

## Transition of an acronym from nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is a global public health concern owing to its substantial contribution to chronic liver diseases. The disease is closely linked to metabolic syndrome (MS), suggesting a common biological pathway and shared disease mechanism for both ailments. Previous studies revealed a close relationship of NAFLD with the components of MS including abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. Hence, a group of experts recently renamed NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD) in order to encompass a more appropriate pathogenesis of the disease. NAFLD was first named to describe a condition similar to alcoholic hepatitis in absence of significant alcohol consumption. However, knowledge pertaining to the etiopathogenesis of the disease has evolved over the past four decades. Recent evidence endorses NAFLD as a terminology of exclusion and suggests that it may often leads to misdiagnosis or inappropriate management of patients, particularly in clinical practice. On the other hand, the new definition is useful in addressing hepatic steatosis with metabolic dysfunction, which ultimately covers most of the patients with such illness. Therefore, it seems to be helpful in improving clinical diagnosis and managing high-risk patients with fatty liver disease. However, it is imperative to validate the new terminology at the population level to ensure a holistic approach to reduce the global burden of this heterogeneous disease condition.

**Key Words:** Nonalcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Redefining; Redefinition of fatty liver disease

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**Core Tip:** A consensus of experts recently renamed nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease. The new definition is advantageous for improving clinical diagnosis and managing high-risk patients with fatty changes in liver.

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## INTRODUCTION

The rising burden of nonalcoholic fatty liver disease (NAFLD) is a global public health concern. This progressive liver disease is a leading cause of chronic hepatic ailments worldwide[1,2]. Recent reports confirm that NAFLD accounts for approximately 8% of the annual 2.14 million global deaths from liver disease[3]. Over the past two decades a substantial elevation in the prevalence of NAFLD has been reported, with strong evidence of a close link between NAFLD and metabolic syndrome (MS)[4]. NAFLD is often found to be associated with the components of MS, such as abdominal obesity, dyslipidemia, hypertension, and hyperglycemia[5]. In addition, the risk factors of NAFLD and MS have also been found to be identical in many studies[1]. Therefore, it has been suggested that both NAFLD and MS follow a common biological pathway as well as a shared disease mechanism. In line with that, a consensus of experts recently renamed NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) so that the term could accurately reflect the pathogenesis of the disease[6]. According to the new definition, MAFLD would be diagnosed if there was evidence of hepatic steatosis in addition to any of the following three conditions, overweight/obesity, type 2 diabetes mellitus, or metabolic dysregulation[7]. The expert opinion was that the new definition is superior for diagnosing NAFLD patients with severe liver injury. Moreover, it is more practical to diagnose high-risk patients and evaluate disease progression in clinical settings[8,9].

## DISCUSSION

Nonalcoholic steatohepatitis (NASH) was first used nearly four decades ago to describe a condition that mimics alcoholic hepatitis in absence of significant alcohol consumption[10]. Initially, the pathology was found to be linked to obesity or obesity-associated disorders. Subsequently, the disease was renamed NAFLD, referring to the absence of any known etiology of liver disease. In the meantime, a detailed understanding of the etiopathogenesis of the disease has evolved as the link between NAFLD, insulin resistance, and other components of MS was explored. Molecular-level investigations explored the role of multiple genetic and cellular mechanisms in the pathogenesis of NAFLD[11]. Epidemiological studies also revealed a number of social, demographic, and clinical determinants responsible for development of NAFLD [12]. Results of the studies described NAFLD as a heterogeneous condition. However, the archaic NAFLD nomenclature, which is a terminology of exclusion, remained unchanged over the years. The inclusion of alcohol in the name and definition is also problematic. In real-life clinical practice, the features of NAFLD often overlap with the characteristics of patients who consume alcohol. Moreover, there is no accepted method to appropriately measure alcohol intake in clinical facilities. Hence, there remains a possibility of misdiagnosis or inappropriate management of patients. Considering the above context, there has been a proposal to change the name since the beginning of this century. As the disease was found to be closely associated with metabolic dysfunction and insulin resistance, the scientific community proposed several names related to metabolic dysfunction, for example, metabolic steatohepatitis, metabolic fatty liver disease, and metabolic-associated fatty liver[10]. Eventually, a consensus of global experts opted for MAFLD.

