https://doi.org/10.54500/2790-1203-2024-4-124-13-19
UDC 616.36-089; 616.15
IRSTI 76.29.30; 76.29.34

Review article

Metabolic-associated fatty liver disease and dyslipoproteinemia. Literature review

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Abstract

The major cholesterol transporter in the circulation, low-density lipoproteins (LDL), should still be considered the most atherogenic lipoprotein species, but not because its contribution to serum cholesterol levels. In most individuals, the atherogenic potential of LDL arises from an increase in the number of small dense LDL particles rather than from its cholesterol content. There is now abundant evidence from cross-sectional and prospective studies showing that LDL particle size is significantly associated with coronary heart disease (CHD) and is a prognostic factor for increased coronary risk.

The purpose of this literature review is aimed to provide a current data description of the prevalence of metabolic-associated fatty liver disease and dyslipoproteinemia in global practice.

Information was searched in Pubmed, ResearchGate, and eLibrary databases. The review included primary studies (both descriptive and analytical), secondary studies (including systematic reviews and meta-analyses), methodological manuals, clinical guidelines, and full-text publications in Russian and English published over the last 10 years.

Therefore, patients suffering from nonalcoholic fatty liver disease have an increased risk of atherosclerosis and cardiovascular disease. The association of nonalcoholic fatty liver disease and atherosclerotic cardiovascular pathologies is based on complex and interrelated mechanisms. According to the literature analysis, the following key pathogenetic links that are connected nonalcoholic fatty liver disease and atherosclerosis can be identified: endothelial dysfunction, lipid profile disorders, increased production of a number of proinflammatory cytokines and inflammatory response, and increased oxidative stress.

Keywords: non-alcoholic fatty liver disease, lipoproteins, cardiovascular diseases, liver diseases, dyslipidemias.

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2024; 4 (124): 13-19
Recieved: 12-08-2024
Accepted: 03-10-2024

Introduction

Metabolic Associated Fatty Liver Disease (MAFLD) is characterized by excessive accumulation of fat in the form of triglycerides (steatosis) in the liver, histologically observed in >5% of hepatocytes. Patients with MAFLD exhibit liver cell damage and inflammation in addition to the excess fat (steatohepatitis). This condition, known as non-alcoholic steatohepatitis (NASH), is histologically indistinguishable from alcoholic steatohepatitis (ASH) [1,2]. The primary transporter of cholesterol in the bloodstream, low-density lipoproteins (LDL), are considered the most atherogenic type of lipoproteins. The LDL levels in most patients increase due to a rise in the number of small, dense LDL particles rather than the cholesterol content within them. To date, there is a wealth of cross-sectional and prospective studies showing that LDL particle size is most strongly associated with ischemic heart disease (IHD) and is a prognostic factor for increased coronary risk [3].

There are several reliable mechanisms linking small, dense LDL particles to the atherogenic process. The rate at which serum lipoprotein particles enter the arterial wall depends on their size, and thus, it is faster for small, dense LDL particles. Elements of the extracellular tissue matrix of the intima-proteoglycans-selectively bind small, dense LDL particles with high affinity, sequestering these lipoproteins in a pro-oxidant environment. Oxidation of LDL facilitates the irreversible deposition of cholesterol in the arterial wall, and numerous studies have shown that small, dense LDL particles are more susceptible to oxidative modification than their larger, lighter counterparts [4]. The increase in the number of small, dense LDL particles is a consequence of a defect in the metabolism of triglyceride-rich lipoproteins. One mechanism may involve the overproduction and prolonged residence time of large, triglyceride-rich very low-density lipoproteins (VLDL) in the postprandial phase [5,6].

MAFLD affects one-third of the global population and is accompanied by dyslipoproteinemia, leading to adverse cardiovascular outcomes. MAFLD has become a highly prevalent chronic, progressive liver disease in Western countries, with a continuously increasing incidence and prevalence, imposing a significant clinical and economic burden [3,7,8]. The prevalence of this disease from 2016 to 2018 was lowest in Africa (13.5%); intermediate in the USA (24%), Europe (23%), and East Asia (27%); and highest in Mexico, Central and South America (31%), the Middle East (32%), and South Asia (33%) [9]. In recent years, with rising living standards and changes in lifestyle and dietary habits, the prevalence of MAFLD has rapidly increased in Asia, becoming a significant public health issue [10,11].
MAFLD is characterized by the accumulation of pathological ectopic fat along with persistent systemic inflammation. This leads to several destructive pathophysiological processes, including alterations in glucose, fatty acid, and lipoprotein metabolism, increased oxidative stress, endothelial dysfunction, and rapid development of systemic atherosclerosis. Ultimately, a dysfunctional cardiometabolic phenotype develops with cardiovascular diseases, which are a leading cause of premature death. Predisposing risk factors include diabetes mellitus, obesity, and dyslipoproteinemia. According to international data, MAFLD affects approximately 15-30% of the working-age population overall, and its prevalence steadily increases to approximately 70-90% among individuals with obesity or type 2 diabetes [3,12,13].

