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METABOLIC DYSFUNCTIONS ASSOCIATED WITH STETOTIC LIVER DISEASE

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Abstract

Metabolic Dysfunction-Associated Stetotic Liver Disease (MASLD) is a significant cause of chronic liver disease, affecting 30% of the global population, and can progress to severe conditions like fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Traditional treatments are limited, so a more integrated approach is necessary. Early identification and modification of risk factors are crucial for preventing complications. MASLD is a major public health concern, causing liver-related morbidity and mortality. A clear assessment and referral pathway is needed for managing severe cases, with lifestyle interventions and cardiovascular risk management being key components. While no specific medication is approved, novel antihyperglycemic drugs show promise. Management should also address liver disease progression, sarcopenia, and adjustments to medications for diabetes and metabolic conditions. The term MASLD replaced Non-Alcoholic Fatty Liver Disease (NAFLD) in 2023 to highlight the disease's connection to metabolic dysfunction. Altered metabolic function can lead to both cardiovascular and liver diseases. Traditional treatment approaches have focused on individual organs, resulting in siloed care. However, because metabolic dysfunction affects the entire body, a more integrated approach involving multiple medical specialists is needed to improve patient outcomes. It suggests that addressing the underlying disease process, rather than solely targeting the cardiovascular or liver-specific issues could be more effective.

Keywords: Non-alcoholic fatty liver disease, Liver cirrhosis, Stetosis Steatohepatitis Diabetes mellitus Metabolic syndrome Fatty liver disease, Obesity.

INTRODUCTION

Cardio-metabolic diseases are the optimal setting to explore the crosstalk between the heart and liver, and the meeting point for multi disciplinary evaluations where cardiologists and hepatologists can find common ground for collaboration. Recent research advances pave the way to a better understanding of the complex pathogenic mechanisms underlying cardiometabolic conditions and their association with car diovascular disease. The liver is at “the core” of several metabolic dis orders and the related histopathological changes range from steatosis, or non-alcoholic fatty liver disease (NAFLD), to steatohepatitis (NASH), to cirrhosis.[1] These states are all associated with various cardiovascular ailments. Recently, experts in the field raised concerns that the nomenclature currently in use (NAFLD) highlights what is not the root-cause of the liver ailment, rather than stressing the dysmetabolic diseases underlying this condition.

For patients consuming more than 140–350 g/week of alcohol for women, and 210–420 g/week for men, a new nomenclature was also introduced: metabolic and alcohol related/associated liver disease (MetALD). The new nomenclature and diagnostic criteria received wide support as they do not carry the stigma attached to the word “fatty”, and have important implications for patient advocacy and public health metabolism. significant implications for numerous chronic non-communicable diseases., carrying marketing surveillance studies to exhibit pleiotropic effects on the liver and the heart.[3]

Furthermore, the Global Burden of Diseases study including 28 million people from 195 countries suggested that there is no safe limit for alcohol use. In order to address these challenges, an international panel of experts in 2020 proposed a new term and definition for metabolic dysfunction- associated fatty liver disease (MAFLD) aiming to replace the term NAFLD.

Unlike NAFLD, MAFLD is a "positive" diagnosis when hepatic steatosis is detected in adults, along with one of the following three criteria: overweight/obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation determined by presence of ≥2 metabolic risk abnormalities.

2. History and Epidemiology:

MASLD is a continuum of chronic hepatic disorder characterized by excessive accumulation of triglycerides within the cytoplasm of hepatocytes. The disease spectrum encompasses a wide range of manifestations, starting from isolated accumulation of triglycerides in hepatocytes and development of steatosis alone or plus one of lobular or portal inflammation or ballooning, known as non-alcoholic fatty liver (NAFL) or currently metabolic dysfunction- associated steatotic liver (MASL).

