

Systematic Review

Beyond weight loss: the long-term effects of glucagon-like peptide-1 receptor agonists in metabolic dysfunction-associated steatohepatitis and fibrosis regression

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ABSTRACT

Metabolic dysfunction-associated steatohepatitis (MASH), a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by hepatic steatosis, inflammation, and fibrosis. Although lifestyle modification is foundational, effective pharmacotherapy is needed, particularly for advanced fibrosis. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) show promise beyond weight loss, but their long-term effects on fibrosis and underlying mechanisms remain unclear. This systematic review evaluates their effects on MASH and fibrosis, mechanisms of action, clinical evidence, and knowledge gaps. A systematic search of PubMed, Embase, Medline, and Cochrane Library identified randomized controlled trials and observational studies evaluating GLP-1 RAs in MASLD, reporting histological or non-invasive markers of fibrosis and steatosis. Comparisons with pioglitazone and vitamin E, alongside cardiovascular and metabolic outcomes, were assessed. GLP-1 RAs improved hepatic steatosis and inflammation, although fibrosis regression varied across trials, some demonstrated MASH resolution without worsening fibrosis, while others reported modest effects. Additional benefits included improvements in weight, glycemic control, lipid profiles, and cardiovascular risk factors. The contribution of direct hepatic versus weight-mediated effects remains unclear, and long-term safety in cirrhosis, including sarcopenia and worsening portal hypertension, requires further investigation. GLP-1 RAs offer promising hepatic and extrahepatic benefits in MASLD, but their effects on fibrosis require confirmation through larger, longer-term trials with robust histological endpoints. Combination therapy, long-term safety, and individualized treatment remain priorities for defining their role as first-line therapy.

Keywords: GLP-1 receptor agonists, Metabolic dysfunction-associated steatohepatitis, Liver fibrosis, Metabolic dysfunction-associated steatotic liver disease, Fibrosis regression

INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is a disease in which fat builds up around the liver (hepatic steatosis) causing inflammation with possibility of future progression to cirrhosis, liver failure, and malignancy. MASH, a type of fatty liver disease formerly categorized as nonalcoholic steatohepatitis (NASH), is primarily known to be associated with underlying metabolic issues (i. e., insulin resistance (IR), obesity, type 2 diabetes mellitus (T2DM), elevated blood pressure, hyperlipidemia).¹ With the concurrent rise of diabetes and obesity worldwide, MASH prevalence has subsequently increased, numbers reaching nearly 3-6% globally.² Amidst a very similar context, MASLD, previously known as nonalcoholic fatty liver disease (NAFLD), encompasses a range of liver disorders within a spectrum, starting from macrovesicular steatosis, which may occur with or without mild lobular inflammation, and progressing to NASH, characterized by hepatocellular injury (ballooning) or perisinusoidal fibrosis.³ The progression of MASH is rather gradual and initially involves simple steatosis, fat accumulation and later culminates into its clinically progressive form with significant hepatocyte scarring, and even hepatocellular carcinoma.⁴ Essentially, while both MASH and MASLD may be linked to obesity, diabetes mellitus, and metabolic syndrome (MetS), MASH is a subset of MASLD that worsens over time.

IR, one of the main hallmarks of MetS and common underlying cause of MASLD, creates an atherogenic, inflammatory and prothrombotic state.⁵ Hence, without adequate insulin signaling, fat cells (adipocytes) become resistant to insulin's anti-lipolytic effect causing an increased breakdown of triglycerides and release of free fatty acids (FFAs) into the bloodstream.⁶

These circulating FFAs in excess are taken up by the liver posing remarkable cytotoxic impacts via induction of lipid peroxidation and increasing hepatocyte apoptosis.⁷ Although the pathophysiology of MASH is rather extensive, in almost all cases, the primary involvement encompasses disruption of hepatocyte cell structure. In response to this chronic liver injury is hepatic fibrosis with the excessive buildup of extracellular matrix (ECM) components, including proteins and collagen.¹

Eventually, the ongoing damage alongside release of numerous immune mediators, alters liver cell composition and structure-especially with increased fibrillar collagen. According to an analysis by Younossi et al nearly 38% of all adults currently have MASLD, the most common liver disease worldwide, with prevalence rates suspected to double by 2040.⁸ This could imply that without efficient global initiatives focusing on related disease risk factors and early preventive measures, the disease may hit a morbid rise. Thus, prompt evaluation on the current clinical burden of MASH/MASLD and its related treatment limitations may be crucial for future health success.

