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MAFLD – a new approach to fatty liver disease

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ABSTRACT

Introduction and purpose
Fatty liver disease associated with metabolic dysfunction (MAFLD) is a term introduced in 2020 to refer to fatty liver disease associated with systemic metabolic dysregulation. The name change from nonalcoholic fatty liver disease (NAFLD) to fatty liver disease associated with metabolic dysfunction (MAFLD) was proposed to focus on the bidirectional interaction between fatty liver disease and metabolic changes and to emphasize the need to evaluate fatty liver disease independently of alcohol consumption and other comorbid causes of liver disease. Fatty liver disease associated with metabolic dysfunction (MAFLD) affects approximately 25% of the general population and more than 50% of patients with metabolic disorders. This new concept of MAFLD may have a broad impact on patients, physicians, healthcare professionals, and various stakeholders regarding fatty liver disease. In this way, MAFLD may influence clinical practice and increase awareness regarding fatty liver disease. This paper identifies differences between the MAFLD and NAFLD diagnoses, areas of benefit, potential limitations, and how the MAFLD terminology has opened up new areas of research.

Materials and methods
To write this article, data bases such as PubMed and Google Scholar were searched using the following terms: MAFLD, NAFLD, obesity, liver diseases, metabolic, fibrosis

Description of the state of knowledge
In May 2020, an international group of experts in Gastroeneterology suggested the acronym MAFLD (fatty liver disease associated with metabolic dysfunction) instead of the previously

used acronym NAFLD (nonalcoholic fatty liver disease). According to the experts, the new acronym more accurately reflects the current knowledge about fatty liver disease - a disease associated with complex metabolic dysfunction. MAFLD was suggested as a more proper term, a superior one, related to the heterogeneity of the clinical picture and course of fatty liver disease under the influence of many factors, including age, gender, hormonal status, ethnicity, diet, alcohol, smoking, genetic predisposition, microbiota and the broadly understood metabolic state. Thus, the final result of MAFLD takes into account the sum of input factors, each of which interacts with others and affects the clinical course of individual disease components and the disease as a whole. It follows that effective treatment of MAFLD will require a systematic analysis of the pathways involved in the disease processes and likely a multifaceted, personalized approach to the patient.

Summary

Nonalcoholic fatty liver disease (NAFLD) is defined as a chronic liver disease characterized by excessive accumulation of fat in the liver without another obvious cause (no excessive alcohol consumption, hepatotoxic drugs, toxins, viral infections, genetic liver diseases), so it is a diagnosis of exclusion. The term NAFLD literally refers to non-alcoholic hepatopathy and does not correlate well with metabolic dysfunction and related cardiovascular risks. Therefore, researchers and scientific societies have taken action to change the terminology. For this purpose, the term MAFLD - metabolic dysfunction-associated fatty liver disease - was proposed. MAFLD has been shown to be an independent risk factor for cardiovascular disease and atherosclerosis. It is better associated with the main risk factors for atherosclerosis and cardiovascular disease than NAFLD, such as dyslipidemia, type 2 diabetes, and hypertension.

Keywords: MAFLD, NAFLD, steatohepatitis, diagnostic criteria, obesity, liver diseases, metabolic, fibrosis

Introduction

Since the introduction of the term nonalcoholic fatty liver disease (NAFLD) into the medical canon, there has been much debate about changing the name to better reflect the nature of the disease and to go beyond the superficial histopathological similarities to alcohol-related liver disease [1-5]. In 2020, an international expert panel, using a two-stage Delphi consensus, proposed the term “metabolic fatty liver disease,” abbreviated as “MAFLD” [6]. MAFLD, like NAFLD, requires evidence of ≥5% fatty liver disease in the absence of concomitant liver disease, including “significant” alcohol consumption, while emphasizing the role of systemic metabolic dysregulation in driving liver disease as a requirement for considering the diagnosis [7]. In addition to changing the name itself, a set of simple positive criteria for diagnosing and evaluating patients for the disease has also been suggested. However, the most important difference between NAFLD and MAFLD diagnosis is not the literal recognition of metabolic dysregulation pathways in the development of the disease, but rather the removal of the exclusion criterion for concomitant liver disease in order to make a final diagnosis [8]. Many studies have shown synergistic effects of concomitant liver disease, including viral hepatitis and concomitant alcohol consumption. Previously, the diagnosis of NAFLD did not take into account their contribution to the individual patient's outcome, and the diagnosis was made on the basis of a list of exclusions of other diseases [9,10]. In short, MAFLD emphasizes the essence of the disease and is no longer related only to the presence or absence of other causes of liver disease. This simple change allows physicians to identify and treat all liver diseases that may be present in a given patient in a holistic manner. The latter is important, considering that in many countries and regions overweight or obesity affects more than 60% of the adult population.