3. Role of metabolic dysfunction in the pathophysiology of MASLD

Metabolic dysfunction refers to the presence of obesity, hyperglycemia, hypertension or dyslipidemia clinically. The primary histological characteristic of MASLD is hepatocellular steatosis, which is thought to be the hepatic manifestation of metabolic syndrome. According to the classic "two-hit theory" of fatty liver, the first hit involves excessive hepatic lipid deposition, and the second hit activates inflammatory cascades and fibrogenesis in hepatocytes after that, which results in non-alcoholic steatohepatitis (NASH) assessed by NAS scores and liver fibrosis classified as F1 to F4 by Metavir scores[10].

Multiple risk factors jointly contribute to the progression of MASLD with dynamic changes from hepatic steatosis and inflammation, nonlinear progression of fibrosis to the recompensation of NAFLD-related cirrhosis, and novel pathophysiological mechanisms, such as impaired partial collagen degradation and hepatocyte regeneration, vascular remodeling and systemic inflammation enhancement, which are involved in the updated natural course of MASLD. [11]

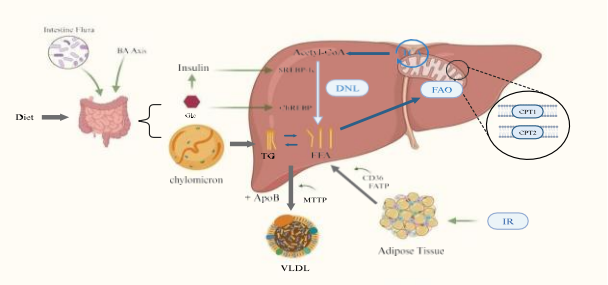

Figure.1: Overview of hepatic triglycerides metabolism. TG, triglycerides; SREBP, sterol regulatory element– binding protein; ChREBP, carbohydrate response element binding protein; FFA, free fatty acid; IR, insulin resistance; CD36, cluster of differentiation 36; FATP, fatty acid transport proteins; VLDL, very-low density lipoprotein; MTTP, Microsomal TG transfer protein; FAO, fatty acid β-oxidation; CPT, carnitine palmitoyl transferase; DNL, de novo lipogenesis

Reduced mitochondrial FAO

Hepatic FAO and mitochondrial turnover are compromised in patients with MASLD. It is necessary for carnitine palmitoyl transferase (CPT) to allow fatty acids to enter mitochondria. CPT1 and CPT2 are found in the two layers of the mitochondrial membrane respectively. CPT is reportedly up regulated and CPT2 is inhibited in patients with MASLD. Overexpression of CPT1A enhances hepatic FAO and lipid autophagy, thus reducing hepatic steatosis in high-fat-diet mice.[12]

4. Management of Diabetes and Other Metabolic Comorbidities:

The management of T2DM patients with liver cirrhosis has be- come an increasingly common scenario with the global increase of obesity, diabetes, and MASLD. There is a clear unmet need in this area, as patients in this population have been rarely studied. Data on glucose monitoring and targets, as well as the use of anti-hyper- glycemic drugs in liver cirrhosis, remain sparse.

Liver parameters					Cardiorenal-metabolic parameters	
	Serum aminotransferase	Liver fat	Liver fibrosis	MASHresolution	Body weight	Cardiorenal benefits
Pioglitazone	↓	↓	↓	Yes	↑	↔
GLP1 RAs	↓	↓	↓	Yes	↓	Yes
GLP1/GIP RAs	↓	↓	Unknown	Unknown	↓	Unknown
SGLT2 inhibitors	↓	↓	Unknown	Unknown	↓	Yes
Insulin	↓	↓	Unknown	Unknown	↑	↔
Metformin	↔	↔	↔	↔	↔	↔
DPP-4 inhibitors	↔	↔	↔	↔	↔	↔

Table: 2 Effects of anti-hyperglycemic drugs on metabolic dysfunction-associated steatotic liver disease.

