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Review Article

Metabolic Dysfunction-Associated Steatotic Liver Disease: A Dark Horse of Metabolic Syndrome

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely related to obesity, type 2 diabetes mellitus, hypertension, and other cardiometabolic risk factors, with an increased risk of cardiovascular events, chronic kidney disease, hepatic and extrahepatic malignancies, and also liver-related outcomes, including liver failure. The nomenclature MASLD has a long evolution history from 1836 to 2023. The term Non Alcoholic Fatty Liver Disease (NAFLD) used previously did not include cardio-metabolic risk factors as diagnostic criteria. By contrast, MASLD should have at least one of the four defined cardiometabolic risk factors. Insulin resistance is nearly universal in patients with MASLD and is present in the liver, adipose tissue, and muscle. Adipose tissue insulin resistance is characterized by increased release of free fatty acids (FFA) from adipocytes (lipolysis) in the fasting state, which accumulate inside the liver and undergo triglyceride formation. Dietary carbohydrates, in the form of dietary sugars (e.g., fructose, sucrose, and glucose), drive the formation and accumulation of intrahepatic fat from de novo lipogenesis (DNL). This review discusses in depth the pathogenesis of hepatic steatosis and inflammation that may lead to hepatic cellular damage, fibrosis, and cirrhosis. The relationship of MASLD with type-2 diabetes mellitus, hypertension, obesity, and lipid abnormalities is also discussed in detail. In fact, MASLD should be viewed as a hepatic manifestation of metabolic syndrome. There are numerous mechanisms that may accelerate atherosclerosis and premature cardiovascular disease (CVD) in patients with MASLD. So MASLD should not be considered as an isolated disease; rather, it should be viewed as part of a spectrum of disease conditions. Its connectivity with other cardio-metabolic conditions highlights the importance of this dark horse of metabolic disorders.

Key words: *Metabolic dysfunction-associated steatotic liver disease, Metabolic syndrome, Cardio-metabolic risk.*

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Introduction:

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease, and its prevalence will likely continue to rise. The presence of MASLD is tightly linked to type 2 diabetes (T2D), obesity and other cardiometabolic risk factors. MASLD is associated with an increased risk of cardiovascular events, chronic kidney disease, hepatic and extrahepatic malignancies, and liver related outcomes, including liver failure and hepatocellular carcinoma (HCC). Therefore, the high socio-economic burden of MASLD poses a global health challenge that needs to be addressed by medical societies and policymakers.[1]

The purpose of this review is to aware medical professionals about the use of updated nomenclature and pathogenesis of fatty liver including their complex relationship with different aspects of metabolic syndrome increasing the risk of cardiovascular disease. This narrative review was constructed by synthesizing published literature from BanglaJol, PubMed-indexed Journals, KASL 2025 MASLD clinical practice guidelines, EASL-EASD-EASO clinical practice guideline of MASLD 2024 etc.

Evolution of nomenclature:

Addison of the United Kingdom named the condition 'fatty liver' in 1836 after observing fat accumulation in the livers of patients with excessive alcohol consumption. In 1857,

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Budd reported that fatty liver development was associated with low physical activity and excessive fat intake. In 1979, American clinicians Adler and Schaffner introduced the term 'fatty liver hepatitis' to describe an Fatty Liver Disease(FLD) associated with diabetes and obesity, characterized by hepatic inflammation and fibrosis, but not related to alcohol consumption. In 1980, Ludwig et al. named the condition 'Non Alcoholic Steato- Hepatitis' (NASH) to describe FLD with histological features of hepatic inflammation and varying degrees of fibrosis in patients without a history of alcohol consumption. The term Non Alcoholic Fatty Liver Disease (NAFLD) was first introduced in 1986 in a review article by Schaffner and Thaler. It has been used for decades as an umbrella term encompassing a wide spectrum of conditions, ranging from simple steatosis to steatohepatitis and cirrhosis. However as there is a strong association between its development and 'metabolic dysfunction,' including obesity, insulin resistance, diabetes, hypertension, and dyslipidemia, Eslam et al. proposed the term 'Metabolic Dysfunction-Associated Fatty Liver Disease' (MAFLD) in 2020. Later in 2023, members of multinational liver societies with a panel of 236 experts from 56 countries worldwide reached a consensus on adopting the terms 'Steatotic Liver Disease'(SLD), with Metabolic dysfunction Associated Steatotic Liver Disease(MASLD) as a subtype.[2] The term MASLD comprises different conditions, including isolated liver steatosis (metabolic dysfunction associated steatotic liver, MASL), metabolic dysfunction associated steatohepatitis (MASH), as well as fibrosis and cirrhosis.[1]

