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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NON-ALCOHOLIC FATTY LIVER DISEASE AND CARDIOVASCULAR DISEASE: ASSOCIATIONS WITH CLINICAL MARKERS AND METABOLIC ALTERATIONS

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Abstract.

Introduction: Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent metabolic disorders and is closely associated with insulin resistance and cardiometabolic risk. In men of working age, NAFLD frequently progresses to hepatic fibrosis and contributes to early cardiovascular remodelling, which significantly increases morbidity and mortality due to cardiovascular complications rather than liver-related outcomes.

Methods: A cross-sectional clinical-analytical study was conducted in 206 men aged 25-60 years with confirmed NAFLD. Liver fibrosis was assessed by FibroScan®. Serum LOX-1, LDLR and LRP-1 levels were measured using ELISA. Echocardiography, carotid intima-media thickness (cIMT), and flow-mediated dilation (FMD) were performed to evaluate cardiovascular function. Statistical analysis included ANOVA and correlation analysis ($p < 0.05$).

Results: Progression of liver fibrosis (F2-F3) was associated with increased insulin resistance, atherogenic dyslipidemia, and reduced hepatic synthetic function ($p < 0.05$). Patients with advanced fibrosis demonstrated early cardiovascular remodelling, including increased cIMT, higher left ventricular mass index, impaired diastolic function (E/e′), and decreased FMD ($p < 0.05$). A significant increase in LOX-1 and a reduction in LDLR and LRP-1 expression indicated a shift toward a pro-atherogenic receptor phenotype ($p < 0.001$).

Conclusion: Hepatic fibrosis in NAFLD is closely associated with an adverse cardiometabolic profile. Elevated LOX-1 levels may serve as an early biomarker of endothelial dysfunction and increased cardiovascular risk, supporting earlier identification and more intensive management of high-risk patients with NAFLD.

Key words. Non-alcoholic fatty liver disease (NAFLD), hepatic fibrosis, insulin resistance, cardiovascular risk, endothelial dysfunction.

Introduction.

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic disorders of the hepatobiliary system and is closely associated with components of the metabolic syndrome. According to epidemiological data, the prevalence of NAFLD in the adult population reaches 25-30%, while in individuals with obesity and insulin resistance it exceeds 60% [1-4]. Among working-age men, the occurrence of hepatic steatosis and fibrotic liver changes is particularly high, contributing to a substantial socio-economic burden [5-7].

The contemporary understanding of NAFLD considers it not as a localized liver pathology but as a systemic metabolic condition characterized by lipotoxicity, oxidative stress, and chronic low-grade inflammation. As the disease progresses from steatosis to fibrosis, structural and functional alterations develop within the vascular wall and myocardium, leading to increased cardiovascular morbidity and mortality. Notably, the leading causes of death in patients with NAFLD are not liver-related complications, but coronary artery disease, cardiac arrhythmias, and chronic heart failure [8-12].

One of the key mechanisms linking NAFLD to cardiovascular remodeling is the dysregulation of lipoprotein metabolism at the receptor level. Upregulation of LOX-1 enhances the uptake of oxidized low-density lipoproteins (oxLDL), promotes endothelial activation, and accelerates atherosclerotic progression [13-16]. Conversely, reduced activity of LDLR and LRP-1 decreases the clearance of circulating lipoproteins, thereby exacerbating atherogenic lipid overload of the vascular wall. These alterations are particularly pronounced in the presence of insulin resistance and visceral obesity [17-20].

Despite growing evidence supporting the metabolic and inflammatory pathways underlying NAFLD, the relationship between alterations in lipid receptor expression, the severity of hepatic fibrosis, and the features of cardiovascular remodeling remains insufficiently understood-especially in male populations of Central Asia, which are characterized by high rates of abdominal obesity and low physical activity.

Objective: To determine the relationship between metabolic disturbances, the degree of hepatic fibrosis, and indicators of cardiovascular remodeling in men with non-alcoholic fatty liver disease.

Materials and Methods.

This study was conducted as a cross-sectional clinical-analytical investigation with elements of prospective follow-up. The research was carried out at the Republican Scientific and Practical Medical Center of Therapy and Medical Rehabilitation (Tashkent, Uzbekistan) during 2022-2024. The study protocol was approved by the local Institutional Ethics Committee (Protocol No. 5 dated 06 March 2022). Written informed consent was obtained from all participants prior to enrolment.

