ANKARA MEDICAL JOURNAL

Review

Ankara Med J, 2023;(4):455-467 // 10.5505/amj.2023.39129

HISTORICAL ASPECTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: STUDIES AND CLASSIFICATIONS

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Submitted: 04.06.2023 // Accepted: 18.12.2023

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide and is currently the second leading indication for liver transplantation. The global obesity pandemic is linked to metabolic syndrome, so the prevalence of NAFLD will increase progressively and become a real burden on the economy and public health worldwide. Assuming that assessment of the history of a disease can improve clinical practice and provide efficient clues for research, the aim of this article is to review the background of nonalcoholic fatty liver disease (NAFLD) in adults and children. We have reviewed the evolution of the definition and classification of NAFLD as a distinct nosological form and started our consideration with the year 1836. The review performed covers the first guidelines issued by the scientific community throughout current clinical guidelines. We have also considered diseases associated with this pathology, from early steps to more recent studies confirming that NAFLD is a risk factor for cardiovascular disease, hepatocellular carcinoma, and other malignancies. This article discloses current differences in the International Classification of Diseases (ICD) 10 and ICD 11. In the updated ICD 11th revision, NAFLD is presented as a separate heading (DB92 - nonalcoholic fatty liver disease), which is closer to modern nomenclature. This classification allows a better understanding of research and clinical approaches to the diagnosis, treatment, and prevention of the disease.

Keywords: Non-alcoholic fatty liver disease, liver steatosis, obesity, metabolic syndrome.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease of metabolic genesis in individuals without exogenous factors of toxic liver damage (e.g., exogenous ethanol), caused by lipid accumulation in liver lobe composing cellular elements, morphologically confirmed by steatosis, steatohepatitis, fibrosis, cirrhosis or adenocarcinoma. NAFLD is diagnosed when lipid accumulation in the form of triglycerides (TG) is more than 5-10% of hepatocyte mass or when more than 5% of hepatic cells contain lipid deposits.[1]

NAFLD includes a wide range of diseases of varying severity with different prognoses: steatosis, nonalcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.[2]

NAFLD is the most common liver disease worldwide and is currently the second leading indication for liver transplantation in the United States, second only to alcohol-related liver disease.[2,3] The highest NAFLD prevalence is in Latin America at 44.37%, then Middle East and North Africa at 36.53%, South Asia at 33.83%, Southeast Asia at 33.07%, North America at 31.20%, East Asia at 29.71%, Asia Pacific at 28.02%, Western Europe 25.10%.[4] In Russia, according to the DIREG2 multicenter study, the prevalence of NAFLD in outpatients was as high as 37.3%.[5]

The rates of decompensated cirrhosis with nonalcoholic steatohepatitis (NASH) are predicted to increase up to 168%, as NASH complicated by hepatocellular carcinoma up to 137% in the period 2015- 2030.[6] As the global obesity pandemic fuels metabolic conditions, the prevalence of NAFLD will increase progressively and become a real burden on the economy and public health worldwide.[4]

Non-alcoholic fatty liver diseases as a separate nosological form: history of definition

T. Addison coined the term "fatty liver" in 1836 when describing the liver in patients suffering from alcohol abuse.[7] In 1838, an Austrian physician and pathologist, Carl von Rokitansky, documented the accumulation of liver fat in hepatic cells in autopsy specimens, suggesting that it might be the cause of cirrhosis of this organ.[8]

Subsequently, for decades, pathologists determined the similarity of changes in the histological structure of the liver observed in patients with diabetes mellitus and obesity.[9, 10]

In 1938, Ch. Connor described fatty liver infiltration, which could lead to cirrhosis in diabetic patients. He reported two cases of bleeding from esophageal varices (one case was fatal because of severe hemorrhage) in patients with diabetes mellitus and fatty liver dystrophy.[11]

In 1958, J. Westwater and D. Feiner reported on histological findings of fatty liver infiltration in obese patients. They confirmed that hepatic test abnormalities and morphological changes improved after weight reduction. In 1962, H. Thaler added certain clinical and pathological descriptions of the disease by investigating liver pathology in diabetes mellitus, which he described as steatosis with an inflammatory response.[12]

In 1960-1970. S.D. Podimova described several cases of liver changes corresponding to steatosis with signs of inflammation in patients who did not abuse alcohol.[13]