Clinical burden and current treatment limitations

In the past several decades, both obesity and diabetes have been at a rise in the United States, with the former often becoming a culprit for the latter. While each disease presents with its own underlying risk factors, etiologies and pathophysiologies, there is much overlap.⁹ In parallel with the increasing epidemic amongst this cohort of patients has also been a rising prevalence of MASLD/MASH. In a systematic meta-analysis review performed by Gancheva et al the coexistence of T2DM and obesity significantly heightens the risk of developing MASH and liver fibrosis, with studies showing an odds ratio of 9.7 in individuals with a BMI over 50 kg/m² and metabolic conditions like T2D.¹⁰ This study alongside many others contributes to the importance of uncovering the interface between diabetes and obesity related MASH progression and the need for early preventative measures. Lifestyle modifications, including diet, exercise and weight loss currently play a crucial role in not only managing both diabetes and obesity, but also reducing liver lipid content and MASLD progression.¹¹ However, the effectiveness of this strategy to combat metabolic dysfunction associated liver disease is consistently limited due to the challenges of patient adherence and long term efficacy.

While lifestyle interventions are often the cornerstone of therapeutic management, they are difficult to keep up for long periods of time and these initiatives independently do not always imply the same benefits for all patients.¹² Therefore navigating alternative pharmaceutical treatment regimens has been a long term course of focus for MASH/MASLD. Several clinical research initiatives have begun to expand the therapeutic horizons of MASH with a mainstream focus on pioglitazone (peroxisome proliferator-activated receptor (PPAR)- γ agonist), vitamin E, and obeticholic acid.¹³ Though characterized as off label therapy for MASH/MASLD, combinations of these drug therapies have been shown to reflect a greater impact on hepatic inflammation and ballooning, with unfortunately no effect on attenuating fibrosis.¹⁴ In a meta-analysis explored by Tincopa et al pioglitazone is associated with weight gain, risk of worsening heart failure and osteoporosis in post-menopausal women.¹⁵ Similarly, while obeticholic acid may potentially resolve MASH, it does not guarantee fibrosis regression, and is contraindicated for patients with complete biliary obstruction and cirrhosis.¹⁶ Thus, not only is the overall efficacy of these drugs limited, but their related contraindications and side effects may also hinder the use in clinical settings. There is a critical need for novel therapies that specifically target the metabolic and inflammatory pathways underlying MASLD and MASH.

Emerging role of GLP-1 RAs

Advancing pharmacological interventions could significantly improve outcomes by addressing the root mechanisms driving disease progression. GLP-1 RAs have been a major pipeline recently, used to treat T2DM, and in many cases approved for weight management. GLP-1 RAs

are a class of medications that work by mimicking the effects of GLP-1, a natural hormone found in our body, augmenting insulin while simultaneously inhibiting glucagon secretion.¹⁷ Essentially, despite maximizing nutrient absorption, food appetite is reduced thereby limiting weight gain. Within the pancreas, GLP-1 regulates the stimulation of insulin secretion by binding to the GLP-1 receptors expressed on islet β -cells, consequently lowering blood sugar levels. In the liver, the receptors modulate elements of signaling pathways including lipolysis, fatty acid oxidation and lipid absorption, which can help in reducing the progression of hepatic diseases.¹⁸ As discussed in the meta-analysis review by Abdelmalek et al beyond their glycemic control, GLP-1 RAs have shown to be beneficial for cardiovascular outcomes, reducing oxidative stress, improving hepatic de novo lipogenesis and the histopathology of MASH. Though significant research has confirmed the positive impact of GLP-1 RAs on improving hepatic steatosis and liver inflammation, more investigation is needed on fibrosis regression.¹⁹ As GLP-1RAs continue to emerge as a pipeline of treatment for various diseases, with further investigation, they may demonstrate promising therapeutic options for MASH/MASLD.

Objectives

Primary objective

Primary objective was to systematically analyze the long-term effects of GLP-1 RAs on MASH and fibrosis reversal in the liver. This includes assessing both clinical and histological improvements in the disease.

Secondary objectives

Understanding mechanism of action

To summarize the physiological and biochemical mechanisms through which GLP-1 RAs produce therapeutic effects in MASLD.

Clinical efficacy and safety

To compare clinical trial data for hepatic versus extrahepatic action of GLP-1 RAs and effects on liver enzymes, insulin sensitivity, body weight, and cardiovascular risk factors.

Comparative effectiveness

To compare relative efficacy and safety profile of GLP-1 RAs with standard treatments (e.g., pioglitazone and vitamin E) for MASLD, with specific emphasis on histologic response and long-term clinical effect.²⁰

Knowledge gaps and future research

To identify areas of current uncertainty and areas of research need and to emphasize high-priority areas of

investigation, including combination regimens, and real-world use of GLP-1 RA therapy.

METHODS

Literature review strategy

Major electronic databases, including PubMed and Google Scholar, were systematically searched for relevant studies published from 2001-2025. The search strategy included keywords such as “GLP-1 receptor agonists,” “MASH,” “fibrosis,” “MAFLD,” “NAFLD,” “liraglutide,” “semaglutide,” and “exenatide” or a combination of the keywords.

Study selection criteria

Studies deemed potentially eligible then underwent full-text review based on predefined inclusion and exclusion criteria. Inclusion criteria included randomized controlled trials, literature reviews, meta-analyses, case reports, and observational studies that evaluated GLP-1RAs in adult patients diagnosed with MAFLD or MASH. Studies were excluded if they were editorials or lacked specific data on the role of GLP-1 RAs in managing MASH.

