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Features of Early Diagnosis of Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus

Urunbayeva D. A., Rakhimova M. E., Juraeva N. T.

Abstract: Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are interrelated pathologies forming the basis of metabolic syndrome. These conditions significantly increase the risk of severe complications, such as fibrosis, cirrhosis, and hepatocellular carcinoma. This article explores the primary pathogenesis theories of NAFLD, including alimentary and metabolic theories, and introduces the novel concept of metabolic dysfunction-associated fatty liver disease (MAFLD). Modern diagnostic approaches, such as ultrasound techniques and biochemical markers, along with the prospects of genetic testing, are discussed in detail. Molecular genetic determination of the I148M polymorphism in the PNPLA3 gene can be recommended for patients with non-alcoholic fatty liver disease (NAFLD) at any stage of disease progression, regardless of the presence or absence of other risk factors for the transition from simple steatosis to non-alcoholic steatohepatitis (NASH). Further studies on larger patient cohorts and in various populations will help refine these findings and potentially develop screening methods for the timely identification of individuals at high risk for adverse NAFLD outcomes.

Relevance

The widespread prevalence of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), along with their interconnection, underscores the necessity for focused consideration of this pathology to optimize approaches to its diagnosis and treatment. As components of metabolic syndrome, these two diseases share similar mechanisms of development and progression, synergistically increasing the risk of adverse outcomes in comorbid patients. Despite their shared pathophysiological mechanisms, the sequence of development between NAFLD and T2DM remains an important issue for investigation [1, 16, 23].

Based on a literature review, two main theories have been identified: the alimentary theory and the metabolic theory. According to the alimentary theory, the primary factor in the pathogenesis is obesity and the excessive accumulation of free fatty acids and triglycerides in the liver, which subsequently leads to insulin resistance and the development of T2DM. In contrast, the metabolic theory suggests that insulin resistance associated with diabetes is the initial trigger, creating conditions for liver damage independent of obesity. Additionally, the review highlights the concept of metabolically associated fatty liver disease (MAFLD), considered the hepatic component of metabolic syndrome [2, 7, 10]. Within this concept, various clinical phenotypes of NAFLD are identified, which determine the pathway of disease progression. Finally, the review discusses pathogenetically justified therapy, emphasizing overcoming insulin resistance, correcting atherogenic dyslipidemia, and restoring liver cell structure and function [4, 7, 8, 20]. Given its high prevalence and the potential severity of its complications, studying the pathogenesis, clinical course, diagnosis, and treatment of NAFLD remains highly relevant.

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Objective

The objective of this article is to summarize current data on the pathogenesis, clinical course, diagnostic approaches, and treatment methods for NAFLD in patients with type 2 diabetes mellitus, as well as to analyze certain genetic risk factors that may influence susceptibility and disease severity.

Materials and Methods

This study analyzed the most relevant domestic and international literature sources containing information on the pathogenesis, diagnosis, and treatment methods for this pathology [19, 23, 26].

Results

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, closely associated with metabolic disorders such as obesity, insulin resistance, and dyslipidemia. Insulin resistance and metabolic dysfunctions are considered key factors in the pathogenesis of NAFLD, particularly in the presence of type 2 diabetes mellitus (T2DM) [26, 28, 32, 33].

T2DM and obesity, especially abdominal obesity, exert significant influence on the course of fatty liver disease associated with metabolic dysfunction, leading to the development of fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC) [3, 5, 25, 30]. Higher risks of disease progression are observed in men over 50 years of age, postmenopausal women, and individuals with multiple cardiometabolic risk factors [1, 5, 32].

It is worth noting that in routine endocrinological practice, liver pathology in diabetic patients is often overlooked, which can have serious consequences [6, 8, 31, 36]. The coexistence of NAFLD and T2DM not only increases the risk of more severe forms of NAFLD and associated hospitalizations but also complicates glycemic control in diabetic patients and promotes the development of atherogenic dyslipidemia [9, 11, 15, 21]. Thus, T2DM and NAFLD often coexist, synergistically increasing the risk of adverse outcomes in affected individuals [3, 22, 28]. At the core of this multifaceted problem lies the liver, which, as the main organ regulating carbohydrate and lipid metabolism, connects NAFLD and T2DM [26, 28, 32, 37].

