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GLP-1 RECEPTOR AGONISTS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: THERAPEUTIC POTENTIAL AND CLINICAL CHALLENGES

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ABSTRACT

Introduction and Purpose: Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), represents the most common chronic liver condition worldwide, strongly linked to obesity and type 2 diabetes. The more severe form, metabolic dysfunction-associated steatohepatitis (MASH), significantly increases risks of cirrhosis, hepatocellular carcinoma, and cardiovascular complications. Currently, effective pharmacological treatments are limited. This review aims to summarize current evidence on the potential role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as therapeutic agents for MASLD/MASH.

Description of the State of Knowledge: GLP-1 RAs, currently used to treat diabetes and obesity, show beneficial metabolic effects through appetite reduction, weight loss, and improved glycemic control. Recent studies indicate that GLP-1 RAs, particularly liraglutide and semaglutide, effectively reduce liver steatosis, hepatic inflammation, and liver enzymes. However, evidence regarding their effectiveness in reducing liver fibrosis remains unclear, highlighting the need for larger and longer studies.

Conclusions: GLP-1 RAs emerge as promising therapeutic options for MASLD and MASH due to their metabolic and hepatoprotective benefits. While preliminary findings support their use, particularly in reducing hepatic steatosis and inflammation, their role in fibrosis regression requires further validation. Future research, involving extensive clinical trials with broader patient populations and standardized dosing protocols, is essential to establish GLP-1 RAs as standard therapy for metabolic liver disease.

KEYWORDS

Non-Alcoholic Fatty Liver Disease, Glucagon-Like Peptide-1 Receptor Agonists, Semaglutide, Liraglutide

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1. Introduction and purpose

1.1. MASLD/MASH: Consequences of Modern Metabolic Disorders

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is currently the most common chronic liver disease worldwide. The global prevalence of MASLD is estimated at approximately 32.4% [1]. Moreover, it has been estimated that in Western countries, up to 60% of obese adults may have MASLD [2, 3]. Closely related to MASLD is its more severe form - metabolic dysfunction-associated steatohepatitis (MASH) which is characterized by lobular inflammation, hepatocellular ballooning, fibrosis, and a substantial risk of progression to liver cirrhosis [4]. According to a screening study, approximately one-third of individuals with MASLD were found to have MASH [2]. The pathogenesis of MASLD is closely linked to metabolic syndrome, as it shares a common underlying mechanism - insulin resistance, along with its key components, including type 2 diabetes (T2D), visceral obesity, hypertension, and dyslipidemia [5]. In the United States, it is estimated that by 2030, half of the adult population will be affected by obesity - a condition that already affects approximately 40% of adults today [6, 7]. Type 2 diabetes is a major factor driving the progression from MASLD to MASH, as well as contributing to the development of liver cirrhosis and hepatocellular carcinoma (HCC) [8]. Approximately 71 % of patients with MASH-associated liver cirrhosis have concomitant type 2 diabetes [9]. Moreover, poor glycemic control is identified as a risk factor associated with enhanced hepatocyte ballooning and progression of liver fibrosis in MASLD/MASH [10]. Current evidence suggests shared pathophysiological mechanisms underlying the reciprocal relationship between MASLD/MASH and T2D, indicating a potential bidirectional association that may further exacerbate cardiovascular outcomes [11, 12]. In individuals without diabetes, MASLD is associated with visceral adipose tissue dysfunction, dyslipidemia, and increased hepatokine secretion - factors that promote insulin resistance and may contribute to the development of T2D [12]. On the

other hand, people with type 2 diabetes often present with elevated liver enzymes and hepatic fat accumulation, independent of body mass index (BMI), and are at greater risk of progressing to advanced liver fibrosis [13, 14]. It is therefore reasonable to assume that the rising prevalence of MASLD and MASH is, at least in part, driven by the global epidemics of obesity and diabetes.

1.2. High-Risk Profile of MASLD and MASH Patients

Patients with MASH are at high risk for severe complications, including portal hypertension, hepatic decompensation, and HCC [15]. Cardiovascular diseases represent the leading cause of mortality in patients with MASLD/MASH, particularly in less advanced disease stages. Notably, MASLD independently elevates cardiovascular risk, irrespective of other established risk factors such as hypertension and dyslipidemia [16]. In the United States, MASH is the second most frequent indication for liver transplantation among men, after alcoholic liver cirrhosis, and it represents the primary indication among women [17].

