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Cardiovascular Implications Of Metabolic Associated Fatty Liver Disease And Non-Alcoholic Fatty Liver Disease: An In-Depth Review

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ABSTRACT

Background: Both Non-Alcoholic Fatty Liver Disease (NAFLD) and Metabolic Associated Fatty Liver Disease (MAFLD) are becoming more well acknowledged as common liver disorders associated with substantial metabolic dysfunction. These conditions, which are marked by hepatic steatosis without binge drinking, are linked to an increased risk of cardiovascular diseases (CVD), an area that has not received enough attention.

Objective: The objective of this study is to compile the most recent information on the cardiovascular effects of MAFLD and NAFLD, looking at their pathophysiological relationships, clinical outcomes, and possible treatment approaches.

Methods: We carried out an extensive assessment of the literature, concentrating on the relationship between MAFLD/NAFLD and cardiovascular health, based on research that were published during the last ten years. The effects on cardiovascular risk factors, the processes relating hepatic steatosis to vascular pathology, and the impact of various liver illnesses on clinical outcomes, such as mortality and cardiovascular events, are important topics of research.

Results: Through a number of processes, MAFLD and NAFLD are significantly linked to an elevated risk of cardiovascular disease. These comprise endothelial dysfunction, insulin resistance, dyslipidemia, and systemic inflammation. Increased risk of myocardial infarction, stroke, and heart failure, as well as accelerated atherosclerosis, have all been associated with the presence of hepatic steatosis. Furthermore, the metabolic syndrome that is frequently linked to chronic liver illnesses increases the risk of cardiovascular disease.

Conclusion: Important factors that contribute to cardiovascular morbidity and death are MAFLD and NAFLD. The necessity for integrated management techniques that address the hepatic and cardiovascular elements of patient care is highlighted by their influence on cardiovascular health. Subsequent investigations have to concentrate on clarifying the exact processes that connect these liver disorders with cardiovascular pathology and assessing the effectiveness of focused therapies to reduce related hazards.

Keywords: *Metabolic Related Fatty Liver Illness, Cardiovascular diseases, and Endothelial dysfunction accurate*

1. INTRODUCTION

Non-alcoholic full of fat liver disease (NAFLD) is becoming more commonplace around the globe **[1,2]** Based on insulin resistance, several investigations have discovered a connection between NAFLD and a number of metabolic illnesses **[3].**

The hallmark of MAFLD is the buildup of fat in the liver without a history of heavy drinking, viral hepatitis, or other liver disorders. It has a tight relationship with dyslipidemia, obesity, and category 2 diabetes—mechanisms of the metabolic set of symptoms. Simple steatosis (fat buildup) to non-intoxicating steatohepatitis, which can advance to cirrhosis and hepatocellular cancer, are all within the spectrum of MAFLD. Because NAFLD can lead to cardiovascular disease and liver-related problems (including cirrhosis and hepatocellular cancer), it is a worldwide health concern. Ace of the main sources of mortality for NAFLD patients is cardiovascular disease **[4].**

Obesity, diabetes, and hypertension that follow metabolic syndrome are thought to be the greatest suggestive of a pathophysiological relationship among NAFLD and CVD mortality. It is noteworthy that individuals with usual body mass index can also have non-alcoholic fatty liver disease; BMI less than 25 kg/m2 is considered non-obese **[5].** Strangely, new research on NAFLD suggests that non-obese patients' metabolic profiles are comparable to those of obese people. One of the main characteristics of MAFLD is insulin resistance, which raises insulin and glucose levels in the blood. This illness raises the risk of cardiovascular diseases (CVD) and encourages atherosclerosis **[6,7].** Research has indicated that a notable cardiovascular risk factor, category 2 diabetes, is additional communal in people with MAFLD. Interestingly, a recent study that separated overweight and non-overweight individuals based on biological sex found that the occurrence of NAFLD was better in the non-overweight female group likened to the male group **[8].**