Definition:

NAFLD is an overarching term that includes all disease grades and stages and refers to a population in which ≥5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (e.g., medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as < 20 g/d for women and < 30 g/day for men).[3] Cardiometabolic risk factors are not included in the diagnostic criteria. NAFLD encompasses the diagnostic categories of Non-Alcoholic Fatty Liver (NAFL), Non- Alcoholic Steato Hepatitis(NASH), and NAFLD-related cirrhosis.[2]

MAFLD was proposed as a diagnosis when hepatic steatosis is confirmed by pathological, radiological, or biochemical examination, along with the presence of overweight/obesity (body mass index [BMI] ≥23 kg/m² for Asians and ≥25 kg/m² for Western populations), type 2 diabetes mellitus (T2DM), or metabolic abnormalities. Unlike NAFLD, the diagnosis of MAFLD does not require the exclusion of excessive alcohol consumption and can be made regardless of the presence of other chronic liver diseases.[2]

MASLD, is defined as the presence of hepatic steatosis diagnosed through imaging or histological examination along with the presence of at least one cardio-metabolic risk factor. Cardio-metabolic risk factors are identified when at least one of the following five conditions is present: (1) BMI ≥ 23 kg/m² in Asians or ≥25 kg/m² in Western populations; or a waist circumference ≥90 cm for men and e≥ 80 cm for women in Asians, or ≥94 cm for men and ≥80 cm for women in Western population according to the World Health Organization (WHO) (2) fasting blood glucose ≥100 mg/dL, postprandial 2-h blood glucose ≥140 mg/ dL, HbA1c ≥5.7%, or a diagnosis of T2DM or antidiabetic medication use; (3) blood pressure ≥130/85 mmHg or anti-hypertensive medication use; (4) triglycerides ≥ 150 mg/dL or lipid-lowering medication use; or high-density lipoprotein cholesterol (HDL-C) < 40mg/dl for men and < 50 mg/dl for women or lipid lowering medication use. It also differs from MAFLD, as significant alcohol consumption must be absent and other causes of SLD must be excluded.[2]

Table-1. Comparison of the definitions and diagnostic criteria of NAFLD, MAFLD, and MASLD[2]

	NAFLD	**MAFLD**	**MASLD**
Term	Includes "nonalcoholic", "fatty"	Excludes "nonalcoholic", emphasizes "metabolic dysfunction"	Replaces "fatty" to "steatotic", emphasizes "metabolic dysfunction"
Diagnosis of hepatic steatosis	Imaging studies or blood biomarkers or liver histology	Imaging studies or blood biomarkers or liver histology	Imaging studies or liver histology
Steatohepatitis	NASH	-	MASH
Amount of alcohol consumption	<30 g/day (M), 20 g/day (F)	Regardless of alcohol consumption	<30 g/day (M), 20 g/day (F)
Criteria for metabolic dysfunction	None	Overweight or obesity, Type 2 diabetes, or presence of ≥2 metabolic risk abnormalities	Presence of any of the cardiometabolic criteria
Inclusion of HOMA-IR, hs-CRP for metabolic risk factors	No	Yes	No
Other cause of steatosis	Exclusion	Inclusion	Exclusion