The cornerstone of the relationship between NAFLD and T2DM, as mentioned earlier, is obesity and insulin resistance. While obesity is widely recognized as a predictor of various diseases, including cardiovascular pathology, coronary artery disease, and certain types of cancer, T2DM is most strongly associated with a high body mass index (BMI) [26, 31, 34]. Approximately 44% of individuals with T2DM are affected by obesity. On the other hand, insulin resistance, an obligatory component of metabolic syndrome (MS), also underpins both T2DM and NAFLD. Insulin resistance is a primary mechanism in NAFLD development, disrupting both carbohydrate and lipid metabolism, leading to lipid accumulation in liver cells [10, 14, 18, 28].

Currently, the prevalence of NAFLD is approximately 25%, with a consistent upward trend. Alarmingly, NAFLD has already become a leading cause of chronic liver diseases worldwide. It often progresses to cirrhosis, HCC, and increased mortality from liver-related and overall causes [25, 28, 30, 33]. Additionally, NAFLD and its complications frequently result in the need for liver transplantation [15, 16, 20]. As previously noted, NAFLD is associated with metabolic dysfunctions and is itself considered a component of MS. In 2020, an international expert consensus statement introduced the term "metabolically associated fatty liver disease (MAFLD)," reflecting both the link between hepatic steatosis and metabolic disorders and the multifaceted nature of this condition, which affects other organ systems and has far-reaching consequences [3, 9, 22].

The coexistence of NAFLD and T2DM is common and poses significant challenges for healthcare systems. However, improved understanding of the disease's natural history, access to new diagnostic methods, and recent evidence of safe and effective treatments have laid the foundation for a paradigm shift in managing this condition in T2DM patients. We are at a critical juncture where the successful

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integration of these new diagnostic and therapeutic advances could significantly improve the quality of life for many patients [8, 36].

Diagnostic Approaches

Various methods are used to diagnose NAFLD, including ultrasound, transient elastography, and biochemical markers. Clinical manifestations of the disease range from asymptomatic to advanced cirrhosis, with symptom severity directly linked to disease progression [16, 27, 29]. Ultrasound is the preferred method for routine screening due to its accessibility and low cost, with sensitivity rates ranging from 60% to 94% [13, 32, 34].

A non-invasive algorithm based on metabolic and anthropometric data (BMI, waist circumference, plasma triglyceride levels, and gamma-glutamyl transferase concentration) known as the fatty liver index (FLI) has been endorsed by some associations for NAFLD diagnosis due to its simplicity. However, most evidence for this algorithm is based on comparisons with ultrasound (a non-gold standard method with low sensitivity), likely overestimating its true efficacy. When FLI was compared to more accurate methods like proton magnetic resonance spectroscopy (1H-MRS), 58% of patients had indeterminate classifications, and only 77% of the remaining 42% were correctly classified [23, 34]. Furthermore, the presence of fibrosis affects its accuracy [25].

Stepwise examination is recommended for patients. Initially, scoring methods based on blood tests, such as the fibrosis index (FIB-4), are used. If fibrosis is suspected, imaging techniques like liver elastography are employed to clarify its stage. Alternatively, blood tests for specific collagen-associated components, such as the ELF test, can be performed. The ELF test quantifies fibrosis-related organic compounds in the blood, including hyaluronic acid (HA), amino-terminal propeptide of procollagen III (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1) [15, 25, 27, 29].

In most cases, liver biopsy is unnecessary for managing patients with fatty liver disease associated with metabolic dysfunction. It is only required to confirm a diagnosis of steatohepatitis or exclude other causes of liver damage [23]. For adults with fatty liver disease associated with metabolic dysfunction, the consistent application of non-invasive diagnostic techniques can halt the progression of liver fibrosis and predict the risk of overall and liver-related complications, including mortality [24, 31].

