Metabolic Dysfunction-associated Steatotic Liver Disease

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**Introduction**

It is evident that there is a link between the onset of dyslipidemia, insulin resistance (IR) and metabolic dysfunction-associated steatotic liver disease (MASLD), since fatty liver disease affects over 75% of people with type 2 diabetes. Additionally, there is a strong epidemiological correlation. The term "non-alcoholic fatty liver disease" should be changed to "MAFLD" according to several studies in 2020–2022. There is a relationship between the development of MASLD and IR as well as serum glucose concentrations and consequently increased endogenous production of triglycerides, all depending on the role of IR as a precipitating factor, even though MAFLD is thought to be of metabolic origin and involved many possible inducing factors. By preventing the process of lipolysis in adipose tissues in the insulin-resistant state, fatty acids into the liver can be increased to yield the same effect. Hepatic steatosis changes the production of adipokines, fatty acid metabolism, and insulin resistance (IR) in skeletal muscles, adipose tissues (AT), and liver, all of which can engage in complementary interactions. Since MASLD is more prevalent in T2DM patients, it may be concluded that MASLD increases the likelihood of developing T2DM. Parts of metabolic syndrome (MetS) can be observed in 90% of MASLD patients.

This fact justifies the change of MASLD nomenclature. Marchesini et al. discovered that, among individuals with hepatic steatosis, the odds ratios for developing liver fibrosis and dysmetabolic steatohepatitis were significantly higher when MetS was present (3.2 and 3.5, respectively). Furthermore, MetS is a helpful biomarker for estimating the possibility of fatty liver associated with obesity. The significance of IR in the pathogenesis of MASLD is supported by some reports. Given that MASLD is a very complicated and mixed disease, it is not reasonable to think of a single hypothesis to describe the pathogenic mechanism. Similar to diabetes and hypertension, MASLD is caused by both environmental and genetic factors. Indeed, an increasing body of research indicates that a variety of environmental factors, such as tobacco exposure and air pollution, influence the development of fatty liver. Notwithstanding the fact that multiple factors contribute to MASLD, a particular concept like abnormal metabolic function or disorder can be used to generalize the etiology of MASLD. According to estimates, there is a 24% global prevalence of MASLD, usually seen in Asia, the US, Europe, and South America with the highest incidences, followed by the Middle East.

**Fatty Liver by Mechanism of Adipokines**

Adipokines are biologically active proteins that exhibit high levels of expression in adipocytes, such as leptin, adiponectin, tumor necrosis factor-α, anti-insulin hormones, and mediators like leukocyte hormone-6 (IL-6) are a few significant adipose hormones. Studies indicated that TNF-α and IL-6 can induce insulin resistance by lessening a cell's sensitivity to insulin. Considered to be two of the key players in the inflammatory response, TNF-α and IL-6 are hormones that induce immunity in the body. It was evident from the research milestones over the past 30 years that led to the first proposal of MASLD's etiology as a parallel-path pathogenesis. It was later revised to multiple paths, which is now referred to as a multifactorial mechanism for MASLD. Together with insulin resistance and buildup of fats, it also involves systemic inflammatory reactions that eventually result in liver fibrosis, hepatitis, and insufficient liver function. Using drugs such as renin-angiotensin system inhibitors (RAS inhibitors), as well as patient's age and iron deposit in body, are risk factors. The primary hormone produced by the body and used for metabolism is insulin. In addition to aiding in tissue growth and development, it keeps blood glucose stable. Maintaining glucose stability requires controlling the breakdown of glycogen and hepatic gluconeogenesis, as well as stimulating insulin receptor-mediated glucose uptake in adipose tissues, cardiomyocytes, and skeletal muscles.

Insulin receptors found in cells and adipose tissues are associated with glucose uptake. The term "insulin resistance" (IR) describes the body tissues' reduced response to insulin stimulation. Changes in the quantity and malfunction of receptors are the causes of this anomaly. In fact, it is not explained by a single factor but rather a number of factors work in concert to result in this metabolic abnormality, including reduced insulin stimulation, aberrant receptor stimulation, or persistent inflammation of the body. It has also been suggested by some scholars that fatty acids cause IR. Lipid buildup in the liver and muscles can result from aberrant fatty acid metabolism. Any given situation will result in a positive feedback loop that raises the blood concentration of insulin as long as the sensitivity to hormonal stimulation is decreased. The rise in serum insulin concentration may induce various physiological effects on different tissues. Despite the fact that fatty acid metabolism will exacerbate insulin resistance, Randle and colleagues first suggested in 1965 that the rise in free fatty acids in serum was also a major factor in the decline in glucose oxidation and the development of IR. Over the past decade, a growing body of research has disregarded this process in favor of focusing on the roles that fatty acids and glucose play in the development of fatty liver disease.