Data extraction process

A comprehensive literature review evaluated the role of GLP-1 RAs in managing MASH, previously referred to as NASH, and associated hepatic fibrosis. 210 total published articles were considered for the purpose of this review, and ultimately 48 were included (see Appendix, Table 1). Following the initial search, titles and abstracts were screened for relevance, as seen in the PRISMA flow diagram. Multiple reviewers conducted the screening process independently. Primary outcomes of interest were histological improvements in MASH, resolution of steatohepatitis, and regression in the fibrosis stage. Secondary outcomes included changes in metabolic parameters such as liver enzyme levels, glycemic control, lipid profiles, body weight, and cardiovascular risk markers. Where available, effect sizes and confidence intervals were recorded to facilitate comparative analysis.

Comparative analysis approach

In addition to evaluating the efficacy of GLP-1RAs, the review included a comparative analysis against other therapeutic agents commonly used in MASH, such as pioglitazone and vitamin E. Particular attention was given to the impact of each intervention on liver fibrosis, metabolic comorbidities, and cardiovascular outcomes.

Subgroup analyses were also considered to identify response patterns across patient populations and GLP-1 receptor agonist formulations. Discrepancies among study results and areas where evidence remains limited were highlighted to emphasize ongoing knowledge gaps and inform directions for future research.

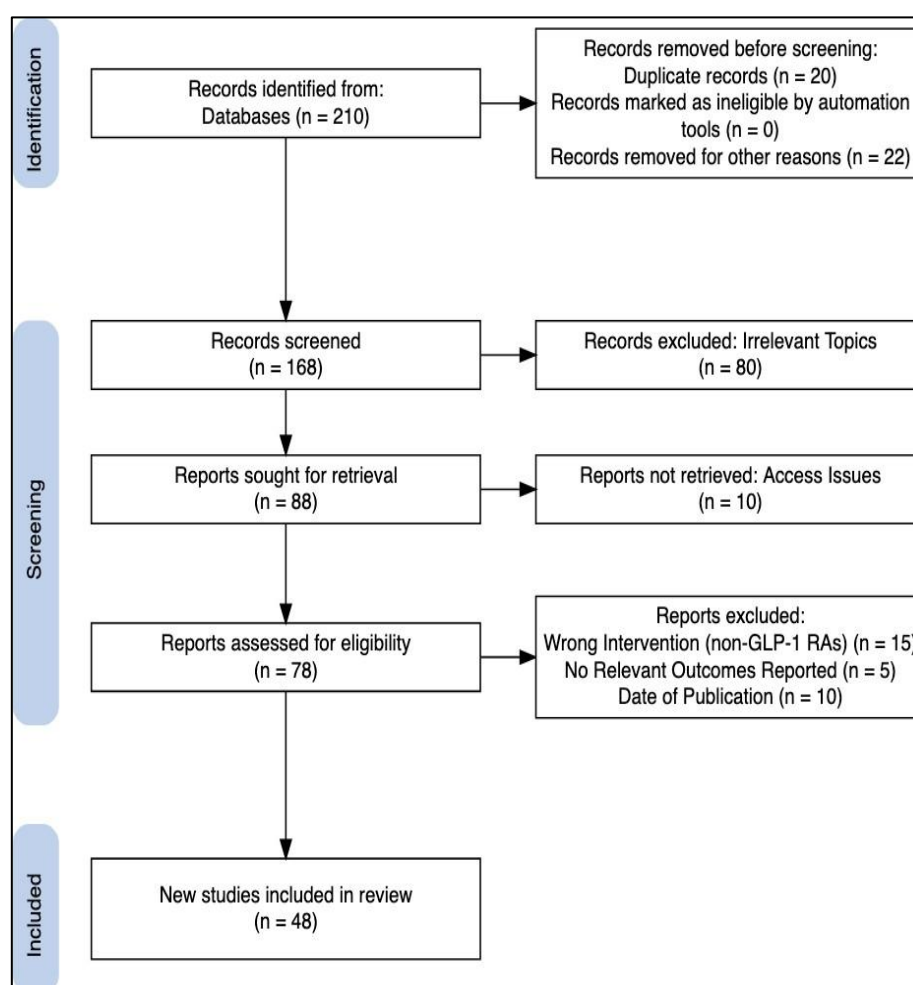


Figure 1: PRISMA flow diagram.

Impact of GLP-1 RAS on MASH

NAFLD is the most common liver disease globally, especially among individuals with T2DM. Despite its prevalence, there are currently no approved medications specifically for NAFLD treatment. However, the emergence of GLP-1 RAs, initially developed for T2D, has brought hope. These agents have shown promising benefits beyond blood sugar control, including weight loss and improved liver fat, inflammation, and fibrosis. The potential of GLP-1 RAs in managing NAFLD and diabetes is a promising development.²¹ Additionally, Nevola et al conducted a multicenter, double-blind, placebo-controlled phase 2 trial and found that treatment with liraglutide improved steatosis and hepatocyte ballooning more than placebo.²¹ Thus, GLP-1 Ras show potential as a treatment option for NAFLD, which allows for the simultaneous management of metabolic dysfunction and liver disease progression in patients with or without T2DM. Similarly, a systematic review and meta-analysis conducted by Liao et al. showed that GLP-1 RAs significantly reduce hepatic fat content, as measured by imaging modalities.²² This study examined how GLP-1 RAs affect adults' visceral and liver fat.

