DOI: 10.20514/2226-6704-2025-15-4-262-274
УДК 616.36-003.826-036-07-085
EDN: MQICUP

И.Г. Никитин, А.В. Стародубова, О.А. Кисляк, Т.Ю. Демидова, Л.Ю. Ильченко

Институт клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, Россия

НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ У ПАЦИЕНТОВ С НОРМАЛЬНОЙ МАССОЙ ТЕЛА: ЭПИДЕМИОЛОГИЯ, АКТУАЛЬНЫЕ ВОПРОСЫ СКРИНИНГА И ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ

I.G. Nikitin, A.V. Starodubova, O.A. Kislyak, T.Yu. Demidova, L.Yu. Ilchenko

Institute of Clinical Medicine, N.I. Pirogov Russian National Research Medical University, Ministry of Health of Russia, Moscow, Russia

Nonalcoholic Fatty Liver Disease in Patients with Normal Body Weight: Epidemiology, Current Issues of Screening and Diagnosis, Approaches to Therapy

Резюме

Неалкогольная жировая болезнь печени (НАЖБП) в настоящий момент времени представляет собой серьезную медико-социальную проблему для общественных систем здравоохранения в связи с ее широким распространением, потенциальным риском развития цирроза печени (ЦП) и гепатоцеллюлярной карциномы (ГЦК). Кроме того, наличие НАЖБП в соматическом континууме пациента сопряжено с достоверно большей частотой развития сердечно-сосудистых событий и сахарного диабета типа 2 (СД2). Наиболее часто НАЖБП регистрируется у пациентов с избыточной массой тела. Отдельного внимания исследователей и клиницистов заслуживают пациенты с НАЖБП, имеющие нормальную массу тела. Несмотря на, казалось бы, относительно благоприятный профиль «метаболического здоровья» риск прогрессирования НАЖБП в ЦП и ГЦК, а также сопряженность с сердечно-сосудистыми событиями в обсуждаемой группе пациентов ничуть не меньше, чем в группе пациентов с НАЖБП и высоким индексом массы тела (ИМТ). Отсутствие ранних симптомов и нарушений со стороны некоторых показателей, характеризующих «метаболическое здоровье» у пациентов с НАЖБП и нормальной массой тела, способствует поздней и несвоевременной диагностике заболевания печени и, как следствие, его прогрессированию и формированию тяжелых сосудистых и метаболических нарушений в последующем. В представленном обзоре авторы предлагают некоторые эпидемиологические данные о распространенности НАЖБП у пациентов с нормальной массой тела, вариантах клинического течения НАЖБП у обсуждаемой группы пациентов и предлагают сделать особый акцент на очевидную необходимость значительно более широкого вовлечения пациентов с нормальной массой тела в клинические и научные исследования, посвященные детальному изучению патогенеза, вопросов организации медицинской помощи и лечения НАЖБП.

Ключевые слова: *неалкогольная жировая болезнь печени, инсулинорезистентность, индекс массы тела, сахарный диабет 2, цирроз печени*

Конфликт интересов

Соавтор статьи Никитин И.Г. является членом редакционной коллегии журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Никитин И.Г. не участвовал в принятии решения о публикации этой статьи.

Соавтор статьи Ильченко Л.Ю. является главным редактором журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Решение о публикации статьи было принято редакционной коллегией без участия главного редактора.

Об иных конфликтах интересов авторы не заявляли

Источники финансирования
Авторы заявляют об отсутствии финансирования

Статья получена 29.01.2025 г.
Одобрена рецензентом 16.03.2025 г.
Принята к публикации 22.03.2025 г.

Для цитирования: Никитин И.Г., Стародубова А.В., Кисляк О.А. и др. НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ У ПАЦИЕНТОВ С НОРМАЛЬНОЙ МАССОЙ ТЕЛА: ЭПИДЕМИОЛОГИЯ, АКТУАЛЬНЫЕ ВОПРОСЫ СКРИНИНГА И ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ. Архивъ внутренней медицины. 2025; 15(4): 262-274. DOI: 10.20514/2226-6704-2025-15-4-262-274. EDN: MQICUP

Abstract
Nonalcoholic fatty liver disease (NAFLD) is currently a serious medical and social problem for public health systems due to its high prevalence, potential development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). In addition, the presence of NAFLD in the patient's somatic continuum is associated with a significantly higher incidence of cardiovascular events and type 2 diabetes mellitus (T2DM). The most frequent NAFLD is registered in patients with excessive body weight. Patients with normal body weight deserve special attention of researchers and clinicians. Despite the seemingly relatively favorable profile of "metabolic health", the risk of progression of NAFLD to CKD and HCC, as well as conjugation with cardiovascular events in this group of patients is no less than in the group of patients with NAFLD and high body mass index (BMI). The absence of early symptoms and abnormalities of some indicators characterizing "metabolic health" in patients with NAFLD and normal body weight contributes to late and untimely diagnosis of liver disease and, as a consequence, its progression and the formation of severe vascular and metabolic disorders in the future. In the presented review the authors offer some epidemiological data on the prevalence of NAFLD in patients with normal body weight, variants of the clinical course of NAFLD in the discussed group of patients and propose to make a special emphasis on the obvious need for a much wider involvement of patients with normal body weight in clinical and scientific studies devoted to a detailed study of the pathogenesis, issues of organization of medical care and treatment of NAFLD

Key words: *non-alcoholic fatty liver disease, insulin resistance, body mass index, diabetes mellitus, liver cirrhosis*

Conflict of interests
Co-author of the article Nikitin I.G. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. Nikitin I.G. did not participate in the decision to publish this article.
Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief.
The authors did not declare any other conflicts of interest

Sources of funding
The authors declare no funding for this study

Article received on 29.01.20254
Reviewer approved 16.03.2025
Accepted for publication on 22.03.2025

For citation: Nikitin I.G., Starodubova A.V., Kislyak O.A. et al. Nonalcoholic Fatty Liver Disease in Patients with Normal Body Weight: Epidemiology, Current Issues of Screening and Diagnosis, Approaches to Therapy. The Russian Archives of Internal Medicine. 2025; 15(4): 262-274. DOI: 10.20514/2226-6704-2025-15-4-262-274. EDN: MQICUP

NAFLD — non-alcoholic fatty liver disease, BMI — body mass index, DM2 — type 2 diabetes mellitus, PEMT —phosphatidylethanolamine N-methyl transferase, HOMA-IR — Homeostasis Model Assessment of Insulin Resistance

NAFLD is a chronic, progressive disease, the cause of which is fat accumulation in hepatic cells and subsequent pericellular inflammation, triggering universal fibrogenesis processes facilitating HC and HCC [1-3]. Of note, NAFLD is a diagnosis by exclusion: while searching for the final diagnostic concept, it is necessary to rule out a number of monogenetic causes — viral, autoimmune, other metabolic liver disorders, which morphologically manifest as steatosis; some drug-induced injuries to the liver, excessive drinking. Since the first description of NAFLD in the late 1990s [1–3], this clinical-morphological hepatic disorder has taken the lead in terms of the incidence and the number of associated HC and transplantation cases in the corresponding statistical reports in Europe and the USA [3]. Moreover, numerous epidemiological experimental development models of some chronic non-infectious disease clearly show that NAFLD morbidity will rise [4, 5]; it means a significant increase in the detection rate of DM2 and cardiovascular conditions as well as associated chronic cardiac failure (CCF).