A total of 206 men aged 25-60 years (mean age 44.8 ± 8.6 years) with confirmed non-alcoholic fatty liver disease (NAFLD) were included. The study sample was ethnically homogeneous (Uzbek population).

Inclusion criteria: Liver steatosis verified by ultrasound or elastography; no history of alcohol abuse (<20 g ethanol/day); negative hepatitis B and C viral markers; absence of autoimmune liver disease; preserved renal function (eGFR > 60 mL/min/1.73 m²).

Exclusion criteria: Liver cirrhosis (METAVIR F4); heart failure class III-IV (NYHA); active inflammatory or oncological disease; use of statins or glucocorticoids within 3 months prior to inclusion.

Assessment of Liver Fibrosis:

Liver fibrosis was assessed using transient elastography (FibroScan®, Echosens, France) and graded by METAVIR scale: F0-F1 -steatosis/minimal fibrosis; F2 - moderate fibrosis; F3 -advanced fibrosis. Patients with F4 were excluded. The rationale for excluding patients with cirrhosis (F4) was to focus on early and intermediate stages of structural remodelling, in which cardiovascular changes are not yet dominated by profound hemodynamic alterations, portal hypertension or advanced cachexia. Including F4 patients could have introduced additional confounding related to cirrhotic cardiomyopathy, thereby obscuring the relationships between fibrosis severity and subclinical cardiovascular remodelling in earlier stages. Steatosis severity was additionally evaluated using the Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI).

Biochemical and Metabolic Parameters:

Fasting blood samples were used to determine: Glucose and insulin with calculation of HOMA-IR (insulin × glucose / 22.5); дipid profile: Total Cholesterol (TC), LDL-C, HDL-C, Triglycerides (TG); liver function markers: alanine Aminotransferase (ALT), aspartate Aminotransferase (AST), Gamma-Glutamyltransferase (GGT), alkaline Phosphatase (ALP), Total Bilirubin; serum albumin and fibrinogen levels.

Expression of LOX-1, LDLR and LRP-1:

Serum concentrations of LOX-1, LDLR and LRP-1 were measured using solid-phase ELISA (R&D Systems, USA). Samples were centrifuged at 3000 rpm and stored at -80°C until analysis.

Cardiovascular Assessment:

- Standard 12-lead electrocardiography.
- Echocardiography (expert-class device, 2.5-3.5 MHz phased-array transducer) with evaluation of: Left Ventricular End-Diastolic Diameter (LVEDD), Left Ventricular End-Systolic Diameter (LVESD), Left Ventricular Ejection Fraction (LVEF), Left Ventricular Mass Index (LVMI), Diastolic function parameters: Transmitral E/A ratio, Tissue Doppler e′/a′ ratio, E/e′ ratio (indicator of left ventricular filling pressure).
- Carotid Intima-Media Thickness (cIMT) measurements (B-mode ultrasound).
- Flow-Mediated Dilation (FMD) of the brachial artery to assess endothelial function.

Statistical Analysis: Data analysis was performed using SPSS 13.0 and GraphPad Prism 9.0. Normality was assessed using the Shapiro-Wilk test. Data were presented as mean ± SD (normal distribution) or median (Q25-Q75) (non-normal distribution). Between-group comparisons were conducted using ANOVA, and correlations were evaluated using Pearson's test. A p-value < 0.05 was considered statistically significant.

Results.

Clinical and Metabolic Characteristics of the Study Population:

Men with NAFLD demonstrated a high prevalence of cardiometabolic risk factors. Obesity was detected in 58% of participants, metabolic syndrome in 52%, arterial hypertension in 46%, type 2 diabetes mellitus in 22%, and active smoking in 41% of cases. These findings indicate a combined disturbance of metabolic regulation and vascular homeostasis in this cohort (Table 1).