Thus, the aim of the current review is to provide an overview of the latest data on the prevalence of metabolic associated fatty liver disease and dyslipoproteinemia in global practice.

Literature Search Strategy

Information retrieval was conducted in the databases Pubmed, ResearchGate, and eLibrary. The review includes primary studies (both descriptive and analytical), secondary studies (including meta-analyses and systematic reviews), methodological guides, clinical guidelines, as well as full-text publications in Russian and English languages published over the last 10 years.

Lipid metabolism in the liver

According to some data, the liver is known to perform approximately 500 metabolic functions, among which the main ones include: protein metabolism — where both anabolic (synthetic) and major catabolic processes occur; carbohydrate metabolism; lipid metabolism— where the liver plays a primary role in the metabolism of neutral fats, fatty acids, cholesterol, and phospholipids; enzyme metabolism and vitamin metabolism; regulation of blood volume and pigment metabolism [3]. The liver is significantly more involved in the metabolism and transport of fats than in their storage. Liver cells, in lipid metabolism, perform the following functions: they absorb cholesterol and phospholipids from the blood and break them down, convert excess carbohydrates into fats when necessary, and synthesize globulins for lipid transport.

The term "lipids" refers to substances that share a common physical property — hydrophobicity. Structurally, lipids are so diverse that they do not have a common chemical structure. Lipids are classified into classes based on molecules with similar chemical structures and shared biological properties. The synthesis of fats occurs during the absorptive period of digestion and is stimulated by insulin. Fats are the most compact form of storing energy, so excess carbohydrates from food are converted into fats and stored in adipocytes. Active fat synthesis occurs in the liver, adipose tissue, and lactating mammary glands. Triacylglycerols (TAGs) constitute a significant mass of lipids in the body, serving as a form of energy storage. Fats, primarily in subcutaneous adipose tissue, perform functions of thermal insulation and mechanical protection [14].

Lipids of different classes vary in structure and functions. Most lipids include fatty acids with complex ether bonds with glycerol, cholesterol, and/or an amide bond with sphingosine amino alcohol. Lipid metabolism involves two main metabolic pathways: endogenous and exogenous. If lipids originate from food, it is referred to as the exogenous metabolic pathway, whereas if they originate from the liver, it is the endogenous pathway. Cholesterol transport in the blood occurs via lipoproteins. The metabolism of individual classes of lipoproteins is closely interconnected. There are various classes of lipoproteins, each characterized by specific functions:

- chylomicrons (CM)
- very low-density lipoproteins (VLDL)
- low-density lipoproteins (LDL)

• intermediate-density lipoproteins (IDL)

• high-density lipoproteins (HDL).

From the liver, cholesterol is exported together with fat in the form of VLDL (very low-density lipoproteins). In capillaries, adipose tissue, and other tissues, lipoprotein lipase (LPL) catalyzes the hydrolysis of fats, and fatty acids are taken up by cells. After most of the fat is lost, VLDL transforms into LDL in the bloodstream as presented in Table 1.

Table 1 - The differences of fat and cholesterol contents of VLDL to LDL

Content	VLDL	LDL	Difference
Fat	50%	7%	43%
Cholesterol	20%	45-50%	-25-30%

Lipoproteins mainly contain cholesterol esters rather than free cholesterol [15]. Patients with MAFLD, especially when accompanied by NASH, are at increased risk of cardiovascular diseases (CVD) [16,17]. It's worth noting that CVD is a leading cause of death among MAFLD patients [15]. Classical risk factors for CVD are often identified in MAFLD [18], and changes in adipose tissue in MAFLD can predict the risk of developing CVD as accurately as standard functional indicators, making MAFLD itself a risk factor for CVD [17,18].

Metabolic associated fatty liver disease and CVD

A large body of research provides evidence that MAFLD is an underestimated and independent risk factor for atherosclerotic cardiovascular diseases (ASCVD). Subclinical cardiovascular diseases and many other risk factors for ASCVD are elevated among patients with MAFLD/NASH. Abdominal obesity, type 2 diabetes, insulin resistance, hypertension, and dyslipidemia — typical components of metabolic syndrome (MetS) [16] — are coexisting pathological conditions often associated with MAFLD, and their coexistence in the same individual increases the likelihood of more advanced forms of MAFLD [17,18,19].