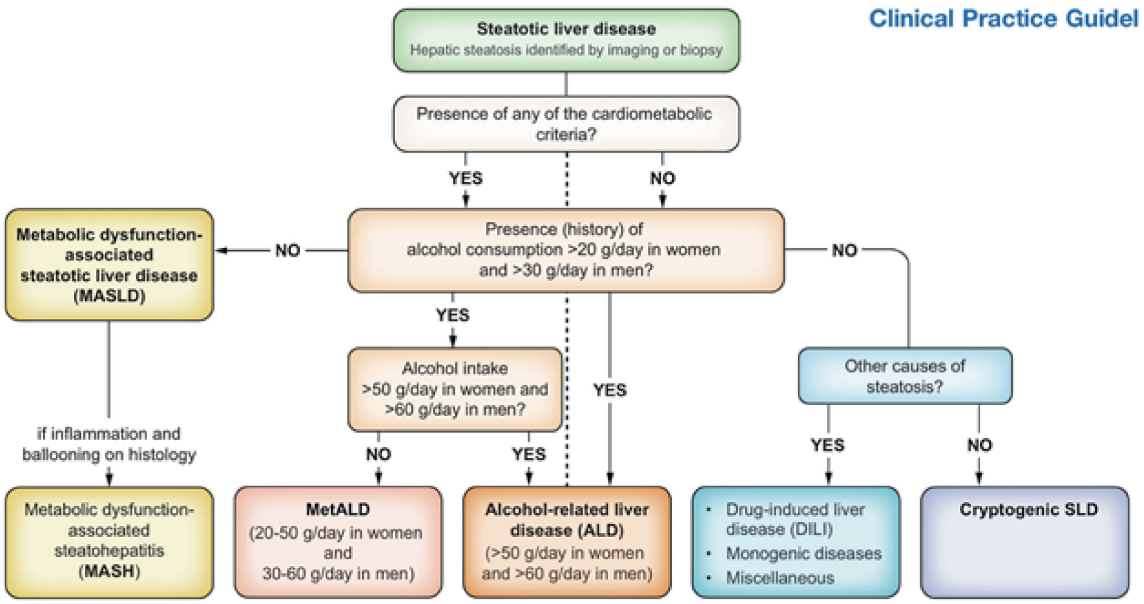

Figure-1: *Algorithm of SLD classification and its subcategories*[1]

Epidemiology

In the most recent meta-analysis, **38%** of adults around the world were shown to have MASLD (years 2016–2019), which was an increase of 50% since 1990–2006. The prevalence seems to be highest in Latin America (44.4%) and lowest in Western Europe (25.1%). These trends are expected to grow, and the global prevalence of MASLD is forecast to reach 55.4% by 2040. However, the Northern Africa and Middle East (MENA) region and Asia are experiencing rapid growth in the MASLD risk factors of obesity and type 2 diabetes mellitus. As a result, the prevalence of MASLD in those areas is also expected to grow. In fact, growth within the MENA region was evident when a study reported that in 2020, the pooled estimated prevalence of MASLD was 39.43% in the general population and 68.71% among T2D patients.[4]

In a recent systematic review and meta-analysis of 63 studies from mostly Asian countries (China/Hong Kong [n=26], South Korea [n=22], Japan [n=14], Sri Lanka [n=1] and Israel [n=1]), investigators reported an incidence rate of **46.13 new cases per 1,000 person-years** (PY). [4]

A cross-sectional study conducted between December 2015 and January 2017 in Dhaka City along with four district towns and four sub district towns (small administrative unit) of Bangladesh with a total of 2782 (1694 men and 1088 women) participants screened by USG of hepatobiliary system showed the overall prevalence of MASLD to be 33.86% (95% confidence interval [CI]: 32.12- 35.64).[5]

Pathogenesis

When energy intake exceeds metabolic needs and disposal capacity, carbohydrates, in the form of dietary sugars (e.g., fructose, sucrose, and glucose), drive the formation and accumulation of intrahepatic fat from de novo lipogenesis (DNL).[3] But it contributes less to the total hepatic triglyceride pool in comparison to fatty acids derived from adipose tissue that account for the majority (60%) of hepatic triglyceride accumulation in MASLD.[6] Insulin resistance is nearly universal in patients with MASLD and is present in the liver, adipose tissue, and muscle. Adipose tissue insulin resistance is characterized by increased release of free fatty acids (FFA) from adipocytes (lipolysis) in the fasting state which accumulate inside the liver and undergo triglyceride formation or mitochondrial â-oxidation.[3] VLDL secretion rate increases linearly with increasing intrahepatic triglyceride accumulation but hepatic VLDL-TG export is inadequate to normalize hepatic triglyceride content.[6] When the amount of intrahepatic FFA overwhelmed the capacity of liver for mitochondrial â-oxidation and formation of triglyceride it is converted to lipotoxic intermediate metabolites (diacylglycerols, ceramides, free cholesterol and lysophosphatidic acid). Mitochondrial dysfunction, endoplasmic reticulum stress, reactive oxygen species formation, and activation of inflammatory pathways (i.e., c-Jun N-terminal kinase, I /nuclear factor B, TLR4) occur by these toxic lipid metabolites. These drive inflammation, cellular injury and fibrosis in the liver. Although in some patients, the development and progression of NASH are driven by substrate overload and insulin resistance, in other patients, disease progression is heavily influenced by genetic factors impacting hepatocyte lipid handling. Genetic polymorphisms have been associated with more advanced liver disease and the development of hepatocellular carcinoma in NASH.[3]