One of the initial stages of atherosclerosis development is endothelial dysfunction. Increased endothelial dysfunction in NAFLD patients is a result of the liver's incapacity to control vaso-provocative chemicals or generate defensive compounds like nitric oxide. Methionine s-adenosylmethionine (SAM), a major basis of methyl in supplementary metabolic events such the formation of phosphatidylcholine and creatine, can be conjugated by the liver in a healthy condition. SAM is then demethylated to produce homocysteine and s-adenosylhomocysteine (SAH). Although the precise process is uncertain, it is thought that individuals with NAFLD have altered methionine metabolism pathways, which results in elevated homocysteine levels in many of them **[9].** Meta-analyses have demonstrated that homocysteine levels in NAFLD patients are consistently higher than in controls **[10].** When homocysteine starts to build up in the blood, it has a number of harmful consequences on inflammation and bleeding. It has been demonstrated that high blood homocysteine levels can lead to oxidative damage to platelets by reducing glutathione reserves that are accessible, which increases platelet activation and the hypercoagulable state **[11].** Additional pathways for persistent inflammation include homocysteine's links to increased oxidative stress, decreased protein folding, and increased endothelial cell dysfunction. Even the liver is negatively impacted by hyperhomocysteinemia; it increases intrahepatic vascular tone and inhibits nitric oxide generation, which exacerbates already severe systemic vascular stress **[12].**

This review's main objective is to assess the major risk of cardiac illness in relation to nonalcoholic fatty liver disease. There are currently no therapies for NAFLD; however, given the link between NAFLD and CVD, managing diabetes, making appropriate lifestyle changes, and using drugs like antihypertensives may be helpful. A review of NAFLD and CVD will increase knowledge of the interactions between disease states and work to enhance patient care, public health recommendations, the costs associated with NAFLD and CVD, and upcoming research and publications.

2. METHODS

Through a thorough search of all papers published between 2000 and 2024, this review methodically investigates the cardiovascular effects of metabolically connected fatty liver disease. Using terms like "metabolic associated fatty liver disease," "cardiovascular risk," and "inflammation," we searched many large databases, including PubMed, Scopus, and Web of Science. Peer-reviewed studies having a human subject focus and data on cardiovascular outcomes related to MAFLD were considered for inclusion. Studies that did not present primary data or had no bearing on cardiovascular consequences were excluded.

Two impartial reviewers reviewed titles, abstracts, and entire texts as part of the selection process. Arguments were used to settle disagreements. A standardized form that contained information on the study design, participant characteristics, and important outcomes pertaining to cardiovascular health and MAFLD was used to retrieve data. We synthesized the data qualitatively, concentrating on finding recurring themes and processes that connect MAFLD to cardiovascular illness.

Metabolic Associated Fatty Liver Disease

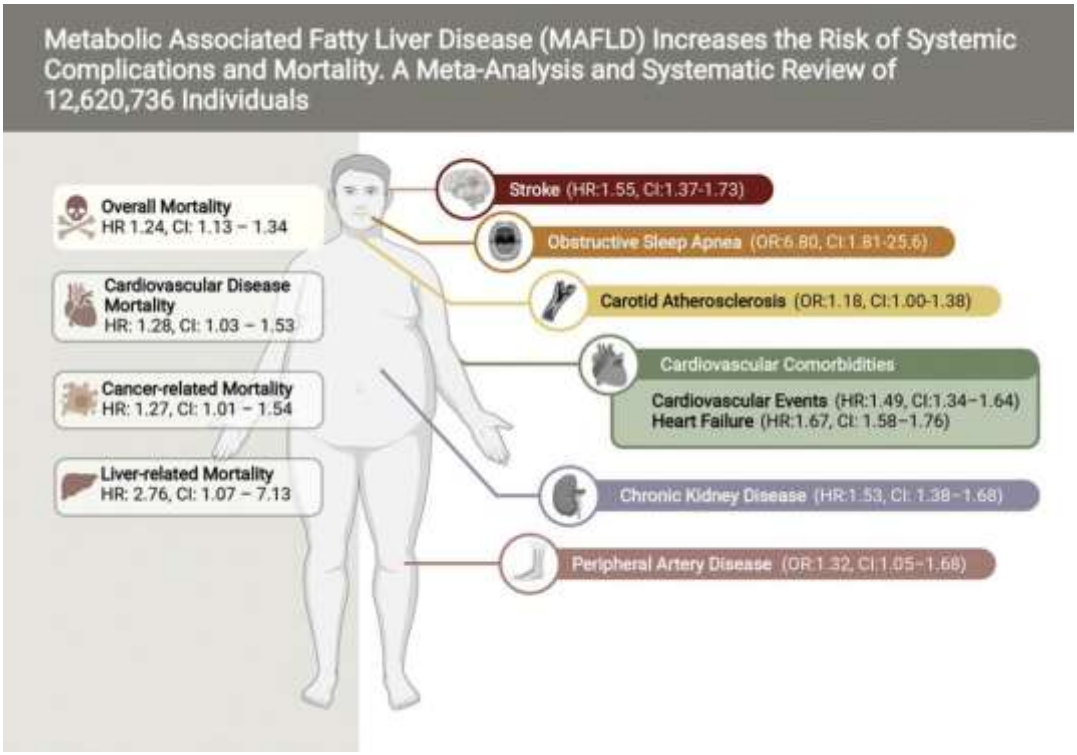

Fig. 1. (MAFLD) Upsurges the major risk of complete complications and mortality [13]

