	**CAP Assessment**	**Steatosis Degree**	**Liver area affected by fatty changes**
	≤238 dB/m	S 0	Normal
	238–260 dB/m	S 1	Lessthan ⅓ (from 11% to 33%)
	260–290 dB/m	S 2	From ⅓ to ⅔ (from 34% to 66%)
	290–400 dB/m	S 3	More than ⅔ (67%)
NAFLD / NASH	kPa Assessment	Fibrosis Degree	Liver area affected by scarring
	2–7 kPa	F0–F1	Normal, minimal
	7.5–10 kPa	F2	Moderates carring
	10–14 kPa	F3	Severes carring
	≥14 kPa	F4	Cirrosis

NAFLD - non-alcoholic fatty liver disease
NASH - non-alcoholic steatohepatitis

According to Table 1, the presence of non-alcoholic fatty liver disease shows a correlation with an increased risk of developing type 2 diabetes, as well as new convincing evidence that the risk varies with the severity of non-alcoholic fatty liver disease. However, it can be confirmed that patients without type 2 diabetes but with non-alcoholic fatty liver disease are also at increased risk of developing type 2 diabetes. The presence and severity of non-alcoholic fatty liver disease are independent risk factors for developing type 2 diabetes.

A fibroscan was performed on 186 patients (women - 76, men - 110), and the assessment of liver stiffness and fibrosis was conducted according to Table 2. The results of the patients are presented in Table 3.

Table 3.
Fibroscan test

Fibroscan	Men (n=110)	Women (n=76)	OR	95%CI	Z statistic	P value
Steatosis Degree						
S0	26 (14.0%)	16 (8.6%)	1.161[α]	[0.57;2.35]	0.414	0.679
S1	20 (10.8%)	12 (6.5%)	1.185[α]	[0.54;2.59]	0.425	0.671
S2	35 (18.8%)	22 (11.8%)	1.145[α]	[0.61;2.17]	0.417	0.676
S3	29 (15.6%)	26 (14.0%)	0.688[β]	[0.36;1.31]	1.150	0.250
Fibrosis Degree						
F0	47 (25.3%)	30 (16.1%)	1.143[α]	[0.63;2.07]	0.443	0.658
F1	39 (21.0%)	29 (15.6%)	0.890[β]	[0.48;1.63]	0.376	0.707
F2	20 (10.8%)	12 (6.5%)	1.189[α]	[0.54;2.59]	0.425	0.671
F3	4 (2.2%)	5 (2.7%)	0.536[β]	[0.14;2.06]	0.907	0.365
Odds ratio: α - OR=1 means that the odds are equal in both groups; β - OR<1 means that the event is directly related and has a chance of occurring in the second group z test statistical not significance P≥0.05						

The chance of developing severe forms of fibrosis stages F2 and F3 in men and women is almost equal, OR = 0.965, 95%CI [0.48;1.96], z = 0.09, p = 0.929. Women are more likely to develop severe forms of steatosis stages S2 and S3 than men, OR = 0.812, 95%CI [0.45;1.47], z = 0.68, p = 0.496.

From the data in Table 1 and Table 2, patients with type 2 diabetes and impaired glucose tolerance showed the following steatohepatitis results: S0 - absence of steatosis in 16 women (21.0%) and 26 men (23.6%). S1 - minimal steatosis in 12 women (15.7%) and 20 men (18.1%). S2 - moderate steatosis in 22 women (28.9%) and 35 men (31.8%). S3 - severe steatosis in 26 women (34.2%) and 29 men (26.3%).

Fibrosis: F0 - absence of fibrosis in 30 women (39.4%) and 47 men (42.7%). F1 - minimal fibrosis in 29 women (38.1%) and 34 men (30.9%). F2 - moderate fibrosis in 12 women (15.7%) and 14 men (12.7%). F3 - severe fibrosis in 4 women (5.2%) and 4 men (3.6%).

Analysis of patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance showed an exacerbation of the degree of steatohepatitis and fibrosis, which can be assessed as predictors of cardiovascular complications in both men and women.

Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis: ALT 25.20 (±17.8 U/L), AST 21.66 (±9.25 U/L), total bilirubin 3.41 (±23.20 mg/dL), direct bilirubin 0.18 (±0.12 mg/dL), CRP 057 (±2.82 mg/dL), glucose 112.35 (±39.17 mg/dL), glycated hemoglobin 5.82 (±1.61%), total cholesterol 196.2 (±43.93 mg/dL), LDL 132.71 (±3656 mg/dL), HDL 49.27 (±12.45 mg/dL), TG 143.30 (±89.58 mg/dL), apoA 1.29 (±0.63 g/L), apoB 1.09 (±1.27 g/L), LP (a) 37.01 (±49.95 mg/dL).

All examined patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease showed increased liver enzyme activity (ALT,

AST, total bilirubin). Blood lipid profile indicators were significantly higher than optimal levels for patients with cardiovascular diseases. There was also a significant increase in liver enzymes, C-reactive protein, triglycerides, and LP(a) in patients with cardiovascular diseases and non-alcoholic fatty liver disease combined with type 2 diabetes and impaired glucose tolerance. Therefore, overweight and obesity, non-alcoholic fatty liver disease can be considered predictors of type 2 diabetes and impaired glucose tolerance.

Discussion

Liver damage in this disease is characterized by fatty degeneration (steatosis) with inflammation and hepatocyte damage (non-alcoholic steatohepatitis, NASH) and fibrosis development. There is a risk of non-alcoholic fatty liver disease progressing to cirrhosis. In 75% of cases, non-alcoholic fatty liver disease is associated with obesity, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, or impaired glucose tolerance.[3,10,11]These pathological processes are risk factors for the progression of atherosclerosis and the development of cardiovascular diseases. Patients with type 2 diabetes mellitus have a higher risk of severe liver disease compared to patients without diabetes.[3] In this case, we are talking about primary non-alcoholic fatty liver disease associated with obesity and carbohydrate and lipid metabolism disorders.

Studies of the frequency and structure of liver damage in patients with abdominal obesity and metabolic syndrome have shown that signs of non-alcoholic fatty liver disease at the steatosis stage are detected in 89% of cases in patients with abdominal obesity, and in 100% of cases in patients with early carbohydrate metabolism disorders and type 2 diabetes mellitus.[12]

Non-alcoholic fatty liver disease is characterized by the excessive accumulation of triglycerides and other cholesterol derivatives in hepatocytes due to an imbalance between the synthesis and utilization of these organic molecules. Non-alcoholic fatty liver disease includes non-alcoholic steatosis and non-alcoholic steatohepatitis (NASH); the latter encompasses a wide spectrum of diseases of varying severity, including fibrosis, cirrhosis, and hepatocellular carcinoma.[1,3]

There is no single proven mechanism for the development of non-alcoholic fatty liver disease. According to one model, the "two-hit" theory, the first "hit" is the excessive influx of free fatty acids (FFAs) into the liver, causing the "second hit" - oxidative stress, which in turn leads to the development of non-alcoholic steatohepatitis and fibrosis.[13] The "first hit" can be induced by tissue insulin resistance. Normally, postprandial insulin elevation leads to reduced lipolysis by inhibiting lipase, decreasing the content of free fatty acids in the blood plasma and liver. However, in the presence of insulin resistance (IR), the opposite process occurs: lipolysis is enhanced, releasing an increased amount of free fatty acids that induce oxidative stress development. Insufficient oxidation of free fatty acids leads to excessive triglyceride accumulation in the liver, secretion of increased amounts of very low-density lipoproteins, and hepatocyte death, resulting in elevated transaminase levels and subsequent fibrosis and cirrhosis.

Bile acids (BAs) are steroid monocarboxylic acids derived from cholanic acid. They are produced in the smooth endoplasmic reticulum of hepatocytes and secreted by liver epithelial cells. Bile acid biosynthesis is one of the important pathways for cholesterol elimination. The human bile acid pool is approximately equally represented by highly hydrophobic cholic, chenodeoxycholic, and deoxycholic acids. Primary bile acids are conjugated with glycine and taurine, increasing their hydrophilicity. They activate nuclear receptors regulating the expression of genes involved in the secretion, transport, and metabolism of primary bile acids, cholesterol, and triglycerides in hepatocytes and plasma.[1,12]In type 2 diabetes mellitus and insulin resistance, bile acid endocrine function is impaired, reducing their absorption, increasing liver fat in-

filtration, disrupting lipid metabolism in the liver and plasma, and accumulating triglycerides and low-density lipoproteins (LDLs). Biliary insufficiency develops, reducing the amount of bile and circulating bile acids, leading to fatty liver disease and cholelithiasis.[2,3]