1. Overweight is currently seen as the main cause and trigger of NAFLD, which is confirmed by the data from large-scale population studies: the incidence of NAFLD grows in parallel with an increase in BMI [1, 4]. At the same time, clinicians can clearly identify two special categories among their patients: first — overweight individuals with *normal* fat content in their hepatic tissue; second — individuals with normal BMI, no insulin resistance and DM2 and with *clinical-morphological signs* of NAFLD. Data from previous epidemiological studies (Dionysos study in Europe) show that the incidence of NAFLD among individuals with normal BMI can be 16–18% [1, 4, 6]. Asian epidemiological studies

among subjects with chronic non-infectious diseases reported NAFLD in 20–22% of population with normal weight; in the analysed cohort, the most common factors of metabolic disorders were hyperuricemia, high pro-inflammatory cytokine levels, age over 50 years old, male sex [3, 7, 8]. The data summarised until now allowed a number of researchers to introduce a new definitive term into clinical practice — "NAFLD in slim individuals/NAFLD in patients with normal body weight" (initially, this phenotype was described as NAFLD in individuals with BMI of < 30 kg/m^2; however, since the body weight is not a diagnostic criterion of NAFLD, the term "NAFLD in slim individuals/NAFLD in patients with normal body weight" was proposed [1, 4]. In this regard, it is advisable to remind obesity classification depending on BMI:

- Deficient body weight: BMI of 18.5 kg/m^2 or less.
- Normal body weight: BMI varies from 18.5 to 25 kg/m^2.
- Pre-obesity: BMI of 25 to 30 kg/m^2.
- Stage 1 obesity: BMI of 30 to 35 kg/m^2.
- Stage 2 obesity: BMI of 36 to 40 kg/m^2.
- Stage 3 obesity: BMI of over 40 kg/m^2, and obesity is usually associated with a pathology.

Despite the fact that NAFLD in individuals with normal body weight is not a rare phenotype of this disease, pathophysiologic mechanisms of its development are still far from being clear. It is obvious that not all people with normal body weight and NAFLD have metabolic disorders, which would made them susceptible to hepatic dysfunction. Therefore, a thorough study of the causes and detailed explanation of the pathophysiologic mechanisms of NAFLD in patients with normal body weight become an important task for future researches and clinical practice. The evaluation of environmental factors, occupational characteristics, genetic status, lifestyle becomes the benchmark in the thorough study of this population. Assuming various causes and possible mechanisms of NAFLD in patients with normal body weight, the disease is likely to develop similar to patients with a higher BMI. This fact can evidence that excessive fat tissue in a patient is not a mandatory condition for non-alcoholic steatohepatitis (NASH), progressive fibrosis, HC and HCC. Moreover, some clinical and pathomorphological studies show both higher severity of liver involvement and higher mortality rates among patients with normal body weight or even lean patients with NAFLD vs. patients with excessive BMI [9].

Given relatively few symptoms of NAFLD and the absence of marked changes in laboratory results and almost normal anthropometric measurements, it is quite challenging for a clinician to suspect a hepatic disorder in individuals with normal body weight.

NAFLD epidemiology in patients with normal body weight

Traditionally, the incidence of NAFLD in the population was nearly always evaluated with the use of a single criterion — BMI, with the normal value being below 25 kg/m^2. This BMI value us used mostly in European or North American epidemiological population-based studies, whereas in numerous similar studies conducted in Asia or Pacific, the normal BMI value is below 23 kg/m^2 [4]. Anyway, when these values are used separately for various populations with normal BMI, the incidence of NAFLD varies greatly and makes 5–34% (**Figure 1**).

A number of factors significantly impacted this marked difference in the NAFLD incidence rates in patients with normal body weight: study design; diagnostic methods used for NAFLD patients; study location; sample uniformity and size; and groups selected for a comparative analysis. Some studies used very thorough and objective methods for NAFLD diagnosis; e.g., fine-needle aspiration of the liver, which used to be the golden diagnostic standard for this disease. In other patients, other methods were used: magnetic resonance imaging with the use of specific applications for processing and interpretation of the data; computer tomography; controlled signal attenuation parameter; traditional ultrasonic examination of the abdominal cavity; and in a number of cases, the diagnosis was based mostly on laboratory result interpretation (transaminase, bilirubin, protein synthesis ability of the liver). As shown in **Figure 1**, the highest NAFLD incidence rates were recorded in India (mostly in males), in people, who look healthy and do not smoke and have sedentary lifestyle. Overall, ethnic population-based studies showed that in Asian males, the insulin resistance rates are almost 3.5 times higher than in African American and Caucasian males. Besides, fat content in the liver of Asian males is almost two times higher than in other ethnic populations [4, 10]. Thus, it can be assumed that this population (males of the Indo-Asian origin) is the most susceptible to NAFLD. One published meta-analysis, which comprises data from 84 studies with the total number of subjects exceeding ten million people, demonstrated that among patients with NAFLD, about 20% of the total number of analysed subjects had normal body weight or were lean (95% CI; 15.9–23.0) [11]. An analysis of the general population in 23 studies, comprising over 113,000 patients irrespective of the presence or absence of NAFLD, demonstrated that just 5.1% of subjects (95% CI; 3.7–7.0) had NAFLD with a normal BMI. At the same time, in 19 studies with over 45,000 of subjects with a normal BMI value, included in the analysis, 11% (95% CI; 7.8–14.1) had NAFLD. It is quire obvious that the data are significantly non-homogenous; however, in Europe in