Table:1 and Figure. 1 show that metabolic-associated fatty liver disease (MAFLD) may worsen the course of nonalcoholic steatohepatitis and fibrosis in MAFLD patients by raising the risk of hyperglycemia, dyslipidemia, and β-cell dysfunction, which can lead to insulin resistance and type 2 diabetes. MAFLD is often accompanied with dyslipidemia, characterized by elevated triglyceride levels and low levels of HDL-C. This lipid profile promotes the formation of atherosclerotic plaque. Studies show that major adverse cardiovascular events (MACE) such as myocardial infarction, stroke, and cardiovascular death are more common in people with MAFLD. MAFLD may exacerbate metabolic health, especially through processes like insulin resistance and type 2 diabetes, and is linked to more severe liver problems.

Cardiovascular diseases

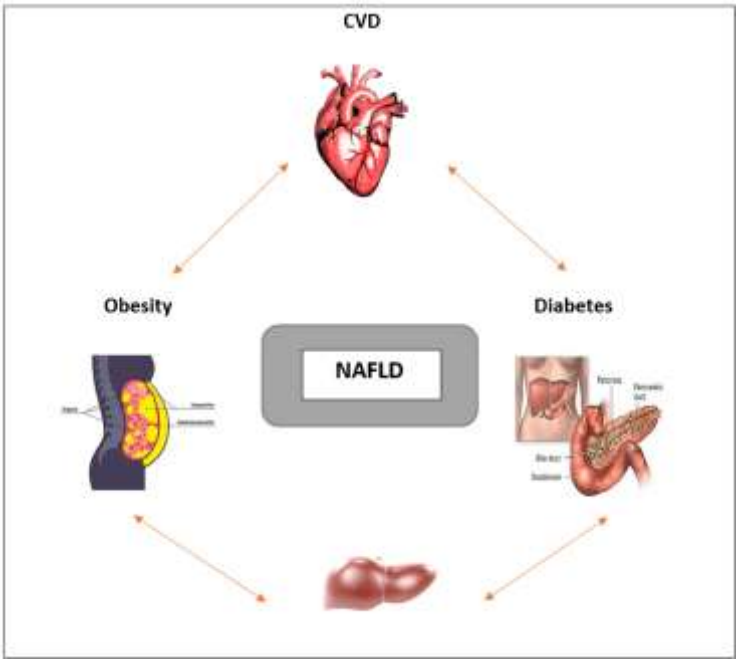

Fig: 2. Cardiovascular implications of metabolic allied fatty liver disease

Long-drawn-out and inflammatory visceral adipose tissue is likely the basis of the postulated underlying processes that connect CVD, CKD, NAFLD, and additional cardiac illnesses, as schematically depicted in Figure. 2. Several substances that may have a role in atherogenesis, insulin confrontation, and (NAFLD) are secreted by this adipose tissue **[14,15].**Regarding the connection between T2DM and NAFLD, as was briefly mentioned above, new research also indicates that changes in gut microbiota may impact the onset and course of NAFLD, potentially by increasing duodenal absorption of various bacterial foods**[16].** In this intricate scenario, the liver may serve as the aimed organ for the ensuing total irregularities as well as the origin of a number of infective intermediaries that may intensify renal, cardiac, and vascular harm. According to **[17,18,19]** NAFLD, particularly its necro-provocative irregular.

In this risky situation as also depicted in Table. 2 and Figure.2 shown in developing indication also proposes that the co-occurrence of overweightness-connected upsurges in fat buildup in the pericardium and kidney may moreover use limited adverse belongings that outcome in physical and practical imbalances in the myocardium, kidney and vasculature.