Table 1. *Summarizes the baseline clinical and anamnestic characteristics of the NAFLD cohort.*

Parameters	NAFLD (n = 206)
Age, years	47.3 ± 0.58
Obesity, n (%)	88 (42.7%)
Body Mass Index (kg/m²)	29.6 ± 0.32
Stress, n (%)	93 (45.1%)
Smoking history, n (%)	16 (7.8%)
Positive family history, n (%)	95 (46.1%)
Physical inactivity, n (%)	187 (90.7%)

Note: *Data are presented as mean ± SD or n (%).*

Liver Enzymes and Inflammatory Activity:

As fibrosis progressed from stages F0-F1 to F2-F3 (Table 2a), a significant increase in ALT levels (34.6 ± 3.5 → 51.1 ± 4.5 U/L; $p < 0.005$) and GGT levels (34.0 ± 3.8 → 58.1 ± 6.2 U/L; $p < 0.005$) was observed, indicating enhanced inflammatory and oxidative hepatocellular injury. The increase in ALP activity ($p < 0.001$) suggests the development of a cholestatic component. These enzymatic shifts reflect the transition from a metabolically compensated steatotic phenotype to an inflammation-driven fibrogenic stage, consistent with the progression toward non-alcoholic steatohepatitis (NASH). The concomitant rise in ALT, GGT, and ALP indicates activation of hepatocyte injury pathways and cholangiocellular stress, suggesting recruitment of hepatic stellate cells and increased extracellular matrix deposition. Such biochemical progression underscores the role of persistent low-grade inflammation and oxidative stress in amplifying both hepatic fibrosis and systemic cardiometabolic risk.

Clinical Significance: The increase in ALT, ALP, and GGT levels as fibrosis progresses from stages F1 to F2 indicates a shift from a metabolically compensated state to an inflammation-driven fibrogenic phenotype, which heightens the risk of: further progression of hepatic pathology, development of endothelial dysfunction, increased cardiovascular risk. The elevation of GGT is particularly important, as it correlates with increased LOX-1 expression and reduced LRP-1 activity, linking these biochemical alterations to vascular and myocardial remodeling. Thus, the observed enzyme dynamics reflect the interplay between hepatic fibrosis and systemic cardiometabolic risk.

Systemic inflammatory activity increased with advancing hepatic fibrosis: fibrinogen levels were higher at stage F2 ($p < 0.05$), while albumin concentrations decreased (44.8 → 41.7 g/L; $p < 0.001$), indicating reduced hepatic synthetic capacity and metabolic decompensation (Table 2b). At the same time, an atherogenic shift in the lipid profile was observed at stages F2-F3, characterized by decreased HDL-C ($p < 0.05$) and increased LDL-C and atherogenic coefficient ($p < 0.01$), reflecting the

Table 2a. *Liver Enzymes and Inflammatory Markers in Patients with NAFLD Depending on the Stage of Fibrosis.*

Parameters	F0 (n = 42)	F1 (n = 91)	F2 (n = 73)	Between-group differences
Total Bilirubin (μmol/L)	12.8 ± 0.8	12.6 ± 0.5	12.7 ± 0.6	$P_{0-1} > 0.05$; $P_{0-2} > 0.05$; $P_{1-2} > 0.05$
ALT (U/L)	34.6 ± 3.5	40.1 ± 2.2	51.1 ± 4.5	$P_{0-1} < 0.05$; $P_{0-2} < 0.005$; $P_{1-2} < 0.05$
AST (U/L)	21.7 ± 1.6	26.1 ± 1.7	27.4 ± 2.5	$P_{0-1} > 0.05$; $P_{0-2} > 0.05$; $P_{1-2} > 0.05$
ALP (U/L)	75.7 ± 3.0	87.4 ± 2.7	91.8 ± 3.0	$P_{0-1} < 0.005$; $P_{0-2} < 0.001$; $P_{1-2} > 0.05$
GGT (U/L)	34.0 ± 3.8	44.0 ± 3.5	58.1 ± 6.2	$P_{0-1} > 0.05$; $P_{0-2} < 0.005$; $P_{1-2} < 0.05$
C-Reactive Protein (mg/L)	4.8 ± 1.7	3.8 ± 0.8	4.4 ± 0.6	$P_{0-1} > 0.05$; $P_{0-2} > 0.05$; $P_{1-2} > 0.05$

Note: *Data are presented as mean ± SD. P_{0-1} - comparison between F0 and F1; P_{0-2} - comparison between F0 and F2; P_{1-2} -comparison between F1 and F2.*

Table 2b. *Metabolic and Protein Blood Parameters in Patients with NAFLD Depending on the Stage of Fibrosis.*