In 1980, the term non-alcoholic steatohepatitis was coined by J. Ludwig et al. (Mayo Clinic, USA) to describe a progressive form of fatty liver disease that histologically resembled alcoholic steatohepatitis. Most of the patients were obese women, and many of them had diabetes mellitus.[14]

In 1983, J. Moran et al. extended these findings to obese children. In the children, abnormal liver enzymes and nonspecific abdominal pain accompanied by steatohepatitis.[15]

In 1986, F. Schaffner and H. Thaler were the first to use the term "nonalcoholic fatty liver disease".[16]

Diseases associated with non-alcoholic fatty liver disease

By the early 2000s, it had already become clear that NAFLD was associated with certain somatic pathologies, with hepatocellular carcinoma, as well as with extrahepatic cancer diseases.[17-26]

Non-alcoholic fatty liver disease and the risk of cardiovascular diseases

In 2004 and 2005, G. Targher and co-authors were the first to report that NAFLD was more closely associated with an increased risk of cardiovascular diseases in patients with type 2 diabetes mellitus.[17,18]

In 2016, G. Targher and co-authors found that patients with NAFLD had a higher risk of cardiovascular diseases, arterial hypertension, atherosclerotic disease, etc., compared with the control group without NAFLD.[19]

In 2021, M. Yoneda and co-authors evaluated the relationship of NAFLD with cardiovascular diseases using a Japanese nationwide database from April 2013 to March 2019. The results of this meta-analysis showed that the identification rate of patients with cardiovascular diseases is higher in NAFLD compared to the control group. Among patients with NAFLD, the frequency of complications with diabetes mellitus and hypertriglyceridemia is high, which in turn can contribute to the development of cardiovascular diseases.[20]

According to a systematic review and meta-analysis of prospective studies published from 1966 to 2021, NAFLD was associated with an increased risk of stroke, myocardial infarction and atrial fibrillation. The

analysis also confirms that mortality from cardiovascular diseases was the same in the groups with and without NAFLD.[21]

Risk of cancer in nonalcoholic fatty liver disease

In 2002, two major studies reported on the risk of hepatocellular carcinoma (HCC) in NAFLD. E. Bugianesi et al. studied patients with hepatocellular carcinoma because of cirrhosis and noted that hypertriglyceridemia, diabetes mellitus, and increased aminotransferases were risk factors for hepatocellular cancer, suggesting that it may represent a late complication of cirrhosis resulting from NASH.[22]

Currently, according to the data provided by the European, American and Italian Liver Foundations, HCC in patients is a definite finality of the natural course of liver diseases, including NAFLD.[2,23,24]

In 2003, H. Sørensen et al. compared data from the Danish general population (7326 people) with alcoholic liver disease or nonalcoholic fatty liver dystrophy. The results showed that the patients with nonalcoholic fatty liver dystrophy had an increased risk of pancreatic cancer and renal cancer.[25]

Various types of extrahepatic cancer, including colorectal adenoma and carcinoma, are currently commonly identified as NAFLD-associated diseases.[26]

According to 2019 data, NAFLD is more associated with an increased risk of gastrointestinal and uterine cancers than with obesity.[27]

National guidelines and clinical recommendations for diagnostics and treatment of non-alcoholic fatty liver

Subsequently, scientific associations around the world began their work on clinical guidelines focused on diagnostic criteria and management of NAFLD. Interestingly, a decade-long gap separates the first clinical and pathological signs of NAFLD from the first recommendations issued by scientific associations. This probably reflects an initial lack of evidence-based data in favor of strong recommendations. Continued growth in incidence, advances in diagnostic techniques, and the results of research and clinical trials of new drug regimens have played a critical role in making the publication and updating of clinical guidelines for NAFLD an ongoing challenge for scientific liver associations.

The Asian Pacific Association issued the first guidelines on NAFLD for the study of the liver (APASL) in 2007. They involved information for clinicians regarding a new common disease.[28,29] Despite the lack of evidence-

based data, the authors were able to formulate general principles in the management of NAFLD. This document, proposed by the Asian Scientific Association, paved the way for the guidelines on NAFLD in Europe.