Endothelial dysfunction accurately

A kind of non-obstructive coronary artery disease (CAD) known as endothelial dysfunction occurs. Chronic chest discomfort is the main symptom of this illness, which tends to afflict more women than men. As an early stage in the pathophysiology of atherosclerosis, endothelial dysfunction, as seen in Table.2 and Figure. 3, is also critical to the development of CVD **[20].** Because of its vasodilatory qualities, nitric oxide (NO) is essential for the health of arteries. In endothelial dysfunction, reduced NO bioavailability is a crucial characteristic. Oxidative stress is caused by increased production of superoxide. Vascular inflammation can be attributed to lipoproteins like ApoC3. particular insulin resistance inside the vascular system **[21].** Further reducing NO availability are elevated levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase (NOS). Impairment of the dilation and constriction of blood vessels. altered blood vessel wall permeability. elevated risk of clotting problems and platelet dysfunction. Individuals who suffer from non-alcoholic fatty liver disease (NAFLD) frequently have high levels of ADMA **[22].**

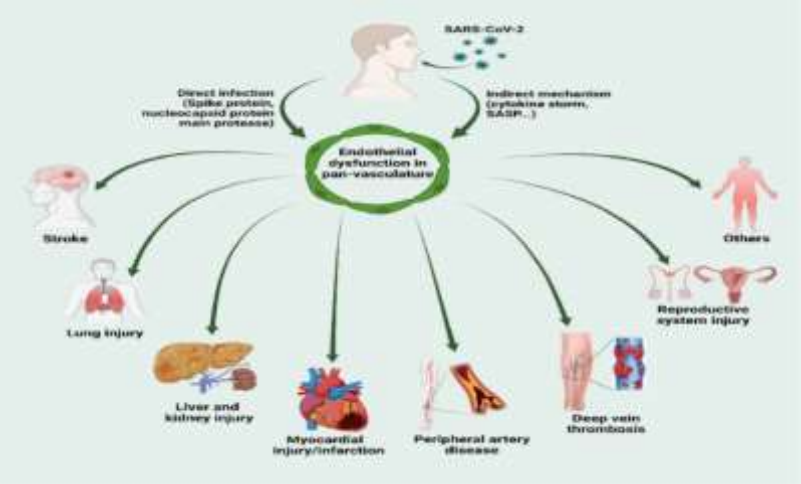

Fig: 3. Endothelial dysfunction in COVID-19 [23]

Table:1. Overview of MAFLD

Aspect	Description
Definition	Fat buildup in the liver without a history of heavy drinking or other liver conditions.
Association	Powerfully related with metabolic set of symptoms, type 2 diabetes, and obesity.
Spectrum	Includes cirrhosis, hepatocellular cancer, non-alcoholic steatohepatitis (NASH), and simple steatosis.

Table: 2. Cardiovascular Risk Factors

Risk Factor	Mechanism	Evidence
Insulin Resistance	Encourages elevated insulin and glucose levels, which exacerbates atherosclerosis.	Patients with MAFLD have a higher prevalence of type 2 diabetes.
Dyslipidemia	Elevated triglycerides and low HDL-C contribute to plaque formation.	Low HDL-C and elevated triglycerides are factors in the development of plaque.
Hypertension	Chronic inflammation and oxidative stress can lead to endothelial dysfunction.	Endothelial dysfunction can result from oxidative stress and chronic inflammation.
Inflammation	Systemic inflammation and oxidative stress damage endothelial cells.	Endothelial cells are harmed by oxidative stress and systemic inflammation.
Oxidative Stress	Contributes to endothelial dysfunction and atherosclerosis.	Contributes to atherosclerosis and endothelial dysfunction.

Table: 3. Cardiovascular Outcomes

Outcome	Description	Evidence
Increased Risk of Cardiovascular Events	increased danger of stroke, myocardial infarction, and other cardiovascular problems.	Research indicates a strong correlation between MAFLD and MACE.
Impact on Mortality	increased death from all causes, with heart disease playing a significant role.	Patients with MAFLD had higher risks of cardiovascular death.
Effect of MAFLD Severity	Increased risk of cardiovascular disease is correlated with MAFLD severity.	Advanced fibrosis and NASH are associated with increased cardiovascular morbidity.

Table: 4. Management and Therapeutic Implications

Strategy	Description	Examples
Lifestyle Modifications	Dietary modifications, physical exercise, and weight loss.	It is advised that all MAFLD patients enhance their cardiovascular and metabolic health.
Pharmacological Treatments	Drugs that address hypertension, dyslipidemia, and insulin resistance.	Antihypertensives, statins, and metformin.
Regular	Cardiovascular risk is continuously	Routine monitoring of glucose, lipid

Cardiovascular Screening	evaluated in MAFLD patients.	profiles, and blood pressure.