Between 10 to 25% of patients with MAFLD may develop NASH, which can progress to liver cirrhosis, hepatocellular carcinoma, and liver failure. The primary cause of mortality in MAFLD patients is ASCVD [7,20]. Patients with MAFLD typically show a significant increase in mean intima-media thickness of the brachiocephalic arteries and a higher prevalence of atherosclerotic plaques [21,22]. Endothelial dysfunction is an early stage in the process of atherosclerosis, preceding its development [23,24], and consequently plays a crucial role in the development of ASCVD. Intraliver endothelial dysfunction has been described in MAFLD [25], indicating that this condition may lead to the onset of atherosclerosis and ASCVD.

Patients with NASH show changes in left ventricular function parameters, even in the absence of a clear reduction in left ventricular ejection fraction, including left atrial dysfunction and subclinical myocardial dysfunction [23, 24]. It has also been noted that MAFLD may affect the condition of heart valves and is significantly associated with an increased risk of aortic valve sclerosis [26]. S. Ballestri et al. report an accelerated incidence of chronic heart failure in this patient population. Moreover, these changes undoubtedly increase the risk of developing arrhythmias, especially atrial fibrillation [25].

The initial stages of liver steatosis involve the ectopic accumulation of triglycerides in the liver. Several sources of fatty acids are used for the hepatic synthesis of ectopically stored triglycerides, but most commonly, they result from increased flux of free fatty acids due to excessive hydrolysis of triglycerides in adipose tissue, driven by the lack of suppression of hormone-sensitive lipase under conditions of insulin resistance. Additionally, there is an increase in intrahepatic de novo synthesis of fatty acids due to carbohydrate excess, as well as absorption from plasma of dietary chylomicrons and hepatic synthesis of VLDL. The assembly of hepatic triglycerides is typically coordinated with the synthesis and secretion of VLDL, whereby intrahepatic triglycerides are stored in intracellular lipid droplets. Liver steatosis occurs when there is an imbalance between lipid accumulation in the liver and lipid clearance, leading to excessive triglyceride accumulation within hepatocyte lipid droplets. Factors contributing to this imbalance include:

• deviations in the relative size of the intrahepatic pool of fatty acids [7].

• the rate of triglyceride synthesis and apolipoprotein B (apoB) production [8].

• the rate of triglyceride lipolysis within lipid droplets [1].

• the rate of beta-oxidation of fatty acids [9].

The formation of small (microvesicular) and large (macrovesicular) lipid droplets is a bidirectional process that can potentially be reduced and/or reversed through interventions that decrease fatty acid uptake and de novo synthesis, reduce triglyceride synthesis, enhance lipolysis, increase fatty acid oxidation, or increase the production and secretion of VLDL.

The average age at first diagnosis of metabolic associated fatty liver disease (MAFLD) is approximately 50 years [27,28], with an increasing prevalence observed in younger populations [29]. Patients diagnosed at a younger age may present with a more severe clinical profile compared to older patients [28]. MAFLD is associated with endothelial dysfunction, elevated systemic inflammation, and ectopic fat deposition in other organs (e.g., pancreas, skeletal muscles, and epicardium). Increasing epicardial fat volume closely correlates with intensified intramyocardial inflammation, endothelial dysfunction, and accelerated atherogenesis [30]. A meta-analysis conducted in 2019 found that metabolic associated fatty liver disease (MAFLD) was associated with all-cause mortality rather than cardiovascular mortality [31]. However, recent research in 2021 indicated that fibrosis stages F3 and F4 were associated with increased liver-related complications and atherosclerotic cardiovascular disease (ASCVD) emerged as the leading cause of mortality in patients with MAFLD [32].

In a prospective cohort study, it was noted that patients with metabolic associated fatty liver disease (MAFLD), who undergo coronary angiography, have an increased likelihood of undergoing percutaneous coronary interventions (PCI) or myocardial revascularization by

coronary artery bypass grafting (CABG). MAFLD is believed to be a hepatic manifestation of metabolic syndrome [33], which raises interest in exploring the interaction between MAFLD and atherosclerosis.

The liver fat content is approximately 80% higher in patients with type 2 diabetes compared to those with metabolic associated fatty liver disease (MAFLD) who do not have diabetes, even when age, gender, and BMI are similar. Liver enzyme levels are not reliable indicators for assessing the severity of intrahepatic fat accumulation [11].