5. Insulin sensitizers:

- **Thiazolidinedione (TZD)**

Thiazolidinedione is a kind of insulin sensitizers with thiazolidinedione ring, which act as potent activators of the nuclear receptor PPARγ. Thiazolidinediones cause decreased liver lipid accumulation and FFA plasma levels by inducing the release of adipokines, encouraging TG storage in adipose tissue, and strengthening the suppressive effect of insulin on lipolysis. As summarized in clinical trials of pioglitazone showed significant improvement in IR, liver steatosis and inflammation compared with placebo.[13]

- **Metformin**

  Metformin inhibits hepatic gluconeogenesis and improves IR in patients with type 2 diabetes. Previous studies indicated that metformin effectively improves systemic inflammation and insulin sensitivity, and reduces body weight. However, it also increases hepatocyte DNL that contributes to hepatic TG accumulation. Although it is clear that metformin could not improve liver histo logical steatosis, it's more often used in combination with other medications at present, such as GLP-1 receptor (GLP-1R) agonists, thiazolidinediones or sodium-dependent glucose transporter 2 (SGLT2) inhibitors

- **ACC inhibitor**

  The first and committed step in DNL is catalyzed by ACCs, which convert acetyl- CoA to malonyl-CoA. Additionally, malonyl-CoA is a signaling molecule that inhibits FAO. ACC inhibitors have been proved efficacious to improve liver steatosis in animal models. While in clinical trials, firsocostat (GS-0976) showed benefit in the improvement of liver lipid accumulation, stiffness and serum liver enzymes, but also led to an increase in serum triglycerides. Another three- part randomized phase 1 study showed similar efficacy on PF-05221304.[14]

- **SCD1 inhibitor**

  SCD1 functions to convert saturated fatty acids to mono unsaturated fatty acids. The activity of SCD1 is increased in patients with MASLD. In mouse models, aramchol (arachidyl- amido cholanoic acid) prevented steatohepatitis and fibrosis by blocking SCD1 and boosting the flow via the transsulfuration pathway, which kept the cellular redox balance stable.

- **DGAT2 inhibitor**

  The last step in DNL is that diacylglycerol acyltrans ferase (DGAT) catalyzes fatty acyl- CoA to diacylg lycerol. Previous studies showed that lower level of DGAT2 expression leads to reduced steatosis in diabetic mice, but hepatocyte damage is exacerbated by lipotoxicity from FFAs. Phase 1 studies indicated that selective DGAT2 inhibitor (PF-06427878) is well tolerated and significantly improves markers of liver function. IONIS-DGAT2Rx is an antisense oligonucleotide inhibitor of DGAT2 expression which prevents LFC in a phase 2 trial.[15]

- **Fatty acid oxidation activators**

  Thyroid hormone receptor (THR) β agonists Mitochondrial dysfunction is involved in the patho physiology of MASLD, and in patients with steato hepatitis exhibit decreased activity of respiratory chain complexes and fatty acid oxidation. It is an appealing therapeutic target for MASLD to stimulate mitochondria function according to recent studies. The thyroid hormone receptor consists of 2 isoforms, namely THRα and THRβ.