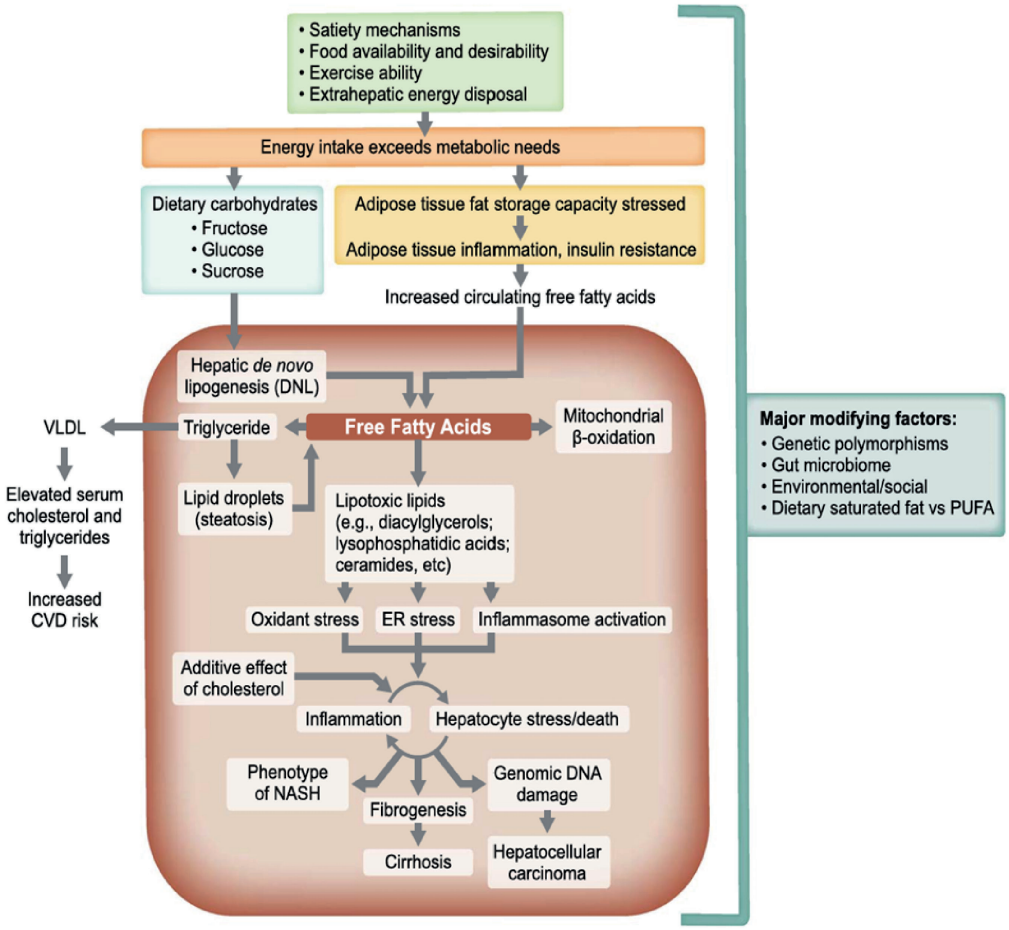

Figure-2: Pathogenesis of MASLD[3]

MASLD and metabolic syndrome

MASLD is considered as the hepatic manifestation of the metabolic syndrome. The metabolic syndrome is defined by clear clinical and laboratory criteria.(Table-II)[7]

Table-II: Criteria for diagnosis of metabolic syndrome[7]