Parameters	F0 (n = 42)	F1 (n =91)	F2 (n =73)	Between-group differences
Glucose (mmol/L)	5.7 ± 0.1	6.19 ± 0.2	7.0 ± 0.3	$P_{0-1} < 0.05$; $P_{0-2} < 0.001$; $P_{1-2} < 0.05$
Urea (mmol/L)	5.04 ± 0.2	5.2 ± 0.1	5.5 ± 0.2	$P_{0-1} > 0.05$; $P_{0-2} > 0.05$; $P_{1-2} > 0.05$
Creatinine (μmol/L)	79.2 ± 1.8	77.5 ± 1.5	75.8 ± 1.6	$P_{0-1} > 0.05$; $P_{0-2} > 0.05$; $P_{1-2} > 0.05$
Fibrinogen (g/L)	339.6 ± 14.2	334.5 ± 7.1	363.8 ± 10.3	$P_{0-1} < 0.05$; $P_{0-2} < 0.05$; $P_{1-2} > 0.05$
Albumin (g/L)	44.8 ± 0.6	44.5 ± 0.4	41.7 ± 0.6	$P_{0-1} < 0.05$; $P_{0-2} < 0.001$; $P_{1-2} < 0.001$

Note: *Data are presented as mean ± SD. P_{0-1} - comparison between F0 and F1; P_{0-2} - comparison between F0 and F2; P_{1-2} -comparison between F1 and F2.*

development of pronounced cardiometabolic risk.

According to elastography data, fibrosis stages were distributed as follows: F0-F1 - 39.8%, F2 -31.1%, F3 - 29.1%. Progression of hepatic fibrosis was accompanied by a consistent increase in insulin resistance: fasting glucose rose from 5.7 ± 0.1 mmol/L (F0-F1) to 7.0 ± 0.3 mmol/L (F2), while insulin levels increased from 12.3 to 18.7 μIU/mL, with a corresponding rise in HOMA-IR ($p < 0.001$).

Clinical Significance:

The increase in glucose levels with advancing fibrosis stages (Table 2b) confirms the association between NAFLD and insulin resistance, indicating a shift toward a diabetogenic metabolic state. Elevated fibrinogen levels demonstrate an enhanced prothrombotic status, which increases the risk of cardiovascular complications. The reduction in albumin reflects depletion of hepatic functional reserve and the transition of the disease into a state of metabolic decompensation.

All of these changes are pathophysiologically consistent with the observed alterations in LOX-1, LDLR, and LRP-1 expression and support the central role of the liver in systemic cardiometabolic regulation.

Cardiovascular Remodelling:

In patients with fibrosis stages F2-F3, significant signs of early cardiovascular remodelling were observed, as presented in Table 3.

Table 3. *Indicators of Early Cardiovascular Remodeling in Patients With NAFLD.*

Parameter	Trend	Significance
Carotid Intima-Media Thickness (cIMT)	↑	$p < 0.01$
Left Ventricular Mass Index (LVMI)	↑	$p < 0.05$
E/e′ Ratio (LV Filling Pressure)	↑	$p < 0.05$
Flow-Mediated Dilation (FMD)	↓	$p < 0.01$

The observed increase in carotid intima-media thickness (Table 3.) and left ventricular mass index, along with a rise in the E/e′ ratio, indicates early structural and functional cardiac remodelling in patients with advanced fibrosis (F2-F3). The significant reduction in flow-mediated dilation (FMD) reflects impaired endothelial function and vascular stiffness. Taken together, these changes suggest the development of subclinical cardiovascular dysfunction even in the absence of overt heart failure. This indicates impaired vascular elasticity, deterioration of left ventricular diastolic function, and reduced endothelium-dependent vasodilation - early signs of cardiac dysfunction that develop even while the ejection fraction remains preserved.

Expression of LOX-1, LDLR, and LRP-1 Receptors:

For the first time, it was demonstrated that the progression of hepatic fibrosis is accompanied by a significant increase in LOX-1 levels ($p < 0.001$), alongside a simultaneous decrease in the expression of LDLR and LRP-1 (both $p < 0.05$). This indicates a shift in the receptor profile toward a pro-atherogenic phenotype, promoting the accumulation of oxidized low-density lipoproteins, endothelial dysfunction, and structural and functional remodelling of the myocardium and vascular wall. In patients with advanced fibrosis (F2-F3), a marked elevation in LOX-1 levels ($p < 0,001$) was observed, in parallel with reduced LDLR and LRP-1 expression (both $p < 0.05$), reflecting a receptor shift favouring vascular atherogenesis. This sequence of pathobiochemical alterations is illustrated in Figure 1.