Over time on an annual basis, 6.3% and 25% of healthy persons will develop metabolic fatty liver disease and fatty liver, respectively. For obstructive sleep apnea (OSA) and the so-called metabolic syndrome, they are nearly identical to include traits like abnormal fasting glucose, obesity, hypertension, and hyperlipidemia, according to medical study conducted in the last ten years. This indicates that MASLD is becoming more common in Asian countries annually. In 2016, a meta-analysis study revealed that Asia had a greater prevalence (27.4%) than either North America (24%) or Europe (23.7%). According to a recent comprehensive analysis, the incidence rate has increased annually over the past decades with the prevalence rate in Asia climbing to 29.62%. While the prevalence in rural areas is significantly lower than in urban areas, indicating that urbanization has a significant impact on obesity and subsequent negative effects on MASLD, the increased prevalence in Asia may be attributed to various socioeconomic factors, sedentary lifestyles, and westernized eating habits. When compared, the prevalence rate also increased with age. Both men and women after menopause have higher prevalence rate, suggesting that estrogen does protect women of childbearing age.

**Correlation between Adipokines and Metabolic Syndrome**

Adipose tissues play a key role in metabolic syndrome by secreting a cytokine or hormone called adipokines, which promote inflammation. Additionally, there is a definitive connection between adiponectin and leptin in the pathogenesis of MASLD. Adiponectin insufficiency is linked to inflammation in the body, as seen in obesity and metabolic syndrome, whereas high leptin concentration promotes inflammation. Furthermore, there is a connection between systemic inflammation and other adipokines such resistin, visfatin, and irisin, while liver cells are shielded from TNF-α-induced apoptosis by adiponectin. For example, consuming excessive number of fruits and eating a high-fat diet may increase the risk of MASLD, but adiponectin as adipocyte-derived protein has been shown to have anti-inflammatory, anti-atherosclerotic, and enhanced insulin sensitivity effects. In individuals with MASLD, serum adiponectin concentration is decreased. Lean body type MASLD may be associated with the consumption of foods high in fructose and saturated fats, as well as innate genetic variables including congenital metabolic abnormalities. Despite that there are patients with normal body weight, the majority of lean MASLD patients may be metabolically obese. At least 5% of Westerners with this trait were reported to have decreased insulin sensitivity and an elevated risk of cardiovascular diseases, even when they did not live a sedentary or obese lifestyle. A Mediterranean diet is linked to lower cardiovascular risk and liver fat level. However, there is conflicting evidence about the impact of the Mediterranean diet on the onset and course of MASLD. The prevalence of the disease, the risk of fatty liver complications and the overall mortality rate were observed to increase with age. Many factors have shown to contribute to this, including reduced liver blood flow, altered cholesterol metabolism, decreased mitochondrial number in liver cells, and altered body composition from sarcopenia to abdominal obesity with ectopic fat deposition, which further leads to insulin resistance. Premenopausal women have a greater overall survival rate and a lower frequency of liver fibrosis and MASLD. Estrogen may provide protection against alterations in body fat distribution (reduced abdominal obesity), variety of metabolic risk factors, and metabolism-related anomalies (differences in lipid metabolism, insulin sensitivity, and inflammatory response). The prevalence of MASLD and the risk of fibrosis are higher in postmenopausal women on hormone replacement treatment than in those who do not. The severity of fatty liver disease rises with the duration of estrogen deprivation in postmenopausal women.

**Prevalence of Metabolic Dysfunction-associated Steatotic Liver Disease**

Some scholars recommended in 2020 that, since fatty liver disease is more closely related to metabolic associated fatty liver disease (MAFLD) than it is to the name NAFLD, which was first introduced in the 1980s and more appropriate to describe the disease. More studies on MASLD have directly proved the connection between metabolic problems and fatty liver, indicating that MASLD is a hot issue of rapidly developing health concern, as the literature statistics have also shown.  Currently, 40% of Asians with MASLD are non-obese individuals. MASLD in non-obese patients is more common in Asian countries but has now become more prevalent in Europe and the United States. In developing countries like India, the ratio is as high as 47%, suggesting that a significant portion of fatty liver disease is occurring in non-obese people. The US is 43.2%, which is equivalent to the reported prevalence of MASLD worldwide.

