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EDITORIAL

From non-alcoholic fatty liver disease to metabolic-associated steatotic liver disease: Rationale and implications for the new terminology

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Abstract

Non-alcoholic fatty liver disease (NAFLD) was the term first used to describe hepatic steatosis in patients with the metabolic syndrome who did not consume excess amounts of alcohol. Alcoholic liver disease (ALD) has many similarities to NAFLD in both pathogenesis and histology. This entity is now the most prevalent chronic liver disease worldwide as a consequence of the epidemic of obesity. Attempts to incorporate the importance of the metabolic syndrome in the development of steatosis resulted in the renaming of NAFLD as metabolic-associated fatty liver disease. This new term, however, has the disadvantage of the use of terms that may be perceived as derogatory. The terms fatty and non-alcoholic have negative connotations in many cultures. In addition, non-alcoholic is not usually a term applicable to pediatric cases of hepatic steatosis. Recently, an international collaborative effort, with participants from 56 countries, after a global consultation process, recommended to change the nomenclature to steatotic liver disease -including metabolic dysfunction- associated steatotic liver disease, metabolic-associated steatohepatitis and metabolic dysfunction-associated ALD. The new terminology is consistent with most of the previously published epidemiological studies and will have a major impact on research into diagnosis, prognosis and treatment.

Key Words: Non-alcoholic fatty liver disease; Steatosis metabolic-associated steatotic liver disease; Nomenclature

Core Tip: Due to the epidemic of obesity, there has been an increase in the prevalence of the metabolic syndrome and hepatic steatosis. The term non-alcoholic fatty liver disease (NAFLD) was given to describe the hepatic manifestation of the metabolic syndrome. Recently the nomenclature has been changed to metabolic dysfunction- associated steatotic liver disease. This removes stigmata associated with the term fatty and include a new entity reflecting both the metabolic syndrome and alcohol as causes of steatosis. These new terms do not alter the inclusion criteria for most of the published studies on NAFLD and will facilitate future studies.

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INTRODUCTION

The excess consumption of alcohol and food was first described in biblical times. Noah, after leaving the ark at the end of the flood, planted a vineyard, consumed too much of the wine he produced and lay naked in his tent (Genesis 9: 21-27). The two daughters of Lot, fearing that there were no men left in the world to provide them with children, made their father inebriated and then became pregnant by him (Genesis 19: 30-38). The Bible also warns against the excess consumption of food and alcohol, "Do not join those who drink too much wine or gorge themselves on meat (Proverbs 23: 19-21). Our failure to comply with these biblical words of advice, has resulted in an epidemic of obesity and alcohol consumption worldwide. As a consequence of this there is now a large increase in obesity and the associated metabolic syndrome resulting in an increase in hepatic steatosis.

STEATOTIC LIVER DISEASE

Steatosis of the liver, or fatty liver, with macrovesicular steatosis and Mallory bodies was described by Addison in 1836 [1]. Connor[2] and Chaikoff *et al*[3] found a link between steatosis and either alcohol consumption or diabetes in 1938. In the 1980s Ludwig *et al*[4] described patients who had a similar feature but denied alcohol consumption. The initial nomenclature was non-alcoholic fatty liver disease (NAFLD). The metabolic syndrome is based on the presence of hypertension, impaired glucose tolerance, elevated triglyceride levels, low high-density lipoprotein and increased abdominal circumference, with some differences between different ethnic groups[5].

Subsequently, NAFLD was noted to be the hepatic manifestation of the metabolic syndrome[6]. NAFLD is now the major cause of chronic liver disease worldwide and one of the main indications for liver transplantation[7]. The definition of non-alcoholic is 30 G per day for a male and 20 g per day for a female. However, many patients who are considered to have NAFLD do in fact have significant alcohol consumption[8].

The pathogenesis of steatotic liver disease involves the development of a dysbiosis, resulting in endogenous alcohol production, increased intestinal permeability, the production of endotoxins, which reach the liver by way of the hepatic portal vein. The insulin resistance that is associated with the metabolic syndrome results in an increase in intrahepatic fat, increased gluconeogenesis and increased free fatty acid levels[9]. In both alcoholic and non-alcoholic steatosis the liver injury is in the parenchyma. Progressive liver injury results in an evolution from simple steatosis, to steatohepatitis, fibrosis and cirrhosis. Lifestyle modifications can decrease and even reverse the disease progression[9].

