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Review

The bidirectional impacts of alcohol consumption and MAFLD for progressive fatty liver disease

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***Abstract*:** Nonalcoholic fatty liver disease (NAFLD), once considered a benign condition, has been associated with several cardiometabolic complications over the past two decades. The worldwide prevalence of NAFLD is as high as 30%. NAFLD requires the absence of a "significant alcohol intake." Conflicting reports have suggested that moderate alcohol consumption may be protective; therefore, the diagnosis of NAFLD previously relied on negative criteria. However, there has been a significant increase in alcohol consumption globally. Apart from the rise in alcohol-related liver disease (ARLD), alcohol, a major toxin, is associated with an increased risk of several cancers, including hepatocellular carcinoma. Alcohol misuse is a significant contributor to disability-adjusted life years. Recently, the term metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed instead of NAFLD to include the metabolic dysfunction responsible for the major adverse outcomes in patients with fatty liver disease. MAFLD, dependent on the "positive diagnostic criteria" rather than previous exclusion criteria, may identify individuals with poor metabolic health and aid in managing patients at increased risk of all-cause and cardiovascular mortality. Although MAFLD is less stigmatizing than NAFLD, excluding alcohol intake may increase the risk of already existing underreported alcohol consumption in this subgroup of patients. Therefore, alcohol consumption may increase the prevalence of fatty liver disease and its associated complications in patients with MAFLD. This review discusses the effects of alcohol intake and MAFLD on fatty liver disease.

Keywords: lean NASH, metabolic dysfunction, obesity, insulin resistance, terminology

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Introduction

Nonalcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ARLD) are the leading causes of chronic liver disease and are associated with high morbidity and mortality.[1] The average pure alcohol consumption worldwide is 5.8 liters per capita.[2] Globally, alcohol consumption has increased significantly in recent years owing to the pandemic.[3,4] Alcohol misuse accounts for 5% of deaths and 5% of disability-adjusted life-years worldwide across all ages. Harmful alcohol consumption leads to death and disability in the early years of life (<40 years of age).[5] It is well known that alcohol consumption can have a synergistic effect and lead to the rapid progression of liver disease in patients with viral hepatitis.[6] However, the effects of alcohol consumption on fatty liver disease have long been debated. Initial studies demonstrated that moderate alcohol consumption might prevent NAFLD; however, later studies have shown that any amount of alcohol consumption increases the risk of progression.[7,8] However, the impact of alcohol consumption on the progression of fatty liver disease has not been addressed in detail. The prevalence of NAFLD is directly proportional to that of overweight and obesity.[9] According to the World Health Organization, 39% of adults aged ⩾18 years are overweight, and 13% are obese. Approximately 39 million children under 5 years and >340 million aged 5–19 years are overweight or obese. Approximately 8% of less than 2-year obese

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children and 80% of 10–14-year-olds will become obese adults.[10] Furthermore, parental obesity increases the risk of childhood obesity.[11] Eventually, by 2050, 60% of males and 50% of females will be obese.[12] This leads to an exponential increase in the worldwide incidence of NAFLD. Although obesity is a major determinant of NAFLD, certain metabolic factors, including genetic factors, the microbiome, and an individual's response to an injury (hit), influence the development of fatty liver. Recently, there has been an ongoing debate on changing the nomenclature of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) to account for metabolic factors that may influence outcomes.[13–15] A large meta-analysis including 3,320,108 individuals reported a 39% prevalence of MAFLD, with 5% of lean and 30% of nonobese individuals being labeled as MAFLD.[16] In this review, we discuss the effects of alcohol consumption and other metabolic factors on fatty liver disease and the pros and cons of renaming NAFLD.

Alcohol and fatty liver: How much is too much?