Researchers reviewed multiple clinical trials from major medical databases until November 2022, focusing on adults with and without T2D or NAFLD. The analysis included 30 studies with over 1,700 participants. GLP-1 RAs significantly reduced visceral fat and fat stored in the liver. These benefits were seen across various groups, including those with T2D, NAFLD, or neither condition. However, the effect on liver fat was insignificant in individuals without T2D.²² Thus, GLP-1 RAs effectively lower harmful fat levels in the body, especially in people with metabolic disorders like T2D and NAFLD, and can potentially be used as a clinical treatment. Recent studies on NAFLD now refer to it by metabolic associated fatty liver disease (MAFLD). GLP-1 RAs may modulate the gut microbiota and bile acid metabolism, which are implicated in the progression of MAFLD. Alterations in the gut-liver axis through these mechanisms can alleviate hepatic dysfunction. MAFLD is a common and progressive liver condition linked to MetS, with risks of fibrosis, cirrhosis, and liver cancer. Disruption of the gut-liver axis, particularly increased gut permeability and altered metabolite absorption, plays a key role in its development. GLP-1 RAs, initially used for T2D and obesity, have shown promise in reversing liver fat buildup through improved glucose control, reduced fat synthesis, enhanced

fat burning, and autophagy. These drugs may also positively influence gut microbiota, further supporting their potential in MAFLD treatment.²³ Thus, by targeting metabolic and microbial pathways, GLP-1 RAs offer a multifaceted therapeutic strategy for improving liver health in MAFLD.

Mechanisms of action

Fasting dyslipidemia in insulin-resistant states is driven by increased hepatic VLDL production. Taher et al found that peripheral and central administration of the GLP-1 RA exendin-4 in a fructose-fed hamster model reduced VLDL triglycerides and apoB100 levels by enhancing fat utilization, lowering glucose and insulin, and decreasing hepatic lipogenesis and inflammation.²⁴ Despite no direct liver GLP-1R activity, effects were mediated through neural pathways. By promoting β -oxidation and reducing lipogenesis, GLP-1 RAs limit lipid availability for VLDL assembly, leading to apoB100 degradation. Thus, GLP-1 RAs may offer a promising therapeutic strategy for addressing dyslipidemia in insulin-resistant states by targeting central regulatory pathways and indirectly modulating hepatic lipid metabolism. Additionally, GLP-1 RAs are emerging as potent therapeutic agents due to their notable anti-inflammatory effects and potential across various diseases. A review by Alharbi highlighted how GLP-1 RAs modulate immune responses by influencing immune cell signaling and inhibiting the NF- κ B pathway, thereby reducing inflammation, cytokine production, and oxidative stress.²⁵ Overall, GLP-1 RAs show strong potential as anti-inflammatory treatments, with ongoing research focused on refining their clinical use and expanding their application to a broader range of inflammatory conditions.

GLP-1 RAs suppress pro-inflammatory cytokines, including TNF- α and IL-6, mitigating inflammation and restoring immune balance.²⁵ Thus, by modulating key inflammatory pathways and dampening cytokine activity, GLP-1 RAs may serve as versatile agents in the management of both metabolic and immune-mediated diseases. T2D significantly increases the risk of atherosclerosis and cardiovascular diseases due to metabolic, inflammatory, and mitochondrial dysfunctions. However, GLP-1 RA treatment has shown promising results in improving mitochondrial function and reducing inflammatory cytokines and adhesion molecules in leukocytes, thereby decreasing leukocyte-endothelial interactions. Additionally, it has been associated with a reduction in carotid intima-media thickness, a marker of atherosclerosis.

Treatment with GLP-1 RAs has been associated with improved mitochondrial function, including enhanced redox state and mitochondrial respiration, which may contribute to reduced hepatic lipid accumulation and inflammation.²⁶ Therefore, GLP-1 RAs may offer significant cardiometabolic protection in T2D patients by improving mitochondrial efficiency and attenuating

vascular inflammation, ultimately reducing the progression of atherosclerosis. Furthermore, Mashayekhi et al explored whether the metabolic benefits of GLP-1 RAs like liraglutide are independent of weight loss and distinct from the effects of boosting natural GLP-1 levels. In a 14-week trial involving individuals with obesity and prediabetes, participants received liraglutide, a low-calorie diet, or the DPP-4 inhibitor sitagliptin. Both liraglutide and diet led to weight loss, but what was particularly intriguing was that liraglutide improved insulin sensitivity and lowered glucose, insulin, and glucagon levels even before significant weight loss occurred. Sitagliptin increased endogenous GLP-1 and GIP but did not improve insulin sensitivity or fasting glucose. These results suggest that liraglutide has unique, weight-independent metabolic effects through direct GLP-1 receptor activation that are not achieved by simply raising endogenous GLP-1 levels. The unique metabolic effects of GLP-1 RAs are an interesting development.²⁷ These findings highlight that liraglutide's metabolic benefits, such as improved insulin sensitivity and glucose regulation, are independent of weight loss and cannot be solely attributed to increased endogenous GLP-1 levels. Thus, this underscores the unique mechanisms through which GLP-1 receptor activation may improve metabolic health in individuals with obesity and prediabetes.