Thus, the progression of hepatic fibrosis in men with NAFLD is associated with increasing insulin resistance, atherogenic alterations in the lipid profile, activation of systemic inflammation, and a decline in hepatic synthetic function. These metabolic disturbances are accompanied by early cardiovascular remodelling and an imbalance in the LOX-1/LDLR/LRP-1 receptor systems, reflecting the systemic nature of the disease and its high cardiometabolic risk.

NAFLD → Fibrosis (progression) → ↑LOX-1, ↓LDLR & LRP-1 → cardiovascular Disease

Figure 1 Pathogenetic model illustrating the relationship between NAFLD, fibrosis progression, and cardiovascular

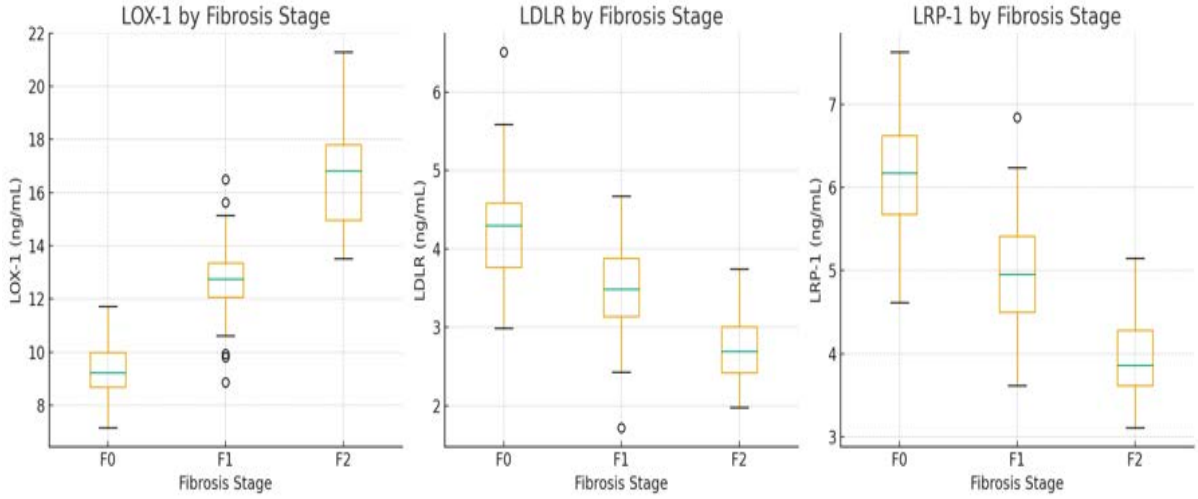

Figure 2. *Box plots showing serum levels of LOX-1 (A), LDLR (B) and LRP-1 (C) in patients with NAFLD stratified by fibrosis stage (F0, F1, F2). The boxes represent the interquartile range (IQR), the horizontal line within each box shows the median, and whiskers denote the 5th-95th percentiles.*