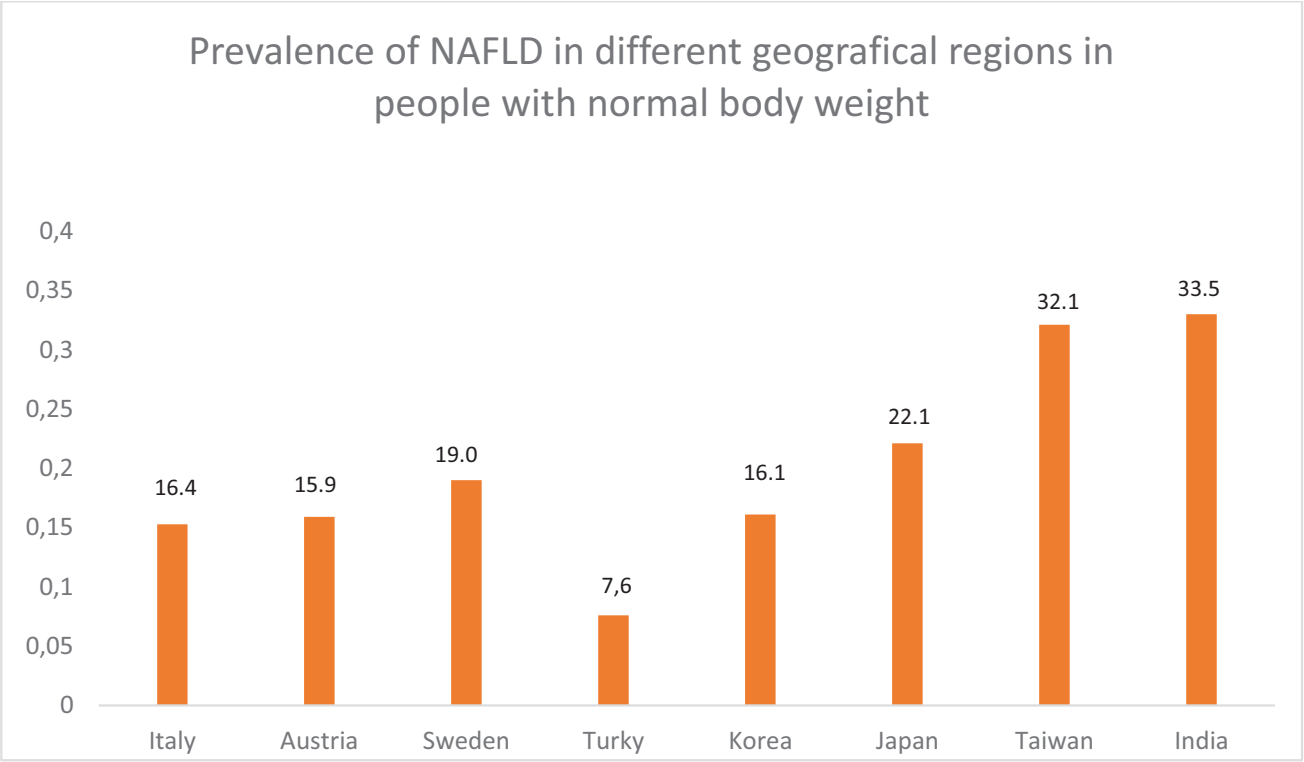

Figure 1.
Prevalence of NAFLD in different geographical regions in people with normal body weight [1, 4]

general, the incidence of NAFLD in individuals with the normal body weight was higher than in other locations. Interesting data were reported in the Global NAFLD/NASH Registry from 18 countries, which demonstrated that approximately 8% of all patients had normal BMI, fewer individual diagnostic signs of metabolic syndrome and a lower rate of hepatic cirrhosis (the sign was evaluated at the first visit to the doctor, taking into account the assumed disease duration) [4, 12].

Current epidemiological data demonstrate growing incidence of NAFLD not only among obese patients, but also in individuals with the normal body weight. Recent studies showed that over the past 15 years, NAFLD morbidity almost doubled: from 5.6% in 2000 to 12.6% in 2023, respectively [11, 12]. Individual population-based studies demonstrate different NAFLD rates in various geographic regions and ethnic groups with overweight, but not obesity (BMI < 30 kg/m^2 for Europeans and < 25 kg/m^2 for Asians). A Hong Kong study in 911 subjects, who met the analysis inclusion criteria and were selected from census databases, showed that the incidence of NAFLD in this population was 19.4%, in Japan — 15.2%, in Belgium — 2.8% [11, 13]. In this regard, the question "How reliable is the use of BMI as a screening benchmark in patients with suspected NAFLD?" remains highly disputable.

Clinical features and laboratory attributes of NAFLD in patients with the normal body weight; outcomes and mortality rates

The results of recent published studies show a tendency that non-obese patients with diagnosed NAFLD have better metabolic health background (**Table 1**).

For instance, fasting plasma triglyceride and glucose levels, high density lipoprotein, adiponectin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and waist circumference in the mentioned population are very often intermediary. The sex and age distribution demonstrates that younger men are the most numerous cohort of patients with NAFLD and normal body weight vs. overweight patients, where women prevail. Besides, according to the results of a multifactor analysis of the aggregate data from the National Health and Nutrition Examination Survey (NHANES III) in the USA, DM2 and arterial hypertension are more common for overweight individuals with NAFLD; in terms of ethnicity, this group included mostly Latin Americans [11, 13]. Nevertheless, a lot of researchers point to the similarity of pathogenetic links of NAFLD development in patients with normal body weight and obese individuals, and emphasise a similarly higher risk of metabolic disorders in both groups vs. general population.

Table 1. Clinical characteristics and mortality associated with NAFLD in non-obese patients

The author of the study	Average age of patients	Region	BMI	The patient's metabolic profile	Mortality rate
Akyuz [8]	41.2+11.8	Turky	23.6+1.3	The predominance of young men, normal blood pressure, higher hemoglobin levels, lower prevalence of metabolic syndrome, less pronounced liver fibrosis	Mortality is similar in patients with NAFLD and obesity
Kim [7]	51.6+9.7	Korea	23.4+1.3	The obvious prevalence of men, higher levels of fasting plasma glucose, insulin, HOMA-IR, uric acid; no differences in metabolic parameters compared with overweight patients	Higher risk of mortality from cardiovascular events and overall mortality compared to patients with normal body weight without NAFLD
Cruz [9]	42.4+8.4	USA	23.1+1.7	The predominance of males, mostly of non-Caucasian origin, a lower prevalence of T2DM, lower levels of cytolysis enzymes and HOMA-IR, a lower degree of steatosis with a morphologically greater severity of inflammation	Higher overall mortality compared to patients without NAFLD
Feldmann [10]	56.7+12.9	Austria	23.6+1.8	Waist circumference, levels of liver enzymes — AST, ALT, GGTP, levels of the main parameters of the atherogenic fraction of the lipidogram, fasting plasma glucose, HOMA-IR had intermediate values between those in healthy people and in patients with NAFLD and obesity	Higher overall mortality compared to patients without NAFLD
Francanzani [5]	45.7+12.9	Italy	23.0+1.2	Less pronounced arterial hypertension and thinner intima media in the carotid arteries	No long-term mortality study has been conducted
Hagstrom [12]	51.4+13.4	Sveden	23.1+2.7	Older age, lower levels of transaminases, and lower representation of NASH as a form of NAFLD at the monitoring initiation stage,	Similar overall mortality with patients with NAFLD without obesity, higher mortality from cardiovascular events
Lee [13]	43.4+6.6	China	20,2+ 1.4	Predominance of males, lower expression of transaminases, intermediate values of fasting plasma glucose and HOMA-IR	No long-term mortality study has been conducted

Fascinating and sometimes very ambiguous are the published data on outcomes and mortality rates in patients with normal body weight and lean patients with NAFLD. For example, studies in the Swedish cohort of patients with NAFLD and normal body weight, despite a relatively favourable prognosis at the beginning of the observation period (during the first three years of the follow-up, there was a lower incidence of an active parenchymal process — steatohepatitis and marked fibrosis), later demonstrated a significantly higher risk of hepatic disorders vs. patients with a higher or even high BMI, including adjustment for age and fibrosis stage by the start of the observation [4, 11]. The obtained data supported significantly higher rates of NAFLD progression in patients with the normal body weight and lean patients. Another cohort-based study conducted among lean patients with NAFLD in Italy, UK, Australia, and Spain, where the total number of subjects was 1,339, with the follow-up period of eight years, showed potential development of diabetes, acute cardiovascular diseases, HCC and other intrahepatic cancer in 8.9% of cases [11, 13]. Even of more interest are the data from the National Health and Nutrition Examination Survey III (NHANES III) registry, with the average dynamic follow-up and periodic examination of patients during 18 years. It has been shown that, for instance, the weighted unadjusted all-cause mortality was higher in patients with NAFLD vs. lean subjects without NAFLD (40.9% vs. 17.9%; $p < 0.001$). The adjusted risk factor of all-cause mortality (HR) in non-obese patients with NAFLD was 2.44 (95% CI; 1.77–3.37) and remained statistically significant even after adjustment for comorbidity, metabolic factors, sex and age, and other demographic parameters. A separate adjustment for demographic variables demonstrated that the cardiovascular mortality was significantly higher in lean patients with NAFLD (15.1% vs. 3.7%; $p < 0.001$). Thus, the cardiovascular mortality in this population grew by 240%! The most common causes of death in patients with the normal body weight and NAFLD were malignancies (25.7%), cardiovascular diseases (21.6%) and infections (13.5%). Another recent study [13], which is of utmost interest, demonstrated that the aggregate all-cause mortality in lean patients

with NAFLD was significantly higher (76.3%) than in patients with NAFLD and normal BMI (51.7%), patients with NAFLD and higher BMI (27.2%) and patients without NAFLD (20.7%) over the ten-year follow-up period. A separate adjustment, which showed the development of cardiovascular conditions in this study, demonstrated in the long-term follow-up the following: 16.9% in lean patients with NAFLD, 5.6% in patients with NAFLD and normal BMI, 8.8% in patients with NAFLD and high BMI; $p < 0.001$.