Extrahepatic benefits of GLP-1 RAS

GLP-1 RAs have shown significant cardiovascular benefits, particularly in reducing the risk of atherosclerotic cardiovascular disease and heart failure. Despite the consistent cardiovascular benefits observed, the number of patients receiving GLP-1 RAs remains low.²⁸ Thus, greater clinician awareness and efforts to improve patient access are needed to bridge the gap between clinical guidelines and real-world usage. Widening the adoption of GLP-1 RAs could significantly improve cardiovascular outcomes in at-risk populations. Furthermore, Ansari et al conducted a systematic review and meta-analysis of 15 trials that evaluated the effects of GLP-1 RAs on weight loss and cardiometabolic health in obese individuals without diabetes.²⁹ The analysis revealed significant weight loss and improvements in systolic blood pressure, diastolic blood pressure, and lipid profiles, including reductions in triglycerides, total cholesterol, VLDL, and LDL, and increased HDL levels. GLP-1 RAs demonstrated consistent benefits across subtypes, contributing to key cardiovascular risk factors. However, they were also associated with a higher risk of gastrointestinal adverse events. This evidence supports using GLP-1 RAs as effective agents for weight loss and cardiovascular health improvement in obese individuals without diabetes.²⁹ Thus, this highlights GLP-1 RAs' potential role beyond glycemic control.

Future research should investigate long-term safety profiles and explore their application in broader populations at risk for metabolic and cardiovascular disease. Therefore, their multifaceted benefits could offer

a valuable strategy in obesity and cardiovascular disease prevention. Another study by Rezaei et al conducted a meta-analysis of randomized placebo-controlled trials to evaluate the effect of GLP-1 RAs on liver enzymes and lipid profiles in patients with NAFLD.³⁰ Twelve studies involving 677 subjects were included, and results showed that GLP-1 RA treatment significantly reduced liver enzymes alanine transaminase, gamma-glutamyl transferase, and alkaline phosphatase, but had no effect on aspartate aminotransferase. GLP-1 RA treatment did not affect lipid profiles, including triglycerides, total cholesterol, HDL, or LDL. The findings suggest that while GLP-1 RAs can improve liver enzyme levels in NAFLD patients, they do not significantly impact lipid levels. Treatment with GLP-1 RAs reduces LDL cholesterol and triglyceride levels in patients with NAFLD.³⁰ Therefore, these results highlight the potential of GLP-1 RAs in targeting hepatic inflammation and injury, even without marked lipid profile improvements. Future studies should explore combination therapies that may amplify both hepatic and lipid benefits. Similarly, Bray et al conducted a systematic review to assess the impact of GLP-1 RAs on inflammation and oxidative stress biomarkers in individuals with T2DM.³¹ The results showed significant reductions in inflammatory markers, including CRP, TNF- α , and MDA, and substantial increases in adiponectin levels. Systolic blood pressure also decreased, which correlated with CRP reduction. These findings highlight the anti-inflammatory and antioxidant effects of GLP-1 RAs, suggesting their potential role in managing inflammation and oxidative stress in T2D and guiding the future development of treatments targeting cardiovascular protection. GLP-1 RAs significantly reduce markers of systemic inflammation and oxidative stress.³¹ Thus, GLP-1 RAs may improve metabolic control and offer cardiovascular benefits through their modulation of systemic inflammation. Further research into their long-term impact on heart disease in diabetes is essential for optimizing therapeutic strategies.

Long-term safety and adverse events

GLP-1 agonists have for the most part demonstrated a favorable safety profile, but concerns do remain, particularly in the context of advanced liver disease. In individuals with cirrhosis, there is a potential risk for sarcopenia stemmed from excessive weight loss. GLP-1 agonists are associated with translocating GLUT4 and the dispersion of mitochondria, which ultimately also results in decrease in "production of mitochondrial ATP necessary for myogenic programme."³²

This implies that GLP-1 agonists could negatively affect muscle regeneration and maintenance, raising safety concerns for cirrhotic patients who are already vulnerable to muscle wasting.³³ Additionally, it is worth noting that weight-loss induced changes in splanchnic circulation may increase the risk for worsening portal hypertension. Gastrointestinal side effects such as nausea, vomiting, and diarrhea are among the most common side effects that have

been noted, possibly even having a long-term impact on comfort and adherence.³⁴ There remains a lack of long-term safety data, specifically in patients with decompensated cirrhosis, emphasizing cautiousness in selection of GLP-1 agonists in this vulnerable group.