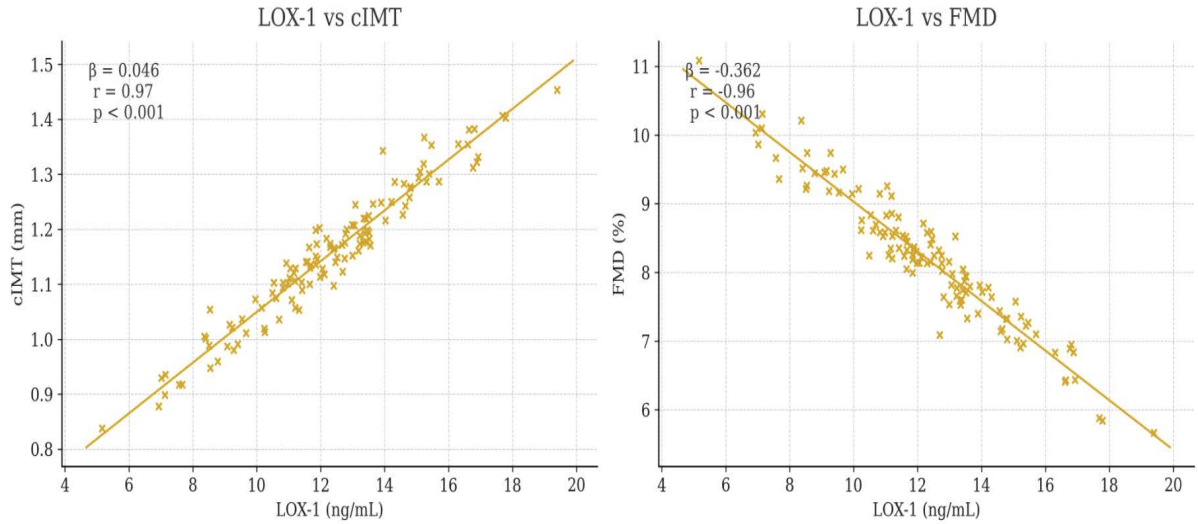

Figure 3. *Scatter plots demonstrating the relationship between serum LOX-1 levels and (A) carotid intima-media thickness (cIMT) and (B) flow-mediated dilation (FMD) in men with NAFLD.*

complications through altered expression of lipoprotein metabolism receptors (↑LOX-1, ↓LDLR, ↓LRP-1).

Increased expression of the LOX-1 receptor and reduced activity of LDLR and LRP-1 contribute to endothelial dysfunction, vascular remodelling, and an elevated risk of cardiovascular disease.

In addition, Figure 2 illustrates the distribution of LOX-1, LDLR and LRP-1 levels across fibrosis stages F0, F1 and F2, demonstrating a stepwise increase in LOX-1 and a parallel decrease in LDLR and LRP-1 with advancing fibrosis.

The association between LOX-1 expression and vascular remodeling is further illustrated in Figure 3. Higher LOX-1 levels were associated with increased cIMT and reduced FMD, supporting the link between pro-atherogenic receptor shifts and early vascular dysfunction.

Discussion.

The findings of this study support the concept of NAFLD as a systemic cardiometabolic disorder that involves not only hepatic parenchymal injury but also cardiovascular structural and functional alterations, as well as dysregulation of receptor-mediated lipid metabolism. The stepwise progression of hepatic fibrosis from F0-F1 to F2-F3 was accompanied by increasing insulin resistance, activation of inflammatory pathways, and a decline in hepatic synthetic capacity. These observations are consistent with recent reports by Bhatia M et al. (2025) and the meta-analysis by Younossi et al. (2023), which characterize NAFLD as a central component of the broader metabolic continuum rather than an isolated liver pathology [3,17].

In the present study we used the conventional definition of non-alcoholic fatty liver disease (NAFLD) as recommended in earlier AASLD and EASL guidelines [11,13]. We acknowledge that recent international consensus statements have introduced the terminology of metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis as a refinement of the NAFLD concept [18].

However, to maintain internal consistency and comparability with the bulk of the literature cited, we retained the NAFLD nomenclature throughout the manuscript.

The increase in fasting glucose and HOMA-IR observed at fibrosis stages F2-F3 in our cohort reflects the deepening of both peripheral and hepatic insulin resistance, accompanied by compensatory hyperinsulinemia. This aligns with the meta-analysis by Chalasani N et al. (2023), which identified insulin resistance as a dominant predictor of fibrosis progression independent of steatosis severity [11].

The significant elevation in ALT and GGT at advanced fibrosis stages reflects enhanced cytolytic and oxidative injury to hepatocytes. The rise in ALP suggests biliary remodelling and cholestatic inflammatory involvement, characteristic of the transition to NASH (non-alcoholic steatohepatitis) as defined in the AASLD guidelines (2023). The reduction in serum albumin at F2 indicates impaired hepatic protein synthesis and metabolic decompensation, while the increase in fibrinogen observed aligns with data reported by Eslam M. et al. (2020), linking NAFLD to a prothrombotic state and endothelial dysfunction [18]. Of particular importance is the early cardiovascular remodelling we identified, evidenced by an increase in carotid intima-media thickness, left ventricular mass index, and impaired diastolic function (elevated E/e′), despite preserved ejection fraction. This corresponds to the model of early subclinical cardiomyopathy associated with NAFLD described by Targher et al. (2016) [6]. The reduction in flow-mediated dilation (FMD) further reflects endothelial dysfunction driven by chronic low-grade inflammation and increased circulating oxidized lipoproteins. This mechanistic link was previously highlighted by Byrne & Targher (2022), who described NAFLD as the "hepatic component of the cardiometabolic phenotype." [10]. A key mechanistic insight from our study is the shift in lipid receptor expression: increased LOX-1 and decreased LDLR and LRP-1 in patients with F2-F3 fibrosis. LOX-1 is the principal receptor for oxidized LDL and is known to drive endothelial inflammation, apoptosis, and atherosclerotic vascular remodeling (Katayama et al., 2022) [14]. Concurrent reduction of LDLR and LRP-1 reduces LDL clearance and promotes vascular lipid deposition, thereby accelerating atherogenesis.