	NCEP ATP III	IDF
Absolutely required	None	Central obesity (waist circumference) ≥94 cm in males or 80 cm in females European origin ≥90 cm in males or ≥ 80 in females
Criteria	Any three of the five criteria below	Central obesity plus two of the four criteria below
Obesity	(1) waist circumference > 40 inches in males, or > 35 inches in females	
Hyperglycemia	(2) fasting glucose ≥100mg/dL or treated for DM	(1) fasting glucose ≥100 mg/dL
Dyslipidemia	(3) TG ≥150 mg/dL or treated for dyslipidemia Or	(2) TG ≥150 mg/dL or treated for dyslipidemia
	(4) HDL cholesterol < 40 mg/dL in males, or < 50 mg/dL in females or under treatment Or	(3) HDL cholesterol < 40 mg/dL in males, or < 50 mg/dL in females or under treatment
Hypertension	(5) > 130 mmHg systolic or > 85 mmHg diastolic or treated for HTN	(4) > 130 mmHg systolic or > 85 mmHg diastolic or treated for HTN

MASLD and Obesity

Fat cells derived from multipotent mesenchymal stem cells that develop into adipoblasts and then to pre-adipose cells. Maturation of this cells depends on a complex signal system. Up-regulation by peroxisome proliferator-activated receptor (PPAR-) is essential, in concert with other transcription factors. These transcription factors give adipocytes great plasticity and a significant ability to adapt to overfeeding by means of hypertrophy and hyperplasia. Within this context, adipose tissue must be viewed primarily as a protective tissue that stores and prevents excessive exposure of other organs to fatty acids resulting in obesity.[6] Android body fat distribution, characterized by increased truncal subcutaneous fat and visceral fat confers a higher risk of insulin resistance irrespective of body mass index (BMI) as visceral fat, which is more metabolically active and inflammatory than subcutaneous fat.[3] Obesity triggers an imbalance in adipose tissue by increasing pro-inflammatory adipokines while reducing anti-inflammatory adiponectin. This promotes activation of several inflammatory pathways but at the cost of adipose tissue insulin resistance. This insulin resistance in turn causes lipolysis resulting in release of excessive FFA in the blood stream. The release of fatty acids from dysfunctional and insulin-resistant adipocytes results in lipotoxicity, caused by the accumulation of triglyceride-derived toxic metabolites such as acylcarnitines and long-chain fatty acyl CoAs, ceramides, diacylglycerols etc. in other tissues (liver, muscle, pancreatic beta cells) and subsequent activation of inflammatory pathways, cellular dysfunction, and lipoapoptosis. The cross talk between dysfunctional adipocytes and the liver involves multiple cell populations, including macrophages(Kupffer cells, with M1> M2 imbalance) and other immune cells, that in concert promote the development of lipotoxic liver disease, a term that more accurately describes the pathophysiology of nonalcoholic steatohepatitis.[6]

MASLD and DM

Increase in plasma FFA concentration also impairs insulin signaling and causes skeletal muscle insulin resistance together with an increase in intramyocellular lipids.[8]

Again adipose tissue and skeletal muscle insulin resistance contributes to hyperglycaemia because of failure of cellular uptake of glucose. This is further complicated by lipotoxicity induced pancreatic beta cell failure. This also offers an attractive hypothesis to explain why impaired glucose tolerance and T2DM in obese insulin-resistant patients with MASLD affect both insulin secretion and insulin action. Besides this increased hepatic gluconeogenesis also occurs in MASLD which contribute to further hyperglycaemia. When screening for diabetes is performed using not only fasting plasma glucose but the gold standard oral glucose tolerance test, prediabetes and T2DM may be 3-fold higher in obese patients with MASLD compared with patients without MASLD.[8] On the other hand studies have shown that MASLD may be present in up to 70% of patients with diabetes whilst the prevalence of biopsy proven MASH (Metabolic Dysfunction Associated Steatohepatitis) in asymptomatic type 2 diabetics with normal liver function tests (LFTs) was 20%.[9] So MASLD and type 2 diabetes mellitus (T2DM) could be considered two sides of the same coin.[10]

In recent years, the gut microbiome (the complex community of microorganisms residing in the intestines) has emerged as a significant player in the relationship between NAFLD and T2DM. Dysbiosis, or an imbalance in the gut microbiota, can result in increased intestinal permeability, which allows bacterial products like lipopolysaccharides (LPS) to translocate into the bloodstream. This translocation can trigger systemic inflammation, further contributing to insulin resistance. Research studies have revealed that individuals suffering from NAFLD often exhibit notable alterations in their gut microbiota composition, which may exacerbate metabolic dysregulation and increase the risk of developing T2DM.[8]

