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EDITORIAL

Metabolic dysfunction-associated steatotic liver disease: A silent pandemic

Arghya Samanta, Moinak Sen Sarma

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Abstract

The worldwide epidemiology of non-alcoholic fatty liver disease (NAFLD) is showing an upward trend, parallel to the rising trend of metabolic syndrome, owing to lifestyle changes. The pathogenesis of NAFLD has not been fully understood yet. Therefore, NAFLD has emerged as a public health concern in the field of hepatology and metabolisms worldwide. Recent changes in the nomenclature from NAFLD to metabolic dysfunction-associated steatotic liver disease have brought a positive outlook changes in the understanding of the disease process and doctor-patient communication. Lifestyle changes are the main treatment modality. Recently, clinical trial using drugs that target 'insulin resistance' which is the driving force behind NAFLD, have shown promising results. Further translational research is needed to better understand the underlying pathophysiological mechanism of NAFLD which may open newer avenues of therapeutic targets. The role of gut dysbiosis in etiopathogenesis and use of fecal microbiota modification in the treatment should be studied extensively. Prevention of this silent epidemic by spreading awareness and early intervention should be our priority.

Key Words: Metabolic dysfunction; Fatty liver; Obesity; Insulin resistance

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Core Tip: Non-alcoholic fatty liver disease is often considered the hepatic manifestation of metabolic syndrome. The new nomenclature of "metabolic dysfunction associated steatotic liver disease" emphasizes the role of disordered metabolism in the pathogenesis. Weight reduction by lifestyle changes is the mainstay of treatment.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a broad spectrum of liver disorders related to dysmetabolic conditions. It is characterized by macrovesicular steatosis with or without hepatocellular ballooning, lobular inflammation, and hepatic fibrosis[1]. NAFLD is the leading cause of hepatic morbidity and mortality worldwide and is now the most common indication of liver transplantation (LT)[2-5]. Thus, NAFLD is associated with exorbitant healthcare costs[6,7]. It affects nearly one third of the adult population[8-11] and 9%-12% of the pediatric population[12-14]. The latest meta-analysis by Younossi *et al*[15], showed a global rise in NAFLD prevalence at an alarming rate- from 25.26% (21.59-29.33) in 1990-2006 to 38% (33.71-42.49) in 2016-2019 ($P < 0.001$)[15]. The prevalence in Asia is following a trajectory similar to that in the western countries[16-18].

THE DEBATE OVER THE NEW NOMENCLATURE: NAFLD *VS* MASLD

NAFLD is usually defined as the presence of steatosis in >5% hepatocytes, detected by imaging or histopathology after exclusion of secondary causes for hepatic steatosis[19]. Pathologically, it is strongly linked to metabolic syndrome, which is a constellation of obesity, hypertension, hyperlipidemia, type 2 diabetes mellitus (T2DM)[20]. Patients with NAFLD are at higher risk of liver-related complications as well as cardiovascular complications and mortality[20,21]. The most common cause of mortality in patients with NAFLD is cardiovascular complications, followed by extrahepatic malignancies and hepatic complications, highlighting the fact that NAFLD is a multisystemic disease[22,23]. Recently, an international expert group proposed to change the existing nomenclature "Non-Alcoholic Fatty Liver Disease" and adopt the acronym MASLD, or "Metabolic dysfunction-Associated Steatotic Liver Disease", thus emphasizing the role of systemic metabolic dysfunction in the etiopathogenesis[24]. The shift in the nomenclature introduces a "positive" diagnostic criteria and highlights the cardiovascular risk profile of these individuals. The new nomenclature thus aims for a better understanding of the disease and patient-physician communication.

The diagnosis of MASLD is based on the detection of steatosis of hepatocytes (diagnosed by imaging, biomarkers, or histology) and at least one feature among the following three - overweight/obesity, type 2 diabetes mellitus and metabolic dysregulation. The criterion of metabolic dysregulation is fulfilled when atleast two features among the following are found: increased waist circumference, hypertension, hyperlipidemia, low level of high-density lipoprotein-C (HDL-C), prediabetes, insulin resistance, and subclinical inflammation. These criteria will ensure the identification of a more homogenous disease condition than NAFLD, overcoming the dilemmas and controversies in defining alcohol intake, thereby encouraging new pathophysiological developments and augmenting clinical studies (as elegantly reviewed by Vargas *et al*[25] in this present issue).

