Editorial

The role of diet in the management of MAFLD—why does a new disease require a novel, individualized approach?

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In 2020, international consensus guidelines recommended renaming a non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD) (1). However, these two terms are not interchangeable. Diagnosis of MAFLD is established while hepatic steatosis (diagnosed by the use of non-invasive methods as well as liver biopsy) is accompanied by overweight/obesity or type 2 diabetes (T2D) or two or more metabolic risk factors, including increased waist circumference (with cut off values specific for the population), arterial hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) (<40 mmol/L in women and <50 mmol/L in men), prediabetes (impaired fasting glucose, impaired glucose tolerance or glycated hemoglobin 5.7–6.4%), insulin resistance [homeostasis model assessment (HOMA) score ≥2.5] and subclinical inflammation (plasma high-sensitivity C-reactive protein level >2 mg/L). Indeed, the introduction of these criteria helps overcome a controversial definition of at-risk alcohol intake and highlights the importance of metabolic factors in the development and progression of the disease (2). However, according to the original definition, NAFLD could have been diagnosed if another liver disease or cause of hepatic steatosis was excluded (3). On the contrary, patients with MAFLD can simultaneously suffer from other chronic liver diseases (1). Therefore, despite a high overlap [estimated in the recent meta-analysis as 81.59%; 95% confidence interval (CI): 66.51–90.82%], MAFLD and NAFLD do not precisely cover the same spectrum of patients and health risks (*Figure 1*) (4).

When the same population is screened for the two diseases, individuals meeting MAFLD diagnostic criteria are characterized by higher body mass index and higher prevalence of metabolic syndrome components, which is accompanied by higher liver enzymes activity, higher scores of the non-invasive liver fibrosis assessment, and higher all-cause mortality despite similar cardiovascular, neoplasm and diabetes-related mortality risk (5). On the contrary, patients who met the definition of NAFLD but not the MAFLD criteria (non-MD-NAFLD) have the lowest levels of transaminase activity and favorable lipid profile, suggesting that in some cases, previously diagnosed as NAFLD liver steatosis is not associated with higher overall clinical risk of adverse outcomes (5). Alcohol intake also has an impact on the clinical presentation of MAFLD: the individuals drinking alcohol regularly (≥30 g/d for males and ≥20 g/d for females) have higher liver enzyme activity and higher AST-to-platelet-ratio index (APRI) score (a non-invasive indicator of fibrosis) but lower levels of metabolic parameters (e.g., glycated hemoglobin and HOMA) then non-drinking patients (4,5). Nevertheless, alcohol intake (as well as a hepatic viral infection) is associated with increased mortality risk in MAFLD patients (4).

Given that MAFLD and NAFLD do not refer to precisely the same condition, the epidemiology and the predisposing factors for the two diseases may differ. Globally, MAFLD affects up to 25% of the population; however, the prevalence of the disease depending on