Epidemiology of MAFLD

The prevalence of MAFLD in developed countries is increasing due to the increasing percentage of diseases predisposing to its occurrence, mainly obesity and type 2 diabetes. The incidence of MAFLD is diverse and depends on both geographical factors and the presence of diseases involved in the pathogenesis of MAFLD, such as obesity, type 2 diabetes and metabolic syndrome. A meta-analysis of 86 studies from 22 countries showed that the global prevalence of MAFLD was 25.2%, the highest percentage was recorded in the Middle East (31.8%) and

South America (30.4%), lower in Europe (23%) and the lowest in Africa (13.5%) [11]. In the National Health and Nutrition Examination Survey (NHANES), the prevalence of MAFLD in 2011–2018 was 34.8%, with a higher incidence in men (38.5% vs 31.1%). The prevalence of MAFLD increased with age, from 23.2% in those aged 18–39 to 43.8% in those over 60 years of age [12]. Chen et al. [13] showed that in a group of 139,170 subjects, the prevalence of MAFLD was 26.1% (men 35.4%, women 14.1%). This study also showed differences in the prevalence of MAFLD depending on the hormonal status of women: 6.1% in premenopause, 16.8% in menopause, 30.2% in postmenopause, which was probably related to the age of the examined. Differences in the incidence of MAFLD were also observed depending on body weight, which results from the pathogenesis of the disease. Among patients with underweight, normal body weight, overweight and obesity, MAFLD occurred in 0.1%, 4%, 27.4% and 59.8% of the study participants, respectively [13]. In the analysis of 116 studies covering 2,667,052 patients with overweight or obesity, the incidence of MAFLD was 50.7% (men 59%, women 47.5%). Significant geographical variation in the incidence of MAFLD was observed in the overweight or obese population. Interestingly, in the Polish population, 87.2% of patients with MAFLD were recorded in this group [14].

Criteria for the diagnosis of MAFLD

Currently, the definition of NAFLD, as given in most guidelines and recent publications, is based on the presence of steatosis in >5% of hepatocytes in the absence of significant current or recent alcohol consumption and other known causes of liver disease. Recently, a set of new "positive" criteria were proposed for the diagnosis of MAFLD regardless of alcohol consumption or other concomitant liver diseases. Suggested criteria for a positive diagnosis of MAFLD are based on evidence of histological (biopsy), imaging, or blood biomarker evidence of hepatic fat accumulation (fatty liver disease) in addition to one of the following three criteria, namely overweight/obesity, presence of type 2 diabetes (T2DM), or evidence of metabolic disorders. Ultrasonography is the most frequently used first-line diagnostic method for the detection of steatosis and is highly recommended. It should be noted that ultrasonography has limited sensitivity, does not reliably detect steatosis <20%, and its performance is suboptimal in individuals with a body mass index (BMI) >40 kg/m2. Measurement of the controlled attenuation parameter (or similar) by vibration-guided transient elastography (FibroScan) is gradually performed in routine clinical practice. Computed tomography or magnetic resonance imaging can be used to diagnose moderate to severe steatosis when available. Magnetic

resonance spectroscopy (MRS) provides quantitative assessment of liver fat but is expensive, has limited availability, and requires specialized software. Therefore, MRI-derived proton density fat fraction, which is close to MRS but more practical, is generally preferred in clinical trials. Until adequately validated in future studies, serum biomarkers of steatosis could replace imaging methods. However, at present this would only be appropriate for large epidemiological studies with markers such as fatty liver index (FLI), given the available data on the diagnostic and prognostic properties of FLI [15–18].

MAFLD and NAFLD - differences

One study compared diagnostic criteria for NAFLD and MAFLD. Of 13,083 cases with completed ultrasound and laboratory data, MAFLD was diagnosed in 4087/13,083 (31.24%) participants, whereas NAFLD was diagnosed in 4347/13,083 (33.23%) in the general population and 4347/12,045 (36.09%) in patients without alcohol consumption or other liver diseases. Compared with NAFLD, patients with MAFLD were significantly older, had a higher BMI, a higher percentage of metabolic comorbidities (diabetes, hypertension), and higher HOMA-IR, lipids, and liver enzymes. MAFLD patients with alcohol consumption were younger and more often male than those without alcohol consumption. Furthermore, they had fewer metabolic disorders but higher levels of liver enzymes. MAFLD patients who consumed alcohol had more advanced fibrosis. This study provides evidence that the MAFLD definition is more useful in identifying patients with fatty liver disease at high risk of disease progression [19].

As it turns out, the diagnosis of MAFLD is crucial in identifying patients at higher risk who would benefit from targeted treatment. Several studies have highlighted that the diagnosis of MAFLD correlates better with higher stage of liver fibrosis and noninvasive markers of fatty infiltration, e.g. shear wave elastrography [20-22]. The knowledge that metabolic dysregulation pathways contribute to severe liver dysfunction highlights the important difference between diagnostic criteria for MAFLD and exclusion criteria of NAFLD in the evaluation of people with this disease.

Moreover, one study conducted by non-gastroenterologists showed that 56% of respondents were unaware that NAFLD was associated with alcohol consumption [23]. Thus, despite the emphasis on the non-alcoholic background of the disease, this term is misinterpreted even among physicians and does not fully reflect the needs of practice.