Of interest are the studies, which show significantly lower serum phosphatidylcholine and lysophospatidylcholine levels and higher glutamate concentrations in patients with NAFLD with normal body weight and lean patients vs. a similar population without NAFLD. Glucose tolerance impairment in patients with NAFLD and normal body weight was similar to that in obese patients with NAFLD; DM2 rates were almost the same (approx. 30%). This proves the idea that fat accumulation in the liver can play a vital role in the development of insulin resistance and DM2 even without obesity [14, 15].

Based on the mentioned studies, the following conclusion can be made: despite less body fat, less marked dyslipidemia, lower transaminase levels, the risk of cardiovascular disease, progressive hepatic conditions, malignancies and all-cause mortality associated with NAFLD in patients with the normal body weight and lean patients is the same or higher than in individuals with a higher BMI. The causes of such an increased risk are still unclear; this phenomenon can be associated with specific NAFLD pathogenesis in non-obese patients.

Hypothesised causes of NAFLD in patients with the normal body weight

Numerous recent clinical and epidemiological studies show a number of important factors facilitating development of NAFLD in patients without excessive body weight. These key factors include environmental factors (diet and eating behaviour), genetic factors, endocrine dysfunction. No doubt, these factors interact and impact the possibility of NAFLD development, often if there is more visceral fat, irrespective of BMI. It allows making an assumption about a "common metabolic pathway" underlying NAFLD, irrespective of the body build.

Environmental factors: diet and eating behaviour

Excessive consumption of saturated fats and animal protein, sucrose and highly refined carbohydrates is the main component in the development of NAFLD [1, 4]. Regular consumption, e.g. of sugar-containing beverages, is closely associated with the development of NAFLD in children and adults. It has been shown that individuals with NAFLD consume three times as many sugared beverages as individuals without NAFLD [16–19]. Fructose is a simple sugar, which, together with glucose, forms sucrose, i.e. table sugar. Experiments and clinical practice have demonstrated that regular fructose consumption significantly boosts steatogenesis de novo in the liver, causing mitochondrial disorientation, marked endoplastic reticulum stress, and reduces fatty acid oxidation, leading to significant shifts in biocoenosis of gut microflora, the most active component of a number of metabolic processes in the body. Such shifts facilitate the development of parenchymatous hepatic inflammation and create conditions for insulin resistance [17]. Regular consumption of fructose and NAFLD development are the subject of numerous studies [4, 16]. For example, correlation between regular fructose consumption and a more advanced stage of fibrosis in patients with NAFLD and higher rates of its active form (steatohepatitis) has been demonstrated; this correlation is clearly observed in children [17].

Until now, the main dietary recommendations for patients with NAFLD were related mostly to individuals with a high body weight. When comparing, for instance, diets with restricted consumption of facts and carbohydrates in obese patients with NAFLD, only restricted consumption of carbohydrates allowed to significantly reduce fat deposits in the liver, together with a reduction in insulin resistance, abdominal obesity and total fat weight [20, 21]. Eight to ten weeks of restricted consumption of highly refined carbohydrates (fructose, glucose) in young men with NAFLD significantly reduced fat deposits in the liver and body weight values and completely normalised liver transaminase, gamma glutamine transpeptidase and total cholesterol. At the same time, liver fat reduction did not depend on changes in the body weight or obesity [22]. Isocaloric sugar replacement with starch for ten days (!) resulted in decrease in visceral fat, total fat in the liver, reduction in insulin resistance and steatogenesis de novo in obese children, who previously reported high daily consumption of sugar (over 50 g daily) [22]. Favourable impact of the diet with low fructose content, low glycaemic load and glycaemic index on the metabolism parameters was observed in children with NASH, who previously consumed significantly more fructose vs. children in general population [17]. Taking into account the mentioned data, the European Association for the Study of the Liver (EASL) recommends that people living with NAFLD follow the Mediterranean diet and exclude fructose and ultra-processed food from their diet [2, 4]. For patients with NAFLD and

the normal body weight, some components of the diet become extremely important. For example, choline deficit in volunteer males caused a significant increase in transaminase levels and fat accumulation in the liver tissue [20]. Other studies in NASH Clinical Research Network [20, 21] demonstrated that choline deficit in the diet of postmenopausal women for a month and a half resulted in significant shift in the liver function tests and was associated with marked hepatic inflammation. Adequate daily choline consumption is 550 mg for men and 425 mg for women; however, the majority of people often fail to consume the required amount of choline [15]. Since choline is a compound found mostly in animal-derived products, the chance of NAFLD in vegans and vegetarians is significantly higher [14, 15, 20, 21].

Choline biosynthesis is actively facilitated by phosphatidylethanolamine N-methyl transferase (PEMT), which catalyses phosphatidylcholine synthesis. Phosphatidylcholine is an integral component of the lipoprotein secretion system, particularly that of low density lipoprotein (LDL), in the liver [15]. Studies show that in individuals with NASH, PEMT expression was lower than in patients with simple steatosis; also, PEMT expression correlated with the platelet levels in the course of fibrosis progression in patients with NASH. It is interesting to note that numerous studies demonstrated a remarkable pattern: lower PEMT expression in lean patients and individuals with normal BMI [23, 24]; in animal models, it has been reported that PEMT -/- mice were protected against obesity, despite fat rich diet. PEMT gene is regulated by oestrogen, that is why choline deficit can be most obvious during menopause, manifesting as body weight gain, a higher risk of insulin resistance and development of NAFLD. To sum up the analysed results, we can conclude that choline deficit, caused by low PEMT expression or insufficient consumption with food, can be associated with potential development of NAFLD and is a condition for condition progression, especially in individuals with normal body weight.

Extremely important environmental factors impacting NAFLD development are smoking and alcohol consumption. Strictly speaking, the diagnostic criteria for NAFLD suggest absence of any significant alcohol consumption; however, currently, significant alcohol consumption has a very broad interpretation. For example, in the USA, the acceptable weekly alcohol consumption for men and women is 294 g and 196 g, respectively; in Europe, these values are lower: 210 g and 140 g, respectively. Values for the Asians are even lower: 140 g for men and 70 g for women [24, 25]. Currently, numerous epidemiological studies evaluate the impact of alcohol consumption on the course of NAFLD. For instance, a detailed examination of the French cohort with NAFLD demonstrated significantly higher mortality rates in patients, who consumed 7 units of alcohol a day (i.e., 56 g of absolute ethanol), while consumption of less than one unit per week was associated with higher survival rates [26, 27]. The impact of alcohol on liver diseases is especially obvious in obese individuals: with BMI > 30 kg/m^2, the liver toxicity of alcohol doubles and significantly increased the chance of HCC [27, 28].

Smoking is another significant factor in NAFLD progression. Large-scale Asian studies demonstrated that fibrosis progression rates in smokers with NAFLD were almost two times higher than in non-smokers in the same cohort [29].

