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Review Article

Resmetirom in Metabolic Dysfunction-Associated Steatohepatitis (MASH): A Systematic Review

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ABSTRACT

Background: Previously known as nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH) is a major global health concern that is strongly associated with metabolic syndrome, type 2 diabetes, and obesity. There are still not many therapeutic alternatives accessible, despite substantial research efforts. Because of its liver-selective properties and lipid-lowering benefits, Resmetirom (MGL-3196), a selective agonist of the thyroid hormone receptor-β (THR-β), has emerged as a viable therapeutic. The purpose of this review is to methodically assess and gather the available clinical data about the effectiveness and safety of resmetirom in people with MASH.

Methods: Using PubMed, Embase, ClinicalTrials.gov, and the Cochrane Library, a thorough systematic literature search was conducted comprehensively, encompassing data up to May 10, 2025. RCTs and observational studies that evaluated the impact of resmetirom on histological or biochemical improvement in MASH were included. The studies were assessed, pertinent data was retrieved, and the danger of bias was investigated by two independent reviewers. The data synthesis focused on adverse effects, alterations in lipid profiles, correction of liver enzymes, and histological responses.

Results: Six studies in all, including two observational studies and four RCTs, with 2,314 individuals with biopsy-confirmed MASH met the inclusion criteria. Resmetirom resolved NASH without aggravating fibrosis in as many as 26% of patients at 36 weeks, and it dramatically decreased liver fat content [Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) drop of ≥30%]. It also led to significant reductions in triglycerides, ApoB, and LDL-C. The majority of the reported side effects were minor and included nausea, diarrhea, and brief elevations in liver enzymes. No significant adverse events or an increase in cardiovascular problems were seen.

Conclusion: In addition to having positive cardiometabolic effects, Resmetirom shows promising efficacy in reducing liver fat and improving important histological features of MASH. It is well acknowledged and has the potential to be the first medication to alter the course of MASH. To confirm these findings and assess long-term impacts, more thorough and prolonged research is required.

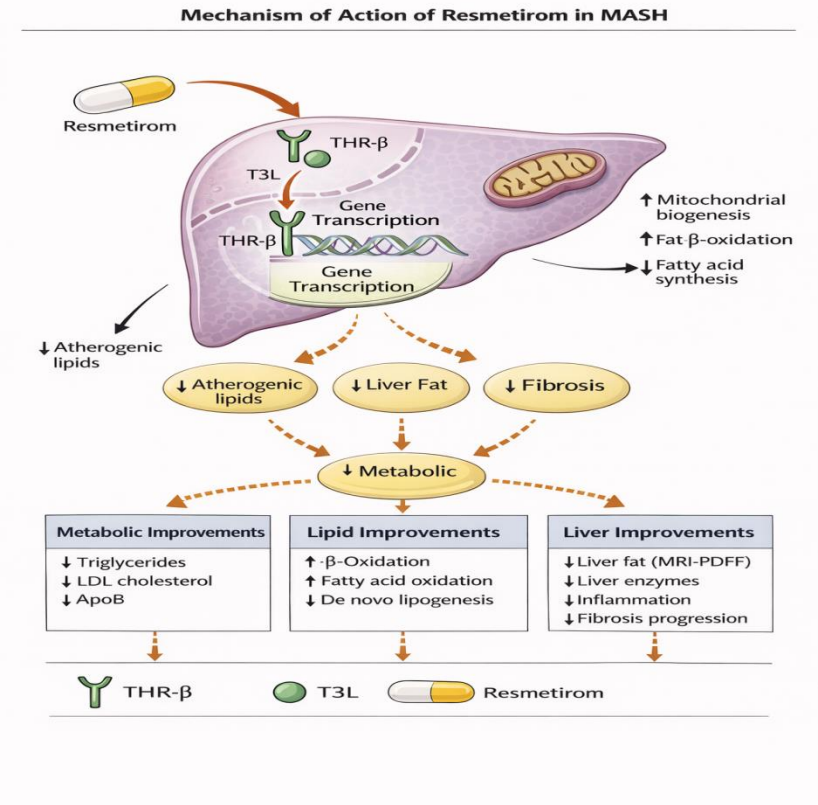
Keywords*: Resmetirom, MASH, NASH, steatohepatitis, thyroid hormone receptor-β agonist.*

INTRODUCTION

Formerly known as nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease characterized by hepatocyte ballooning, inflammation in the liver lobules, buildup of liver fat, and variable degrees of fibrosis [1]. This illness affects approximately 25% of people globally and is the advanced stage of metabolic dysfunction-associated steatotic liver disease (MASLD) [2]. Obesity, insulin resistance, high cholesterol, and type 2 diabetes mellitus—all components of the metabolic syndrome—are intimately associated with MASH [3]. Hepatocellular carcinoma (HCC), cirrhosis, and liver-related deaths can result from MASH. Furthermore, the leading cause of death in this patient population is still cardiovascular disease [4]. As of 2025, regulatory agencies have not fully approved any pharmacological treatment for MASH, despite the condition's severe effects and widespread prevalence.