In 2010, the European Association for the Study of the Liver (EASL) summarized the results of the 2009 NAFLD/NASH Special Conference.[30] This article outlined expert opinions regarding the diagnosis and treatment of patients with NAFLD. The main ones are:

1) In patients with elevated alanine aminotransferase (ALT) on the biochemical blood count or with hepatic steatosis on ultrasound, noninvasive methods to assess fibrosis should be the first-line procedure.

2) In patients with other chronic liver diseases, an ultrasound examination should be performed to identify metabolic risk factors and steatosis.

3) During elective surgical procedures, such as bariatric surgery for obesity (high risk of NASH) and cholecystectomy (common risk factors between NAFLD and cholelithiasis), liver biopsy should be performed.

4) Treatment of patients with NAFLD should primarily include weight loss (5-10% weight loss may be sufficient to normalize aminotransferase and improve liver architectonics with steatosis), lifestyle changes, and physical exercises.

In 2012, a collaborative effort of the three major American Hepatology Associations, the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association, and the American College of Gastroenterology, published a regulatory document on NAFLD. They proposed:

1) Screening family members for NAFLD is not recommended;

2) Assessment of fibrosis by noninvasive diagnostic methods in patients with NAFLD is a useful tool for identification of fibrosis and/or cirrhosis;

3) Liver biopsy for suspected NAFLD should be considered in patients with other comorbid chronic liver disease;

4) Metformin has no significant effect on liver morphology and is not recommended as a specific treatment for NASH;

5) Vitamin E (α-tocopherol) administered at a daily dose of 800 IU/day can improve liver histology in adult patients with NASH without diabetes and, therefore, can be considered as first-line pharmacotherapy for the patients;

6) Ursodeoxycholic acid (UDCA) is not recommended for the treatment of NAFLD;

7) Omega-3 fatty acids can be considered for the treatment of hypertriglyceridemia in NAFLD patients;

8) Statins should not be used for specific treatment of NASH; they can only be used to treat dyslipidemia in patients with NAFLD.[31]

In 2014, the World Gastroenterology Organization published its regulatory document on basic principles of diagnosis and treatment of NAFLD.

Here are some of them:

1) NAFLD and NASH are a serious global pandemic public health problem and affect both rich and poor countries;

2) Diet and exercise should be recommended for all patients;

3) Not everyone with fatty liver dystrophy needs aggressive therapy;

4) Liver puncture biopsy should be performed in patients who have risk factors for NASH and/or other liver diseases; 5) NAFLD and NASH are also an increasing problem in pediatric patients, including those under ten years of age.[32]

Consensus and practice guidelines based on recommendations from national associations were also published between 2007 and 2014. These include the Italian Association for the Study of the Liver (AISF), 2010 Chinese Association for the Study of Liver Diseases, 2011, Korean Association for the Study of the Liver, 2013, Japanese Society of Gastroenterology and Japanese Society of Hepatology, 2015.[33-36]

Classification of nonalcoholic fatty liver disease

Since the 1920s, Austrian, Swedish, and Spanish authors have reported on the association of arterial hypertension, diabetes mellitus, obesity, hyperuricemia, and cardiovascular disease. Over the past years, several international organizations have tried to form a reference of what is included in the terms "metabolic syndrome" and "insulin resistance," proposing different definitions for them.[37]

A considerable amount of information has recently been published supporting the change in the nomenclature of nonalcoholic fatty liver disease to metabolic fatty liver disease (MFLD). "Consensus" statements have been made, as well as a number of articles that have attempted to emphasize the need for this change.[38]

In 2020, an international expert consensus statement was issued. The statement proposed a new concept - metabolically associated fatty liver disease (MAFLD). According to the authors of this consensus, this interpretation of the disease allows both focusing on the systemic and multifactorial pathogenesis of liver parenchyma damage and making medical care more personalized for various clinical options of comorbidity associated with MAFLD.[39,40]

Nevertheless, is this really the case? In 2021, Sh. Singh et al., in their study on the pathogenesis of NAFLD, deeply disagreed with a possible change in the nomenclature of this disease. In their opinion, NAFLD is a heterogeneous disease with different pathogenetic mechanisms, one of which is liver steatosis caused by metabolic dysfunction. The authors believe that instead of changing nomenclature without strong scientific support, efforts should be directed toward understanding the pathogenesis of NAFLD in different populations, which can potentially help develop new therapeutic options.[38]

Russian experts who compile clinical guidelines agree with the authors of the NAFLD Consensus but nevertheless recommend clinicians use the WHO-approved codes in their daily practice, as specified both in the current ICD-10 and in the soon-to-be-released ICD-11.[1]

The International Classification of Diseases is a regulatory document with generally accepted statistical classification of diagnoses. It is used in public health to standardize methodological approaches and international comparability of materials.[41] The current ICD 10th revision was adopted by the World Health Assembly in 1990 in Geneva and has been translated into 43 languages, being used in 117 countries.

