Review Article

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and the Emerging Role of Resmetirom: A Comprehensive Review

Waqas Ahmed

PhD Scholar, Institute of Translational Medicine, Shenzhen University, China

Abstract

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), previously referred to as nonalcoholic fatty liver disease (NAFLD), is increasingly recognized as the hepatic manifestation of metabolic syndrome. In 2023, international hepatology societies updated the nomenclature from NAFLD to MASLD, emphasizing metabolic dysfunction as the central pathophysiologic driver. This spectrum of liver disease ranges from benign steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Despite its high global prevalence, MASLD has historically lacked approved pharmacologic therapies. Recent advances in therapeutics have introduced **Resmetirom**, a selective thyroid hormone receptor-beta (THR-β) agonist, which has shown promising results in reducing hepatic fat and improving histological endpoints. This review explores the epidemiology, pathogenesis, diagnosis, and therapeutic potential of Resmetirom in the treatment of MASLD.

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Correspondence
Waqas Ahmed
PhD Scholar, Institute of Translational Medicine
China

Introduction

MASLD has emerged as a leading cause of chronic liver disease globally, paralleling the rise in obesity, type 2 diabetes mellitus (T2DM), and other components of the metabolic syndrome. In June 2023, a major international consensus redefined NAFLD as MASLD to better reflect the underlying metabolic dysfunction and to improve disease identification and management in clinical practice (1). This nomenclature includes patients with hepatic steatosis and at least one cardiometabolic risk factor, including overweight/obesity, T2DM, hypertension, or dyslipidemia (2). MASLD encompasses a broad clinical spectrum, from simple steatosis (previously called NAFL) to metabolic dysfunction-associated steatohepatitis (MASH), which is histologically characterized by steatosis, hepatocyte ballooning, lobular inflammation, and varying degrees of fibrosis (3).

Globally, MASLD affects nearly 25–30% of the adult population, making it the most common chronic liver disease (4). The disease burden is particularly high in South Asia, the Middle East, and Western countries, driven by increasing rates of insulin resistance and sedentary lifestyles (5). Despite this, MASLD often remains underdiagnosed due to its asymptomatic nature in early stages. Furthermore, until recently, there were no approved pharmacological treatments for MASLD or MASH, emphasizing the urgent need for targeted therapeutics.

Pathophysiology of MASLD

The pathogenesis of MASLD is multifactorial and complex. Central to its development is **insulin resistance**, which promotes increased lipolysis and free fatty acid delivery to the liver. This is compounded by hepatic **de novo lipogenesis**, reduced mitochondrial β-oxidation, and impaired export of triglycerides in very-low-density lipoproteins (6). The resulting **lipotoxicity** and accumulation of toxic lipid intermediates initiate hepatocellular injury, oxidative stress, endoplasmic reticulum stress, and activation of inflammatory pathways (7). The "multiple-hit hypothesis" suggests that MASLD progression involves a series of parallel insults including adipokine dysregulation, gut microbiota changes, and genetic susceptibility (8).

Genetic polymorphisms, such as **PNPLA3 (rs738409)** and **TM6SF2 (rs58542926)**, have been shown to influence disease severity and risk of fibrosis (9). Histologically, MASLD progression to MASH and fibrosis is associated with hepatocellular ballooning and infiltration of inflammatory cells. Without intervention, MASH can lead to cirrhosis and hepatocellular carcinoma, even in non-cirrhotic stages (10). These insights into pathogenesis have informed the development of targeted treatments such as **Resmetirom**, which act on lipid metabolism and inflammation pathways.

Diagnosis of MASLD

The diagnosis of MASLD is based on the presence of hepatic steatosis—detected either by imaging or histology—in the context of at least one cardiometabolic risk factor and in the absence of other chronic liver diseases or significant alcohol intake (11). Commonly used imaging modalities include **ultrasound**, **controlled attenuation parameter (CAP)** via FibroScan, and **MRI-proton density fat fraction (MRI-PDFF)**, the latter being the most accurate non-invasive tool to quantify liver fat (12).