The stages of ARLD and NAFLD are similar. Regular alcohol consumption for 15 days leads to the development of fatty liver (steatosis) in 90–100% of individuals.[17] Continued misuse for more than 6 months leads to alcohol-associated hepatitis in 10–35% of individuals, and 8–20% of individuals who misuse alcohol for a prolonged duration (5–10 years) develop cirrhosis.[18] The spectrum of NAFLD is similar to ARLD, which includes simple steatosis [nonalcoholic fatty liver (NAFL)] in the initial stages, followed by associated inflammation termed nonalcoholic steatohepatitis (NASH), and then slowly progressing to cirrhosis. Approximately 30% of the population with or without risk factors have fat accumulation in the liver (NAFL).[19] Of them, 10% develop NASH. Approximately 30% of patients with NASH progress to severe liver disease.[19] NAFLD and ARLD produce histologically similar features at all stages.[20] In patients with NAFLD who consume alcohol, it is challenging to differentiate ARLD and NAFLD as these two share strikingly similar histological and molecular biological features at all stages of disease and demonstrate identical polymorphisms in the patatin-like phospholipase domain-containing 3 gene (PNPLA3).[20–22] In fact, NAFLD was considered as an endogenous alcohol-related fatty liver disease due to increased fermentation products of carbohydrates to ethanol in patients with NAFLD.[23] Table 1 describes the similarities between NAFLD and ARLD. Therefore, the distinction between the two conditions must be made on clinical grounds, biochemical tests, and a history of alcohol consumption.[24,25] Therefore, NAFLD is a diagnosis of exclusion requiring the absence of significant alcohol consumption. The definition of "significant alcohol consumption" vary across different guidelines: European Association for Study of the Liver (EASL) considers consumption of ⩾30 g/d for men and ⩾20 g/d for women as significant, while American Association for the Study of Liver Disease (AASLD) considers ⩾21 standard drinks/week or ⩾294 g/week for men and ⩾14 standard drinks/week or ⩾196 g/week for women as significant alcohol consumption.[26,27] On the contrary, the cut-off of Asian guidelines differ from AASLD and EASL, which consider ⩾70 g/week (one standard drink per day) for women and ⩾140 g/week (two standard drinks per day) for men as significant alcohol consumption based on national institutes of health guidelines for clinical trials on NASH.[28] Alcohol consumption above these limits is suggestive of ARLD.[27]

Table 1. Similarities among NAFLD and ARLD.

Variables	NAFLD	ARLD
Pathogenesis	Increased insulin resistance – increased hepatic lipid uptake, synthesis and reduced degradation and secretion	Increased fatty acid synthesis, decreased fatty acid oxidation and VLDL secretion
Natural history	Steatosis-steatohepatitis-cirrhosis	Steatosis-steatohepatitis-cirrhosis. However, the progression in stages is faster than NAFLD

(Continued)

Table 1. (Continued)

Variables	NAFLD	ARLD
Hormone levels	Increased insulin (due to insulin resistance) and leptin	Insulin (impaired pancreatic function) and leptin levels are normal to reduced
Genetic effects	Polymorphisms in rs738409 of PNPLA3 is associated with increased risk of NAFLD	Polymorphisms in rs738409 of PNPLA3 is associated with increased risk of alcohol-related fatty liver disease
Other polymorphisms involved in disease progression/ predisposition[29–31]	ADIPOQ, LEPR, APOC3, PPAR, SREBP, TM6SF2, TLR4	TM6SF2, CYP2E1, KRAS, HFE, MTHFR, TLR4, PNPLA2
Alcohol metabolizing enzymes	ADH, ALDH, CAT and CYP2E1 increased in early stages	ADH, ALDH, CAT and CYP2E1 increased in early stages
Microbiota changes	(1) Increased Bacteroidetes and Ruminococcus and (2) decreased bacterial diversity	Lower abundance of the phyla Bacteriodetes and Firmicutes, with a proportional increase in the abundance of the Gram-negative phylum Proteobacteria and the Gram-positive phylum Actinobacteria. Increased Gram-negative Alcaligenes and Gram-positive Corynebacterium
mRNA	miR-34a, miR-122, miR-155, miR-192	miR-19b, miR-27a, miR-34a, miR-103,miR-107, miR-155, miR-182, miR-192 miR-122 may be protective
ASGPR mediated endocytosis	Normal/increased	Decreased
Lipid peroxidation	Increased TBARS and oxidized glutathione	Increased TBARS and oxidized glutathione with reduced glutathione
Intestinal permeability	Decreased	Significantly decreased
Laboratory variables	Increase in ALT >> AST (early stages)	Increase in AST >> ALT (early stages)
Lipid profile	Hypertriglyceridemiea	Hypertriglycerdemia

ADH, alcohol dehydrogenase; ADIPOQ, adiponectin-encoding gene; ALDH, aldehyde dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; APOC3, apolipoprotein C3; ARLD, alcohol-related liver disease; ASGPR, asialoglycoprotein; CAT, catalyse; CYP, cytochrome; LEPR, leptin receptor; NAFLD, nonalcoholic fatty liver disease; PNPLA3, patatin-like phospholipase domain-containing 3 gene; PPAR, peroxisome proliferator-activated receptors; SREBP, sterol regulatory element binding proteins; TBARS, Thiobarbituric acid reactive substances; TM6SF2, transmembrane 6 superfamily member 2; VLDL, very low-density lipoprotein.

