Resmetirom as a Selective Thyroid Hormone Receptor-Beta Agonist in the Management of NAFLD/NASH and MASLD/MASH: A Narrative Literature Review

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a growing global health burden associated with fibrosis progression, cirrhosis, hepatocellular carcinoma, and increased cardiovascular risk. Despite the increasing prevalence of MASLD/MASH, effective pharmacological treatment options have historically been limited. Resmetirom, a selective thyroid hormone receptor-beta (THR-beta) agonist, has recently emerged as a novel liver-directed therapy targeting key metabolic mechanisms involved in disease progression. This narrative literature review aimed to evaluate the mechanism of action, clinical efficacy, safety profile, and therapeutic potential of resmetirom in the management of MASLD/MASH. A structured literature search was conducted using PubMed, ScienceDirect, and SpringerLink to identify relevant studies published between 2015 and 2025. Eligible publications included randomized controlled trials, extension studies, systematic reviews, meta-analyses, clinical practice guidance documents, and regulatory reports evaluating the efficacy and safety of resmetirom.

Current evidence indicates that resmetirom selectively activates hepatic THR-beta, promoting fatty acid β-oxidation, enhancing mitochondrial function, reducing hepatic triglyceride accumulation, and improving cholesterol metabolism. Phase II and phase III clinical trials, including the pivotal MAESTRO-NASH trial, demonstrated significant reductions in liver fat content, improvements in liver enzymes and atherogenic lipid parameters, and favorable histological outcomes, including MASH resolution and fibrosis improvement. Resmetirom also consistently reduced low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B, suggesting potential cardiometabolic benefits beyond improvements in liver histology. The most commonly reported adverse events were mild-to-moderate gastrointestinal symptoms. In conclusion, resmetirom represents a significant therapeutic advancement in MASLD/MASH and the first liver-directed pharmacological therapy approved for selected patients with non-cirrhotic MASH and moderate-to-advanced fibrosis. Although long-term outcome data remain limited, current evidence supports its role as a promising metabolic-based treatment for improving both hepatic and cardiometabolic outcomes.

Keywords: Resmetirom; THR-beta agonist; MASLD; MASH; NAFLD; NASH; liver fibrosis.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has emerged as one of the most prevalent chronic liver diseases worldwide and represents a major public health challenge [14, 20]. MASLD encompasses a spectrum of liver pathology ranging from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), previously termed non-alcoholic

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steatohepatitis (NASH), which is characterized by hepatocellular injury, inflammation, and progressive fibrosis [1, 2, 15]. Recent international consensus recommendations have adopted the MASLD/MASH nomenclature to better reflect the central role of metabolic dysfunction in disease pathogenesis and progression. The increasing prevalence of obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus has contributed substantially to the growing global burden of MASLD, with recent estimates suggesting that nearly one-third of the adult population worldwide is affected by hepatic steatosis. Furthermore, MASLD has become a leading indication for liver transplantation and is increasingly recognized as a major contributor to liver-related morbidity and mortality [14, 15, 20].

The clinical significance of MASLD extends beyond the liver. Patients with MASLD/MASH frequently exhibit obesity, dyslipidemia, hypertension, insulin resistance, and type 2 diabetes mellitus, reflecting the systemic nature of the disease [2, 17]. Importantly, cardiovascular disease remains the leading cause of death among individuals with MASLD and often exceeds the risk of liver-related mortality in non-cirrhotic populations [17]. Disease progression is largely driven by persistent metabolic dysfunction, lipotoxicity, oxidative stress, chronic inflammation, and fibrogenesis, ultimately leading to cirrhosis, hepatic decompensation, and hepatocellular carcinoma in a subset of patients [1, 2]. Among the histological features of MASLD/MASH, fibrosis stage has consistently been identified as the strongest predictor of long-term clinical outcomes, emphasizing the importance of therapies capable of preventing or reversing fibrosis progression. Despite the substantial disease burden associated with MASLD/MASH, therapeutic options have historically been limited. Lifestyle modification, including dietary intervention, weight reduction, and increased physical activity, remains the cornerstone of management and can improve steatosis and metabolic risk factors [5, 15]. However, long-term adherence is often challenging, and many patients continue to experience disease progression despite intensive lifestyle interventions. Consequently, considerable efforts have been directed toward developing pharmacological therapies that target key mechanisms involved in hepatic lipid accumulation, inflammation, and fibrosis. The recent emergence of liver-directed metabolic therapies represents a significant shift in the treatment paradigm from supportive management toward mechanism-based intervention [5, 15].