**Table 1 Potential positive implications and challenges related to transition of nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease**

Positive implications	Challenges
Useful in overcoming the dichotomization of NASH and non-NASH in clinical practices	Obtain a global acceptance as some researchers consider the name change premature and inappropriate
Facilitate diagnosis and evaluation of disease progression in high-risk patients	Underestimation of actual prevalence of the disease using the criteria of MAFLD
Improve awareness of physicians, healthcare providers and patients	Further clarification and stratification of the definition to guide decision-making and assess prognosis of the disease
Improve physician-patient communication	Address the patients with fatty changes in liver in absence of metabolic derangements
Improve clinical diagnosis and patient care	Deal with lean or undernourished individuals with hepatic fatty changes
Reduce confusion and stigma regarding the disease	Lack of information regarding genetic risk factors, phenotyping measurements, body fat content, and alterations in gut microbiota in the new definition
Increase public attention and improve health policy actions	Determine the outcome variable of ongoing clinical trials where “improvement in NASH” is one of the endpoints

MAFLD: Metabolic dysfunction-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis.

It is assumed that the new definition would improve clinical diagnosis (Table 1). The term MAFLD annulled two different NAFLD entities, simple steatosis and NASH, and conceptualized the fatty changes in the liver as a disease process. Therefore, the redefinition of MAFLD would help to overcome the dichotomization of NASH and non-NASH, and facilitate the assessment of disease severity in clinical practice[13]. A recent study reported that the switch from NAFLD to MAFLD increased the awareness of physicians regarding the management of the disease[14]. However, changes in nomenclature may have potential implications for ongoing clinical trials in which “improvement in NASH” is an outcome variable. It is possible to redefine the outcomes of clinical trials based on the existing MAFLD framework, but there remains certain disagreement regarding the new terminology and its definition that need to be addressed[15]. The new criteria may underestimate the actual prevalence of the disease, as reported in a recent study[8]. It may also exclude patients without metabolic disturbances. A recent review found that metabolic derangements may be absent in 30% of the patients diagnosed with NAFLD[5]. The new definition is also not clear regarding concomitant liver diseases such as drug-induced, viral or auto-immune liver disease. Apart from individuals with high body mass index, NAFLD has also been reported in lean and nonobese adults. It is assumed that visceral adiposity and differences of metabolic adaptations may play a potential role in the pathogenesis of hepatic steatosis in lean adults[16]. Alterations in gut microbiota can also be a contributing factor in developing NAFLD in lean and undernourished adults[16]. Moreover, there is evidence in support of a significant relationship between a positive family history of metabolic traits and NAFLD, particularly in lean patients with a fatty liver[17]. Individuals with a family history of metabolic traits are likely to develop complications of NAFLD at a younger age[18]. Therefore, body fat content, rate of weight gain, and family history of metabolic traits need to be considered when constructing a new conceptual framework to define MAFLD. It seems that diagnosis of cryptogenic cirrhosis attributable to metabolic derangements would be easier using the new definition of MAFLD, as cryptogenic cirrhosis was found to be associated with obesity and diabetes[19]. Nevertheless, a more insightful opinion is required to establish an accurate definition so that the term incorporates individuals with hepatic fatty changes in the absence of metabolic derangements. Moreover, there should be definitive guidelines regarding inclusion of genetic risk factors, phenotypic measurements, dietary intake, visceral adiposity, and alterations in gut microbiota in the definition.

## CONCLUSION

As more than one-fourth of the global population have NAFLD. Emphasis should be given to appropriate understanding of etiopathogenesis of the ailment[20]. To that end, an appropriate term is required so that it can reflect the entire pathophysiology of

the disease and cover the whole population with perturbed accumulation of hepatic fat. The new definition seems to address hepatic steatosis with metabolic dysfunction, which ultimately covers most of the cases with such illness. It is also useful for improving clinical diagnosis and managing high-risk patients with fatty changes in the liver. Therefore, the shift in terminology from NAFLD to MAFLD has already attained global endorsement. However, validation of the new term at the population level is warranted to ensure a holistic approach to reduce the global burden.

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