Is alcohol protective in NAFLD? Does the amount of alcohol or type of beverage matter?

Consumption of alcohol in light (1.0–9.9 g/d) to moderate (10.0–29.9 g/d; 10.0–19.9 g/d for women) amount is not uncommon in patients with NAFLD.[32] A large cross-sectional study of 2475 participants from the Framingham Heart Study cohort with hepatic steatosis (HS) demonstrated that the prevalence of HS increases proportionately with an increasing number of drinks.[33] Even <7 drinks/week increased the risk of steatosis by 15%. Furthermore, steatosis was noted in >50% of individuals who consumed >21 drinks/week.[33] The authors reported that the type of beverage was significantly associated with the risk of steatosis (beer >> wine).[33] A similar

study by Mitchell *et al.*[34] reported lower fibrosis levels among wine drinkers. Of the 187 patients with biopsy-proven NAFLD assessed for alcohol consumption based on recall methods, 39% had never consumed alcohol, 49% were current drinkers, and 12% were past drinkers. Current drinkers reported 20 (2.3–60) g/week of alcohol consumption over 18 years, and past drinkers reported 38 (1.5–221) g/week of alcohol consumption over 21 years. Approximately 39% of alcohol consumers had a history of binge intake, and 10% had a history of alcohol intake above the recommended limit of 140 g/w in females and 210 g/w in males more than 10 years prior to inclusion. Compared with lifetime abstainers, modest (<70 g/week) alcohol consumption was associated with lower advanced fibrosis [Odds ratio (OR), 0.29; 95% CI 0.1–0.87; $p=0.02$] even after adjusting for homeostatic model assessment for insulin resistance (HOMA-IR), sex, and total lifetime alcohol consumption; whereas moderate (⩾70 g/week) alcohol consumption was not (OR, 0.23, 95% CI 0.02–2.55; $p=0.21$). A non-binge pattern was associated with a lower risk of advanced fibrosis (OR 0.33, 95% CI 0.13–0.81; $p=0.01$), but not a binge consumption pattern (OR 0.53, 95% CI 0.13–2.10; $p=0.37$) when compared with abstainers. Approximately 12.5% of exclusively wine drinkers, 22.7% of exclusively beer drinkers, and 35% of abstainers had advanced fibrosis. The authors concluded that modest wine consumption might be associated with a lower risk of advanced fibrosis. It is unknown whether this study was prone to recall bias in reporting alcohol consumption. Modest alcohol consumption in NAFLD may be associated with a lower risk of steatohepatitis, fibrosis, and hepatocellular carcinoma (HCC).[35,36]

In contrast, a large population-based study of 367,612 individuals reported that even light alcohol consumption (<10 g/day in women and <20 g/day in men) is associated with increased liver-related and all-cause mortality in patients with elevated alanine transaminase (ALT) levels.[37] Furthermore, light alcohol consumption is associated with an increased risk of HCC in patients with advanced fibrosis.[38] In fact, even light alcohol consumption increases the risk of insulin resistance and impairment in fasting glucose levels.[39] A recent systematic review of six longitudinal studies worldwide reported that even light and moderate alcohol consumption leads to rapid progression of liver disease in patients with NAFLD.[40] It is well known that binge drinking increases PRO-C3, a marker of the type of III collagen (the interstitial matrix formation), without any change in C3M and C4M (a marker of basement membrane degradation.[41] An acute binge of alcohol leads to a 10-fold increase in fibrogenesis markers in healthy and NAFLD patients leading to an increased risk of disease progression.[34,41] Alcohol is a toxin associated with at least 4% of cancers globally.[42] More than one lakh cancers were caused by light to moderate alcohol consumption in 2020 alone.[42] Approximately 21% of liver cancer cases are attributable to alcohol consumption.[43] Alcohol is associated with the rapid progression of liver disease and increases mortality risk, irrespective of the etiology.[44–47] Alcohol intake in any amount is harmful to patients with NAFLD, and the inclusion of an arbitrary cut-off for alcohol intake in the definition of NAFLD can be considered a flaw.

Key point: Alcohol consumption, regardless of the type, is harmful to patients with NAFLD.