Accumulation of large amounts of fat in the liver leads to insulin resistance and excessive production of both glucose [34-39] and very low-density lipoproteins (VLDL) [39,40], resulting in hyperglycemia, hypertriglyceridemia, and reduced HDL cholesterol levels.

The role of LDL in the development of NAFLD

Disruption in the regulation of lipid metabolism in the fatty liver is accompanied by increased production of very low-density lipoproteins (VLDL).

Subsequent studies have focused on LDL subclasses, particularly small dense LDL (sdLDL), which are particularly atherogenic and increased in metabolic syndrome and hepatic steatosis [41]. The dyslipidemia profile associated with hepatic obesity is characterized by elevated levels of LDL particles (including sdLDL) and reduced levels of HDL particles, correlating with intrahepatic lipid accumulation [42]. Small dense low-density lipoproteins (sdLDL) represent a distinct subclass of LDL particles associated with metabolic disorders [33]. Conversely, the relationship between sdLDL levels and the severity of MAFLD is unclear. It has been found that levels of sdLDL, measured in the blood of MAFLD patients, positively correlate with the NAFLD Activity Score (NAS), indicating the degree of hepatic steatosis and fibrosis. This association provides evidence of MAFLD development in the context of elevated sdLDL levels [42].

Particles of small dense low-density lipoproteins (sdLDL) compared to large LDL particles exhibit increased penetration through the arterial wall, longer plasma half-life, low affinity to the LDL receptor, higher susceptibility to glycation, and low resistance to oxidative stress, all indicating high atherogenicity. In patients with elevated levels of sdLDL particles, the risk of developing ischemic heart disease and fatty liver disease increases approximately threefold compared to individuals with predominantly large buoyant LDL particles [43]. Furthermore, it is hypothesized that the concentration of small dense LDL particles serves as a better surrogate marker for the severity of coronary heart disease than the concentration of LDL cholesterol [43].

Therefore, it can be hypothesized that the particle size of LDL may itself serve as a valuable indicator for assessing the risk of cardiovascular complications and as a marker for the development of MAFLD. Further research involving patient groups with multiple risk factors will help establish the importance of LDL particle size compared to the classical lipid profile in individuals with prior cardiovascular events.

Conclusion

Non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD) are increasingly prevalent conditions that are often underdiagnosed and underestimated as risk factors for cardiovascular disease (CVD) morbidity and mortality. Advanced diagnostic strategies are needed to detect NAFLD and MAFLD early. Existing methods such as ultrasound-based transient elastography (FibroScan) for assessing liver stiffness and steatosis are valuable for disease staging and longitudinal monitoring.

Therefore, patients with non-alcoholic fatty liver disease are at an increased risk of developing atherosclerosis and cardiovascular diseases. The mechanisms underlying the development of atherosclerotic vascular lesions and metabolic associated fatty liver disease are intricately interconnected.

Based on the literature analysis, the following key pathogenetic factors linking non-alcoholic fatty liver disease and atherosclerosis can be identified: endothelial dysfunction, disturbances in lipid profiles, increased production of certain pro-inflammatory cytokines, inflammatory response, and enhanced oxidative stress. These findings confirm the possibility of an independent correlation between dyslipoproteinemia and metabolic associated fatty liver disease. Patients with metabolic associated fatty liver disease are at high risk of developing systemic atherosclerosis and cardiovascular diseases [41–45]. Awareness of comorbidities is crucial for clinicians encountering various subclinical markers indicative of atherosclerosis in practice. Patients with metabolic associated fatty liver disease should undergo early detection and diagnosis of dyslipidemia, which enhances disease prognosis and risk stratification, optimizes long-term clinical outcomes, enables appropriate interventions, and reduces cardiovascular mortality. Further exploration of pathophysiological mechanisms to identify new therapeutic and preventive targets, as well as early biomarkers for optimal diagnosis of these diseases, is crucial in defining the incidence and mortality rates of cardiovascular and liver pathologies in the population.

Authorship. Authors equally contributed to this work.

Conflict of interest statement. The authors declare no conflicts of interest.