Genetic factors

There is no doubt that obesity is the most significant independent risk factor of NAFLD, even with adjustments to sex, arterial hypertension, age, and metabolic health markers (homocysteine, lipid profile, transaminase, uric acid, fasting plasma glucose levels). It is obvious that there is a specific cohort of patients, who do not develop NAFLD even with obesity and chronic excessive calorie consumption. At the same time, it is well-known that there is J-shape correlation between NAFLD and BMI. It is worth noting that the risk of liver disorders is also significantly higher in individuals with BMI below 19 kg/m^2 [1, 5, 6, 9]. All this evidences the presence of a genetic component in the development of NAFLD — candidate genes, the activity of which can be associated both with NAFLD development and a protective role in its prevention.

The studies of gene *PNLPA3* polymorphisms in the development and progression of NAFLD are well-known [23, 30, 31]. For example, the single nucleotide polymorphism, associated with I148M (rs738409) replacement in gene *PNPLA3,* is the key genetic risk factor of NAFLD, while identification of this polymorphism is an advisable component of examination of patients with NAFLD in numerous clinical guidelines in the European Union and USA [23]. Close association between NAFLD development and progression and polymorphisms of genes *MBOAT7* (membrane of domain O-acyltransferase 7) and *TM6SF2* (antigen 2 of transporter 6 transmembrane family) has been identified. It is worth noting that all these studies were conducted only in obese or overweight individuals, whereas in patients with NAFLD with the normal body weight or lean patients, the study of genetic polymorphism of a number of candidate genes is described in very disorganised and sporadic publications [1, 4, 23]. Therefore, of note is a study of Japanese researchers [4], who evaluated the incidence of NAFLD in various communities of obese and overweight patients and patients

with the normal body weight. The authors conclude that genotype PNLPA3 rs738409 (GG, homozygotic variant) doubles the risk of NAFLD in patients with the normal body weight vs. obese and overweight patients, who did not have mutation in this gene. At the same time, using the BMI-based classification, there were no differences in the incidence of genetic variants of genes *MBOAT7* and *TM6SF2* in the mentioned groups of patients. One European study [4] in 187 Austrian citizens showed a higher incidence of the risk allele (rs738409) of gene *PNLPA3* in individuals with NAFLD and the normal body weight vs. obese and overweight patients: patients with the normal body weight had the risk allele in 4% of cases, whereas other patients had this allele only in 0.3% of cases. Similar rare studies in patients with the normal body weight and NAFLD, conducted in various geographic locations (Europe, South and Southeast Asia, Japan), demonstrated the same pattern: the incidence of the risk allele rs738409 of gene *PNLPA3* was significantly higher in patients with the normal body weight and lean patients with NAFLD vs. obese and overweight individuals [4, 23].

The risk allele AA of variant V175M (rs7946) in gene *PEMT*, causing the loss of its activity, was reported 1.7 times more often in the group of patients with NAFLD vs. controls [23]. Other genetic polymorphisms of *PEMT* (rs4646343, rs3761088, rs12325817) were associated with intensive triglyceride accumulation in hepatic cells because of restricted choline diet [4, 23]; allele variants rs 4646365 and 1531100 were associated with higher rates of NAFLD diagnosis in menopausal women. Detailed exome sequencing in pooled results from two patients with NAFLD and six healthy individuals showed that only allele variant rs7946 in gene *PEMT* and rs2290532 in the gene associated with oxysterole (*OSBPL10*) were closely related to NAFLD [23], whereas another study [32], where the close association between allele rs7946 of *PEMT* gene and the risk of NAFLD was shown, did not observe any association between variants of gene *OSBPL10* with NAFLD.

Another group of very diverse genetic disorders is lipodystrophies. This group is characterised by a common phenotype: adipose tissue deficit without obvious nutritional deficiency and active metabolism [33, 34]. A typical pattern of these conditions is NAFLD, the pathogenetic mechanisms of which are based on the inability of the body to accumulate lipids in the form of fats. For these conditions, typical pathogenic variants of genetic mutations have been identified, which are often family-related: genes encoding hormone sensitive lipase (*LIPE*), perilipin 1 (*PLIN1*), peroxisome proliferator-activated receptor gamma (*PPARG*), lamin A/C (*LMNA1*), v-akt murine thymoma viral oncogene homolog (*AKT2*), and cell death-inducing DFFA-like effector (*CIDEC*) [4, 33]. Hepatic steatosis in such patients is observed almost in 100% of cases, thus assuming that NAFLD in lean individuals can be a specific type of ectopic fat accumulation, the mechanisms of which are similar to lipodystrophy. Later, the definition was given to the concept of polygene risk, related to insulin resistance and marked reduction in fat mass in the lower limbs, which are the integral signs of lipodystrophy. Later researches showed that the polygene index of the risk of lipodystrophy is closely associated with NAFLD, severe fibrosis and reduction in fat mass in the lower limbs [34].

Endocrine and other factors of NAFLD development in patients with the normal body weight

Endocrine disbalance is another factor of NAFLD. It is well known that the risk of NAFLD is significantly higher in postmenopausal women [4, 35]. This fact can be explained by the loss of oestrogen protection together with increasing body weight, dyslipidaemia and impaired glucose tolerance. Another known hormonal factor of NAFLD and NASH is hyperandrogenism, irrespective of resistance and obesity. An increased circulating testosterone level was associated with a higher degree of steatosis, higher levels of proinflammatory cytokines and fibrosis stage in middle-aged women [35]. A completely separate form of liver damage is NAFLD in patients with hypothyroidism. Hormone replacement therapy has obvious favourable effect on steatosis regression, reduction of fibrosis, and biochemistry normalisation [36]. Currently, there are no proper studies of the characteristics of the endocrine profile in patients with NAFLD and normal body weight.

When thinking about possible pathophysiological components of NAFLD development in individuals with the normal body weight, it is essential to mention the studies, which demonstrated synergetic effects of fats and fructose on oestrogen deficit development, which causes damage to hepatic cell functions [35]; similar correlation was found between choline deficit and oestrogen levels, which can be associated with a higher risk of NAFLD in the population under discussion. For instance, the average hepatic fibrosis score in postmenopausal women with NAFLD was significantly higher vs. premenopausal women with NAFLD, despite almost the same level of choline consumption with food. Besides, it should be remembered that oestrogens are a potent *PEMT* expression regulator: reduced oestrogen production is associated with lower *PEMT* expression, which is one of the most important pathophysiological mechanisms of NAFLD development in postmenopausal women caused by chronic choline deficit [4, 15, 16, 20].

Key considerations of NAFLD screening and therapy in patients with the normal body weight

Currently, there are no generally recognised and accepted recommendations for patients with NAFLD and normal body weight, despite high incidence of NAFLD and unfavourable outcomes in the population in question; none of the professional medical communities currently recommends screening among patients with NAFLD and normal body weight. For example, the practical guidelines of the American Association for the Study of Liver Diseases (AASLD) do not recommend regular NAFLD screening even in high risk groups (DM2, obesity) due to the lack of scientific evidence, which could prove the efficiency of various diagnostic approaches, therapy regimens and, as a result, economic justification and adequate advantages of the screening. There are various, sometimes completely opposite, opinions in this regard. Some specialists still recommend examination of patients with an obvious risk of hepatic disorders: individuals with DM2 or metabolic syndrome (MS); patients over 50 years of age. It is possible to use relatively simple laboratory and imaging devices, forecasting algorithms (complete blood count, blood biochemistry, abdominal ultrasound examination, various scales) to form an idea of the degree of fibrosis and to forecast the rates of its progression [37, 38]. However, to the contrary, the European and Asian guidelines propose screening among patients at the highest risk of NAFLD, including patients with DM2 and obesity [38]. At the same time, numerous local clinical guidelines and recommendations admit the presence of NAFLD in individuals with the normal body weight and lean patients, especially in those who show the signs of metabolic syndrome or belong to the Asian population. It is obvious that the development of consensus guidelines for the screening, therapy, forecast, and evaluation of long-term risks is essential for the optimal management of ***all*** patients with NAFLD.