Comparative efficacy with pioglitazone and vitamin E

Given the safety consideration, it is essential to compare the efficacy of GLP-1RAs alongside other pharmacological options such as pioglitazone and vitamin E. Pioglitazone has demonstrated efficacy in improving hepatic steatosis, lobular inflammation, and in some cases fibrosis regression.²⁰ While making significant improvements in biochemical and histological features of NASH, it is worth noting that it comes with a cost: weight gain.³⁵ This presents a clinical challenge in patients with obesity and IR. On the other hand, vitamin E has shown to have antioxidant effects, especially in non-diabetic individuals. While one study did find significant improvements in liver inflammation and histology in patients with MASLD, more studies are needed to verify its long-term efficacy and safety profile.³⁶ In contrast, GLP-1RAs offer promising benefits not only on hepatic outcomes, but also MetS. Studies directly comparing GLP-1 RAs to agents like pioglitazone and vitamin E are lacking, making it hard to truly determine their relative therapeutic value. Further research is needed to guide clinical decision making.

DISCUSSION

Clinical implications of GLP-1 RAs in MASLD/MASH management

GLP-1RAs represent a particularly encouraging therapeutic option for MASLD, especially among patients who also contend with obesity or T2DM. The American Diabetes Association notes that agents in this class can attenuate fibrosis and help resolve steatohepatitis, in part by normalizing the raised plasma aminotransferase concentrations frequently seen in MASLD.³⁷ Through these mechanisms, the development of hepatic fibrosis may be curtailed and disease trajectory potentially stalled or reversed. Trial data likewise indicate that GLP-1 RAs reduce circulating markers of hepatocellular injury and fibrogenesis.³⁸ By tempering the progression toward cirrhosis, these drugs can meaningfully improve long-term outlook for affected patients. In individuals with advanced cirrhosis who might otherwise be candidates for transplantation, such therapy may offer a valuable alternative.³⁹ A treatment capable of lessening reliance on liver transplantation underscores how transformative GLP-1 RAs could become within the MASLD treatment landscape.

Challenges and gaps in current evidence

Although short-term investigations report histologic gains, robust long-term evidence of fibrosis regression remains

scarce. Several factors contribute to this shortfall, chief among them the absence of sufficiently large and sufficiently prolonged trials needed to establish durable treatment effects.⁴⁰ Confirming genuine fibrosis regression would additionally require paired liver biopsy. A separate review similarly observes that while liraglutide and semaglutide improve markers of metabolic dysfunction, extended trial durations are required before statistically robust conclusions can be drawn.⁴¹ Lengthening and enlarging subsequent studies will therefore be pivotal to corroborate present observations and to delineate the long-term safety, effectiveness, and clinical role of GLP-1RAs in metabolic dysfunction.

How long GLP-1RA therapy should be maintained remains undefined, as reported treatment windows span widely, from roughly 12 weeks to as long as 12 months.⁴² Such variability reinforces the call for additional study to pinpoint the most beneficial treatment duration. The durability of benefit, and the degree to which treatment length shapes steatohepatitis resolution and the slowing of cirrhosis, are still being characterized. Patient-level considerations, including MASLD severity, the presence of T2DM, and individual therapeutic responsiveness, likely also influence how long treatment ought to continue. Further work is warranted to account for these modifiers and to formulate explicit recommendations on optimal GLP-1RA treatment length that maximize patient benefit. A structured diagnostic strategy will be central to achieving those outcomes. Biomarkers may eventually support this effort, yet the current evidence base is too limited to depend on them for firm conclusions. Pinpointing biomarkers capable of forecasting the response to GLP-1RA therapy could enable individualized treatment and better patient-specific results.⁴³

Potential for combination therapy approaches

Pairing GLP-1RAs with sodium-glucose cotransporter-2 (SGLT2) inhibitors holds considerable appeal. Available data point to complementary, mutually reinforcing metabolic actions between the two classes. Relative to either drug alone, the combination can produce clinically meaningful declines in glycated hemoglobin (HbA1c), body weight, and systolic blood pressure.

Consequently, combined use has been linked to better cardiovascular and renal results, reflected in fewer hospitalizations for conditions such as decompensated heart failure and chronic kidney disease.⁴⁴ Work by Li et al further documents the gains in glycemic control and weight reduction achievable with this dual regimen.⁴⁵ Collectively, these observations illustrate how combination therapy can address the layered needs of patients burdened by coexisting metabolic and cardiovascular disease. Engaging several pathophysiologic pathways at once not only sharpens clinical benefit but also furnishes an integrated framework for sustained disease control.

Combining GLP-1RAs with other glucose-lowering

agents, including farnesoid X receptor (FXR) agonists and peroxisome proliferator-activated receptor (PPAR) agonists, may confer added value, though this question warrants dedicated study and additional trials. Such pairings could carry particular relevance for fibrosis management. As one illustration, semaglutide used alongside antifibrotic agents has yielded encouraging effects on hepatic steatosis and liver biochemistry, even as durable evidence of fibrosis improvement remains outstanding.⁴⁶

Numerous trials are presently examining these combinations to better define their advantages.