LEAN NAFLD

The prevalence of NAFLD showed a rising trend similar to the rising burden of obesity[26,27]. In contrast, lean patients with NAFLD were also detected. In the meta-analysis by Young *et al*[28], 11% and 25% of the general and NAFLD populations, were identified to be "lean NAFLD" respectively[29]. Metabolic profile was more deranged in lean NAFLD patients than healthy controls. These patients also had a higher prevalence of insulin resistance, metabolic syndrome and higher levels of pro-inflammatory mediators[30,31]. On the contrary, lean NAFLD patients have more favorable histologic features than obese NAFLD patients[31].

The ethnicity of the study population should be considered for correctly defining lean MAFLD patients. Body mass index (BMI) cutoffs depending on the ethnicity of the individual have been recommended to define "lean MAFLD". The cutoffs for defining lean MAFLD are BMI < 25 kg/m^2 for Caucasians and < 23 kg/m^2 for Asians[32]. The prevalence of lean NAFLD has been found to be 5%–45% in the Asian population and 5%–20% among Europeans[33]. Further studies are needed to better characterize the newly-defined lean MAFLD patients.

T2DM AND NAFLD

Presence of concomitant T2DM accelerates the disease progression in NAFLD, as patients with concomitant T2DM and NAFLD had higher rates of advanced fibrosis and adverse outcomes compared to NAFLD without T2DM[10]. Furthermore, the concomitant NAFLD and T2DM causes increased liver-related, cardiovascular complications as well as overall mortalities[10]. Other complications of T2DM like diabetic retinopathy, nephropathy, and polyneuropathy, have

been detected more frequently in diabetes patients with coexisting NAFLD[34-36]. Therefore, a novel diagnostic score has been recommended for T2DM patients with NAFLD[37]. Those with an FIB-4 score of more than 1.3 have a higher risk of developing severe disease[38]. Recent NAFLD guidelines recommend that T2DM populations be screened for NAFLD [24].

NAFLD AND METABOLIC SYNDROME

NAFLD is considered as the hepatic manifestation of metabolic syndrome[39]. In the meta-analysis by Ballestri *et al*[40], NAFLD was associated with incident metabolic syndrome in 5-year follow-up. On the other hand, another study by Ma *et al*[41] demonstrated that patients with metabolic syndrome had a higher risk of developing NAFLD. While comparing the new term 'MASLD' with the traditional definition of 'NAFLD', Lin *et al*[42] found higher proportions of metabolic comorbidities in patients with MASLD, emphasizing the impact of positive diagnostic criteria.

DIAGNOSTIC EVALUATION

Liver biopsy is the gold standard to assess disease activity and severity. The severity of liver fibrosis has been identified as the most important prognostic factor and is independently linked with hepatic outcomes in NAFLD patients. Sanyal *et al*[2], in an elegantly done prospective study of 1773 adult patients with NAFLD, found that F3, and F4 fibrosis were associated with increased risk of hepatic complications and death, after adjustment for age, sex, race and diabetes status.