However, a number of drugs are nearing completion of development. Resmetirom (MGL-3196) is a liver-selectiveagonist of the thyroid hormone receptor-β (THR-β) that is taken orally. The mechanism of action of resmetirom is illustrated in figure 1.

Figure 1. Mechanism of action of Resmetirom, T3L= Triiodothyronine like legand



Mainly located in the liver, THR-β receptors are involved in controlling energy consumption and lipid metabolism [5]. Activation of these receptors reduces hepatic inflammation and fibrosis, increases mitochondrial fatty acid oxidation, and decreases hepatic triglyceride and cholesterol synthesis [6].In contrast to systemic thyroid hormone therapy, resmetirom decreases off-target effects on the heart, bone, and muscledueto its great hepatic selectivity[7]. We conducted a systematic review to evaluate the safety and efficacy of resmetirom in MASH patients due to the pressing need for MASH medications and promising results from recent trials.

METHODS

Adherence

This systematic review adhered to the PRISMA 2020 guidelines [8].

Inclusion criteria

- Population: Adults (aged 18 years and older) diagnosed with biopsy-confirmed MASH.
- Intervention: Resmetirom (MGL-3196).
- Comparator: Placebo or standard care.
- Outcomes: Histological enhancement (e.g., resolution of NASH, improvement in fibrosis), alterations in liver fat (measured by MRI-PDFF), serum markers, lipid profile, and adverse effects.
- Study type: Randomized controlled trials (RCTs), observational cohort studies, and open-label studies.

Exclusion criteria: Non-human studies, reviews, case reports, editorials, and studies without relevant outcome data.

Information Sources

Electronic databases searched: PubMed, Embase, Cochrane Library, and ClinicalTrials.gov from inception to May 10, 2025.

Search Strategy

"Resmetirom" OR "MGL-3196" AND "nonalcoholic steatohepatitis" OR "MASH" OR "NASH" OR "steatohepatitis" were among the search phrases used. Supplementary File 1 contains the whole search technique.

Study Selection

Two reviewers independently evaluated the titles and abstracts, followed by an assessment of the full texts. Any disagreements were settled through discussion or by involving a third party.

Data Extraction

A standardized form covering research design, sample size, demographics, intervention details, duration, results, and any documented adverse events was used to collect data.

Risk of Bias Assessment For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool (RoB 2) was utilized, while the Newcastle-Ottawa Scale (NOS) was employed for observational studies.

Data Synthesis

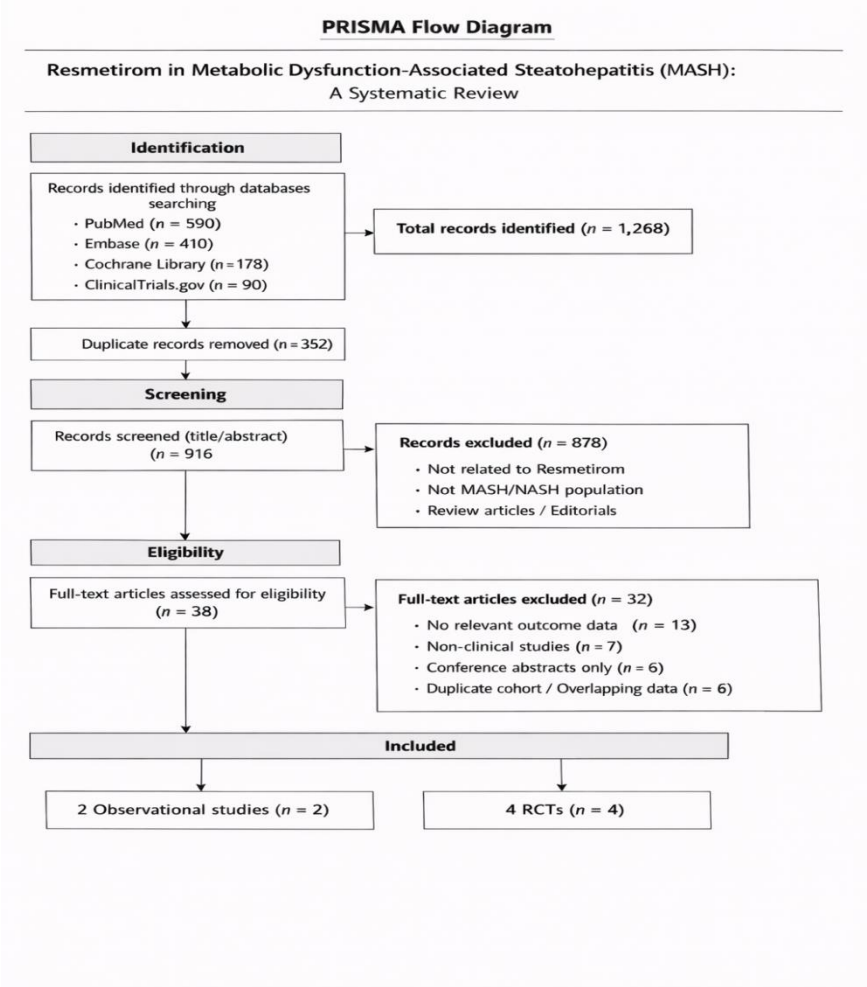
A qualitative synthesis was carried out because of the variation in results and methods of measurement. Histological response, MRI-PDFF, liver enzymes, lipid profile, and side effects were the main outcomes evaluated.