According to the American Association for the Study of Liver Diseases (AASLD), the global prevalence of non-alcoholic fatty liver disease ranges from 6.3% to 33%, and non-alcoholic steatohepatitis from 3% to 5%, depending on the studied population and examination method.[3]

Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes by 1.5–5.5 times.[12] The prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes is 70–90%.[14] The prevalence of non-alcoholic fatty liver disease also increases with increasing body mass index (BMI): with morbid obesity, almost all patients have non-alcoholic fatty liver disease, with steatohepatitis in 25–70%. With the combination of obesity and type 2 diabetes, non-alcoholic fatty liver disease is found with a frequency of 5–20% to 75%, according to various authors.[13,15] Non-alcoholic fatty liver disease is not only associated with other components of metabolic syndrome - arterial hypertension, dyslipidemia, but is also its "unofficial" component. Non-alcoholic fatty liver disease, like type 2 diabetes, is a proven risk factor for cardiovascular diseases, increasing the occurrence of cardiovascular events and mortality by 1.2–6.2 times.[12,13,16,17]

Since there is no definitive answer as to whether insulin resistance and hyperglycemia (type 2 diabetes) are causes or complications of non-alcoholic fatty liver disease,[14] the overall relationship between non-alcoholic fatty liver disease and type 2 diabetes can be described as a "two-way street".[13] On one hand, non-alcoholic fatty liver disease precedes the development of type 2 diabetes, with its presence associated with an increased risk of the latter, the degree of risk being directly proportional to the severity of non-alcoholic fatty liver disease. The prevalence of type 2 diabetes is higher among those with non-alcoholic fatty liver disease than in the general population. On the other hand, in individuals with diabetes, the presence of non-alcoholic fatty liver disease worsens glycemic control and increases the already high risk of macrovascular complications.[18-20]

The pathogenesis of non-alcoholic fatty liver disease is represented by the two-hit hypothesis.[21,22] In the first stage, against the background of visceral obesity and impaired glucose tolerance, lipolysis increases, leading to elevated serum free fatty acid concentrations due to increased synthesis and inhibition of their oxidation in mitochondria, resulting in triglyceride accumulation and reduced fat excretion by hepatocytes. This creates conditions for the formation of liver fat degeneration - steatosis. Additionally, fatty hepatosis, regardless of its causes, can contribute to hyperinsulinemia due to decreased insulin clearance.[7,12,23,24]In the second stage of disease development, further accumulation of free fatty acids exerts direct lipotoxic effects on pancreatic beta cells and hepatocytes, stimulating glycogenolysis in the liver and predicting the increase of insulin resistance and hyperinsulinemia. Prolonged hypertriglyceridemia under insulin resistance conditions disrupts endothelial-dependent vasodilation, causing oxidative stress, resulting in lipid peroxidation products, reactive oxygen species, and cytokines, which are major risk factors for early atherosclerosis. Aldehydes, products of lipid peroxidation, are potent stimulators of stellate cells, leading to increased collagen synthesis (fibrogenesis) and neutrophil chemotaxis. As a result, with reduced hepatocyte membrane protective properties against lipotoxicity, direct or oxidative stress-mediated mitochondrial damage, tissue respiration uncoupling, hepatocyte apoptosis, and necrosis occur, activating fibrogenesis.

In the pathogenesis of non-alcoholic fatty liver disease, impaired adipose tissue function also plays a role. Adipocytes of visceral adipose tissue secrete

large amounts of free fatty acids directly into the portal vein, becoming not only a substrate for the formation of atherogenic lipoproteins but also inhibiting insulin binding to hepatocytes, leading to hyperinsulinemia and increasing insulin resistance. Secretion of adipokines and cytokines is also impaired, contributing to steatosis, inflammation, and fibrosis, and in the absence of adequate treatment, cirrhosis.[12,25,26] Elevated free fatty acid levels in the blood, even in healthy individuals, contribute to increased production of intercellular adhesion molecules, endothelial endothelin-1, E-selectin, and PAI-1, which are indicators of a procoagulant state, impaired vascular reactivity, and systemic inflammation. Non-alcoholic fatty liver disease increases the risk of thrombosis due to endothelial-leukocyte-platelet dysfunction.[27] Endothelial dysfunction occurs independently of insulin resistance and traditional risk factors. Non-alcoholic fatty liver disease promotes atherosclerosis progression, as evidenced by the relationship between the intima-media thickness of the carotid artery, brachiocephalic trunk arteries, coronary arteries, and the degree of liver histological changes. Research indicates that non-alcoholic fatty liver disease is characterized by specific cellular reactions inducing systemic endothelial dysfunction and unique cellular responses in fibrosis formation. Fibrosis in non-alcoholic fatty liver disease is characterized by sinusoidal capillarization, serving as a trigger for the cascade of systemic endothelial dysfunction.[26]