Resmetirom (MGL-3196) is an orally administered, liver-directed, selective thyroid hormone receptor-beta (THR-beta) agonist developed to address the metabolic abnormalities underlying MASLD/MASH. THR-beta is highly expressed in hepatocytes and plays a critical role in regulating hepatic lipid metabolism, fatty acid oxidation, cholesterol homeostasis, and energy expenditure [7, 13]. By selectively activating hepatic THR-beta while minimizing stimulation of THR-alpha receptors in cardiac and skeletal tissues, resmetirom aims to reduce hepatic steatosis and improve cardiometabolic risk factors without inducing the systemic adverse effects associated with non-selective thyroid hormone analogues. Recent phase II and phase III clinical trials have demonstrated significant reductions in liver fat content, improvements in atherogenic lipid parameters, and favorable histological outcomes, including MASH resolution and fibrosis improvement in selected patient populations [7, 9, 10]. These findings ultimately led to the regulatory approval of resmetirom as the first liver-directed pharmacological therapy for adults with non-cirrhotic MASH and moderate-to-advanced fibrosis. This narrative literature review aims to critically evaluate the current evidence regarding the mechanism of action, clinical efficacy, safety profile, and therapeutic role of resmetirom in MASLD/MASH [13, 16]. In addition, the review discusses the broader clinical implications of selective THR-beta activation, compares resmetirom with other emerging therapeutic approaches, and highlights key challenges and future directions in the evolving management of metabolic liver disease [3, 13, 19].

MATERIALS AND METHODS

Study Design

This study used a structured narrative literature review design. This approach was selected to provide an integrated synthesis of mechanistic, clinical, and safety evidence regarding resmetirom in NAFLD/NASH and MASLD/MASH. Although the literature search was conducted systematically, this review was not designed as a full PRISMA-based systematic review because no formal risk-of-bias assessment, PRISMA flow diagram, or quantitative meta-analysis was performed.

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Search Strategy

A structured literature search was conducted using PubMed, ScienceDirect, and SpringerLink. The search terms included combinations of the following keywords: "resmetirom," "MGL-3196," "thyroid hormone receptor beta agonist," "THR-beta agonist," "NAFLD," "NASH," "non-alcoholic fatty liver disease," "non-alcoholic steatohepatitis," "MASLD," "MASH," "metabolic dysfunction-associated steatotic liver disease," and "metabolic dysfunction-associated steatohepatitis." The search was limited to articles published between 2015 and 2025 and written in English. The literature search was performed on 15 November 2025. Titles and abstracts were screened for relevance to the mechanism, efficacy, safety, and therapeutic role of resmetirom in NAFLD/NASH or MASLD/MASH. Full-text articles were then reviewed to determine eligibility. Priority was given to peer-reviewed randomized controlled trials, extension studies, systematic reviews, meta-analyses, clinical reviews, and recent regulatory or practice guidance documents relevant to resmetirom therapy.

Inclusion and Exclusion Criteria

Inclusion Criteria: Articles were included if they were published between 2015 and 2025, written in English, and focused on NAFLD/NASH or MASLD/MASH. Clinical studies were eligible if they evaluated resmetirom as a therapeutic intervention and reported at least one efficacy or safety outcome, including changes in MRI-PDFF, liver fat content, liver enzymes, lipid parameters, NASH/MASH resolution, fibrosis improvement, insulin resistance, adverse events, or treatment tolerability. Review articles, systematic reviews, meta-analyses, and practice guidance documents were also included if they provided relevant clinical, mechanistic, or regulatory context for resmetirom therapy.