Definitions of NAFLD and MAFLD

NAFLD was diagnosed based on the presence of fat in the liver and the absence of other causes of fatty liver. The current diagnosis of NAFLD requires (1) evidence of HS by imaging or histology, (2) no significant alcohol consumption, (3) no competing causes of HS, and (4) no coexisting causes of chronic liver disease. Research efforts have led to significant progress in our understanding of the disease. However, this term is arguably heterogeneous. Recently, the term MAFLD required the presence of fat in the liver along with two other metabolic factors that predispose an individual to develop fatty liver.

Diagnosis of MAFLD[48]

Demonstration of fat in the liver by histology, blood biomarkers, noninvasive markers, or imaging techniques in a patient with type 2 diabetes mellitus or an overweight or obese individual [body mass index (BMI) ⩾23 kg/m^2 for Asians or ⩾25 kg/m^2 for Caucasians] is termed MAFLD. In the absence of obesity or diabetes, a lean individual with liver fat is required to have at least two metabolic risk factors to label him/her as MAFLD. These metabolic factors include the following:

(a) Abdominal obesity: waist circumference ⩾102/88 cm in Caucasian men and women (⩾90 cm in Asian men and ⩾80 cm in Asian women)
(b) Hypertension: blood pressure ⩾130/85 mmHg or on specific drug treatment
(c) Triglycerides ⩾150 mg/dl (⩾1.70 mmol/l) or specific drug treatment
(d) HDL (high density lipoprotein)-cholesterol < 40 mg/dl or (<1 mmol/l) for men or <50 mg/dl (<1.3 mmol/l) for women or specific drug treatment
(e) Prediabetes [i.e., fasting glucose levels 100–125 mg/dl (5.6–6.9 mmol/l), or 2 h postload glucose levels 140–199 mg/dl (7.8–11.0 mmol) or HbA1c (glycated hemoglobin) 5.7% to 6.4% (39–47 mmol/mol)]
(f) Insulin resistance, that is, HOMA-IR score ⩾2.5
(g) High-sensitivity C-reactive protein level >2 mg/l

Does changing the term affect the outcomes?

A recent study by Huang *et al.*[49] evaluating 12,480 individuals with HS diagnosed on ultrasonography reported that both definitions of NAFLD and MAFLD had similar accuracy in predicting neoplasm-related, cardiovascular-related, and diabetes-related mortality. However, MAFLD definition was more strongly associated with overall mortality. This may be due to the wider definition of MAFLD. More patients in the MAFLD group had a higher prevalence of metabolic dysfunction, fibrosis scores, alcohol consumption, smoking, and other diseases contributing to liver disease, including viral hepatitis. The correlation between MAFLD and the NAFLD definition was highly concordant (kappa 0.76). Similar studies have reported that MAFLD can not only predict higher overall mortality but also higher cardiovascular mortality, even in asymptomatic patients.[50–52] Furthermore, few studies have reported an increased risk of systemic diseases, including cardiovascular, cerebrovascular, and renal diseases, in patients identified using the MAFLD definition.[53,54]

Key point: Although the concordance between NAFLD and MAFLD is high, MAFLD may better identify individuals at a higher risk of all-cause mortality. The term MAFLD can improve metabolic health by shifting the care of such individuals from hepatology-centric to multidisciplinary care.

Is lean NAFLD a distinct entity? Can we include lean NAFLD under the umbrella term MAFLD?

The average BMI of the Asian population is lower than that of the Western population and, therefore, has lower cut-off points for defining obesity.[55,56] Lean NAFLD is defined as an individual with normal BMI (<25 kg/m^2 for non-Asians and <23 kg/m^2 for the Asian population) demonstrating histological or noninvasive characteristics of NAFLD/NASH.[48] Although phenotypically lean NAFLD individuals are of normal weight, they are considered to be metabolically unhealthy and referred to as metabolically obese normal-weight individuals.[57] Lean NAFLD individuals have higher visceral fat deposition, lower subcutaneous leg fat (which is protective against cardiometabolic diseases), impaired insulin secretion, higher insulin resistance, and carotid intima-media thickness leading to increased all-cause and cardiovascular mortality.[58] A few reports have suggested that despite the apparent healthier phenotype, lean NAFLD patients display the entire histological spectrum of NASH, including steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis.[59–61] Conversely, it has been reported that patients with lean NAFLD without metabolic dysfunction may have less severe histological inflammation, fibrosis, and lesser incidence of cardiovascular events and mortality compared to obese NAFLD.[52,62,63] A recent meta-analysis including 85 articles and 539,358 patients reported that approximately 15% of the overall population in Asia and 9% in the West have lean NAFLD.[64] Furthermore, 31% and 15.5% of NAFLD patients in Asian and Western populations, respectively, were lean. The authors reported that patients with lean NAFLD had lower waist circumference, blood pressure, and HOMA-IR, and fewer patients had diabetes mellitus without any difference in lipid profile parameters. The authors concluded that lean NAFLD individuals are less metabolically unhealthy than obese and overweight NAFLD individuals, and overreliance on metabolic dysfunction may exclude a significant proportion of lean NAFLD patients.[64] A similar study from India reported poor applicability of MAFLD criteria for lean NAFLD individuals due to lack of metabolic dysfunction.[65]