Taken together, the observed sequence -**NAFLD → Fibrosis → LOX-1 activation → Endothelial dysfunction → Cardiac and vascular remodelling** - constitutes a unified pathogenetic continuum explaining the heightened cardiovascular event risk in this patient population. These findings are consistent with the EASL Guidelines (2024), which identify fibrosis stage as the strongest prognostic determinant, surpassing steatosis severity or transaminase levels.

An important methodological limitation of our study is the lack of formal multivariate regression analyses adjusting for key cardiometabolic confounders such as age, body mass index, HOMA-IR and LDL-C. Although fibrosis stage and LOX-1 levels showed consistent associations with cIMT, LVMI and FMD in unadjusted analyses, these relationships cannot be interpreted as fully independent of coexisting obesity, hypertension, diabetes and dyslipidemia. Therefore, our findings should be viewed as evidence of strong associations between fibrosis severity, pro-atherogenic receptor shifts and subclinical cardiovascular remodelling in men with NAFLD, rather than definitive proof of an independent causal effect.

Conclusion.

The results of this study confirm that non-alcoholic fatty liver disease (NAFLD) in working-age men represents a systemic disorder affecting not only the hepatobiliary system but also the cardiovascular system.

A key pathogenic mechanism identified in this study is the upregulation of LOX-1 expression in parallel with reduced expression of LDLR and LRP-1, which together form a pro-atherogenic metabolic receptor profile that contributes to endothelial dysfunction and accelerated atherosclerotic progression. Thus, hepatic fibrosis in NAFLD should be considered an integrated marker of cardiometabolic risk, reflecting synchronous pathological changes in the liver, vascular wall, and cardiac tissue.

Clinical Implications

• Assessment of hepatic fibrosis using FibroScan® should be incorporated into the routine diagnostic evaluation of patients with NAFLD.

• Circulating LOX-1 may serve as an early biomarker of vascular complications.

• Patients with fibrosis stages F2-F3 require intensified management of metabolic risk factors (glycemia, lipids, body weight, blood pressure).

• At these stages, early initiation of cardioprotective therapy (SGLT2 inhibitors, GLP-1 receptor agonists, statins) is justified.

• Multidisciplinary management (cardiology + hepatology + endocrinology) is essential to reduce the risk of cardiovascular progression.

Future Directions.

Further research should aim to clarify the causal relationships between fibrosis severity and the development of cardiovascular complications. Long-term prospective studies are needed, as well as molecular investigations into the regulation of LOX-1, LDLR, and LRP-1 under metabolic stress conditions. Targeted therapeutic modulation of these receptors may represent a promising strategy to reduce cardiovascular risk in patients with NAFLD.

Study Limitations.

This study was conducted in a cohort of men of a single ethnic origin, which may limit generalizability. The cross-sectional study design does not allow for establishing causality. Serum levels of LOX-1, LDLR, and LRP-1 may not fully reflect their tissue-level expression. In addition, a small group of apparently healthy individuals initially examined for descriptive comparison was not included in the final inferential analyses because of the pronounced imbalance in sample size and the lack of systematic measurements for all study variables; therefore, the present work should be considered a single-arm study of men with NAFLD.

Conclusions.

1. Patients with NAFLD demonstrate a high prevalence of cardiometabolic risk factors, including obesity (58%), metabolic syndrome (52%), arterial hypertension (46%), and type 2 diabetes (22%).

2. The progression of hepatic fibrosis (F2-F3) is associated with a significant increase in insulin resistance and atherogenic alterations in the lipid profile ($p < 0.001$).
3. Elevated ALT, GGT, and ALP levels reflect increasing cytolytic and cholestatic liver injury.
4. At fibrosis stages F2-F3, early signs of cardiovascular remodelling were observed, including left ventricular mass index elevation, carotid intima–media thickening, and impaired diastolic function ($p < 0.05$).
5. Increased LOX-1 levels and reduced expression of LDLR and LRP-1 constitute a pro-atherogenic receptor profile that links fibrosis progression to vascular complications.
6. NAFLD should be regarded as a systemic cardiometabolic disease, requiring early prevention of cardiovascular events.

Conflict of interest.

Authors declare about not having financial and personal interests.

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