Exclusion Criteria: Articles were excluded if they were not written in English, were unrelated to resmetirom or metabolic liver disease, did not provide relevant clinical or mechanistic information, or focused primarily on other therapeutic agents without extractable resmetirom-specific data. Research protocols, conference abstracts, letters, editorials, and press releases without sufficient clinical data were not used as primary evidence. Duplicate publications and articles with insufficient methodological or bibliographic information were also excluded.

Data Extraction and Synthesis

Data extracted from eligible publications included study design, study population, sample size, fibrosis stage, resmetirom dose, duration of treatment, comparator group, primary and secondary outcomes, biochemical parameters, imaging outcomes, histological findings, lipid profile changes, adverse events, and major study limitations. Evidence was synthesized narratively by comparing findings across study designs, trial populations, dosing regimens, outcome measures, and follow-up duration. No statistical pooling or meta-analysis was performed due to heterogeneity in study design, patient characteristics, endpoints, and outcome reporting.

RESULTS AND DISCUSSION

Pathophysiology of MASLD/MASH

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a complex multisystem disorder characterized by excessive hepatic lipid accumulation in the setting of cardiometabolic dysfunction. The current “multiple-hit” hypothesis proposes that insulin resistance, adipose tissue dysfunction, altered gut microbiota, oxidative stress, chronic inflammation, and genetic susceptibility interact simultaneously to promote disease development and progression. Insulin resistance plays a central role by increasing adipose tissue lipolysis and hepatic free fatty acid influx, leading to triglyceride accumulation, lipotoxicity, and hepatocellular injury [1, 2]. These metabolic disturbances are further exacerbated by mitochondrial dysfunction and oxidative stress, which activate inflammatory signaling pathways and contribute to progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) [1, 2]. Persistent hepatocellular injury and inflammation stimulate activation of hepatic stellate cells, resulting in extracellular matrix deposition and progressive fibrosis [6]. Fibrosis stage is recognized as the strongest predictor of liver-related morbidity and mortality in MASLD/MASH

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and is closely associated with the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma. In addition, MASLD is strongly linked to obesity, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease, highlighting its systemic nature beyond the liver [17]. This multifactorial pathophysiology underscores the need for therapies that target underlying metabolic dysfunction and fibrosis progression, providing the biological rationale for selective thyroid hormone receptor-beta agonists such as resmetirom [5, 6, 13].

Mechanism of Action of Resmetirom

Resmetirom is an orally administered, liver-directed, selective thyroid hormone receptor-beta (THR-beta) agonist designed to address key metabolic abnormalities underlying MASLD/MASH [7, 13]. THR-beta is the predominant thyroid hormone receptor isoform expressed in hepatocytes and plays a critical role in regulating lipid metabolism, mitochondrial function, and cholesterol homeostasis. Selective activation of hepatic THR-beta enhances fatty acid β-oxidation, promotes mitochondrial biogenesis, increases energy expenditure, and reduces intrahepatic triglyceride accumulation, thereby directly targeting hepatic steatosis, a central feature of MASLD/MASH. In addition to reducing hepatic fat content, THR-beta activation modulates cholesterol metabolism through upregulation of hepatic low-density lipoprotein receptor expression and increased clearance of circulating atherogenic lipoproteins [9, 10, 13]. These effects contribute to reductions in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), triglycerides, and other cardiometabolic risk markers observed in clinical studies of resmetirom. Unlike non-selective thyroid hormone analogues, resmetirom exhibits preferential hepatic activity and minimal activation of THR-alpha, thereby reducing the risk of adverse cardiac and skeletal effects traditionally associated with systemic thyroid hormone stimulation. The therapeutic rationale for resmetirom extends beyond hepatic steatosis [13, 17]. MASLD/MASH is increasingly recognized as a systemic metabolic disorder characterized by insulin resistance, dyslipidemia, chronic inflammation, and elevated cardiovascular risk [17]. Consequently, therapies capable of simultaneously improving liver histology and cardiometabolic parameters may provide broader clinical benefits. By targeting a fundamental pathway involved in hepatic lipid handling and cholesterol metabolism, resmetirom represents a mechanistically distinct therapeutic approach that addresses both hepatic and systemic manifestations of metabolic liver disease [13, 17].