Serum biomarkers and scoring systems, such as the **Fibrosis-4 Index (FIB-4)**, **NAFLD Fibrosis Score (NFS)**, and **AST to Platelet Ratio Index (APRI)**, are used to assess fibrosis severity (13). **Liver biopsy** remains the gold standard for diagnosing MASH and assessing fibrosis stage but is limited by invasiveness, cost, and sampling variability (14). Increasingly, noninvasive tests and elastography are being used for risk stratification in clinical and research settings.

Management of MASLD

To date, **lifestyle intervention** remains the cornerstone of MASLD treatment. Weight loss of 7–10% has been associated with improvements in steatosis, inflammation, and fibrosis (15). A Mediterranean-style diet, regular physical activity, and management of comorbidities such as diabetes and hyperlipidemia are essential.

Pharmacologic treatments, prior to the advent of investigational agents, were limited to off-label use of **pioglitazone** and **vitamin E**. Pioglitazone improved histological features in diabetic MASH but has side effects like weight gain and fluid retention (16). Vitamin E, as an antioxidant, showed benefit in non-diabetic patients but has raised concerns about long-term safety (17).

Several investigational therapies are in development, including **GLP-1 receptor agonists (e.g., semaglutide)**, **FXR agonists (e.g., obeticholic acid)**, **pan-PPAR agonists (e.g., lanifibranor)**, and **THR-β agonists** like **Resmetirom** (18). Among these, Resmetirom has emerged as a leading candidate due to its favorable efficacy and safety profile.

Resmetirom: Mechanism of Action and Development

Resmetirom (MGL-3196) is an oral, liver-directed **selective thyroid hormone receptor-β (THR-β) agonist**. THR-β is highly expressed in hepatic tissue and regulates genes involved in lipid metabolism and mitochondrial function. By selectively stimulating THR-β, Resmetirom enhances hepatic fatty acid oxidation, reduces lipogenesis, and improves lipid homeostasis without the systemic effects seen with non-selective thyroid hormones (19).

In preclinical studies, Resmetirom showed potent activity in reducing liver fat and fibrosis in animal models of NASH. This laid the foundation for a series of successful human clinical trials.

Clinical Trials of Resmetirom

In a **Phase 2 trial**, Resmetirom demonstrated significant reduction in hepatic fat content by **MRI-PDFF** at 12 and 36 weeks. At week 12, 56% of patients achieved ≥30% reduction in liver fat compared to 9% in the placebo group (20). Improvements were also observed in ALT, AST, LDL cholesterol, and triglyceride levels.

The **MAESTRO-NASH Phase 3 trial**, published in 2023, included over 950 patients with biopsy-proven MASH and fibrosis (F1–F3). Resmetirom (80 and 100 mg) met both primary endpoints:

- **Resolution of NASH** without worsening of fibrosis in 25–30% of patients.
- **Improvement of fibrosis by ≥1 stage** in 24% of patients versus 14% with placebo (21).

The **MAESTRO-NAFLD-1 trial**, which focused on non-invasive endpoints, showed significant reductions in liver fat and improvements in lipid profiles, confirming Resmetirom's systemic metabolic benefits (22).

Safety and Tolerability

Resmetirom has shown a **favorable safety profile** in both Phase 2 and 3 trials. The most common adverse events were **mild gastrointestinal symptoms**, such as nausea and diarrhea, which were generally transient. Importantly, Resmetirom did not cause cardiac side effects or thyroid hormone imbalance, underscoring its tissue selectivity (23). No signal of hepatotoxicity was observed during long-term treatment.

Conclusion

MASLD represents a significant public health challenge due to its high prevalence, progressive nature, and lack of approved treatments. The renaming from NAFLD to MASLD reflects a paradigm shift toward recognizing the central role of metabolic dysfunction. While lifestyle modification remains foundational, novel agents such as Resmetirom offer hope for disease modification. As the first-in-class THR-β agonist, Resmetirom has demonstrated efficacy in resolving NASH, reducing liver fat, and improving fibrosis with good safety in advanced clinical trials. Ongoing research and long-term outcome data will further clarify its role in the management of MASLD and MASH.

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Authors Contribution	
Dr Waqas Ahmed	Conception of study design, acquisition, analysis, and interpretation of data.
	Drafting and methodology, data interpretation
	Analysis and interpretation of data for work & Data Collection