The World Health Organization reports that the number of people suffering from fatty liver disease is rising worldwide, and that the percentage of adults over the age of 18 who have type 2 diabetes has climbed from 4.7% in the 1980s to 9% in 2018. Thus, metabolic fatty liver is seen as a systemic disease, particularly in relation to cardiovascular issues, in addition to affecting the liver. Nowadays, older adults with cardiovascular disease make up roughly 25% of individuals with fatty liver disease. Over the past 30 years, there has been a global increase in the prevalence of non-obese MASLD patients. However, studies have shown that non-obese MASLD patients had lower rate of hypertension, hyperuricemia, and abnormal fasting glucose when compared to their obese counterparts. However, these patients do not reflect healthy individuals with normal metabolisms; rather, they simply do not appear to be obese. Lean MASLD patients have a higher chance of undiagnosed visceral fat buildup, dyslipidemia, and hypertension when compared to the control group. APRI (Aminotransferase-to-Platelet Ratio Index) and the NAFLD fibrosis score (NFS), FIB-4 index, and current liver stiffness measurement (LSM) are among the non-invasive assessment techniques for liver fibrosis that are currently widely utilized in clinical practice. In order to determine whether a patient has liver fibrosis, APRI applies a formula based on the patient's blood platelet count and GOT, as they will have a decrease in platelet value and an increase in GOT.

The abnormality of PNPLA3 gene, ethnic background, diet, alcohol consumption, genetic defect, intestinal flora, and other factors are associated with the prevalence of MASLD. As a result, MASLD patients' course and reaction to treatment differ significantly. According to epidemiological research, the incidence of MASLD could reach 21.9% in the US and up to 31% in Asia. However, the incidence of MASLD verified by biopsy exceeded to 61% in the US, but such test is rarely performed on Asian patients. The areas with the highest distribution of fat are visceral and subcutaneous adipose tissues, which have varying fat properties. Although the intrahepatic fat content of obese individuals is higher, 45% of them fall into the metabolically healthy category since they do not exhibit any metabolic disorder symptoms. It's uncertain if these individuals are superior to others who are metabolically healthy and of normal weight, as they are less likely to get cardiovascular issues. However, 30% of individuals who are normal weight have metabolic syndrome, which increases their risk of cardiovascular disease. This is due to the fact that visceral fat, as opposed to subcutaneous fat, is linked to a higher risk of metabolic abnormalities, and thus, the distribution and properties of fat, as well as their location like peripheral fat, are more significant factors in predicting metabolic risk than fat quantity.

**MASLD and Chronic Systemic Inflammation**

Lately, the definition of MASLD and DAFLD (dysmetabolism-associated fatty liver disease) have become comparable. In addition to suggesting a different nomenclature, Polyzos and Mantzoros promoted using the term DAFLD for the diseases. According to Polyzos, elevated levels of these adipokines are linked to the onset of metabolic syndrome-related disorders and obesity. The pathophysiology of MASLD may involve cytokines released by fat. Despite the fact that MASLD does not yet have a viable treatment, weight loss has the potential to stop the disease's progression and repair the liver's pathological and histological abnormalities. In obese patients, inflammatory response is increased and promoted by most adipokines (leptin, TNFα, IL-6, and IL-18). Thus, anti-inflammatory drugs and adiponectin can be used. A growing amount of research connects low-grade bodily inflammation with obesity. Due to the fact that these inflammations seem to play a significant role in liver dysfunction in obese patients, who cannot be excluded for MASLD diagnosis, some patients may be misdiagnosed with infectious hepatitis. Therefore, it is crucial to rule out alcoholic liver disease, viral infections, autoimmune hepatitis, drug-induced liver damage, etc.

Body Mass Index (BMI≥25 kg/m2 or Asian BMI≥24 kg/m2) is part of the diagnostic criteria of MASLD. Nonetheless, waist circumference rather than BMI is thought to be a more accurate measure of visceral fat accumulation. For instance, dual energy X-ray measurement (DXA) can be used to assess the waist circumference directly in young athlete who has high body mass index (due to high muscle mass) with normal waist.  As a result, there is compelling evidence linking metabolic dysfunction to both the primary etiology of MASLD and its sequelae. It is evident that MASLD/DAFLD is a dynamic metabolic disease marked by changes in many metabolic parameters over time. In fact, age, ethnicity, gender, lifestyle, genetic or epigenetic variants, and metabolic syndrome can all have distinct effects on one another over time. The many DAFLD phenotypes are mostly brought on by genetic, environmental, or metabolic abnormalities.