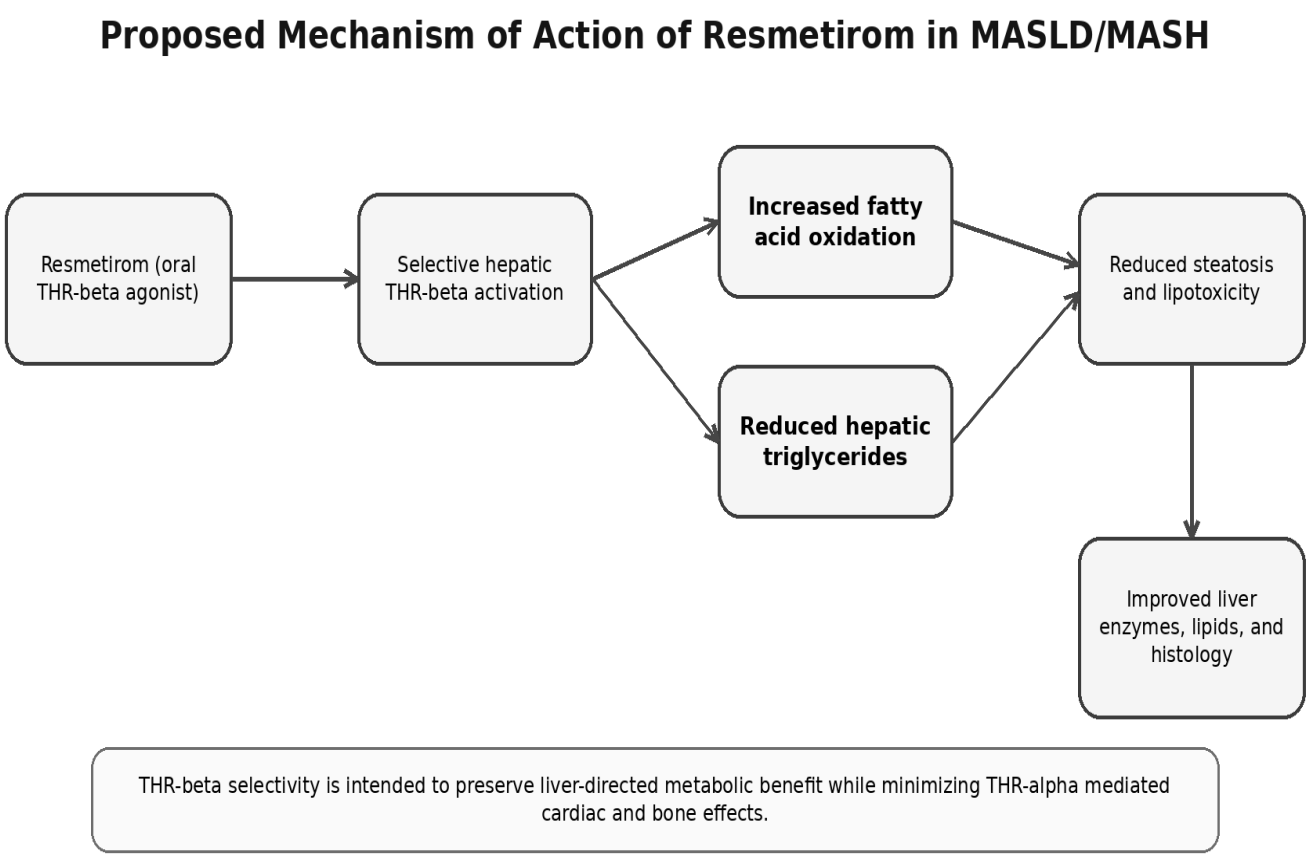

Figure 1. Proposed mechanism of action of resmetirom in MASLD/MASH.