Currently, there are no direct indication of the screening and therapy of NAFLD in patients with the normal body weight in many guidelines. A lot of important and fundamental questions arise: e.g., Is the visceral fat, and not the total body fat content, a more significant factor of NAFLD in patients with the normal body weight vs. obese patients? If the answer is "yes", then are there currently more efficient alternatives to the use of BMI as an obesity marker for the NAFLD screening? There are a number of published studies promoting the idea that waist circumference is a more accurate indicator of adipose tissue distribution in the body, meaning that this is a better method for identification of a cohort with a significantly higher risk of cardiovascular diseases [1-3, 38, 39]. However, the widespread introduction of this simple and inexpensive diagnostic approach as a standard measure of obesity, especially in primary case settings, requires complete transformation of the diagnostic process. Waist circumference measurement will be an important component of obesity diagnosis, especially in patients with normal BMI. The fundamental question can sound as follows: "Is NAFLD in individuals with the normal body weight a separate clinical entity, which requires specific diagnostic and therapeutic approaches, or is it a subtype of the classic obesity-related NAFLD, responding to weight management, management of hyperlipidemia, arterial hypertension and insulin resistance?". Even in patients with the normal body weight with clinical and morphological signs of NAFLD, many metabolic health parameters are significantly altered: there are differences in triglyceride levels, waist circumference, log HOMA-IR, age, waist circumference vs. patients with the normal body weight, who does not suffer from NAFLD [38]. This fact allows drawing a conclusion that NAFLD in individuals with the normal body weight is a form of liver damage similar to that in obese patients [3]. At the same time, individuals with the normal body weight and NAFLD have a higher risk of hypertriglyceridemia, insulin resistance, central obesity and hyperuricemia vs. obese patients [3, 39].

We believe that this is essential to emphasise the attitude of the cohort under discussion to the diet and exercises. Numerous studies demonstrated that in overweight and obese patients with NAFLD, loss of 5% of the baseline weight is associated with clinical and laboratory stabilisation of NAFLD in 75% of cases [40]. It was found out later that a similar pattern can be observed in patients with NAFLD and normal body weight: after the loss of some weight (no more than 5% of the baseline value) and exercises, 57% of patients with the normal body weight showed repression of clinical and laboratory signs of NASH [22]. It is believed that the results can evidence that weight management and controlled exercises are useful and universal therapeutic approaches in the management of ***all*** patients with NAFLD.

Recently, drug management of NAFLD has been changing rapidly, and new approaches have been appearing; at the same time, it is essential to understand whether medicinal products developed for drug management of classical obesity-related NAFLD, are equally efficient for NAFLD patients with the normal body weight, which requires large-scale clinical trials. Such clinical trials should be conducted without delay, and potential efficacy of some drugs should be evaluated, e.g., of sodium-glucose linked transporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1) agonists, obeticholic acid, pioglitazone and saroglitazar, a fixed combination of antagonists of glucose-dependent insulinotropic peptide/glucagon-like peptide 1.

Despite a lot of common pathophysiological components of NAFLD in individuals with various body weight, it is necessary to clearly define the key aetiological and pathophysiological factors, environmental factors, genetic characteristics in order to shape an individualised approach to the selection of the therapy and management of NAFLD patients with the normal body weight. The role of various diet factors and a specific nutrition composition have hardly been studied and compared to other significant risk factors of NAFLD in patients with the normal body weight. Numerous studies consistently prove the correlation between hepatic dysfunction and choline deficit, which is known to have a specific phenotype of diet-mediated obesity resistance. But are there any other nutrient factors, which might facilitate NAFLD development; and if there are any such factors, then how do they interact with functional genetic variants, as it can be observed, e.g., between choline and PEMT? Also, it is highly possible that there are other, yet unknown, environmental factors, for instance, biological or herbal supplements, promoting NAFLD development in individuals with the normal body weight.

Recent attempts to use cluster analysis turned out to be very interesting; it allows identifying five various diabetes subtypes, each of which is very specific in terms of patient characteristics and the risk of complications [39, 41]. It is obvious that the use of this classification model for patients with non-homogenous disease brings about more targeted therapy and management approaches as compared to a universal principle, which is currently applied. It is quite possible that a similar cluster analysis could be used also to characterise NAFLD progression: from the group of patients with relatively benign disease progression to patients with severe and progressive condition, which allows developing various therapeutic strategies for the patient management. Besides, studies in the group of NAFLD patients with the normal body weight should continue in order to evaluate the incidence of this form of disease in various geographical locations and ethnicities and to thoroughly analyse eating habits. An objective idea of the long-term sequelae of NAFLD in individuals with the normal body weight, characteristics of this disease variant, its progression rates and progression-promoting factors is the essential condition for the development of an adequate therapeutic strategy in the patient population in questions.

Other environmental factors such as intestinal dysbiosis, malnutrition, long-term drug therapy, parenteral feeding are the subject of a separate discussion and analysis of other, very versatile mechanisms of NAFLD development, including patients with the normal body weight [42, 43].

Therefore, NAFLD in patients with the normal body weight is a frequent clinical condition. The phenotype of these patients does not demonstrate (at least externally) any signs of metabolic illness as compared, e.g., to patients with NAFLD and obesity. It can be assumed that NAFLD developing in patients with the normal body weight and in lean patients is a clinical situation promoted by a composition of several conditions: diet, geographical location and ethnicity, genetic factors, age, and eating habits. At the same time, like with many things in life, a patient with the normal body weight is not the primary target of an attending physician trying to diagnose NAFLD and the rate of disease progression. Diet, choline consumption, alcohol consumption, menstrual function, age, ethnicity and geographical location, as well as hormone status evaluation are the subject of a separate examination in NAFLD patient with the normal body weight. In order to lower the NAFLD incidence in the population under discussion, a thorough development of screening for such patients, which is not tied to BMI values, is required. This patient cohort needs further thorough study; a therapeutic strategy should be actively developed, and patients should take more active part in clinical trials to evaluate the value and significance of diagnostic approaches and planned therapy.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Никитин И.Г.: окончательное утверждение публикуемой статьи, согласие принять на себя ответственность за все аспекты работы и гарантия того, что все вопросы, связанные с точностью и добросовестностью любой части работы, могут быть надлежащим образом исследованы и урегулированы

Стародубова А.В.: существенный вклад в разработку концепции или планировании научной работы, либо получение, анализ или интерпретацию работы

Кисляк О.А.: существенный вклад в разработку концепции или планировании научной работы, либо получение, анализ или интерпретацию работы

Демидова Т.Ю.: составление черновика рукописи

Ильченко Л.Ю.: существенный вклад в разработку концепции или планировании научной работы, либо получение, анализ или интерпретацию работы

Contribution of authors:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Nikitin I.G.: Final approval of the published article, agreement to assume responsibility for all aspects of the work, and a guarantee that all issues related to the accuracy and integrity of any part of the work can be properly investigated and resolved