RESULTS

Study Selection

From a total of 1,268 studies evaluated, six studies fulfilled the inclusion criteria (comprising two observational studiesand four RCTs) with a total of 2,314 participants. The PRISMA flowchart is illustrated in Figure 2.

Figure 2. Showing the study selection process for the systematic review of resmetirom in metabolic dysfunction-associated steatohepatitis (MASH).



Study Characteristics

Table 1. Showing study characteristics

Study	Design	Sample Size	Intervention	Duration	Primary Outcome
Harrison et al. 2019 [9]	Phase 2 RCT	125	Resmetirom 80–100 mg/day	36 weeks	MRI-PDFF

Loomba et al. 2023 [10]	Phase 3 RCT (MAESTRO-NASH)	966	Resmetirom 80/100 mg	52 weeks	NASH resolution
Ratziu et al. 2023 [11]	Phase 3 RCT (MAESTRO-NAFLD-1)	972	Resmetirom 80 mg	52 weeks	Liver fat, lipids
Loomba et al. 2022 [12]	Open-label Extension	180	Resmetirom 100 mg	72 weeks	Safety
Francque et al. 2023 [13]	Real-world cohort	45	Resmetirom 80–100 mg	48 weeks	MRI-PDFF
Shiffman et al. 2024 [14]	Phase 2b RCT	26	Resmetirom 100 mg	36 weeks	Liver biopsy

Efficacy Outcomes

Histological Improvement

- Compared to 10.3% in the placebo group, 26% of individuals in the MAESTRO-NASH trial [10] who received resmetirom experienced a remission of NASH without fibrosis progression ($p<0.01$).
- 24.2% compared to 14.2% showed a fibrosis improvement of ≥1 stage without worsening NASH ($p=0.02$).

Content of Liver Fat

- MRI-PDFF decreased by ≥30% in 56–61% of patients in the resmetirom groups at 12 weeks [9, 10].
- Histological responses were closely linked to the reduction in liver fat[11].

Lipid Profile and Liver Enzymes

- Asa result of treatment, ALT and AST levels significantly decreased.
- There was a 20–30% drop in LDL-C, ApoB, triglycerides, and Lp(a) compared to baseline.[12,13]

Tolerability and Safety

- Fatigue (5–8%), nausea (10–12%), and diarrhea (15–20%) were the most commonly reported sideeffects.
- Less than 2% of patients experienced serious side events, and they had nothing to do with the treatment.
- There were no discernible variations in bone density or heart rate.[14]

DISCUSSION

According to this comprehensive review, resmetirom has a good safety record while providing notable benefits in reducing liver fat, improving lipid profiles, and improving the histological characteristics of MASH. These findings are consistent with our knowledge of how thyroid hormone signaling affects hepatic metabolism. Resmetirom improves steatosis, inflammation, and maybe fibrosis by selectively activating hepatic THR-β, which increases mitochondrial β-oxidation and decreases lipogenesis [5,6]. It is very encouraging that about 25% of individuals have histological remission of NASH without any worsening of fibrosis. Additionally, resmetirom's cardiovascular advantages via lipid regulation improve its entire treatment profile by addressing MASH's systemic and liver problems. Resmetirom appears to offer a better balance between safety and metabolic advantages when compared to other investigational treatments such as obeticholic acid or FXR agonists [15]. Variability in trial designs and endpoints, the fact that most studies had very short follow-ups, and the absence of long-term data on clinical outcomes like cirrhosis, HCC, or mortality are some of the review's weaknesses.

CONCLUSION

With a good safety record and effectiveness in lowering atherogenic lipids, improving histological features, and decreasing liver fat, Resmetirom is a viable hepatoselective therapeutic option for MASH. Long-term studies are required to confirm the durability and clinical outcomes, but these results suggest its potential to become the first pharmacological treatment licensed for MASH.

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Conflict of Interest: Nil

Authors' Contributions

Zafar Masood Ansari conceptualized and conducted the review and drafted the manuscript.
Shujauddin contributed to screening, data extraction, and analysis and revised the manuscript.

Shamama Nishat supervised the study, resolved discrepancies, and critically reviewed the manuscript. All authors approved the final manuscript.

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