The PRECIDENTD trial, for instance, is assessing the joint cardiovascular and renal impact of GLP-1RAs together with SGLT2 inhibitors.⁴⁴ Such investigations are intended to clarify how combination strategies might reshape the care of metabolic and cardiovascular disease. Their findings should prove decisive in informing future guidelines and refining treatment approaches for patients with intricate comorbidity profiles.

Future research directions

A pressing requirement exists for larger, longer trials employing biopsy-verified histology to substantiate the influence of GLP-1RAs on fibrosis regression. Existing studies, including several evaluating semaglutide, have encouragingly reduced hepatic fat and inflammation yet stop short of demonstrating definitive fibrosis improvement.⁴⁷ Adequately powered, extended trials anchored by biopsy-confirmed histologic endpoints will be necessary to establish the true effect of GLP-1RAs on fibrosis regression. Despite promising reductions in liver fat and inflammation reported for semaglutide, conclusive proof of meaningful fibrosis benefit has not yet emerged.¹⁹ A further priority is clarifying how GLP-1RAs affect hepatic decompensation and portal hypertension in patients with established cirrhosis. Although these agents appear to lower the likelihood of cirrhosis progression and complications in non-cirrhotic populations, their behavior in patients who already have cirrhosis remains uncertain. Analyses such as that by Kanwal et al underscore the importance of deeper inquiry into these endpoints.^{40,48} This emphasizes the urgent need for focused research into the safety and efficacy of these therapies in advanced liver disease. Elucidating their effect on established cirrhosis could substantially inform clinical decision-making and enhance patient outcomes.

CONCLUSION

GLP-1 RAs have arisen as a promising therapeutic class in the treatment of MASLD and MASH, demonstrating consistent improvements in hepatic steatosis, inflammation, and metabolic dysfunction. Their multifaceted effects, ranging from enhanced insulin sensitivity, weight loss to anti-inflammatory effects and lipid metabolism regulation, all aid in positioning them

uniquely among current pharmacologic options. Although GLP-1 RAs show potential in slowing fibrosis progression, current evidence remains inconclusive, mainly due to the lack of long-term trials with biopsy-confirmed assessments of fibrosis regression.

Their use in patients with advanced liver disease, particularly those with cirrhosis, also requires caution due to safety concerns such as sarcopenia and altered splanchnic circulation. Regardless, their ability to reduce the requirement for liver transplantation in high-risk populations is a major clinical advantage. Compared to traditional therapies such as pioglitazone or vitamin E, GLP-1 RAs offer broader benefits, however direct head-to-head comparisons are limited.

Combination therapies involving GLP-1 RAs and other agents such as SGLT2 inhibitors, or FXR agonists have all shown amplified clinical benefits when used in combination, potentially optimizing outcomes in patients with overlapping metabolic and cardiovascular comorbidities.

Given their broad range of effects, GLP-1 RAs may have a potential role as first-line therapy in patients with MASLD and metabolic dysfunction, especially when treatment is tailored to a patient's individual health profile and comorbidities. Future research must prioritize large-scale trials with clear histological endpoints, stratified by disease severity, comorbidities and biomarker driven treatment response. These studies will be a vital turning point in defining the optimal duration, safety profile and the positioning of GLP-1 RAs in the treatment hierarchy for MASLD and MASH. GLP-1 RAs ultimately hold notable potential to reshape the therapeutic landscape for metabolic liver disease; however, their full clinical utility is still unfolding.

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APPENDIX

Table 1: Summary of key findings from selected studies in the literature review.