Pathophysiological mechanisms between NAFLD and CVD

From the combination of these common risk factors, it is problematic to determine a particular influence of NAFLD to augmented major risk of CVD. NAFLD and CVD are in cooperation symptoms of end-organ injury of the metabolic set of symptoms are shown in Table.3. The underlying processes involving many pathways simultaneously are quite complicated and relate NAFLD to CVD (Figure. 1). Pathophysiological pathways **[24,25,26]** that connect NAFLD and CVD. Adverse cardiometabolic outcomes are strongly associated **[27].** Possibly through mechanisms other than those associated with overweight and obesity **[28,29].**

Specifically, augmented triglyceride buildup in the liver is caused by raised up lipid uptake and amplified rates of DNL in non-alcoholic fatty liver disease **[30].** This is accompanied by an excess of large, triglyceride-enriched VLDL particles that are secreted and aid to activate liver fat for conveyance to peripheral tissues **[31].** Further significant characteristics of NAFLD include irregular glucose metabolism and hepatic insulin confrontation, which are essential to the pathophysiology of both NAFLD and CVD **[32,33].** In addition to visceral obesity along with a typically elevated body weight and the accompanying systemic inflammation, illnesses of glucose metabolism in NAFLD patients can also be linked to a greater buildup of defective ectopic fatty tissue **[34].** This situation involves not only a higher liver fat content but also a build-up of pancreatic ectopic dysfunctional adipose tissue, which is fundamentally linked to insulin confrontation and beta cell dysfunction **[35,36].**

Hyperhomocysteinemia is another factor contributing to the growth of endothelial dysfunction. Reduced glutathione reserves owing to elevated homocysteine levels in the serum cause oxidative stress, which is linked to worsened NO production, heightened vascular resistance, and increased platelet activation **[37,38,39,40**]. Both adults and children with NAFLD have higher plasma levels of homocysteine **[41,42].** On the other hand, homocysteine levels were lower in steatohepatitis patients than in non-patients **[43].** Due to a procoagulant imbalance, patients with NAFLD may also be additional vulnerable to atherosclerotic cardiovascular disease.

Effects of NAFLD on Mortality and Morbidity from Cardiovascular Disease

A significant death rate from liver disease in general is linked to both heart failure with maintained ejection fraction (HFpEF) and heart failure with decreasing ejection fraction (HFrEF) **[44].** However, certain cohort studies **[45,46,47,48,49,50]** presented that NAFLD patients had a high cardiovascular mortality rate. Others were unable to corroborate this link **[51,52].** Most research on this subject found that relationships between NAFLD and CVD held true regardless of known hypertension, or dyslipidemia **[53,54,55,56].**

Insulin resistance and disturbances in glucose metabolism have a most important role in the growth and evolution of non-alcoholic fatty liver disease and are important factors in the pathophysiology of cardiovascular disease. A current meta-analysis including 11 studies and 8346 individuals revealed that patients with NAFLD and concurrent T2DM had a twofold higher risk of CVD manifestation likened to those deprived of NAFLD (OR 2.20; 95% CI 1.67–2.90) **[57].**

3. CONCLUSION

In conclusion, early NAFLD stages already result in an elevated personal cardiovascular risk. When NAFLD is diagnosed, a thorough examination of cardiovascular risk and subclinical atherosclerosis should be conducted. Improved recognition of high-risk individuals who may advantage from therapeutic treatments might be made possible by this, helping to alleviate the intolerable global illness burden linked to the current pandemic period (Covid-19). Cardiovascular and metabolic disorders. The cornerstones of NAFLD prevention and therapy are dietary adjustments, weight reduction, increased physical activity, and adoption of a low-carb or Mediterranean diet. While there isn't yet a single medication licensed to treat liver disease, statins should be used to address concurrent cardiovascular risk factors. Because MAFLD is associated with workings of the metabolic set of symptoms such as insulin resistance, it has important consequences for the cardiovascular system. The illness affects overall mortality in addition to raising the risk of cardiovascular events. (Table.4) To effectively address liver-related and cardiovascular risks, a multimodal strategy involving lifestyle modifications, medication, and routine cardiovascular monitoring is necessary.

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