Starodubova A.V.: Significant contribution to the development of the concept or planning of scientific work, or the receipt, analysis or interpretation of work

Kislyak O.A.: Significant contribution to the development of the concept or planning of scientific work, or the receipt, analysis or interpretation of work

Demidova T.Yu.: Drafting of the manuscript

Ilchenko L.Yu.: Significant contribution to the development of the concept or planning of scientific work, or the receipt, analysis or interpretation of work

Список литературы/References:

1. Feldman M., Friedman L.S., Brandt L.J et al. Gastrointestinal and Liver Disease. Pathophysiology, diagnosis, management. Sleisinger and Fordtran's, Elsevier, 11th Edition, 2021. p.2488
2. Younussi Z., Anstee Q.M., Marietti M. et al. Global burden of NAFLD and NASH: trends, predictors, risk factors and prevention. Nat Rew Gastroenterol Hepatol. 2018; 15(1): 11-20 https//: doi: 10.1038/nrgastro.2017.109
3. Ye Q., Zou B., Yeo Y.H. at al. Global prevalence, incidence and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(8): 739-752 https//: doi: 10.1016/S2468-1253(20)30077-7
4. DiStefano J.K., Gerhard G.S. NAFLD in normal weight individuals. Diabetologia & Metabolic Syndrome, 2022; 14:45 https//:doi.org/10.1186/s13098-022-00814-z
5. Francanzani A.L., Petta S., Lombardi R. at al. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease and association with visceral obesity. Clin Gastroenterol Hepatol. 2017; 15(10): 1604-1611 https//:doi: 10.14309/ctg.0000000000000326
6. Estes C., Razavi H., Loombra R. et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden disease. Hepatology. 2018;67(1):123 — 133 https//: doi: 10.1002/hep.29466
7. Kim H.J, Lee K.E, Kim D.J. at al. Metabolic significantce of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch intern Med. 2004; 164(19):2169-2175 https//: doi: 10.1001/archinte.164.19.2169.
8. Akyuz U., Yesil A., Yilmaz Y. Characterization of lean patients with nonalcoholic fatty liver disease: potential role of high hemoglobin levels. Scand J Gastroenterol. 2015; 50(3): 341-346 https//: doi: 10.3109/00365521.2014.983160. Epub 2014 Dec 26.
9. Cruz ACD, Buganesi E., Gerge J. at al. 379 characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology. 2014;146(5): S-909 https//: doi: 10.1016/S0016-5085(14)63307-2
10. Feldman A., Wernly B., Strebinger G et al. Liver-related mortality is increased in lean nonalcoholic liver fatty liver disease compared to overwieght and obese subjects. J Gastrointest Liver Dis. 2021; 30(3): 366-373 https//: doi: 10.15403/jgld-3622
11. Yanoussi Z.M., Yilmaz Y., Yu M.L. at al. Clinical and patient-reported outcomes from patients with nonalcoholic fatty liver disease across the world: data from the global non-alcoholic steatohepatitis (NASH)/non-alcoholic fatty liver disease (NAFLD) registry. Clin Gastroenterol Hepatol. 2021; 20(10): 2296-2306.e6 https//:doi.org/10/1016/j.cgh.2021.11.004
12. Hagstrom H., Nasr P., Ekstedt M. at al. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: a long-term follow-up study. Hepatol Commun. 2018;2(1): 1236-1249 https//: doi: 10.1002/hep4.1124
13. Lee M., Yee H.Y., Li X. et al. 2019 GLOBAL NAFLD Prevalence: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2022; 20(12):2809-2817.e28 https//:doi: 10.1016/j.cgh.2022.12.002
14. Kim S., Fenech M.F., Kim P.J. Nutritionally recommended food for semi — to strict vegetarian diets based on large-scale nutrient composition data. Sci Rep. 2018;8(1):4344 https//: doi: 10.3390/ijms21124479
15. Wallace T.C., Bluzstjan J.K., Caudill M.A. at al. Choline: the under-consumed and underappreciated essential nutrient. Nutr Today. 2018;53(6): 240-253 https//: doi: 10.1097/NT.0000000000000302
16. DiStefano J.K., Fructose-mediated effects on gene expression and epigenetic mechanisms associated with NAFLD pathogenesis. Cell Mol Life Sci. 2020;77(11): 2079 — 2090 https//: doi: 10.1007/s00018-019-03390-0.
17. DiStefano J.K., Shaibi G.Q. The relationship between excessive dietary fructose consumption and pediatric fatty liver disease. Pediatr Obes. 2020;16: e12759 https//: doi: 10.1111/ijpo.12759
18. Jones R.B., Alderete T.L., Kim J.S. at al. High intake of dietary fructose in overweight/obese teenagers associated with depletion of Eubacterium and Streptococcus in gut microbiome. Gut Microbes. 2019;10(6): 712 — 719 https//: doi: 10.1111/ijpo.12759
19. Russo E., Leoncini G., Esposito P. at al. Fructose and uric acid: major mediators of cardiovascular disease risk starting at pediatric age. Int J Mol Sci 2020;21(12): 4479 https//: doi: 10.3390/ijms21124479
20. Parry S.A., Hodson L. Influence of dietary macronutrients on liver fat accumulation and metabolism. J Investig Med. 2017; 65(8): 1102-1115 https//: doi: 10.1136/jim-2017-000524.
21. Nakatsuka A., Matsuyama M., Yamaguchi S. at al. Insufficiency of phosphatidylethanolamine N-methyltransferase is risk for lean non-alcoholic steatohepatitis. Sci Rep. 2016;6: 21721 https//: doi: 10.1038/srep21721
22. Chalasani N., Younussi Z., Lavine J.E. at al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from American association for the study of liver diseases. Hepatology. 2018;67(1): 328-357 https//: doi: 10.1002/hep.29367
23. Martin K., Hatab A., Athwal V.S. at al. Genetic contribution to non-alcoholic fatty liver disease and prognostic implications. Curr Diab Rep. 2021; 21(3):8 https//: doi: 10.1007/s11892-021-01377-5
24. Bale G., Vishnubhotla R.V., Mitnala S. at al. Whole-exome sequencing identifies a variant in phosphatidylethanolamine — N-methyltransferase gene to be associated with lean-nonalcoholic fatty liver disease. J Clin Exp Hepatol. 2019;9(5): 561-568 https//: doi: 10.1016/j.jceh.2019.02.001
25. DiStefano J.K. NAFLD and NASH in postmenopausal women: implications for diagnosis and treatment. Endocrinology.2020; 161(10):bqaa134 https//: doi: 10.1210/endocr/bqaa134
26. Decraecker M., Dutartre D., Hiriart J.B. at al. Long-term prognosis of patients with alcohol-related liver disease or non-alcoholic fatty liver disease according to metabolic syndrome or alcohol use. Liver Int. 2021;42(2): 350-362 https//: doi: 10.1111/liv.15081