1.3. Current Management of MASLD and MASH: Lifestyle First, Drugs Emerging

Due to the long-standing absence of approved drug therapies, lifestyle modification has remained the cornerstone of managing MASLD and MASH. Current clinical guidelines emphasize the importance of regular physical activity combined with a calorie-restricted diet, particularly in individuals with obesity. The primary goal is to achieve a weight loss of 7-10%, which has been consistently associated with improvements in liver steatosis, reductions in plasma aminotransferase levels, decreased cardiovascular risk, and even resolution of MASH [13, 18, 19]. Resmetirom is currently the first and only pharmacological agent, provisionally approved by the FDA in March 2024 in the United States for the treatment of MASH with fibrosis. Additionally, resmetirom is under review by the European Medicines Agency [20].

1.4. Therapeutic Potential of GLP-1 RAs for Metabolic Liver Disease

GLP-1 receptor agonists (GLP-1 RAs) support metabolic health and weight loss through several biological mechanisms [11, 21]. They are currently approved for the treatment of type 2 diabetes and obesity, owing to their ability to improve blood glucose regulation and suppress appetite and caloric intake [22, 23]. Large randomized controlled trials (RCTs) evaluating GLP-1 RAs have consistently demonstrated their beneficial impact on reducing the risk of adverse cardiovascular events, all-cause mortality, and progression of nephropathy in patients with type 2 diabetes [24-26]. GLP-1 RAs are currently under evaluation as a therapeutic option for MASH in individuals both with and without type 2 diabetes [27]. Findings from phase 2 clinical trials indicate that semaglutide, along with another GLP-1 RA, liraglutide, significantly enhanced histological resolution of MASH when compared to placebo [28, 29]. Emerging evidence supports the effectiveness of GLP-1 receptor agonists in the treatment of MASLD and MASH. Although their precise mechanisms of action remain incompletely understood, these are likely multifactorial. Importantly, the beneficial effects of GLP-1 RAs appear to extend beyond mere weight reduction. In patients with MASLD/MASH, treatment with GLP-1 RAs may alleviate hepatic inflammation and reduce liver steatosis, however, their impact on liver fibrosis remains uncertain. GLP-1 receptor agonists represent a promising therapeutic option for patients with MASLD/MASH, conditions that, despite their high global prevalence and serious long-term complications, have long lacked effective pharmacological treatment.

1.5. From NAFLD/NASH to MASLD/MASH: Updated Nomenclature

The terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been revised by an international panel of experts in 2023 to metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), respectively. The updated terminology and definitions more accurately reflect the metabolic origin of the disease and have been considered less stigmatizing. It is important to note that the new criteria are largely consistent with the previous ones, with 98% of individuals previously diagnosed with NAFLD or NASH meeting the updated definitions of MASLD and MASH [30]. For these reasons, this review adopts the new nomenclature, although some of the cited studies used the former terms.

1.6. Purpose of the Review: Exploring GLP-1 RAs in Liver Disease

The aim of this review is to provide a comprehensive overview of the current evidence, drawn from the most recent and methodologically robust studies, regarding the role of GLP-1 receptor agonists in the treatment of MASLD/MASH. We seek to explore their potential impact on the course of these conditions and their complications and limitations associated with GLP-1 RAs therapy, as well as key challenges that need to be addressed in future clinical trials before these agents can be officially approved as a treatment for MASLD.

2. Description of the state of knowledge

2.1. Systemic Actions and Receptor Distribution of GLP-1

Glucagon-like peptide 1 (GLP-1) is an incretin hormone primarily involved in stimulating insulin secretion from pancreatic beta cells in response to elevated blood glucose levels, while simultaneously suppressing glucagon production from alpha cells [31]. In addition, GLP-1 slows gastric emptying and intestinal movement, thereby decreasing glucose absorption and aiding in the regulation of post-meal spikes in glucose and triglyceride levels. Beyond its effects on digestion, GLP-1 also promotes the sensation of fullness by directly influencing the central nervous system [32, 33]. GLP-1 acts on multiple organ systems by directly stimulating its receptors or indirectly via neural and hormonal signals. These mechanisms influence the function of the cardiovascular system, liver, adipose tissue, kidneys, and brain [32]. GLP-1 receptors (GLP-1 R) is primarily found in the distal ileum, colon, pancreatic alpha and beta cells, and within the central nervous system. Although its presence is less pronounced, GLP-1 receptors are also distributed in the heart, lungs, kidneys, vascular system, and peripheral nerves [32, 33]. According to some studies, GLP-1 receptors are also expressed in human hepatocytes, but their expression is reduced in patients with MASH [34, 35].