As a result of this a new nomenclature was proposed: metabolic dysfunction-associated fatty liver disease (MAFLD) [10]. This term was felt to reflect the importance of metabolic factors in the etiology of MAFLD and to assist in providing a better understanding of this entity by patients.

There are, however, problems with this nomenclature as well. For example, not all cases of MAFLD are seen in patients with obesity. This is reflected in the term lean NAFLD[11]. In many of these patients a history of drinking sweet sugary beverages or soda with artificial sweeteners may be present. Some patients with cirrhotic liver disease suspected to be caused by MAFLD may not have fat in the liver when assessed by biopsy. The change to MAFLD has been suggested to have been premature[12].

Treatment for MAFLD is mainly based on lifestyle changes. Clinical trials with anti-obesity treatments, lipid-lowering agents and insulin sensitizers in the main were not successful. There is concern that concentrating just on metabolic factors could impede the development of other therapeutic mechanisms[13]. In addition, in many trials the end-point selected was a decrease in the NASH score and not in the more important degree of fibrosis or clinical end-points including cardiovascular events or death[14]. Other factors affecting the development of steatosis include the intestinal microbiome, genetic factors including PNPLA3 mutations[15], and sarcopenia.

Recently, the name has been revised once more. A global consultation process using the well-established Delphi technique was performed from 2020 to 2023[16-18]. This involved 236 participants from 56 countries. The terms non-alcoholic and fatty were rejected for use since they were associated with a stigma in terms of patient understanding. Steatosis was chosen to replace “fatty”. The new nomenclature to be recommended was metabolic dysfunction-associated steatosis liver disease (MASLD).

The presence of at least one of the five cardiometabolic risk factors is essential to make the diagnosis. The previous diagnosis of non-alcoholic steatohepatitis (NASH) was recommended to be replaced by metabolic dysfunction associated steatohepatitis (MASH). Cryptogenic steatotic liver disease was coined to cover those cases with no clear cause.

Metabolic dysfunction-associated ALD (MetALD) is a new term to describe those cases with excessive alcohol consumption. This entity has not been previously defined and will now have to be investigated further in appropriate clinical trials.

CONSEQUENCES OF THE CHANGE IN NOMENCLATURE

The change in nomenclature preserves the existing data on natural history of the disease, biomarkers and clinical trials, which is very important. An analysis of the European NAFLD registry cohort has found that 98% of the participants would fulfill the new criteria for MASLD[19]. In addition, a study of 1333 patients from Hong Kong with NAFLD found that only 4 (0.3%) of patients did not meet the new MASLD criteria[20].

The diagnosis of MASLD has an advantage of removing the stigma associated with the term fatty, and patient advocacy groups were consulted as part of the process. The importance of this effect differs between different cultures [21].

Steatotic liver disease reflects the range of causes of hepatic steatosis and permits characterization of fibrotic severity – for example MASH with stage 3 fibrosis. It is to be noted that disease stage and severity are not changed in this new definition and will still be valid with the increasing use of non-invasive testing for determining these parameters.

There is a strong similarity between the metabolic criteria for diagnosing MASLD and those previously suggested for MAFLD. The new definition of MASLD is based on simple and accessible clinical criteria and biological measurements without the need for specialized testing for insulin resistance such as homeostasis model assessment of insulin resistance. There may be a place for subsequent testing in the minority of patients with hepatic steatosis in the absence of cardiometabolic risk factors.

The new classification also enables subgroups to be included within the umbrella term steatotic liver disease. This includes medications and rare genetic diseases in children. The newly defined term MetALD reflects the importance of alcohol consumption in the development of steatosis, even in the absence of metabolic factors.

CONCLUSION

This new nomenclature for the most common liver disease worldwide is important for developing a cohesive definition between groups worldwide which will enable extensive data collection with implications for the development of personalized medical therapeutic and enabling incorporation of existing data sets. The public health implications of this are likely to be very significant.

FOOTNOTES

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