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Clinical Efficacy in NAFLD/NASH and MASLD/MASH

The clinical efficacy of resmetirom has been evaluated in multiple phase II and phase III trials using imaging, biochemical, and histological endpoints [7, 9, 10]. In the phase II randomized controlled trial conducted by Harrison et al. (2019), resmetirom produced significant reductions in hepatic fat content measured by MRI-PDFF, accompanied by improvements in liver enzymes and atherogenic lipid parameters. These findings provided proof-of-concept that selective THR-beta activation could effectively reduce hepatic steatosis while simultaneously improving metabolic risk factors [7]. The pivotal phase III MAESTRO-NASH trial subsequently established the histological efficacy of resmetirom in patients with biopsy-confirmed MASH and fibrosis. At week 52, NASH resolution without worsening of fibrosis occurred significantly more frequently in patients receiving resmetirom than in those receiving placebo. Similarly, fibrosis improvement of at least one stage without worsening of disease activity was achieved in a greater proportion of treated patients. These outcomes are clinically meaningful because fibrosis stage remains the strongest predictor of liver-related morbidity and mortality in MASLD/MASH [6, 10]. Collectively, the available evidence suggests that resmetirom not only reduces hepatic fat accumulation but also favorably influences the histological progression of disease.

Effects on Lipid Profile and Cardiometabolic Risk

Beyond its liver-directed effects, resmetirom has shown favorable effects on atherogenic lipid parameters. Clinical trial data indicate reductions in LDL cholesterol, triglycerides, apolipoprotein B, and other lipid-related markers [9, 10, 13]. This is particularly important because cardiovascular disease is a major cause of morbidity and mortality among patients with NAFLD/NASH and MASLD/MASH. Therefore, the lipid-lowering effect of resmetirom may provide additional clinical value beyond improvement in liver histology. Cardiovascular disease remains the leading cause of death among patients with MASLD/MASH and often exceeds the risk of liver-related mortality in non-cirrhotic populations [17]. The close association between hepatic steatosis, insulin resistance, systemic inflammation, and atherogenic dyslipidemia has led to recognition of MASLD as a multisystem metabolic disorder rather than an isolated liver disease [2, 17]. Therefore, therapies capable of improving both hepatic pathology and cardiovascular risk factors may provide broader clinical benefits. The lipid-lowering effects observed with resmetirom, including reductions in LDL cholesterol, apolipoprotein B, and triglycerides, may be particularly relevant in this context, although dedicated cardiovascular outcome studies are still required [9, 10, 13]. However, the extent to which these lipid changes translate into reduced cardiovascular events remains uncertain. Most available trials were designed primarily to assess liver-related endpoints rather than long-term cardiovascular outcomes [7, 9, 10]. Future studies should therefore evaluate whether improvements in lipid parameters are associated with measurable reductions in cardiovascular morbidity and mortality [13, 16].

Safety and Tolerability

Overall, resmetirom has demonstrated an acceptable safety and tolerability profile in clinical trials. The most commonly reported adverse events are gastrointestinal, particularly diarrhea and nausea [8, 9, 10]. In the MAESTRO-NASH and MAESTRO-NAFLD-1 programs, serious adverse events were generally similar across treatment and placebo groups, although gastrointestinal symptoms were more frequent among patients receiving resmetirom [9, 10]. Current prescribing and regulatory information also emphasizes the need to monitor for potential hepatotoxicity and gallbladder-related adverse reactions. The safety profile of resmetirom is encouraging, but long-term safety data remain necessary [13, 16]. Because NASH/MASH is a chronic disease, many patients may require prolonged therapy. Future studies should evaluate sustained treatment response, drug adherence, safety in patients with multiple comorbidities, interactions with lipid-lowering or antidiabetic medications, and outcomes in broader real-world populations.

