FEATURES OF THE COURSE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN

TYPE 2 DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

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ОСОБЕННОСТИ ТЕЧЕНИЯ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ ПРИ

САХАРНОМ ДИАБЕТЕ 2 ТИПА И НАРУШЕНИИ ТОЛЕРАНТНОСТИ К ГЛЮКОЗЕ

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БАУЫРДЫҢ АЛКОГОЛЬСІЗ МАЙЛЫ АУРУЛАРЫНЫҢ ҮДЕРІСТЕРІНІҢ ЕРЕКШЕЛІКТЕРІ

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**Abstract**

Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT) are common diseases with a high risk of developing cardiovascular diseases (CVD), the leading cause of disability and death. Our aim is to develop new methods for screening, prevention, and treatment of CVD in patients with NAFLD, T2DM, and IGT. We studied 216 patients with CVD and NAFLD, T2DM, and IGT. NAFLD was defined according to AASLD recommendations. Diabetes was defined as HbA1c ≥6.5%, glucose ≥7 mmol/L, self-assessment, or use of antidiabetic drugs. IGT was defined as HbA1c 5.7–6.5% or glucose 5.6–7 mmol/L. We performed fibroscan on 186 patients and analyzed liver enzyme activity, C-reactive protein, glucose, and lipid profile. It was found that the combination of NAFLD with T2DM and IGT exacerbates the degree of steatohepatitis and fibrosis, which may predict the development of CVD in both men and women. All patients with CVD and NAFLD showed increased liver enzyme activity and lipid levels. Additionally, patients with CVD and NAFLD combined with T2DM and IGT had increased levels of CRP, TG, and LP(a). Thus, NAFLD can be an early predictor and factor in the development of diabetes and metabolic syndrome, requiring further investigation to establish causality.

Keywords: Non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2DM), impaired glucose tolerance (IGT), cardiovascular diseases (CVD), metabolic syndrome.

**Аңдатпа**

Бауырдың алкогольсіз майлы ауруы (БАМА) және 2 типті қант диабеті (2 типті ҚД) немесе глюкозаға төзімділіктің бұзылуы (ГТБ)-бұл жүрек-қан тамырлары ауруларының (ЖҚА) даму қаупі жоғары жалпы аурулар, мүгедектік пен өлімнің негізгі себебі. Біздің мақсатымыз-БАМА, 2 типті ҚД және ГТБ бар емделушілерде ЖҚА скринингінің, алдын алудың және емдеудің жаңа әдістерін әзірлеу. Біз ЖҚА және БАМА, 2 типті ҚД және ГТБ бар 216 пациентті зерттедік. БАМА AASLD ұсыныстары бойынша анықталды. Қант диабеті HbA1c ≥6,5%, глюкоза ≥7 ммоль/л, өзін-өзі бағалау немесе диабетке қарсы препараттар бойынша анықталды. ГТБ–HbA1c 5,7–6,5% немесе глюкоза 5,6-7 ммоль/л. Біз 186 пациентке фиброскан жасадық және бауыр ферменттерінің, С-реактивті ақуыздың, глюкозаның және липидті профильдің белсенділігін талдадық. БАМА-ның 2 типті ҚД және ГТБ-мен үйлесуі стеатогепатит пен фиброздың дәрежесін күшейтетіні анықталды, бұл ерлер мен әйелдерде ЖҚА дамуын болжай алады. ЖҚА және БАМА бар барлық науқастарда бауыр ферменттерінің белсенділігі мен липидтер деңгейінің жоғарылауы байқалды. Сондай-ақ, ЖҚА және БАМА бар пациенттерде 2 типті ҚД және ГТБ-мен бар пациенттерде ТГ және ЛП(а) деңгейінің жоғарылауы байқалды. Осылайша, БАМА қант диабеті мен метаболикалық синдромның дамуының ерте болжаушысы және факторы болуы мүмкін. Сондықтан да себеп-салдар байланысын орнату үшін қосымша зерттеулерді қажет етеді.

Түйін сөздер: Бауырдың алкогольсіз майлы ауруы (БАМА), 2 типті қант диабеті (2 типті ҚД), глюкозаға төзімділіктің бұзылуы (ГТБ), жүрек-қан тамырлары аурулары (ЖҚА), метаболикалық синдром.

**Аннотация**

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

исследовали 216 пациентов с ССЗ и НАЖБП, СД 2 типа и НТГ. НАЖБП определялась по рекомендациям AASLD. Диабет определялся как HbA1c ≥6,5%, глюкоза ≥7 ммоль/л, самооценка или антидиабетические препараты. НТГ - HbA1c 5,7–6,5% или глюкоза 5,6–7 ммоль/л. Мы провели фиброскан 186 пациентам и анализировали активность печеночных ферментов, С-реактивного белка, глюкозы и липидного профиля. Установлено, что сочетание НАЖБП с СД 2 типа и НГТ усугубляет степень стеатогепатита и фиброза, что может предсказывать развитие ССЗ у мужчин и женщин. У всех пациентов с ССЗ и НАЖБП отмечалось повышение активности печеночных ферментов и уровня липидов. Также у пациентов с ССЗ и НАЖБП в сочетании с СД 2 типа и НТГ наблюдалось повышение уровня СРБ, ТГ и ЛП(а). Таким образом, НАЖБП может быть ранним предиктором и фактором развития диабета и метаболического синдрома, требующим дальнейших исследований для установления причинно-следственной связи.