As mentioned earlier, the MAFLD diagnosis eliminates the criterion of excluding concomitant liver disease in order to make a final diagnosis, which is one of the main advantages compared to the traditional definition of NAFLD. This is evidenced by studies showing that people with liver diseases such as hepatitis B or hepatitis C, diagnosed with MAFLD, have significantly increased complications, both intra- and extrahepatic [24]. The additional diagnosis of MAFLD in addition to the already established diagnosis of hepatitis B contributed to an increased rate of complications and mortality [25]. Moreover, in the study conducted by Zheng et al. [26], out of 780 patients who underwent liver biopsy, 773 were diagnosed with MAFLD. In turn, among patients with MAFLD, 66 were found to have excessive alcohol consumption. This group also had high levels of gamma-glutamyltransferase and a larger area of fatty liver parenchyma compared to patients with MAFLD without concomitant liver disease. Assessment of these results would not be possible in the context of the "old" definition of NAFLD due to restrictive nature of NAFLD, containing the requirement to exclude concomitant liver disease.

To compare NAFLD with MAFLD, Zhang et al. examined the burden of cardiovascular and renal disease in adults with MAFLD and NAFLD in a cross-sectional study. Based on nine surveys conducted over 18 years from 1999 to 2016, they observed that the prevalence and absolute number of MAFLD cases significantly increased and were higher than those of NAFLD. The MAFLD group had significantly higher odds of all components of the metabolic syndrome (hypertension, dyslipidemia, diabetes, obesity), especially diabetes (OR = 5.73, 95% CI: 5.10–6.45) and central obesity (OR = 17.05, 95% CI: 15.32–18.97), compared with the non-MAFLD group. Patients with MAFLD also had a significantly higher 10-year risk of myocardial infarction and stroke in the course of cardiovascular diseases (OR = 3.2, 95% CI: 2.8–3.6 vs. OR = 3.7, 95% CI: 3.4–4.1). A statistically insignificant upward trend in the incidence of any chronic kidney disease was also observed in both NAFLD and MAFLD groups. Thus, it has been proven that the absolute cardiorenal burden may be higher in MAFLD than in NAFLD [27].

Various observational studies have shown that MAFLD better identifies patients with advanced liver fibrosis compared to NAFLD. Lin et al. [28] in one of the influential considerations on this topic showed that noninvasive liver fibrosis scores were significantly higher in MAFLD than in NAFLD. These results were further confirmed by the study by Yamamura et al. [29] who found that liver stiffness on elastography was higher in MAFLD than in NAFLD (7.7 vs. 6.8 kPa, respectively). Furthermore, Huang et al. [30] showed that patients diagnosed with MAFLD alone had higher disease severity assessed by histological and laboratory parameters compared to patients diagnosed with NAFLD alone.

It may also be surprising that MAFLD showed associations with lung diseases compared to NAFLD diagnosis, including poorer lung function and higher mortality rates associated with COVID-19 infection. The study by Miao et al. [31] compared the association of lung function parameters in patients diagnosed with MAFLD versus NAFLD. After adjustment for age, sex, obesity scores, smoking status, and alcohol consumption, individuals with MAFLD had significantly lower predicted forced vital capacity (88.27±17.60% vs. 90.82±16.85%, $P<0.005$) and lower forced expiratory volume in 1 second (FEV1) (79.89±17.34 vs. 83.02±16.66%, $P<0.005$) than individuals diagnosed with NAFLD.

Another advantage of using MAFLD over NAFLD is the increased identification of individuals with high-risk features of progressive liver disease. One research reviewed 17 studies with both NAFLD and MAFLD diagnoses, including a total of 9,808,677 individuals. This study found that the prevalence of MAFLD was 33.0%, with a prevalence of NAFLD of 29.1%. A surprising fact of this work was that of all cases of fatty liver disease identified in the combined studies, 15.1% were identified as MAFLD alone. Several studies have shown that a large increase in the number of patients diagnosed was performed in Asian populations. This indicates that the new diagnostic criteria are better suited to identify patients than the traditional NAFLD diagnosis label [32,33]. Although this has been replicated in other reports, there are geographic differences in this increase in the identification of significant fatty liver disease.

Summary

Early diagnosis of MAFLD is important because implementing appropriate treatment for this condition prevents hepatic and cardiovascular complications. Changing definitions and detailed criteria for diagnosing fatty liver disease show how diverse the etiology of this condition and its clinical picture are.

In conclusion, there are clear clinical, research, and, above all, patient benefits of using the MAFLD definition over the NAFLD terminology. MAFLD establishes a clear diagnosis with a set of positive diagnostic criteria that allow physicians to better adapt their practice to individuals at high risk of complications or other comorbid metabolic diseases. Therefore, the term “MAFLD” is undoubtedly a step in the right direction to reduce the stigma associated with the NAFLD diagnosis, increase public awareness, and improve clinical care.

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