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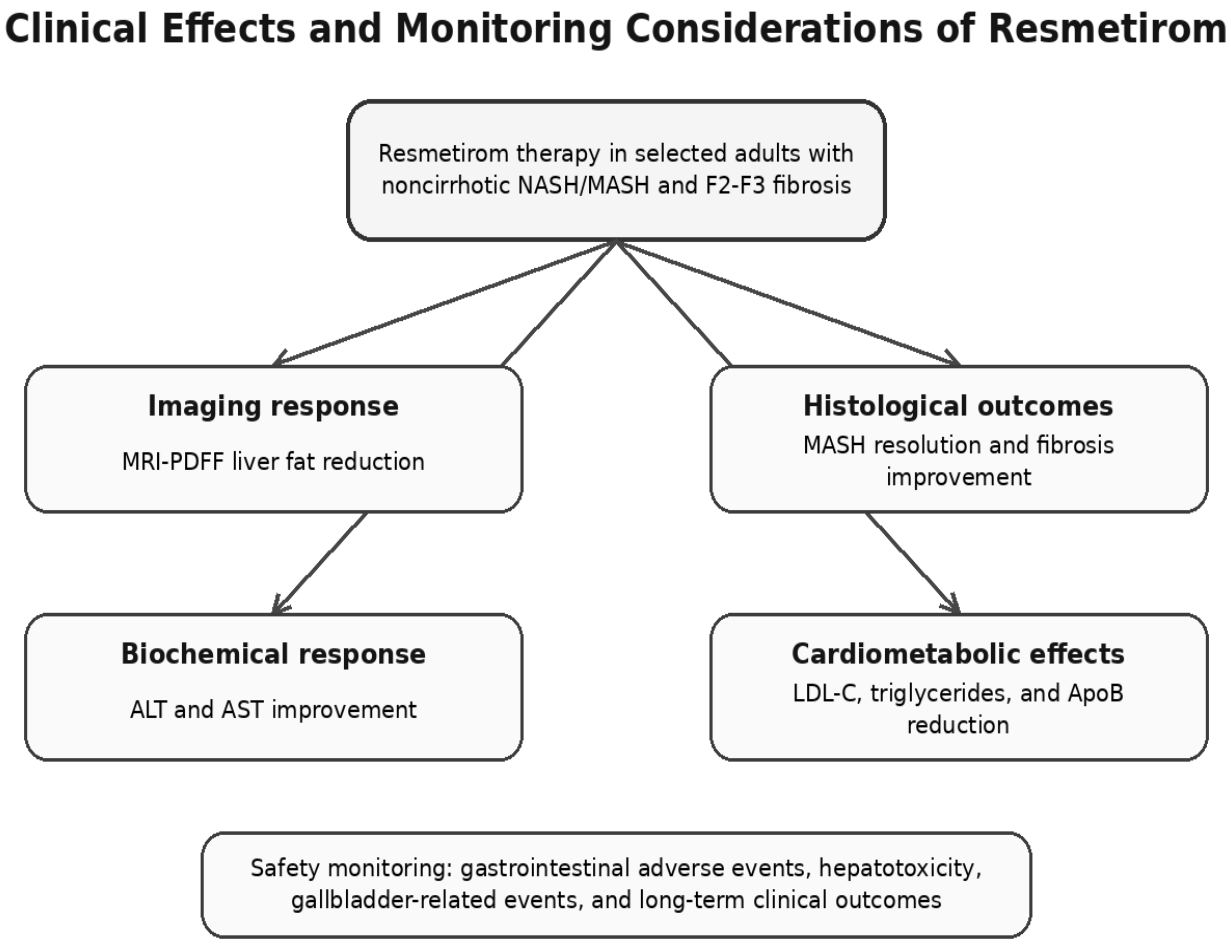

Figure 2. Clinical effects and monitoring considerations of resmetirom therapy.