**Clinical Diagnosis and Prognosis of MASLD**

Being present in roughly 25–30% of individuals, almost 70% of T2DM patients, and almost all obese patients, metabolic fatty liver disease has grown to be a major global health concern. The following criteria are used, and at least one condition must be met to diagnose MAFLD: 1. Presence of serum biomarkers; 2. No excessive alcohol use (defined as 20g or less per day for women and 30g per day for males); and 3. No other secondary cause of hepatic steatosis. Over the last few decades, MASLD has been linked to cardiovascular, metabolic, and chronic renal disorders in addition to serious liver-related consequences. Although the pathophysiology of MASLD is well recognized to be complex, insulin resistance, abdominal obesity, and type 2 diabetes are all strongly associated with chronic liver disease. Numerous studies have shown that metabolic syndrome, obesity, and type 2 diabetes might hasten the onset and course of MAFLD. Given these strong correlations, Loria, Lonardo, and Carulli decided that MASLD should be renamed with words like insulin resistance or metabolism-related. In 2020, there were two major statements that discussed updating and revising the definition of fatty liver disease in addition to suggesting that NAFLD be renamed as metabolic association fatty liver disease (MAFLD). These publications stated that the presence of hepatic steatosis (determined by imaging, histological examination, or blood biomarker) plus at least one of the following metabolic criteria can be used to diagnose MAFLD: 1. Being overweight; 2. Given a diabetes diagnosis; and 3. Metabolic syndrome showing higher waist circumference, low HDL cholesterol, low HDL, hypertension, hypertriglyceridemia, insulin resistance: HOMA-IR > 2.5). High-sensitivity C-reactive protein (hs-CRP>2 mg/L) or at least two risk variables are commonly regarded as the sole indicators of MAFLD. The histology has minimal predictive value but can forecast the course of fibrosis. It is therefore best to take individuals with advanced fibrosis (F3 and F4) into consideration when making a diagnosis. Compared to healthy groups, this stage is predictive with rising hepatic and extrahepatic morbidity and mortality. There is a significant increase in the risk of cardiovascular disease (HR: 1.55, 95% CI: 1.11-2.15), HCC (HR: 6.55, 95% CI: 2.14-20.03), overall mortality (HR: 1.29, 95% CI: 1.04-1.59), and liver cirrhosis (HR: 3.2, 95% CI: 1.05-9.81).

Interventional treatment is not necessary for patients with early-stage F0-F2 MASLD since they do not appear to be liver disease. Reducing the risk of cardiovascular disease and addressing metabolic risk factors like diabetes are important for these individuals. The hallmark of MASLD is disruption of the body's adipokines, which is linked to systemic inflammation. Paleoesophageal reflux, esophageal cancer, gallstones, gallbladder cancer, cholangiocarcinoma, pancreatic cancer, papilloma of the esophagus, colon polyps, and fatty liver disease are examples of digestive illnesses associated with obesity. Thirty percent of adults and forty to seventy percent of healthy people have MASLD, a chronic liver disease. For individuals with MASLD, liver fibrosis has a dismal prognosis. Along with liver illness, MASLD also involves cancer, arrhythmia, depression, ischemic cerebral infarction, sleep apnea, dementia, myocardial lesions, chronic renal disease, ovarian cancer, polycystic ovary syndrome, and heart failure and ischemia heart disorders. In MASLD, weight loss and a change in lifestyle can help with both primary and secondary cardiovascular disease prevention. Both primary and secondary prophylaxis with aspirin and statins may be appropriate for MASLD patients who are high-risk for cardiovascular disease. It is well known that new anti-diabetic medications like GLP-1 receptor agonists and SGLT2 inhibitors lower the incidence of T2DM.

**Conclusion**

The American Association of Liver Medicine has introduced a new definition for metabolic fatty liver disease (MASLD) in June 2023: metabolic dysfunction-associated steatotic liver disease. It is the result of pertinent research and clinical procedures related to earlier definitions that are more suited for patient care. It is also a more accurate terminology, as it recognizes an increased risk of myocardial infarction, ischemic stroke, heart failure, and arrhythmias, that are associated with MASLD, a systemic disease that affects the brain and causes depression, sleeplessness, and dementia. Risk factors for the progression of MASLD include age, iron deposition, diabetes, metabolic syndrome, alcoholism, renin-angiotensin system inhibitors, and metabolic syndrome.

Every year, over 25% of healthy individuals’ livers will develop fatty liver, 6.3% of MASLD, and some percentage of liver fibrosis, cirrhosis, or even cancer. Indicators for tracking the severity of liver disease in MASLD patients include hyaluronic acid, GPT, and other serum markers. As the prevalence of obesity increases, MASLD is one of the most important causes of liver disease in adults and children worldwide, even though there are cases of MASLD with lean body physique. Generally, being overweight in childhood and adolescence is associated with an increased risk of future MASLD, so liver-related morbidity or mortality can be predicted at a younger age. MASLD has the highest risk of comorbidities such as liver-related diseases, as well as metabolic abnormalities, causing significant pressure on national and social health care expenditures.