MASLD and Hypertension

Hypertension has long been demonstrated to be associated with MASLD, studies revealing a high prevalence of MASLD in hypertensive patients, even without the risk factors for liver steatosis. On the other hand numerous research data showed that MASLD is an independent risk factor for hypertension.[11] Recently, there have been reports about correlation between essential hypertension and MASLD. More than 50% of MASLD cases were found in patients with hypertension in the absence of other risk factors for liver disease. The frequency of MASLD in patients with isolated hypertension (without concomitant obesity and diabetes mellitus (DM) is three times higher than in healthy persons of similar age and sex. The greatest number of MASH cases (80%) was diagnosed in the group of non-dippers — persons with a lack of nocturnal decrease in blood pressure, which was associated with high insulin levels. On the other hand the prevalence of hypertension was 37.6% in patients with MASLD and increased to 46.7% in patients with MASH.[11] There are many theories that explain how MASLD can induce hypertension. These theories are systemic inflammation, insulin resistance (IR), increased vasoconstriction and decreased vasodilation, arterial stiffness, increased oxidative stress and genetic and epigenetic modifications.[12]

MASLD is strongly associated with increased levels of inflammatory cytokines, such as tumor necrosis factor á (TNF-á), interleukin 6 (IL-6), and C-reactive protein (CRP). These TNF-á and IL-6 are responsible for the up regulation of Renin Angiotensin System (RAS) components, especially increasing angiotensinogen production in the liver and kidney, promoting angiotensin-related hypertension. Insulin is responsible for vasodilatation through nitric oxide (NO) production, and in reverse, insulin resistance (IR) stimulates vasoconstriction, leading also to hypertension. Another mechanisms behind IR and hypertension are the activation of sympathetic nervous system and the renal sodium retention. Asymmetric dimethylarginine (ADMA) is a recently discovered marker of endothelial dysfunction and atherosclerosis. ADMA is endogenously responsible for the inhibition of nitric oxide synthase (NOS), therefore causing the inhibition of vasodilatation. ADMA levels are significantly higher in patients with MASLD (liver being the main site of elimination).[12]

The resistance and compliance of the arteries are determined by two main structural components: elastin and collagen. Their quantity is kept stable by the interplay between production and degradation. Disruption of this balance, stimulated by low grade inflammatory context, might lead to reduced quantities of normal elastin and overproduction of altered collagen, therefore leading to increased arterial stiffness. Although there are consistent data that prove the link between hypertension and MASLD, genetics research is limited regarding this association. Adiponectin (ADIPOQ) gene (which encodes adiponectin) polymorphisms have been indicated to be the link between hypertension and MASLD. Another gene that was investigated was angiotensin receptor type 1 (AGTR1). In a recent prospective cohort study, the gain-of function A1166C (rs5186) variant in the AGTR1 gene represented a strong predictor for incident MASLD and associated hypertension.[12]

Cardiovascular disease and NAFLD

Obesity, T2DM, and metabolic syndrome are characterized by over secretion of VLDL driven by the high plasma FFA concentration and hepatic flux of fatty acids. Increased hepatic VLDL secretion lowers high-density lipoprotein cholesterol levels and leads to increased small, dense, low-density lipoprotein cholesterol molecules, the typical triad of MASLD.[6] Again MASLD has been suggested to be linked to oxidative stress. The production of reactive oxygen species (ROS) in MASLD is responsible for the oxidation of low-density lipoproteins (LDL), which induces the transformation of the macrophages into foam cells. This is the first step of the atherosclerotic lesion development.[12]

The association of MASLD with the metabolic syndrome and T2DM led to the connection between fatty liver and the development of cardiovascular disease (CVD). There are numerous mechanisms that may accelerate atherosclerosis and premature CVD in patients with MASLD. Hyperglycemia per se is an established factor for CVD, as well as the typical atherogenic dyslipidemia in MASLD driven by VLDL over secretion. It is known that individuals