Thus, according to the European Association for the Study of the Liver (EASL) recommendations, screening for carbohydrate metabolism disorders in patients with non-alcoholic fatty liver disease is necessary, while screening for non-alcoholic fatty liver disease in patients with type 2 diabetes is recommended regardless of liver enzyme levels. Screening for other components of metabolic syndrome, representing a cluster of atherosclerosis risk factors, is also advisable.[13,28,29] The screening method for non-alcoholic fatty liver disease in patients with type 2 diabetes is liver ultrasound,[30] which detects moderate and severe steatosis and has advantages in diagnosing non-alcoholic fatty liver disease at the cirrhosis stage, especially in asymptomatic patients.[31] Non-invasive diagnostic methods include the FibroMax test (α-2-macroglobulin, haptoglobin, apolipoprotein A1, γ-glutamyl transpeptidase (GGT), and total bilirubin), the FibroMeter test (α-2-macroglobulin, γ-glutamyl transpeptidase, urea, prothrombin index (%), platelets) for differentiating fibrosis from cirrhosis, and elastometry to assess liver elastic properties changes based on reflected vibration impulses and their subsequent computer analysis at all fibrosis stages.[32]

Considering the increased risk of adverse outcomes, regular diabetes screening for non-alcoholic fatty liver disease and rapid lifestyle changes to slow disease progression are emphasized. Patients with impaired glucose tolerance and diabetic non-alcoholic fatty liver disease can benefit from early referral to cardiovascular specialists to reduce the risk of cardiovascular events and mortality.[27] Therefore, the pathogenic mechanisms of non-alcoholic fatty liver disease and type 2 diabetes are closely interconnected. Both diseases can mutually aggravate each other, increasing the risk of cardiovascular diseases and significantly raising the likelihood of liver fibrosis in patients.[33] Patients with non-alcoholic fatty liver disease will benefit from frequent monitoring, and rapid lifestyle changes should be initiated at early disease stages to prevent the progression of type 2 diabetes, which can significantly increase morbidity and mortality. Patients with impaired glucose tolerance and diabetic non-alcoholic fatty liver disease may also benefit from early cardiovascular risk assessment. Pharmacological agents should aim to improve glycemic control, reduce fibrosis, and protect the cardiovascular system.[27]

Limitations It is important to take into account the many limitations of this study when evaluating the results. First,

the diagnostic standards and procedures applied in the included research vary significantly from one another. Second,the generalizability of the results is restricted by the absence of data from control group. This study is a diagnostic study without control groups and number of patients is not enough to generalize the study findings. All of the gaps in this review should be addressed in future research to provide more comprehensive information. Thus, the study results emphasize the importance of combating overweight, obesity, and non-alcoholic fatty liver disease as risk factors for type 2 diabetes and impaired glucose tolerance, and the need for further research to identify causative links between these conditions, as specific causes remain insufficiently studied. A deeper understanding of these connections will allow the development of more effective strategies for preventing and treating metabolic disorders.

What's known? Non-alcoholic fatty liver disease is associated with obesity, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, or impaired glucose tolerance. Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes by 1.5–5.5 times.

What's new? Patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance have an increased degree of steatohepatitis and fibrosis, which may predict the development of cardiovascular complications in both men and women

Conclusion

Our task was to develop innovative approaches to screening, preventing, and treating cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance.

Non-alcoholic fatty liver disease can be considered an early indicator and key factor in the development of type 2 diabetes and other clinical manifestations of metabolic syndrome. The study showed that patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance have an increased degree of steatohepatitis and fibrosis, which may predict the development of cardiovascular complications in both men and women. Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis showed significant increases in these indicators in patients with cardiovascular diseases and non-alcoholic fatty liver disease, especially in the presence of type 2 diabetes and impaired glucose tolerance. All examined patients showed increased liver enzyme activity and lipid levels, indicating the impact of these diseases on the liver and metabolism.

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