2.2. Glycemic Control, Weight Loss, and Cardiovascular Protection

GLP-1 receptor agonists (such as exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide, and semaglutide) enhance the physiological activity of endogenous GLP-1 through various biological mechanisms outlined in the previous paragraph. These agents effectively lower blood glucose levels, especially postprandial and reduce HbA1c while also promoting weight loss. Unlike native GLP-1, which is rapidly broken down by dipeptidyl peptidase-4 (DPP-4) within approximately 1.5 minutes [36]. GLP-1 RAs are structurally modified to resist DPP-4 degradation, enabling sustained action and allowing for daily or weekly administration. The reduction in glycated hemoglobin (HbA1c) typically ranges from 1% to 2% and follows a dose-dependent pattern. This effect is influenced both by patient-specific factors, such as baseline HbA1c levels, initial body weight, duration of type 2 diabetes, and by characteristics of the GLP-1 receptor agonist used. These include whether the agent is short-acting (e.g., exenatide administered twice daily, lixisenatide) or long-acting (dulaglutide, albiglutide, subcutaneous semaglutide), its pharmacological potency, and its impact on weight reduction [26, 37, 38]. Long-acting formulations tend to provide better glycemic control, particularly for nocturnal and post-meal glucose levels, and therefore generally achieve greater HbA1c reductions compared to short-acting agents. Beyond glycemic control, GLP-1 RAs have shown significant benefits in preventing complications related to T2D [24-26]. A substantial amount of research now supports that therapy with long-acting GLP-1 RAs leads to favorable results in individuals with type 2 diabetes, including improvements in cardiovascular outcomes, mortality, and kidney function. Based on data from the meta-analysis by Kristensen et al. [39], including seven large placebo-controlled cardiovascular outcome trials, involving over 56000 participants, GLP-1 RAs were shown to reduce the risk of major adverse cardiovascular events (MACE) by 12%. Additionally, treatment with these agents led to a 12% reduction in all-cause mortality, a 9% reduction in the risk of hospitalization for heart failure, and a 17% reduction in the risk of renal function decline, primarily due to a decreased incidence of macroalbuminuria. These findings highlight the cardioprotective and renoprotective effects of GLP-1 RAs and support their use as an effective strategy for reducing morbidity and mortality in patients with T2D. As a result, these drugs are now considered first-line therapy for individuals with T2D and existing atherosclerotic cardiovascular disease or a history of cardiovascular events [40]. By decreasing appetite and enhancing satiety, particularly after meals, GLP-1 RAs contribute to weight reduction through reduced caloric intake [25]. Depending on the specific agent and dosage, treatment can lead to weight loss ranging from 5,7% to -16%, with semaglutide demonstrating the most potent effect [38, 41-43]. This appetite-suppressing property has led to their approval for the treatment of obesity, even in patients without T2D [44, 45]. Current clinical guidelines recommend reducing calorie intake combined with regular physical activity, with the goal of achieving a weight loss of 7-10% in individuals with obesity and MASLD/MASH. This degree of weight reduction has been shown to significantly improve liver enzymes, hepatic steatosis,

inflammation, and fibrosis, and to slow disease progression [18, 19]. However, achieving and maintaining substantial weight loss over time is difficult. Many dietary approaches fail to produce lasting results, while physiological mechanisms often promote weight regain [46]. Taken together, the positive metabolic impact of GLP-1 RAs suggests their potential value in treating MASLD.