Author(s)	Main results
Wang and Friedman (2023) ¹	Reviewed fibrosis mechanisms in MASH, emphasizing translational insights and potential therapeutic targets.
Luthra and Sheth (2025) ²	TARGET-NASH data showed that disease severity strongly predicts progression and clinical outcomes in MASH.
Portincasa et al (2024) ³	Summarized MASLD pathogenesis and therapeutic landscape, highlighting lifestyle and pharmacological approaches.
Eskridge et al (2023) ⁴	Surveyed patients and physicians; revealed significant gaps in awareness, diagnosis, and management of MASLD/MASH.
Radu et al (2023) ⁵	Confirmed strong link between NAFLD and metabolic syndrome, with shared pathophysiology in insulin resistance and inflammation.
Bugianesi et al (2010) ⁶	Demonstrated insulin resistance as a central feature in NAFLD pathogenesis.
Sears and Perry (2015) ⁷	Showed role of fatty acid metabolism in insulin resistance, contributing to NAFLD development.
Younossi et al (2025) ⁸	Provided updated global epidemiology of MASLD, showing rising prevalence worldwide.
Mokdad et al (2001) ⁹	Identified continuing epidemics of obesity and diabetes in the U.S., precursors to MASLD.
Gancheva et al (2024) ¹⁰	Found diabetes significantly increases risk of MASH progression.
Prabhakar et al (2020) ¹¹	Showed diet and lifestyle modifications improve NAFLD and T2DM outcomes.
Wong (2024) ¹²	Reviewed lean MASH, highlighting unique risk profiles and disease mechanisms.
Nguyen et al (2024) ¹³	Discussed emerging MASLD therapies and their effects on plasma lipids.
Hu et al (2024) ¹⁴	Reviewed new drug pipeline for MASLD/NAFLD, including GLP-1 agonists and FXR agonists.
Tincopa et al (2024) ¹⁵	Summarized new and emerging treatments for MASH with focus on antifibrotic and metabolic pathways.
Zhao et al (2024) ¹⁶	Meta-analysis showed obeticholic acid improves histology in NASH but with safety concerns (pruritus, lipid changes).
Drucker (2018) ¹⁷	Explained GLP-1 biology, mechanisms of action, and broad therapeutic applications.
Mantovani et al (2021) ¹⁸	Meta-analysis: GLP-1 RAs improve liver enzymes, histology, and metabolic markers in NAFLD/NASH.
Abdelmalek et al (2024) ¹⁹	Reviewed GLP-1 RAs role in MASH management, showing efficacy in weight and liver outcomes.
Mazhar et al (2023) ²⁰	Systematic review: Vitamin E and pioglitazone effective for NAFLD/NASH, though with safety limitations.
Nevola et al (2023) ²¹	Reviewed current and future perspectives of GLP-1 RAs in NAFLD.
Liao et al (2023) ²²	Meta-analysis: GLP-1 RAs reduce visceral and ectopic liver fat, independent of diabetes status.
Rochón et al (2024) ²³	Gut-liver axis linked to MASLD; GLP-1 RAs show hepatoprotective effects through metabolic and microbiome pathways.
Taher et al (2014) ²⁴	Showed GLP-1 agonism reduces hepatic VLDL overproduction and lipogenesis in insulin resistance.
Alharbi (2024) ²⁵	Demonstrated anti-inflammatory role of GLP-1 RAs with clinical implications.
Luna-Marco et al (2023) ²⁶	GLP-1 RAs improve mitochondrial function and reduce inflammatory markers in T2DM patients.
Mashayekhi et al (2024) ²⁷	Found liraglutide improves insulin sensitivity independent of weight loss.
Marx et al (2022) ²⁸	GLP-1 RAs reduce atherosclerotic cardiovascular risk in T2DM.
Ansari et al (2024) ²⁹	Meta-analysis: GLP-1 RAs are effective for weight loss and cardiometabolic improvement in obesity without diabetes.
Rezaei et al (2021) ³⁰	Meta-analysis: GLP-1 RAs improve lipid and liver profiles in NAFLD patients.
Bray et al (2021) ³¹	GLP-1 RAs improve biomarkers of inflammation and oxidative stress in RCTs.
Huang et al (2024) ³²	Serum GLP-1 linked to sarcopenia and myogenic differentiation.
Morris et al (2022) ³³	Found GLP-1 RAs are safe and effective in patients with cirrhosis.
Bettge et al (2016) ³⁴	Systematic analysis: nausea, vomiting, and diarrhea common AEs with GLP-1 RAs.
Lutchman et al (2007) ³⁵	Discontinuation of pioglitazone leads to recurrence of NASH features.
Chee et al (2024) ³⁶	Systematic review: Vitamin E improves serum markers and histology in MASLD.
ADA Committee (2025) ³⁷	Updated standards of care for diabetes, including MASLD comorbidity evaluation.
Nowak et al (2025) ³⁸	Reviewed therapeutic potential of GLP-1 RAs in MASLD.
Kanwal et al (2024) ³⁹	GLP-1 RAs reduced risk of cirrhosis and complications in MASLD patients.
Kanwal et al (2021) ⁴⁰	Proposed clinical care pathway for NAFLD risk stratification and management.
Barritt et al (2022) ⁴¹	Reviewed GLP-1 RAs in NASH, obesity, and diabetes, guiding hepatologists.
Yabutt et al (2023) ⁴²	Comprehensive review of GLP-1 receptor-based therapeutics for liver disease.
Jianping et al (2021) ⁴³	Meta-analysis: GLP-1 RAs improve NAFLD parameters with acceptable safety.
Scheen (2024) ⁴⁴	Reviewed additive cardiometabolic effects of GLP-1 RAs and SGLT2 inhibitors.
Li et al (2022) ⁴⁵	Meta-analysis: GLP-1 RA + SGLT2i combo safe and effective in T2DM.
Yin et al (2023) ⁴⁶	Identified GLP-1 as a potential therapeutic target for NAFLD.
Targher et al (2025) ⁴⁷	Reviewed advances in incretin therapies for MASLD, including dual/triple agonists.
Havranek et al (2025) ⁴⁸	GLP-1 RAs shown to improve MASLD outcomes in clinical settings.