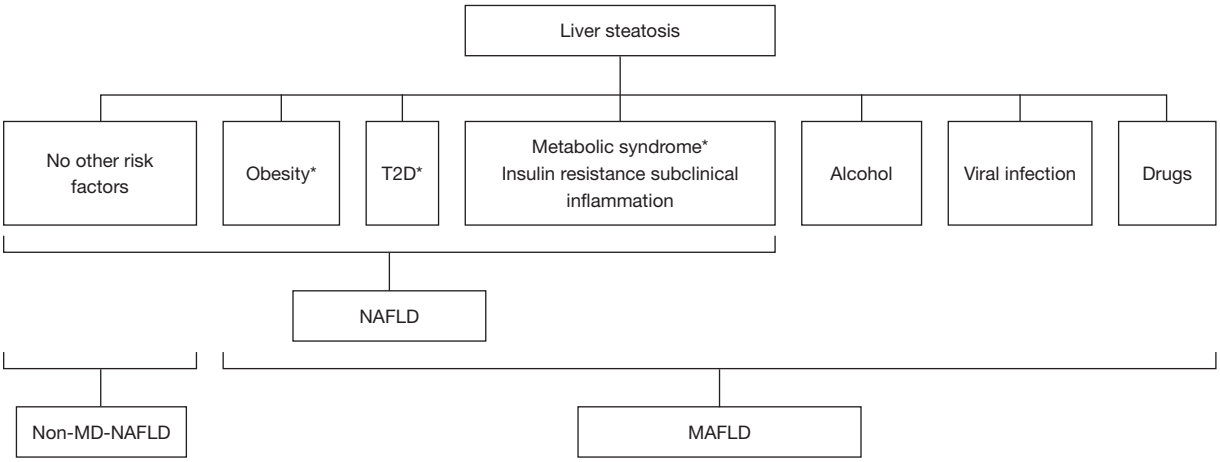

Figure 1 Different spectra of patients with NAFLD and MAFLD. Due to the broader diagnostic criteria, MAFLD covers subgroups of patients with liver steatosis secondary to exposure to toxic factors and viral infection. In turn, NAFLD also refers to individuals in whom metabolic risk factors or comorbidities do not accompany liver steatosis (non-MD-NAFLD). Notably, the risk factors and comorbidities can be present in various combinations in MAFLD patients making this population very heterogeneous. *, comorbidities and conditions crucial for MAFLD diagnosis may also co-exist in NAFLD patients. T2D, type 2 diabetes; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic-associated fatty liver disease; non-MD-NAFLD, met the definition of NAFLD but not the MAFLD criteria.

the region may vary from 1.2% to 59% and is probably underestimated due to a high number of undiagnosed T2D cases (5). Apart from methodological differences between the epidemiological studies, local, mainly dietary factors, seem to play a role in these discrepancies. For instance, in a recent prospective cohort study conducted in China, Zhang *et al.* found that consumption of preserved eggs can increase the risk of liver steatosis, particularly in this population, independently of traditional risk factors. Out of 15,883 participants from the Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIH) study, free of liver diseases, cancer, and cardiovascular disease at baseline, 3,683 cases of liver steatosis were diagnosed based on abdominal ultrasonography during 56,002 person-years of follow-up. After an adjustment for sociodemographic characteristics, lifestyle risk factors, total energy intake, egg intake, and eating patterns, the risk of liver steatosis occurred to correlate positively with the frequency of preserved egg consumption with multivariable hazard ratios 1.05 (95% CI: 0.98, 1.14) for <1 time/week to 1.26 (95% CI: 1.09, 1.46) for ≥2 times/week (6). The authors explain this association by the fact that preserved eggs contain a significant amount of lead oxide, while exposure to heavy metals is considered a risk factor of liver steatosis (7). However, from the point of view of MAFLD diagnostic criteria, the population included in the study was heterogenic and included both metabolically healthy individuals and those presenting features of the metabolic syndrome (overweight, hypertension, hyperlipidemia, and diabetes). Therefore, the results of this and similar studies focusing on the impact of dietary factors on liver steatosis, including individuals not meeting the metabolic criteria, cannot be directly translated to patients with MAFLD.

Since our understanding of the role of diet in MAFLD development and progression is still limited, there is a need for studies aiming to identify general and population-specific diet components that may predispose to the development of the disease. The role of dietary interventions in MAFLD management is crucial since no pharmacological treatment is currently being approved for this purpose, and several compounds are being evaluated in clinical trials yet (8). Notably, due to the broad diagnostic criteria, patients with MAFLD do not constitute a homogenous group, and several subtypes of the disease, requiring a specific dietary approach, can be distinguished (*Figure 1*) (9). For instance, meta-analyses point out that in overweight and obese individuals with liver steatosis, 7–10% reduction of body weight due to caloric restriction may result in significant improvement of the disease course reflected by liver enzymes activity and histologically assessed liver steatosis and inflammation with less certain impact on fibrosis (10). However, patients with

alcoholic steatohepatitis and liver cirrhosis are frequently at risk of malnutrition and may require nutrition therapy with increased caloric and nutrient supply (9). The dietary recommendations for the individuals representing other MAFLD phenotypes, e.g., overweight with viral hepatitis or diabetic with a history of alcohol intake/abuse, are to be established yet. There is a need for prospective studies assessing the course of different MAFLD phenotypes depending on the dietary treatment in different populations. However, before such studies are conducted, re-analyses of the previous prospective epidemiological studies considering the prognosis for patients meeting the diagnostic criteria for different MAFLD phenotypes could provide valuable information (as was done for the NHANES III study in the context of MAFLD-associated health risks) (4,5).

In summary, the transition in terminology from NAFLD to MAFLD has several implications, including a need for a novel therapeutic approach covering dietary recommendations. Therefore, further research is required to establish evidence-based guidelines for the management of different MAFLD phenotypes, especially in the aspect of dietary interventions.

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