2.3. Potential direct Hepatocellular Effects of GLP-1 RAs

Recent in vitro studies have provided growing evidence that GLP-1 receptor agonists may exert direct effects on hepatocytes in the treatment of MASLD and MASH by modulating key molecular pathways involved in lipid metabolism [47-49]. These agents have been shown to reduce hepatic steatosis by inhibiting de novo lipogenesis, promoting fatty acid β-oxidation, and improving mitochondrial function and autophagy [50-52]. On the genetic level, GLP-1 RAs downregulate the expression of lipogenic and metabolic regulators such as SREBP-1c, PPARγ, ACSL1, FABP1, and FOXA1, which play a critical role in lipid accumulation and transport in hepatocytes [48, 49, 53, 54]. These effects are believed to be mediated by activation of intracellular signaling pathways, particularly AMPK, PI3K/AKT, and Wnt/β-catenin, contributing to enhanced lipid clearance, reduced lipotoxicity, and anti-inflammatory responses [48, 55-57]. While some studies have confirmed the expression of GLP-1 receptors in human hepatocytes and demonstrated receptor-dependent mechanisms of action [47, 58], others suggest that the beneficial hepatic effects of GLP-1RAs might be indirect, resulting from systemic improvements such as weight loss and glycemic control [49, 59, 60]. Recent receptor silencing experiments in hepatocyte models have shown that inducted by GLP-1 RAs gene modulation is significantly reduced when GLP-1 receptor is inhibited, supporting the hypothesis of direct hepatocyte-specific action [48]. Although the debate about the presence of GLP-1 receptors in liver tissue is still ongoing, GLP-1 RAs have demonstrated an ability to modulate key disrupted metabolic pathways, making them a promising candidate for therapeutic intervention in MASLD.

2.4. The Effect of GLP-1 Receptor Agonists on Liver Steatosis

Among GLP-1 RAs, liraglutide has been the most extensively studied. Clinical trials consistently report reductions in body weight (typically between 2.2% and 6.4%) [61] accompanied by decreased liver fat content (ranging from 19% to 44%) as assessed by imaging modalities such as MRI [62-64]. A clear relationship has been established between the extent of weight loss and the improvement in liver steatosis. In comparative study, liraglutide has outperformed other antidiabetic agents like metformin and gliclazide in reducing hepatic fat [65]. Additional agents such as dulaglutide and exenatide have also shown favorable outcomes [66-68]. Dulaglutide not only improves liver enzymes but has also been associated with resolution of hepatic steatosis in specific populations, such as women with polycystic ovary syndrome [69, 70]. Higher doses of dulaglutide may offer enhanced efficacy, as suggested by Frias et al trial [71]. Exenatide, has also been shown to significantly reduce hepatic triglyceride content and epicardial fat, benefits not observed with other oral hypoglycemics [67].

2.5. Impact of GLP-1 Receptor Agonists on Liver Enzymes and Hepatic Cytolysis Markers

A meta-analysis by Mantovani et al demonstrated that GLP-1 RAs treatment significantly reduced circulating ALT levels compared to placebo or reference therapies, with a pooled weighted mean reduction of approximately 7 IU/L. Likewise, GLP-1 RAs significantly lowered serum GGT levels, with reductions of about 11 IU/L. However, no significant change was observed in AST levels across these pooled studies [72]. Individual clinical trials have also supported these findings. For instance, Loomba et al [73] in a 48-week study involving semaglutide 2.4mg once a week, patients treated with this GLP-1 RA experienced significant improvements in ALT levels compared to placebo, with a higher proportion achieving clinically relevant reductions (≥17 units) [74]. This was accompanied by meaningful reductions in AST and GGT concentrations as well, highlighting the comprehensive hepatic benefit of semaglutide. The impact of GLP-1 RAs on hepatic cytolysis enzymes, primarily ALT and AST, is clinically relevant, as elevations in these enzymes correlate with hepatic inflammation and increased risk of progressing to more severe liver conditions, including MASH and cirrhosis [75]. Various GLP-1 RAs, including exenatide, dulaglutide, liraglutide, and semaglutide, have shown effectiveness in lowering these cytolysis markers [76]. For example, exenatide treatment resulted in normalization of ALT levels in approximately 40% of diabetic patients initially presenting elevated liver enzymes [77]. Dulaglutide has similarly demonstrated significant enzyme reductions within six months [69], while liraglutide showed dose-dependent improvements, particularly at a 1.8 mg/day dosage [78]. Semaglutide further confirmed dose-dependent efficacy in reducing ALT levels, achieving maximal improvements around

weeks 28–30 of treatment initiation, closely linked with weight loss [28, 79]. Overall, GLP-1 RAs provide a consistent positive effect on liver enzymes and hepatic cytolysis markers, particularly ALT and GGT, although their impact on AST may vary depending on the specific study or drug dosage. Table 1. presents a summary of the most important beneficial effects of GLP-1 RAs in MASLD discussed in this review.