Several non-invasive tests have been developed as diagnostic and prognostic tools in patients of NAFLD as liver biopsy is invasive and less preferred for disease monitoring. Imaging to detect and quantify hepatic steatosis has gained prominence with advances of computerized tomography (liver attenuation index) and magnetic resonance imaging (magnetic resonance imaging proton density fat fraction-MRI-PDFF)[43-45]. Multiparametric MRI, which consists of MR spectroscopy, MR elastography and T1 mapping, has demonstrated high diagnostic accuracy, comparable to liver histology[45,46]. Similar multiparametric CT sequences that can evaluate the hepatic attenuation, liver segmental volume ratio, splenic volume, and liver surface nodularity score, have shown encouraging results as an alternative diagnostic tool to identify advanced fibrosis in NAFLD patients[47]. MRI-PDFF response has been studied as a potential surrogate for histologic improvement after treatment of NAFLD. Several studies have shown a clear correlation between a reduction in MRI-PDFF (usually taken as a ≥ 30% relative reduction) and improvement in the NAFLD activity score, resolution of NASH, and fibrosis[48,49]. Boursier *et al*[50], in a large cohort of 1097 patients, compared the prognostic efficacy of fibrosis index based on 4-factors (FIB4), transient elastography (TE) and liver biopsy. The results showed that FIB4 and TE showed good accuracy for the prediction of liver-related events (LRE), with Harrell's C-indexes > 0.80 [0.817 (0.768-0.866) *vs.* 0.878 (0.835-0.921), respectively, $P = 0.059$], as compared to liver biopsy. The authors proposed a stepwise algorithm to accurately stratify NAFLD patients based on their risk for LRE: compared to patients with "FIB4 < 1.30", those with "FIB4 ≥ 1.30 then TE < 8.0 kPa" had a similar risk of LREs [adjusted hazard ratio (aHR) 1.3; 95%CI 0.3–6.8], whereas the risk of LREs significantly increased in patients with "FIB4 ≥ 1.30 then TE 8.0-12.0 kPa" (aHR 3.8; 95%CI 1.3–10.9), and even more for those with "FIB4 ≥ 1.30 then TE > 12.0 kPa" (aHR 12.4; 95%CI 5.1–30.2).

However, we need to keep in mind a major limitation of using these non-invasive methods to diagnose and monitor hepatic steatosis is that it provides no information on the underlying etiology or associated risk factors.

TREATMENT

As NAFLD is a systemic disease of disordered metabolism, a multi-disciplinary approach is of utmost importance for the treatment. Weight reduction by lifestyle changes and dietary interventions is the cornerstone of treatment in obese and lean NAFLD patients[19,51]. The beneficial effects of lifestyle modifications have been consistently found to be helpful in the resolution of hepatic steatosis in both lean Asian and Caucasian NAFLD patients[51-53]. Medical treatment with glucagon-like peptide receptor agonists, sodium-glucose cotransporter-2 inhibitors, and peroxisome proliferator-activated receptor-γ agonists was able to improve inflammation and fibrosis, as well as reduction in blood pressure, better glycemic control and lipid profile[54-56]. Bariatric surgery is an effective treatment for a select group of patients who are non-responsive to dietary interventions and exercise or unable to lose weight through lifestyle changes. It can improve both histological characteristics of NASH as well as mortality due to cardiovascular complications[57]. Lim *et al*[58] studied the usefulness of endoscopic bariatric therapies such as intragastric balloon, endoscopic sleeve gastroplasty, and duodeno-jejunal bypass liner in reducing weight and found better results as compared to standard medical therapy. With extensive research into the therapeutic options in the pipeline, treatment strategies for NAFLD treatment are promising[59].

FUTURE PERSPECTIVE

Further prospective studies are the need of the hour to develop more accurate diagnostic tools for advanced fibrosis in NAFLD and to explore the underlying pathophysiological mechanisms linking NAFLD with other conditions. More in-depth research on gut microbiota in the etiopathogenesis of NAFLD and its role in the therapeutics is warranted. Most

randomized clinical trials of available drugs do not reflect the proper scenario, due to the limitations of therapeutic targets, drug safety, and other factors. This current review by Vargas in this issue serves as a valuable resource for researchers seeking a comprehensive understanding of NAFLD and tries to address these issues[25].

CONCLUSION

NAFLD must be evaluated as a multisystemic metabolic disorder. It may lead to liver-related complications, thus the need for multidisciplinary screening and disease management cannot be over emphasized. Routine screening for NAFLD is recommended in patients with metabolic syndrome. Lifestyle intervention remains the most important treatment modality. The global pandemic of NAFLD poses significant social and economic burden; thus it is of utmost importance to create widespread awareness in order to make early interventions and achieve better outcome.

FOOTNOTES

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