Ключевые слова: Неалкогольная жировая болезнь печени (НАЖБП), сахарный диабет 2 типа (СД 2 типа), нарушение толерантности к глюкозе (НТГ), сердечно-сосудистые заболевания (ССЗ), метаболичсекий синдром.

**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 microvascular 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 (Ng et al., 2022a; Younossi et al., 2016). 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 (Estes et al., 2018).

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 (Kasper et al., 2021; Estes et al., 2018; Li et al., 2019). 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 (Estes et al., 2018). 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 (Duell et al., 2022a). Non-alcoholic fatty liver disease is the focus of close attention from physicians of various specialties and, according to epidemiological studies, is considered one of the most common diffuse liver diseases today (Huang et al., 2012a).

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 (Ng et al., 2022a; Ratziu et al., 2010; Marchesini et al., 2003a).

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 (Hassen et al., 2022; Toth, 2012). 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 (Ratziu et al., 2010; Hassen et al., 2022; Toth, 2012).

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 (Ng et al., 2022a; Duell et al., 2022a; Huang et al., 2012a). In type 2 diabetes mellitus and insulin resistance, bile acid endocrine function is impaired, reducing their absorption, increasing liver fat infiltration, 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 (Younossi et al., 2016; Estes et al., 2018; Huang et al., 2012a; Charlton et al., 2002).

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 (Toth, 2012).

Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes by 1.5–5.5 times (Duell et al., 2022a; Toth, 2012). The prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes is 70–90% (Sanyal et al., 2021). 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 (Hassen et al., 2022; Taylor et al., 2020). 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 (Duell et al., 2022a; Hassen et al., 2022; Shang et al., 2022; Younossi et al., 2019; Huang et al., 2012b).

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 (Charlton et al., 2002; Sanyal et al., 2021), the overall relationship between non-alcoholic fatty liver disease and type 2 diabetes can be described as a "two-way street" (Angulo, 2002). 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 (Marchesini et al., 2003b; Marchesini et al., 2003c; Chen et al., 2017; Khan et al., 2019; Kitade et al., 2017; Kotronen & Yki-Järvinen, 2008; Seppälä-Lindroos et al., 2002).

The pathogenesis of non-alcoholic fatty liver disease is represented by the two-hit hypothesis (Toth, 2012; Muzurović et al., 2021a; Katsiki et al., 2016). 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 (Duell et al., 2022b; Caussy et al., 2021; Kim & Cho, 2017; Targher et al., 2020). 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 (Charlton et al., 2002; Duell et al., 2022b; Eckel et al., n.d.; Musso et al., 2003; Chen et al., 2023; Duell et al., 2022c; Muzurović et al., 2021b; Ng et al., 2022b; Zhao et al., 2022). 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 (Marchesini et al., 2003b; Mantovani et al., 2021a). 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 (23, 43). Fibrosis in non-alcoholic fatty liver disease is characterized by sinusoidal capillarization, serving as a trigger for the cascade of systemic endothelial dysfunction (Toth, 2012).

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 (Hassen et al., 2022; Vanjiappan et al., 2018). The screening method for non-alcoholic fatty liver disease in patients with type 2 diabetes is liver ultrasound (Angulo, 2002; Sanyal et al., 2015), which detects moderate and severe steatosis and has advantages in diagnosing non-alcoholic fatty liver disease at the cirrhosis stage, especially in asymptomatic patients (Hassen et al., 2022; Charlton et al., 2002; Hazlehurst et al., 2016). 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 (Jali et al., 2015).

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 (Mantovani et al., 2021b). 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 (Ciardullo et al., 2020). 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 (Tziomalos et al., 2012).

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**

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 CF UMC NNCC (Table 1).

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 (Seko et al., 2018) and ≥30, 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 (Kasturiratne et al., 2013). 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 (Lallukka & Yki-Järvinen, 2016; Mantovani et al., 2018; Targher, 2020). Lean patients were defined as having a body mass index (BMI) <23 kg/m2 for Asians and BMI <25 kg/m2 for other races. Patients were considered overweight if their BMI was in the range of 23–27.5 kg/m2 for Asians and 25–30 kg/m2 for other races. Obese patients were defined as BMI >27.5 kg/m2 for Asians and BMI >30 kg/m2 for other races (Weinstein et al., 2018; Yoneda et al., 2021).

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 (Narasimhan et al., 2010).

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.

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%).

**Discussion and Results**

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.

**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.

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.

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**Conflict of Interest**

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

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**Appendix**

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

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Men (n=90)** | **Women (n=126)** |
| Type 2 Diabetes | 24 (11.11%) | 14 (6.4%) |
| Impaired Glucose Tolerance | 19 (8.8%) | 7 (3.2%) |
| Non-alcoholic Fatty Liver Disease | 110 (50.9%) | 76 (60%) |
| Liver Fibrosis | 99 (45%) | 75 (34.7%) |

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 | Less than 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 | Moderate scarring |
| 10–14 kPa | F3 | Severe scarring |
| ≥14 kPa | F4 | Cirrosis |

NAFLD - non-alcoholic fatty liver disease

NASH - non-alcoholic steatohepatitis

Table 3

| Fibroscan | S0 | S1 | S2 | S3 | F0 | F1 | F2 | F3 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Men (110) | 23.6% | 18.1% | 31.8% | 26.3% | 42.7% | 30.9% | 12.7% | 3.6% |
| Women (76) | 21% | 15.7% | 28.9% | 34.2% | 39.4% | 38.1% | 15.7% | 5.2% |