Comparison With Other Emerging Therapies

The therapeutic landscape of NASH/MASH is rapidly evolving. Other emerging treatments include glucagon-like peptide-1 receptor agonists, dual incretin agonists, fibroblast growth factor analogues, peroxisome proliferator-activated receptor agonists, and combination therapies [11, 12, 19]. GLP-1 receptor agonists may be particularly useful in patients with obesity and type 2 diabetes because they promote weight loss and improve glycemic control. In contrast, resmetirom directly targets hepatic lipid metabolism through THR-beta activation. This difference in mechanism suggests that resmetirom may be especially useful for patients with noncirrhotic NASH/MASH and moderate to advanced fibrosis, while incretin-based therapies may be more beneficial for patients in whom obesity and glycemic dysregulation are dominant drivers. In the future, combination approaches may become important because NASH/MASH is a multifactorial disease involving steatosis, inflammation, insulin resistance, lipotoxicity, fibrosis, and cardiometabolic dysfunction. Nevertheless, the safety, sequencing, and additive efficacy of combination therapy require further investigation. Incretin-based therapies have emerged as another promising treatment class for MASH. Semaglutide has demonstrated significant rates of NASH resolution and substantial weight reduction, while newer dual agonists such as tirzepatide have shown encouraging reductions in liver fat content and metabolic risk factors. Because resmetirom primarily targets hepatic lipid metabolism through THR-beta activation whereas incretin-based therapies exert broader effects on appetite regulation, body weight, and glucose metabolism, future combination strategies may provide synergistic benefits across multiple pathogenic pathways involved in MASH progression.

Limitations of Current Evidence

Although current evidence supports the therapeutic potential of resmetirom, several limitations should be acknowledged [13, 16]. First, clinical trials differ in patient characteristics, fibrosis stage, treatment duration, dose

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selection, and endpoints. Second, many outcomes are based on surrogate markers, imaging findings, or histological endpoints rather than long-term clinical outcomes such as hepatic decompensation, transplantation, liver-related mortality, and cardiovascular events. Third, most studies have focused on selected trial populations, which may not fully represent patients with advanced comorbidities, cirrhosis, or diverse ethnic and geographic backgrounds. Fourth, long-term post-marketing safety data remain limited. Therefore, while resmetirom represents a major therapeutic advance, its long-term role in clinical practice should continue to be evaluated through ongoing outcome trials, real-world evidence, and updated clinical practice guidelines [3].

Clinical Implications and Future Perspectives

The regulatory approval of resmetirom represents a landmark development in hepatology, marking the transition from lifestyle-based management alone toward targeted pharmacological therapy for MASLD/MASH [3, 4, 18]. Nevertheless, several important questions remain unresolved. Current approval is primarily supported by surrogate endpoints, including reductions in liver fat content, histological improvement, and fibrosis regression, rather than definitive clinical outcomes such as hepatic decompensation, hepatocellular carcinoma, liver transplantation, or mortality [4, 18]. Consequently, long-term follow-up studies are required to determine whether improvements observed in clinical trials translate into sustained reductions in liver-related and cardiovascular events [13, 16]. The rapidly evolving therapeutic landscape of MASLD/MASH also raises questions regarding optimal treatment sequencing and combination therapy. Emerging agents such as semaglutide, tirzepatide, fibroblast growth factor analogues, and antifibrotic compounds target complementary pathogenic pathways and may provide additive benefits when used alongside resmetirom [11, 12, 13, 19]. Future research should focus on identifying predictors of treatment response, evaluating combination strategies, and generating real-world evidence across diverse patient populations [13, 16]. These investigations will be critical for defining the long-term role of resmetirom within precision medicine approaches to MASLD/MASH management [3, 13].