Further, the presence of fat in liver can be due to multiple causes, including malabsorption syndromes, celiac disease, inflammatory bowel disease, unmeasured excessive alcohol intake, Wilson's disease, and use of hormonal drugs.[66] Such individuals may lack metabolic dysfunction

but have simple steatosis and a lesser incidence of fibrosis. It is well known that fibrosis is a major determinant of outcomes in patients with NAFLD.[67,68] MAFLD may identify patients who are at risk of advanced fibrosis and poorer cardiovascular outcomes.[69] It may be prudent to label lean individuals with pure HS (after the exclusion of other relevant causes) as pre-MAFLD.

Key point: Lean individuals with NAFLD and no metabolic dysfunction may be missed by the positive criteria of MAFLD.

What are the advantages and disadvantages of renaming NAFLD?

As discussed above, the criteria for MAFLD may underestimate a significant proportion of patients with lean NAFLD. This may be advantageous for those lean individuals without metabolic dysfunction as mislabeling them as MAFLD would have increased the psychological stress and cost burden to the healthcare systems. Second, the understanding of the disease pathogenesis and treatment armamentarium has significantly increased in the last two decades.[70–72] Renaming NAFLD may substantially affect therapeutic targets. The term NAFLD is now known to every physician and nonphysician, and changing the term may confuse recently educated individuals.[73,74] However, recent studies from a few centers had reported a clear and easy understanding when the term NAFLD was renamed to MAFLD among primary care physicians, specialists, and the general population.[75–78] On the contrary, MAFLD may include several other concomitant individuals with liver disease. A recent study including 1076 patients with chronic hepatitis B reported concomitant MAFLD in 27.5% of patients, and MAFLD was independently associated with an increased risk of liver-related clinical events and mortality.[79] MAFLD definition may increase the number of individuals being labeled as metabolically unhealthy with fatty liver disease.[80] However, the simplistic criteria of MAFLD make it easily acceptable.[14] For example, patients with prediabetes or diabetes and HS (MAFLD) have a significantly higher incidence of cardiovascular, cerebrovascular, and chronic kidney disease.[59] Therefore, the current criteria of MAFLD are simplistic and easily understandable.

Key point: The proportion of patients with "fatty liver disease" may increase with broad positive criteria of MAFLD. However, such simpler criteria are easy to educate primary care physicians and specialists who can identify individuals who are at higher risk of cardiovascular diseases.

Alcohol and MAFLD

The diagnosis of MAFLD is dependent on the presence of metabolic factors and does not include alcohol consumption. Approximately 25% of patients with MAFLD and 29% of patients with NAFLD have a history of harmful alcohol consumption.[81] This may lead to a high risk of underreporting alcohol consumption among this group of patients. Alcohol Use Disorders Identification Test-consumption (AUDIT-C), hair, and urinary ethyl glucuronide are helpful screening instruments for identifying ARLD and treating it accordingly.[81] A study evaluating 86 patients with biopsy-proven NAFLD and alcohol consumption reported that irrespective of the assessment method, moderate alcohol consumption was associated with advanced fibrosis, particularly in patients with NAFLD and diabetes mellitus.[82] The authors reported a better correlation between alcohol consumption assessed with a short version of the AUDIT-C and clinical interview than with AUDIT-C and phosatidylethanol (Peth) or clinical interview and Peth.[82] Therefore, dual-etiology fatty liver disease (concomitant MAFLD and ARLD) was defined as an individual meeting the criteria for MAFLD with significant consumption of alcohol, defined as consumption of >3 drinks per day in men and >2 drinks per day in women or binge drinking (defined as >5 drinks in males and >4 drinks in females, consumed over 2 h). Another similar study from Japan reported that even mild alcohol intake was associated with a significant increase in the prevalence of advanced fibrosis in patients with MAFLD.[69] A individual can therefore be labeled as alcohol-associated fatty liver disease (AAFLD) with a metabolic component (having significant alcohol intake and metabolic dysfunction) or MAFLD with an alcohol component or both alcohol and metabolic fatty liver disease apart from pure AAFLD and MAFLD.[24] The term NAFLD cannot be used in patients who consume significant alcohol as it is mutually exclusive with AAFLD.

