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REVIEW

Metabolic dysfunction–associated steatotic liver disease and cardiovascular disease

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INTRODUCTION

According to recent estimates, steatotic liver disease affects about 30% of the global population, and there has been a significant 16% increase in cases between 1991 and 2019.[1] In November 2023, the American Association for the Study of Liver Diseases adopted new terminology for nonalcoholic fatty liver disease to reduce stigmatization, inclusion, and reflection of cardiometabolic risk factors in the disease process. One must consider metabolic risk factors to diagnose metabolic dysfunction–associated with steatotic liver disease (MASLD). MASLD refers to steatotic liver disease associated with cardiometabolic risk factors.[2] The previous terminology, NAFLD, has now been replaced with MASLD.

Steatotic liver disease is characterized by fat accumulation in liver cells caused by altered lipolysis. In addition, inflammation occurs due to lipid peroxidative damage to the cell membranes of the hepatocytes, resulting in fibrosis caused by the activation of HSCs. MASLD is defined as the presence of steatotic liver disease along with at least 1 cardiometabolic risk factor and the exclusion of alcoholic liver disease. Most patients with MASLD do not exhibit any symptoms, and initial presenting signs are typically related to portal hypertension. There are several algorithms used for the diagnosis and estimation of steatosis, including fatty liver index, which estimates steatosis using body mass index (BMI), waist circumference, serum triglycerides, and gamma-glutamyl transferases. Other predictive scores include NLFS (nonalcoholic fatty liver disease liver fat score), which predicts liver fat content using aminotransferases and fasting insulin levels, and LAP score (lipid accumulation product), which identifies the risk of liver disease as well as cardiovascular disease (CVD) using fasting triglyceride levels and waist circumference.[1]

Imaging such as liver ultrasound is used in combination with these scores to demonstrate a hyperechoic liver accurately and reliably in steatosis. CT of the liver is also an accurate diagnostic tool, but its limitation is its inability to grade the level of steatosis. On the other hand, MRI can delineate the grade of steatosis and has been suggested as an alternative to liver biopsy, which is definitive for diagnosis but is limited due to its cost and the need for expert operators.[1] In addition, to help diagnose MASLD, doctors should take a detailed history to evaluate metabolic risk factors and alcohol use history, hepatitis B and C screening, and screening for genetic and autoimmune causes of steatotic liver disease (alpha-antitrypsin deficiency, hemochromatosis, primary biliary cirrhosis, primary biliary cholangitis, autoimmune hepatitis, etc).[3]

Metabolic syndrome is a well-established concept clustering cardiometabolic risk factors defined as increased waist circumference, increased triglycerides (>150 mg/dL), reduced HDL (<40 in men; <50 in women), hypertension (systolic blood pressure ≥ 130 and diastolic blood pressure ≥ 85 mm Hg), and increase fasting glucose (>100 mg/dL).[2] Currently, metabolic syndrome's definition does not include steatotic liver disease; however, there is a growing body of evidence associating the two. As evident,

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LAP, lipid accumulation product; MASLD, metabolic dysfunction–associated steatotic liver disease; NLFS, nonalcoholic fatty liver disease liver fat score.

MASLD is a multiorgan disease that increases the risk of diabetes, chronic kidney disease, CVD, and subsequent arrhythmogenic complications.[2]

To improve the outcomes of patients who have both MASLD and CVD, it is essential to have a thorough understanding of how these 2 conditions are related. This review provides a brief overview of the latest research and pathophysiological studies in this area to help better understand this topic.

DISCUSSION

CVD is a leading cause of death among individuals with MASLD.[3] Unfortunately, it is often underappreciated despite being an independent risk factor for CVD, with the severity of CVD varying with the degree of liver fibrosis.[3] The relationship between MASLD and CVD is intricate and involves metabolic, inflammatory, and vascular pathways.[4] Common risk factors for steatotic liver disease and CVD increase the chances of atherosclerotic disease in this population.[4]

Steatotic liver disease is closely linked to insulin resistance, reported in as many as 75% of the steatotic liver disease population, leading to lipolysis and dyslipidemia.[5] Insulin resistance is associated with increased inflammatory markers.[5] This systemic inflammatory state and dyslipidemia potentially contribute to the development of cardiovascular complications in patients with MASLD. A study conducted by Park and colleagues reinforced these findings. It showed elevated levels of blood sugar, triglycerides, apolipoprotein B, C-reactive protein, and decreased levels of HDL in cases compared to controls after adjustment for confounders.[6]

In addition, insulin resistance contributes to the visceral deposition of adipose tissue, which contributes significantly to intramyocardial inflammation, endothelial dysfunction, and accelerated atherosclerosis.[3] Given this inflammatory state in MASLD, experts have also suggested an imbalance between coagulation factors leading to a hypercoagulable state, increasing the risk of CVD.[7] Tripodi et al[7] studied this relationship in a case-control study, which showed a statistically significant increase in factor VIII levels (procoagulant) and a decrease in protein C in patients with steatotic liver disease. Furthermore, this imbalance was also proportional to the intima-media thickness. This mechanism is also described in Figure 1.[8]