According to the ICD-10 codes, the diagnosis of NAFLD is made by the leading clinical disease, syndrome and/or symptom:

K76.0 - fatty liver degeneration not classified under other headings;

K73.0 - chronic persistent hepatitis, not classified under other headings;

K73.9 - chronic hepatitis unspecified;

K74.6 - other and unspecified cirrhosis of the liver.[41]

For NAFLD diagnosis, ICD-10 recommends code K76.0 (fatty degeneration of the liver not classified under other headings). For clinically confirmed NAFLD or cirrhosis, code K 74.6 (other and unspecified cirrhosis of the liver) is recommended. Given the long history of the classification of NAFLD as a distinct nosological form,

the first papers which were issued long before the release of ICD-10 revision, one can inadvertently conclude that ICD-10 coding for NAFLD is imperfect.

Undoubtedly, since the entry into force of ICD-10 (in Russia, it was approved as an official document in 1997 by order of the Ministry of Health), a real breakthrough in gastroenterology occurred: new diagnostic tools and techniques appeared, new mechanisms of etiology and pathogenesis were identified, as well as new potential therapeutic goals. Thus, the classification in the field of gastroenterology is actively evolving, due to which there is a need to edit it. Nowadays, we are still encouraged to use the ICD-10 classification for coding diagnoses, which is already far from the current classification of gastroenterological diseases, especially in terms of hepatology.

Such inconsistencies exist both in hepatology and in other areas of medicine. Therefore, a revision of the ICD has long been necessary. To date, ICD-11, which was adopted by the WHO in 2019, has been developed; the official beta version, available on the Internet, has been developed in the Russian Federation.

In ICD-11, which is still planned to be approved in the Russian Federation, NAFLD will have the codes corresponding to its international name:

DB92 - nonalcoholic fatty liver disease

DB92.0 - nonalcoholic fatty liver disease without nonalcoholic steatohepatitis

DB92.1 - non-alcoholic steatohepatitis

DB92.Y - other clarified non-alcoholic fatty liver disease

DB92.Z - nonalcoholic fatty liver disease, not specified

DB93 - hepatic fibrosis or cirrhosis

DB93.0 - hepatic fibrosis

DB93.1 - peripheral cirrhosis

DB93.2 - definite liver fibrosis or cirrhosis.[42]

ICD-11 is clear to be more closely aligned with modern nomenclature. Finally, the special codes "nonalcoholic fatty liver disease" and "nonalcoholic steatohepatitis" have been introduced. They eliminate the existing contradictions in ICD-10.

Thus, with the introduction of ICD-11, the scientific and statistical approaches to the classification of diagnoses will coincide. In the future, science will continue to move forward, and the understanding of liver diseases will deepen. Perhaps we will see how the nomenclature will differ from the fixed structure of the classification.

Conclusion

We can conclude that a thorough understanding of the history of NAFLD as a distinct nosology allows us to better understand the disease itself as well as anticipate directions for future research. From early assumptions to current research, NAFLD has been shown to be an independent risk factor for cardiovascular disease, hepatocellular carcinoma, and other malignancies. However, as in practical medicine, we cannot move forward without proper and clearly defined statistics.

The updated International Classification of Diseases 11 revision (ICD-11) eliminates the current contradictions of ICD 10 about NAFLD. In ICD-11, it is allocated in a separate heading (DB92 - nonalcoholic fatty liver disease), which is closer to up-to-date nomenclature. This classification contributes to a better understanding of research and clinical approaches to the diagnosis and treatment of the disease.

Ethical Considerations: Since public data and related literature were analyzed in our study, there was no ethical violation.

Conflict of Interest: The authors declare no conflict of interest.

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