Table 1 Summary and Critical Interpretation of Key Evidence on Resmetirom in NAFLD/NASH and MASLD/MASH

Study	Design	Sample Size (N)	Duration	Population	Primary Endpoint	Key Findings	Major Limitation
Harrison et al., 2019	Phase II RCT	125	36 weeks	Biopsy-confirmed NASH	MRI-PDFF change	Reduced liver fat and improved lipids	Small sample
Harrison et al., 2021	Open-label extension	78	36 weeks	Phase II completers	Long-term efficacy	Sustained benefit	No placebo
Harrison et al., 2023	Phase III	969	52 weeks	NAFLD/NASH	Safety/efficacy	Improved LDL-C, ApoB, liver fat	Histology not primary
Harrison et al., 2024	Phase III MAESTRO-NASH	966	52 weeks	MASH with fibrosis	MASH resolution/fibrosis	Histological benefit	Long-term outcomes unknown
Suvarna et al., 2024	Meta-analysis	Multiple	Variable	MASLD/MASH	Efficacy/safety	Overall benefit	Few trials
Patel et al., 2024	Narrative review	N/A	N/A	MASH	Evidence synthesis	Summarized evidence	Secondary source
Chen et al., 2025	Guidance update	N/A	N/A	MASLD/MASH	Implementation	Monitoring recommendations	Not primary data
Udaikumar et al., 2025	Comparative review	Variable	Variable	MASLD/MASH	Comparative efficacy	Complementary role	No direct RCT

The table summarizes the principal clinical studies evaluating resmetirom in MASLD/MASH. Early phase II investigations established proof-of-concept by demonstrating substantial reductions in hepatic fat content and improvements in metabolic parameters. Subsequent phase III trials, particularly the pivotal MAESTRO-NASH

study, provided robust evidence of histological benefit, including MASH resolution and fibrosis improvement. Collectively, these studies support resmetirom as an effective liver-directed therapy for selected patients with noncirrhotic MASH and moderate-to-advanced fibrosis. Nevertheless, long-term outcome data regarding hepatic decompensation, cardiovascular events, transplantation, and mortality remain limited, highlighting the need for continued post-marketing surveillance and real-world effectiveness studies.

CONCLUSION

Resmetirom, a selective thyroid hormone receptor-beta agonist, represents a significant advancement in the treatment of MASLD/MASH. By targeting hepatic lipid metabolism through selective THR-beta activation, resmetirom effectively reduces liver fat accumulation, improves atherogenic lipid profiles, and promotes histological improvement in selected patients with noncirrhotic disease and moderate-to-advanced fibrosis. Evidence from phase II and phase III clinical trials has demonstrated clinically meaningful benefits in steatosis reduction, MASH resolution, and fibrosis improvement, ultimately leading to regulatory approval as the first liver-directed pharmacological therapy for MASH.

Beyond its hepatic effects, resmetirom may offer broader cardiometabolic benefits because of its favorable effects on LDL cholesterol, triglycerides, and apolipoprotein B. However, important questions remain regarding long-term durability, real-world effectiveness, cardiovascular outcomes, and optimal use in combination with emerging therapies such as GLP-1 receptor agonists and dual incretin agonists. Overall, resmetirom should be viewed as a landmark therapeutic development that signals the transition from lifestyle-based management alone toward targeted metabolic treatment of MASLD/MASH. Ongoing long-term studies and post-marketing evidence will further define its role within the evolving therapeutic landscape of metabolic liver disease.

Conflicts of Interest

The authors declare no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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Data Availability Statement

The data supporting this review are available from the cited references.

Ethical Approval

Not applicable, as this study is a literature review and did not involve human participants or animal subjects.

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