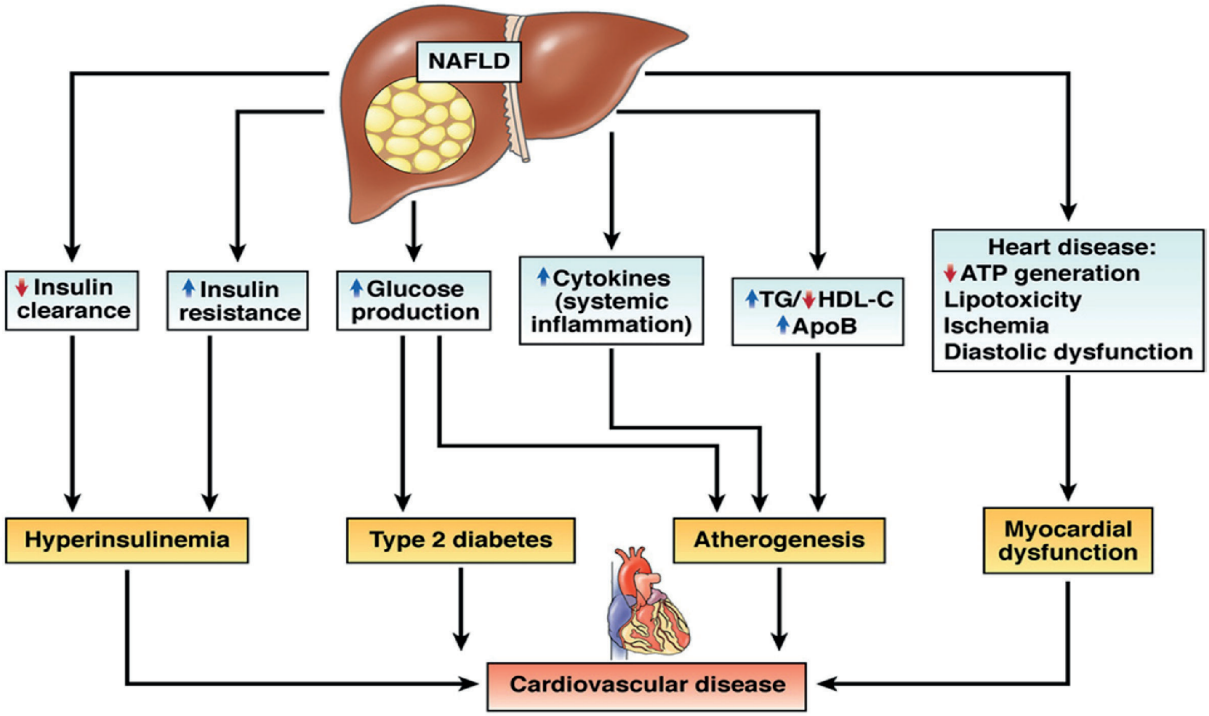

Figure-3: *CV risk factors that coexist in patients with MASLD* [12]

with MASLD are characterized by abnormal endothelial function. Increased fatty acids impair endothelial cell insulin signaling and nitric oxide production in a dose-dependent manner through the activation of the inhibitor B kinase / nuclear factor B pathway. Again hyperinsulinemia from increased insulin secretion due to insulin resistance and decreased insulin clearance by liver correlates with the severity of hepatic steatosis and chronically elevated plasma insulin levels may promote atherogenesis. Again increased myocardial triglyceride accumulation is observed in obesity and T2DM which is associated with myocardial insulin resistance and impaired ventricular energy metabolism. Hepatic triglyceride content correlates inversely with myocardial glucose uptake and metabolism as measured by positron emission tomography as the phosphocreatine/ adenosine triphosphate ratio. There is a close correlation between MASLD and myocardial steatosis and early diastolic dysfunction.[6]