Funding. This study was supported by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant No. BR21881970, Title: Development of new screening, prevention, and treatment methods for atherosclerotic cardiovascular diseases to prevent early mortality in patients with atherosclerosis). The sponsors had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Бауырдың метаболикалық майлық ауруы және дислипопротеинемия. Әдебиеттерге шолу

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Түйіндеме

Қан айналымдағы холестериннің негізгі тасымалдаушысы төмен тығыздықтағы липопротеидтер (ТТЛП) әлі де липопротеидтердің ең атерогендік түрі ретінде қарастырылады, дегенмен, оның қан сарысуындағы холестерин деңгейіне қосқан үлесі үлкен рөл атқармайды. Адамдардың көпшілігінде ТТЛП атерогендік потенциалы оның құрамындағы холестериннен емес, ұсақ әрі тығыз ТТЛП бөлшектерінің көбеюінен туындайды. Қазіргі уақытта ТТЛП бөлшектерінің мөлшері жүректің ишемиялық ауруымен (ЖИА) байланысы бар екенін дәлелдейтін, сонымен қатар, коронарлық тәуекелдің жоғарылауының болжамды факторы бола алатынын көрсететін көлденең қималық және проспективтік зерттеулер бар.

Бұл шолудың мақсаты - әлемдік тәжірибеде метаболикалық байланысты майлы бауыр ауруларының және дислипопротеинемияның таралуы туралы ағымдағы деректердің сипаттамасын беру.

Ақпаратты іздестіру Pubmed, ResearchGate және eLibrary дерекқорлары арқылы жүргізілді. Шолу соңғы 10 жыл ішінде жарияланған алғашқы зерттеулер (сипаттау және аналитикалық), қосымша зерттеулер (жүйелі шолулар мен мета-талдауларды қоса), әдістемелік нұсқаулықтар мен клиникалық нұсқаулар, сондай-ақ орыс және ағылшын тілдеріндегі толық мәтінді басылымдарды қамтыды.

Алкогольсіз майлы бауыр ауруы бар науқастарда атеросклероздың және жүрек-қан тамырлары ауруларының даму қаупі жоғары. Бауырдың алкогольсіз майлы аурулары мен жүрек-қан тамырларының атеросклеротикалық патологиялары күрделі және өзара байланысты механизмдерге негізделген. Әдебиеттерді талдау негізінде бауырдың алкогольсіз майлы ауруы мен атеросклерозды байланыстыратын келесі негізгі патогенетикалық байланыстарды анықтауға болады: эндотелий дисфункциясы, липидті профильдің бұзылуы, қабынуға қарсы цитокиндердің мен қабыну реакциясының жоғарылауы, сонымен қатар, тотығу стрессінің жоғарылауы.

Түйін сөздер: бауырдың алкогольсіз майлы ауруы, липопротеидтер, жүрек қан тамырларының ауруы, бауыр ауруы, дислипидемиялар.

Метаболически-ассоциированная жировая болезнь печени и дислипопротеинемия. Обзор литературы

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Резюме

Липопротеиды низкой плотности (ЛПНП), по-прежнему следует рассматривать как наиболее важный показатель липидного профиля в крови. Показатель потенциала ЛПНП у большинства людей возникает за счет возрастания количества мелких плотных частиц ЛПНП, а не за счет содержания в нем холестерина как такового. На нынешнем этапе имеется множество данных перекрестных и проспективных исследований, представляющих что размер частиц ЛПНП в наибольшей степени связан с ишемической болезнью сердца (ИБС) и является прогностическим фактором повышенного коронарного риска.

Цель настоящего обзора предоставление описания текущих данных по распространенности метаболически ассоциированной жировой болезни печени и дислипопротеинемии в мировой практике.

Поиск информации осуществлялся в базах данных Pubmed, ResearchGate, и eLibrary. В обзор включены первичные исследования (как описательные, так и аналитические), вторичные исследования (включая мета анализы и систематические обзоры), методические пособия, клинические руководства, а также полнотекстовые публикации на русском и английском языках, опубликованные за последние 10 лет.

Следовательно, пациенты, страдающие метаболически ассоциированной жировой болезню печени, имеют высокую вероятность развития атеросклероза и сердечно-сосудистых заболеваний. В основе метаболически ассоциированной жировой болезни печени и атеросклеротических сердечно-сосудистых патологий лежат сложные и взаимосвязанные механизмы. На основании проведенного анализа литературы можно подчеркнуть очередные ключевые патогенетические звенья, связывающие метаболически ассоциированную жировую болезнь печени и атеросклероз: эндотелиальная дисфункция, нарушение липидного профиля, усиление выработки ряда провоспалительных цитокинов и воспалительной реакции и усиление окислительного стресса.

Ключевые слова: неалкогольная жировая болезнь печени, липопротеиды, сердечно-сосудистые заболевания, болезнь печени, дислипидемии.