Table 1. Summary of the outcomes of GLP-1 receptor agonist (GLP-1 RAs) use presented in this review

Outcome	Reported effect of GLP-1 RAs	Benefit	Key supporting studies (referenced in the review)
Body-weight reduction	−5.7% to −16% depending on molecule and dose, semaglutide shows the greatest loss	Yes	Blackman 2016 [41], Rubino 2021 [42], Wadden 2013 [43], Trujillo 2021 [38]
Hepatic steatosis	Liraglutide lowers liver fat by 19-44%, similar benefits seen with dulaglutide and exenatide	Yes	Petit 2016 [62], Vanderheiden 2016 [63], Yan 2019 [64], Kuchay 2020 [68], Dutour 2016 [67]
Histological MASH resolution	Liraglutide 1,8 mg: 39% vs 9% placebo, Semaglutide 0,4 mg: 59% vs 17% placebo; pooled OR ≈ 4.1 for resolution without fibrosis worsening	Yes	Armstrong 2016 [29], Newsome 2021 [28]
Fibrosis (histology)	No significant regression overall	No	Armstrong 2016 [29], Newsome 2021 [28]
Fibrosis (non-invasive indices)	Decrease in APRI, FIB-4, NFS and liver stiffness reported in observational cohorts (liraglutide)	Yes	Ohki 2012 [80], Colosimo 2021 [81], Tan 2022 [82]
ALT	Pooled mean change −7 IU/L vs control, dose-dependent normalisation with semaglutide	Yes	Mantovani 2021 [72], Loomba 2023 [73], Klonoff 2008 [77], Cusi 2018 [69], Armstrong 2013 [78] Newsome 2021 [28] Newsome 2019 [79]
AST	No significant pooled change, falls with high-dose semaglutide in one RCT	Unclear	Mantovani 2021 [72], Loomba 2023 [73]
GGT	Pooled mean change −11 IU/L vs control; improved with semaglutide	Yes	Mantovani 2021 [72], Loomba 2023 [73], Klonoff 2008 [77], Cusi 2018 [69], Armstrong 2013 [78] Newsome 2021 [28] Newsome 2019 [79]

2.6. Promising Anti-Steatohepatitis Effects with Limited Fibrosis Evidence

Emerging evidence positions GLP-1 RAs as promising agents for metabolic dysfunction-associated steatohepatitis (MASH), though their impact on liver fibrosis remains less clear. The first proof of concept signal came from a 48 week, placebo-controlled study in 52 overweight adults with biopsy-confirmed MASH. Daily liraglutide 1.8 mg resolved steatohepatitis in 39% of participants versus 9% on placebo, and it also showed improvement on fibrosis progression (9% vs 36%). Relative risk of MASH resolution was 4.5 (95% CI: 1.1–18.9; p = 0.017), independent of diabetes status. However, it is important to note the small sample size of this study, and that the NAFLD Activity Score (NAS) did not differ, perhaps suggesting the 1.8 mg dose was not optimal for broader histologic change [29]. The larger 72 week semaglutide trial (n = 320) extended these findings. Once a day injections produced stepwise gains in weight loss, enzyme normalization and steatohepatitis resolution, peaking at 59% with the 0.4 mg dose versus 17% on placebo. In this trial ≥80% of patients on doses of semaglutide 0.2 mg/day or higher achieved an improvement in NAS, compared with 44% of controls [28]. Despite these metabolic and inflammatory benefits, an improvement in fibrosis stage failed to reach statistical significance, with absolute response rates of 32 - 49% against 33% for placebo. Pooling both of these RCTs (liraglutide and semaglutide) shows a quadrupling of the odds of MASH resolution without fibrosis worsening (OR ≈ 4.1), yet no definitive advantage for fibrosis regression itself (OR ≈ 1.5, p = 0.06) [72]. This pattern implies that longer treatment horizons or larger cohorts may be required to detect improvements in liver fibrosis stage. Beyond biopsy trials, smaller observational studies report that liraglutide lowers surrogate fibrosis indices such as APRI [80], fibrosis 4 index (FIB-4) [81], NAFLD Fibrosis Score (NFS) and liver stiffness on elastography [82]. These markers support a modest anti-fibrotic signal, but they do not yet replace histological confirmation. The underlying reasons for the absence of fibrosis improvement, despite its occurrence with ≥10% weight loss in lifestyle intervention studies remain unclear [21, 83]. There