Outcome and prognosis of MASLD

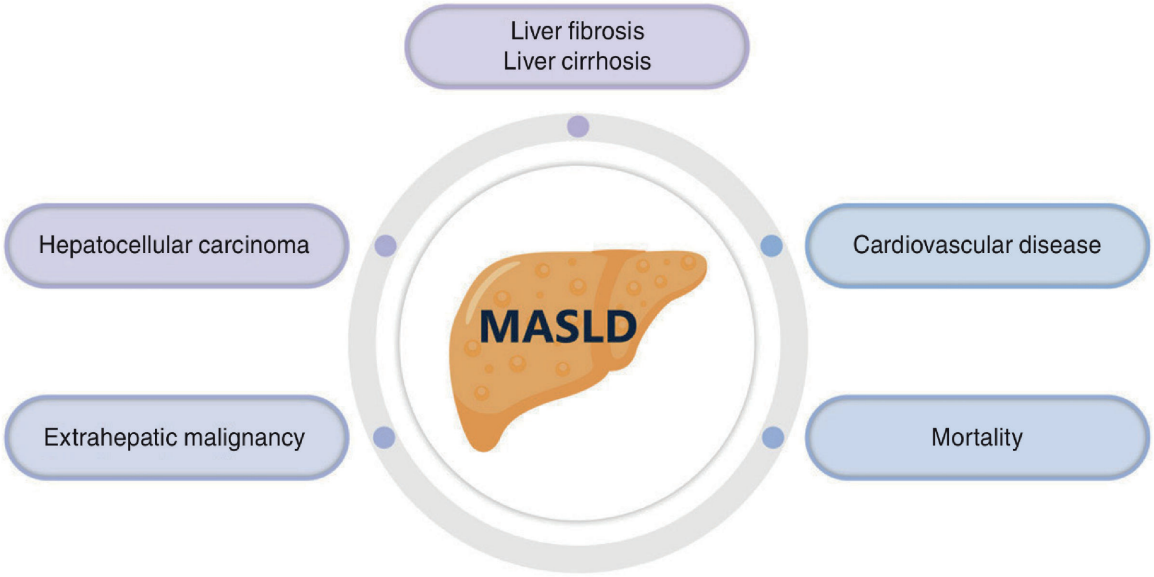

Figure-4: Outcome and prognosis of MASLD.[2]

In a recent meta-analysis of 79 studies on MASLD diagnosed through histological or imaging methods, the incidence of CVD was reported as 24.77 cases per 1,000 person-years. Additionally, the meta-analysis reported a CVD-related mortality rate of 4.5 deaths per 1,000 person-years.[13] Another meta-analysis comprising 36 studies on MASLD further confirmed a significant elevation in the risk of CVD-related mortality (HR 1.30, 95% CI 1.08–1.56).[14]

A meta-analysis of 151 studies published since 2000 reported that among overweight individuals with MASLD, the prevalence of liver fibrosis (F1–4) was 46.6% (95% CI 26.6–67.7), that of advanced fibrosis (F3–4) was 6.7% (95% CI 4.4–10.0), and that of cirrhosis (F4) was 2.5% (95% CI 1.6–3.7). In overweight individuals with MASH, the prevalence was even higher, with the prevalence of liver fibrosis at 72.6% (95% CI 49.4–87.8), that of advanced fibrosis (F3–4) at 19.4% (95% CI 7.6–41.1), and that of cirrhosis (F4) at 1.7% (95% CI 0.4–6.6).[15]

In patients with cirrhosis related to MASLD, the annual incidence of Hepatocellular carcinoma (HCC) exceeds 1.5% which therefore, warrants surveillance for HCC in patient of suspected cirrhosis related to MASLD. In addition MASLD is also associated with a 1.5- to 2-fold increase in the prevalence of gastrointestinal cancers, including esophageal, gastric, pancreatic, and colorectal cancers. (Figure-4)[2]

During a median follow-up of 14.2 years, the all-cause mortality in patients with biopsy-proven MASLD (n=10,568) and matched controls (n=49,925) was 28.6 and 16.9/1,000 person-years, respectively. All-cause mortality was higher in patients with MASLD than in matched controls (adjusted HR 1.93, 95% CI 1.86–2.00).[15] A meta-analysis revealed that the leading causes of death in MASLD were cardiovascular disease, extrahepatic malignancy, and liver-related events.[17]

Conclusion

MASLD usually does not occur in isolation rather it is part of broader spectrum of metabolic dysfunction ranging from insulin resistance to full blown metabolic syndrome. In fact it is hepatic manifestation of metabolic syndrome. The inter relationship between MASLD and other component of metabolic syndrome reflects the driver role of MASLD for progression of metabolic syndrome consisting of diabetes mellitus, hypertension, obesity and hyperlipidaemia increasing the risk of cardiovascular morbidity and mortality.

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