Genetic Factors and Implications

NAFLD and liver fibrosis are heritable traits. Cohort studies, including 60 pairs of twins (42 monozygotic and 18 dizygotic), have demonstrated heritability of steatosis based on fat fraction density (MRI-PDFF) and liver fibrosis via magnetic resonance elastography [16, 37]. Retrospective family studies indicate a familial association of NAFLD with cirrhosis [29]. Prospective studies on probands with NAFLD-cirrhosis and their first-degree relatives have shown an 18% risk of fibrosis progression among relatives, significantly higher than in the general population. Further population studies on familial cirrhosis histories in NAFLD patients are needed [15, 29]. Modern genetic diagnostic methods identify predispositions to NAFLD by analyzing gene polymorphisms linked to lipid metabolism, inflammation, and insulin resistance. For example, mutations in PNPLA3 (rs738409) and TM6SF2 genes are associated with increased NAFLD risk. These insights enable precise disease forecasting and personalized treatment strategies [19, 24].Key genetic risk factors include polymorphisms in PNPLA3, TM6SF2, and MBOAT7 genes. The PNPLA3 I148M variant is recognized as a significant genetic determinant influencing susceptibility and disease severity. Mutations in TM6SF2 and MBOAT7 are linked to more severe NAFLD forms, such as steatohepatitis and fibrosis. Identifying these genetic traits allows for personalized medical strategies, improving care for patients with NAFLD and T2DM and enhancing their quality of life [25, 29]. Further studies on genetic risk factors are essential to refine diagnostic methods and develop effective treatments. Recent advances in genetic research underscore the need for targeted therapies to address NAFLD [29, 30].

Genome-wide association studies have identified multiple loci linked to NAFLD and non-alcoholic steatohepatitis (NASH). Research on these genes has expanded understanding of NAFLD's genetic basis. The I148M mutation in the PNPLA3 gene, which encodes the adiponutrin enzyme, disrupts triglyceride metabolism. Carriers of the PNPLA3 I148M allele have higher liver fat content and increased risks of steatohepatitis, fibrosis, and cirrhosis. This allele is a key genetic determinant of NAFLD [29, 37].

Polymorphisms in genes regulating liver lipid remodeling, such as PNPLA3, are strongly associated with susceptibility to the NAFLD spectrum, from steatosis to NASH and fibrosis [21, 25, 29].

Conclusions

Non-alcoholic fatty liver disease (NAFLD) is a serious condition that requires timely diagnosis and appropriate treatment. It is essential to remember that prevention and control of the main risk factors play a crucial role in mitigating this pathology.

Currently, patients with NAFLD are often overlooked because practicing physicians rely on low-sensitivity screening tools, such as plasma aminotransferase measurements and liver ultrasound. The availability of simple diagnostic tests that can be widely utilized by practitioners, combined with access to inexpensive, safe, and more effective medications, is expected to revolutionize disease management in the near future [3, 30]. We anticipate that, encouraged by recent advances in diagnostic (e.g., enhanced imaging and plasma biomarkers/genetic tests) and therapeutic (e.g., pioglitazone) developments, screening and early intervention for NAFLD will become the standard of care for all patients with type 2 diabetes mellitus (T2DM) [3, 23].

The primary genetic factor influencing the progression of hepatic steatosis to non-alcoholic steatohepatitis (NASH) is the PNPLA3 I148M polymorphism. The mutant protein accumulates on the surface of hepatocyte lipid droplets, disrupting lipid utilization and contributing to the development of hepatic steatosis. Additionally, the I148M polymorphism promotes the accumulation of lipids in liver cells. Lipid accumulation triggers the transformation of hepatic stellate cells into myofibroblast-like cells that secrete collagen, leading to an increase in nonfunctional connective tissue in the liver and the development of fibrosis [6, 20].

Molecular-genetic testing for the I148M polymorphism in the PNPLA3 gene can be recommended for patients with NAFLD at any stage of the disease, regardless of the presence or absence of other risk factors for the progression of simple steatosis to NASH. Further research involving larger patient cohorts and diverse populations will help refine these findings and may lead to the development of screening methods that can identify individuals at high risk of adverse NAFLD outcomes. Identifying these genetic characteristics will enable the creation of personalized strategies that improve the effectiveness of medical care for patients with NAFLD and T2DM, ultimately enhancing their quality of life.

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