27. Chang Y., Cho Y.K., Kim Y. et al. Nonheavydrinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: a cohord study. Hepatology. 2019;69(1): 64-75 https//: doi: 10.1002/hep.30170
28. Hajifathalian K., Torabi Sagvand B., McCullough A.J. Effect of alcohol consumption on survival in nonalcoholic fatty liver disease: a national prospective cohort study. Hepatology. 2019;70(2): 511-521 https//: doi: 10.1002/hep.30226
29. Okamoto M., Miyake T., Kitai K. at al. Cigarette smoking is a risk factor for the onset of fatty liver disease in nondrinkers: a longitudinal cohort study. PLos ONE. 2018; 13(4): e0195147 https://doi.org/10.1371/journal.pone.0195147
30. Тихомирова А.С., Кисляков В.А., Байкова И.Е. и др. Клинико-морфологические параллели полиморфизма гена PNLPA3 у пациентов с неалкогольной жировой болезнью печени. Терапевтический архив. 2018; 90(2): 85-89. Tikchomirova A.S., Kislyakov V.A., Baykova I.E. at al. Clinical and morphological parallels of PNLPA3 gene polymorphism in patients with non-alcoholic fatty liver disease. Therapeutic archive. 2018; 90(2): 85-89 [In Russian] https//: doi. org/10.26442/terarkh.201890285-88
31. Никитин И.Г., Тихомирова А.С., Жинжило Т.А. и др. Связь цирроза печени в исходе неалкогольной жировой болезни печени с полиморфизмом гена PNLPA3/rs738409. Архивъ внутренней медицины. 2020; 10(2) :148 — 154. Nikitin I.G., Tikchomirova A.S. Zhinzhilo T.A. at al. Association of liver cirrhosis in the outcome of non-alcoholic fatty liver disease with polymorphism of the PNLPA3/rs738409 gene. The Russian Archives of Internal Medicine. 2020; 10(2): 148-154 [In Russian] https//:doi.org/10.20514/2226-6704-2020-10-2-148-154
32. Lin H., Wong G.L., Chan A.W. at al. Association of genetic variations with NAFLD in lean individuals. Liver Int. 2022;42(1): 149 — 160 https//: doi: 10.1111/liv.15078
33. Akinci B., Onay H., Demir T. et al. Clinical presentations, metabolic abnormalities end-organ complications in patients in patients with familial partial lipodystrophy. Metabolism. 2017;72: 109 — 119 https//: doi: 10.1016/j.metabol.2017.04.010
34. Brown R.J., Araujo-Vilar D., Cheung P.T. et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. J Clin Endocrinol Metab. 2016;101(12): 4500 — 4511 https//: doi: 10.1210/jc.2016-2466
35. Petta S., Gliresi A., Bianco J. at al. Insulin resistance and hyperandrogenism drive steatosis and fibrosis risk in young females with PCOS. PlosONE, 2017;12(11): e0186136 https//: doi: 10.3390/nu13061848
36. Lonardo A., Ballestri S., Mantovani A. at al. Pathogenesis of hypothyroidism-induced NAFLD: evidence for a distinct disease entity? Dig Liver Dis. 2019;51(4): 462 — 470 https//: doi: 10.1016/j.dld.2018.12.014
37. Youngs R., Caviglia G.P., Govaero O. at al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. J Hepatol. 2021; 75(4): 786 -794 https//: doi: 10.1016/j.jhep.2021.05.008
38. Schattenberg J.M., Anstee Q.M., Caussy C. at al. Differences between current clinical guidelines for screening, diagnosis and management of nonalcoholic fatty liver disease and real-world practice: a targeted literature review. Expert Rev Gastroenterol Hepatol. 2021;15(11): 1253-1266 https//: doi: 10.1080/17474124.2021.1974295
39. Bjorkstrom K., Franzen S., Eliasson B. at al. Risk factors for severe liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol. 2019;17(13):2769-2775.e4 https//: doi: 10.1016/j.cgh.2019.04.038
40. Hamurcu Varol P., Kaya E., Alphan E. et al. Role of intensive dietary and lifestyle interventions in the treatment of lean nonalcoholic liver disease patiettents. Eur J Gastroenterol Hepatol. 2020;32(10): 1352-1357 https//: doi: 10.1097/MEG.0000000000001656.
41. Ahlquist E., Storm P., Karajamaki A. et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018;6(5)361 — 369 https//: doi: 10.1016/S2213-8587(18)30051-2
42. Lee G., You H.J., Bajaj J.S. at al. Distinct signatures of gut microbiome and metabolites associated with significant fibrosis in non-obese NAFLD. Nat Commun. 2020;11(1):4982 https//: doi: 10.1038/s41467-020-18754-5.
43. Gibilino G., Sartini A., Gitto S. at al. the other side of malnutrition in inflammatory bowel disease (IBD): non-alcoholic fatty liver disease. Nutrients.2021;13(8): 2772 https//: doi: 10.3390/nu13082772

Информация об авторах

Никитин Игорь Геннадиевич — доктор медицинских наук, профессор, заведующий кафедрой госпитальной терапии им. академика Г.И. Сторожакова Института клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, ORCID ID: http://orcid.org/0000-0003-1699-0881, e-mail: igor.nikitin.64@mail.ru

Стародубова Антонина Владимировна — доктор медицинских наук, профессор, заведующая кафедрой факультетской терапии Института клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, ORCID ID: http://orcid.org/0000-0001-9262-9233, e-mail: lecebnoedelo@yandex.ru

Кисляк Оксана Андреевна — доктор медицинских наук, почетный профессор кафедры факультетской терапии Института клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, ORCID ID: http://orcid.org/0000-0002-2028-8748, e-mail: kisliakoa@mail.ru

Демидова Татьяна Юльевна — доктор медицинских наук, заведующая кафедрой эндокринологии Института клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, ORCID ID: http://orcid.org/0000-0001-6353-540X, e-mail: t.y.demidova@gmail.com

Ильченко Людмила Юрьевна — доктор медицинских наук, профессор кафедры госпитальной терапии им. академика Г.И. Сторожакова Института клинической медицины ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, ORCID ID: http://orcid.org/0000-0001-6029-1864, e-mail: ilchenko-med@yandex.ru

Information about the authors

Igor G. Nikitin — Doctor of Medical Sciences, Professor, Head of the Department of Hospital Therapy named after Academician G.I. Storozhakov, Institute of Clinical Medicine, N.I. Pirogov Russian National Research Medical University, Ministry of Healthcare of the Russian Federation, Moscow, ORCID ID: http://orcid.org/0000-0003-1699-0881, e-mail: igor.nikitin.64@mail.ru

Antonina V. Starodubova — Doctor of Medical Sciences, Professor, Head of the Department of Faculty Therapy of the Institute of Clinical Medicine of the Russian National Research Medical University named after N.I. Pirogov of the Ministry of Health of the Russian Federation, Moscow, ORCID ID: http://orcid.org/0000-0001-9262-9233, e-mail: lecebnoedelo@yandex.ru

Oksana A. Kislyak — Doctor of Medical Sciences, Honorary Professor of the Department of Faculty Therapy of the Institute of Clinical Medicine of the Russian National Research Medical University named after N.I. Pirogov of the Ministry of Health of the Russian Federation, ORCID ID: http://orcid.org/0000-0002-2028-8748, e-mail: kisliakoa@mail.ru

Tatyana Yu. Demidova — Doctor of Medical Sciences, Head of the Department of Endocrinology, Institute of Clinical Medicine, Russian National Research Medical University named after N.I. Pirogov, Ministry of Health of the Russian Federation, ORCID ID: http://orcid.org/0000-0001-6353-540X, e-mail: t.y.demidova@gmail.com

Lyudmila Yu. Ilchenko — Doctor of Medical Sciences, Professor of the Department of Hospital Therapy named after Academician G.I. Storozhakov of the Institute of Clinical Medicine of the Russian National Research Medical University named after N.I. Pirogov of the Ministry of Health of the Russian Federation, ORCID ID: http://orcid.org/0000-0001-6029-1864, e-mail: ilchenko-med@yandex.ru

Автор, ответственный за переписку / Corresponding author