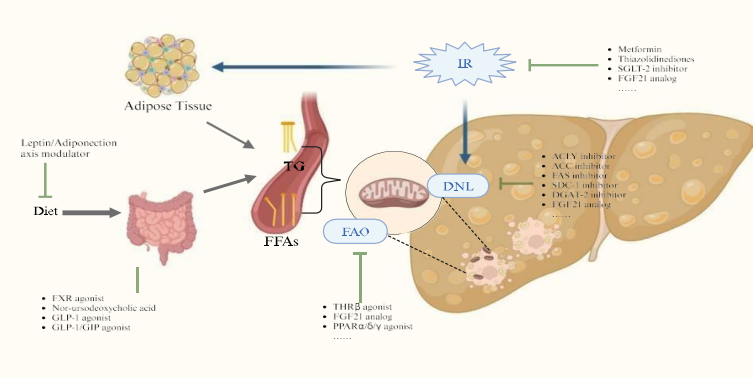

Figure3: Medications targeting at metabolic dysfunction of MASLD. DNL, de novo lipogenesis; FAO, fatty acid β-oxidation; IR, insulin resistance; GLP, glucagon-like peptide; GIP, glucose-dependent insulinotropic peptide; FXR, farnesoid X receptor; FGF, fibroblast growth factor; TG, triglycerides; FFA, free fatty acid; THR, thyroid hormone receptor; PPAR, proliferator-activated receptor.

- **Statins and bempedoic acid**

  Statins are at "the core" of cardiovascular disease prevention and treatment. The American Heart Association advises their use in a public health approach in all people with high cardiovascular risk. Animal studies have provided some evidence that statins may improve MASLD/MASH. Statins do not appear to reduce liver fat, but might mitigate the risk linked with MASLD through their lipid lowering, anti-inflammatory, antioxidant and anti-fibrotic effects.[16]
  Bempedoic acid reduces cholesterol levels via down regulation of ATP-citrate lyase and upregulation of AMP-activated protein kinase (AMPK). Its primary effect is the reduction of cholesterol synthesis in the liver. Reductions of gluconeogenesis and plasma levels of C-reactive protein (by AMPK activation) are additional potentially beneficial ef fects of bempedoic acid.[18]

- **Ezetimibe**
  Ezetimibe reduces intestinal absorption of cholesterol and has an additive LDL-C lowering effect when added to statins, with reduction in cardiovascular events. In an early study, ezetimibe in combination with a low-fat diet reduced visceral adipose tissue, intrahepatic triglycerides and serum markers of inflammation in obese patients with insulin resistance and presumed MAFLD. The impact of ezetimibe on MASLD/MASH was explored in a few post-hoc analyses of RCTs.
- **Sodium-glucose cotransporter 2 inhibitors**
  Sodium-glucose cotransporter 2 inhibitors (SGLT2i) help improve glycemia in T2DM by promoting urinary glucose excretion, and are also beneficial for treatment of heart failure through a number of mechanisms that go beyond osmotic diuresis. Dapaglifozin and empa glifozin are now recommended for the treatment of heart failure with reduced, mildly reduced or preserved ejection fraction, and there is a high prevalence of heart failure with preserved ejection fraction among patients with MASLD. Additionally, recent data from meta-analyses of RCTs showed that SGLT2i improve liver function parameters and metabolic outcomes among patients with MASLD and MASH.[17]
- **Glucagon-like peptide-1 receptor agonists**
  Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for treatment of T2DM and for chronic weight management in overweight and obese patients. Among all molecules in development for treating MASH, semaglutide stands out with the most robust evidence on cardiovascular outcomes, with 2 RCTs available in patients with T2DM and obesity.[19,20]

Conclusion:

The increased understanding of MASLD has brought about a name change to the disease, creating greater awareness. MASLD is the most common cause of chronic liver disease and is the leading cause of liver-related morbidity and mortality. There is no doubt that all stakeholders must be involved in tackling the public health threat of obesity and obesity-related diseases, including MASLD. A simple and clear assessment and referral pathway is essential to en sure that patients with more severe MASLD are identified and the new term of MASLD and prior terminologies are still used concurrently in daily clinical practice and scientific communication.

While the initial diagnosis of MASLD hinges upon the presence of at least 1 altered anthropometric, clinical, or laboratory parameter indicating metabolic dysfunction, it has been pointed out that various cardio metabolic risk factors may carry different weight depending on their association with insulin resistance, which is the major etiological factor of the disease. Reaching truly global consensus on these additional issues within a flexible and further evolving SLD framework will help us further clarify the pathophysiology, develop efficient treatment strategies, and summon public awareness to a disorder seen in the liver but having consequences far beyond.

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All authors are contributed equally

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