Obese patients with a BMI $>33.4\,kg/m^2$ tend to avoid alcohol misuse more than nonobese individuals.[83] A recent study including 134 morbidly obese patients who underwent sleeve gastrectomy

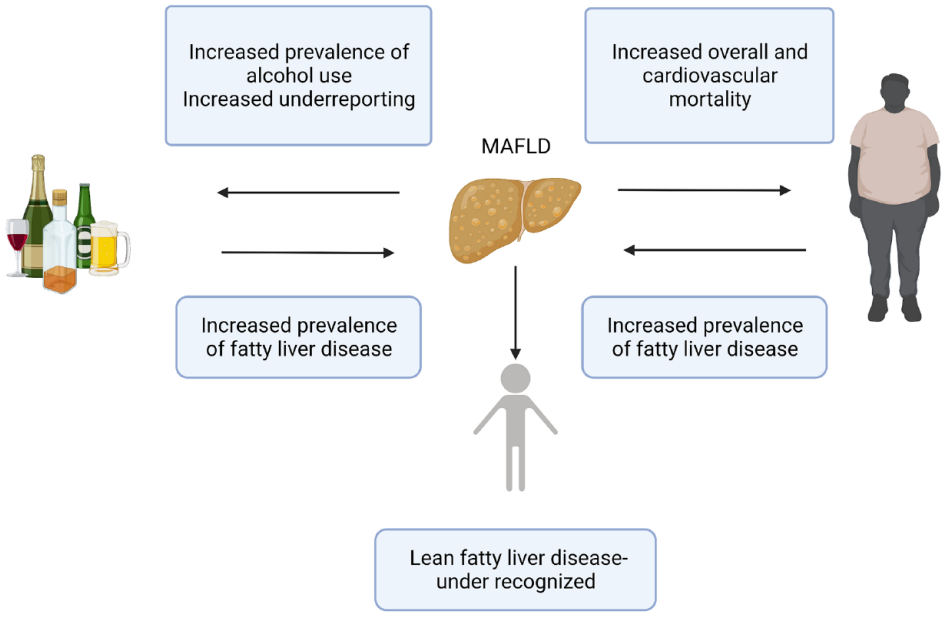

Figure 1. The bidirectional impacts of alcohol and metabolic dysfunction-associated fatty liver disease on fatty liver disease.
MAFLD, metabolic dysfunction-associated fatty liver disease.

and simultaneous liver biopsy reported that advanced fibrosis was associated with MAFLD rather than alcohol consumption.[83] The positive criteria of MAFLD may thus be an essential determinant of fibrosis in morbidly obese individuals rather than alcohol consumption, insulin resistance, or dyslipidemia. However, further studies are required to confirm these unique findings. A recent large population study including 12,656 individuals from the National Health and Nutrition Examination Survey cohort reported MAFLD in 27%, ARLD in 9%, and dual etiology in 4%.[84] Interestingly, the authors noted that both MAFLD [adjusted hazard ratio (aHR) 1.21, 95% CI 1.13–1.30] and excessive alcohol consumption (aHR 1.14, 95% CI 1.04–1.26) were associated with an increased risk of mortality.[84] Furthermore, the presence of MAFLD, irrespective of alcohol consumption, increases mortality risk.

Key point: Alcohol consumption increases the risk of fibrosis and mortality in patients with MAFLD.

Conclusion

Obesity and alcohol abuse are the leading causes of disease worldwide. The positive criteria defining MAFLD and the significant increase in alcohol consumption in recent years may exponentially increase the risk of progressive fatty liver disease (Figure 1). Therefore, dietary changes and policies to curtail alcohol consumption are necessary. In addition, future research should focus on developing therapeutic targets for MAFLD.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Anand V. Kulkarni: Conceptualization; Data curation; Writing – original draft.

Shiv Kumar Sarin: Conceptualization; Project administration; Supervision; Writing – review & editing.

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