Lee et al[4] recently published a retrospective cohort study on the Korean population that evaluated the relationship between MASLD and CVD using nationwide health screening data from 2009. They concluded that MASLD is an independent risk factor for myocardial infarction. It has been observed to be distinct from the traditional risk factors associated with myocardial infarction.[4] Huang et al[9] delved into the relationship between MASLD and atherosclerosis, with results showing a significant correlation between MASLD and carotid plaque formation. However, a high amount of these patients were also found to have diabetes (21%), obesity (26%), hypertension (57), dyslipidemia (45%), and lack of exercise (77%). Despite not finding a direct correlation between MASLD and cardiovascular events, they deduced this association to their common risk factors, disease pathogenesis, and pathways, including oxidative stress, dyslipidemia, insulin resistance, endothelial dysfunction, and aberrations in lipid metabolism, as mentioned before. They could not establish if MASLD is associated with CVD independent of the metabolic risk factors.[9] Another study published by Semmler and colleagues discovered no association between steatotic liver disease and CVD after adjustment for age, sex, and metabolic dysfunction. They concluded the cardiovascular risk to be secondary to metabolic derangements rather than liver disease.[10]

To counter the above argument, VanWagner and colleagues the direct relationship of steatotic liver disease with cardiovascular changes. A cross-sectional study in patients who concurrently underwent CT quantification of the liver fat and comprehensive echocardiography with myocardial strain measured by speckle tracking was evaluated for cardiac dysfunction. Patients with steatotic liver disease were noted to have subclinical cardiac remodeling.[11] However, many of these findings were attributed to obesity and visceral adipose tissue in these patients with some independent co-relation.[11] After adjusting for other risk factors for heart failure and BMI, the authors concluded that MASLD is independently associated with heart remodeling.

Further studies that support the idea of shared risk factors and, hence, screening for MASLD and CVD simultaneously are evident in the following findings. Wu et al[12] specifically studied the role of diet soft drink consumption of MASLD; a positive correlation was noted due to their secondary effects on obesity and metabolic syndrome. Emerging evidence also suggests that adherence to the Mediterranean diet might benefit cardiovascular risk factors by reducing hyperlipidemia.[13] While MASLD can have multiple causes, studies indicate a correlation between alcohol consumption and its development. The research by Kang and Oh[14] highlights that flushing, triggered by alcohol intake, is a noteworthy risk factor for MASLD in Korean men. Interestingly, Chen and colleagues studied the correlation between social determinants of MASLD and cardiovascular risk. They included patients with MASLD, following them up for 63 months. Higher social status was associated with a lower overall cardiovascular mortality (sub-HR: 0.71 [0.57–0.88], $p = 0.0018$) but a higher incidence of CVD (sub-HR: 1.36 [95% CI: 1.10–1.68], $p < 0.0001$) in this population.[15] It is possible that the reason for lower rates of metabolic risk factors in specific neighborhoods could

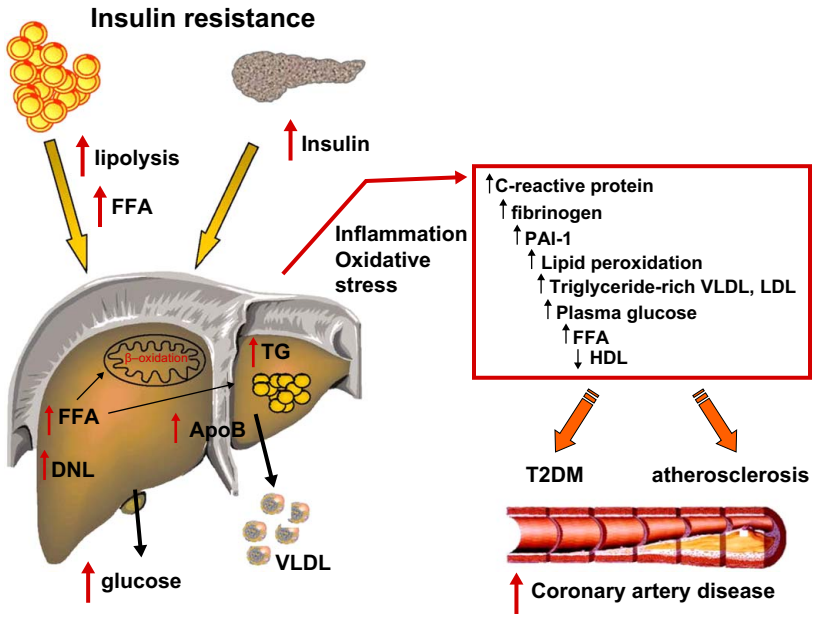

FIGURE 1 Intricate relationship and pathophysiology of insulin resistance with steatotic liver disease and, eventually, cardiovascular disease. Reprinted from Gaggini et al.[8] http://creativecommons.org/licenses/by/3.0.

be due to their higher physical environment scores, as shown in the study by Mujahid et al.[16] These scores are a combination of walkability and the availability of healthy foods, which may impact the BMI and overall quality of life. Interestingly, this study found that women in neighborhoods with better physical environments had lower BMIs, while men had higher BMIs.

SUMMARY

There is a debate surrounding the connection between MASLD and CVD. While some argue they are directly linked, others believe they share common risk factors and causal pathways. Nevertheless, the discussion suggests that MASLD can cause damage to blood vessels, leading to atherosclerosis due to oxidative stress and endothelial dysfunction. In addition, the prothrombotic state in patients with MASLD can contribute to strokes and heart attacks. Despite the association between the two and the resulting morbidity, there is a lack of robust evidence establishing a direct relationship between MASLD and CVD. Further studies studying prevention, outcomes, and treatment will contribute significantly to the field. In addition, awareness regarding this association among health care providers is of utmost importance to screen for CVD in patients with MASLD due to their shared risk factors, improving outcomes in this population.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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