are several potential causes why early GLP-1 RAs trials have not mirrored their steatohepatitis success with parallel fibrosis gains: short study duration, limited sample size, heterogeneity in disease severity and genetics, and the intrinsic sampling error of liver biopsy itself. Collectively, randomized and observational data indicate that GLP-1 RAs consistently resolve steatohepatitis and improve metabolic parameters, establishing them as viable candidates for MASH therapy. Yet convincing evidence of fibrosis reversal is still pending, highlighting the need for long-term phase 3 programmes and better non-invasive fibrosis endpoints.

3. Summary

3.1. Future directions

Future research into the use of GLP-1 receptor agonists for MASLD should address several important aspects. First, larger clinical trials with extended treatment durations are necessary to confirm the effectiveness of GLP-1RAs in improving liver-related outcomes, particularly morbidity and mortality among patients with more severe stages of liver disease. Key future direction involves exploring the effectiveness of approved therapeutic doses in clinical practice, since current evidence comes from trials using different dosing regimens that may limit direct applicability. Furthermore, robust studies specifically targeting non-diabetic populations with MASLD are urgently required, as the majority of existing trials primarily included individuals with diabetes, thus limiting generalizability. Future studies should also delve into personalized medicine aspects, including genetic factors and metabolic predictors, to better identify individuals who are likely to benefit most from treatment with GLP-1RAs [84, 85]. Additionally, considering sex-related differences in the prevalence and response to treatment observed in MASLD, future adequately powered trials should aim to investigate potential gender-specific therapeutic effects of GLP-1RAs [86]. Finally, emerging dual agonists such as tirzepatide, which targets both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, present promising therapeutic options. Investigating these novel agents could substantially improve management approaches in obesity, diabetes, and MASLD [87-89]. Thus, comprehensive and carefully designed clinical trials evaluating these multidimensional aspects are crucial to clarify and enhance the role of GLP-1RAs in treating MASLD.

3.2. Conclusions

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its severe form, metabolic dysfunction-associated steatohepatitis (MASH), are emerging as significant public health issues due to their rising global prevalence, closely linked to obesity and type 2 diabetes. MASLD and MASH not only carry risks of progressive liver disease and cirrhosis but also significantly elevate cardiovascular risk, becoming a critical factor in morbidity and mortality. Lifestyle modifications remain the cornerstone of MASLD and MASH management, particularly through weight reduction achieved by dietary interventions and physical activity. However, maintaining sustained weight loss is challenging, and pharmacological options have been limited until recently. Resmetirom has recently been provisionally approved for MASH treatment with fibrosis in the United States, marking a significant advancement in pharmacotherapy. This review explored the potential of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), highlighting their multifaceted mechanisms, including improvements in glycemic control, appetite suppression, weight loss, and potential direct hepatocellular actions. Clinical evidence demonstrates that GLP-1 RAs, notably liraglutide and semaglutide, consistently reduce liver fat content and improve hepatic enzyme profiles. Their beneficial effects extend beyond metabolic improvements, showing promise in histological resolution of steatohepatitis. These beneficial effects are presented in Table 1. However, despite encouraging results, definitive evidence for fibrosis improvement remains inconclusive, likely due to limitations such as small sample sizes and short trial durations. The adoption of GLP-1 RAs in clinical practice for MASLD and MASH treatment is promising but necessitates larger and longer-term studies to better understand their full therapeutic potential, especially regarding fibrosis reversal. This review emphasizes the need for future research to overcome current limitations and firmly establish GLP-1 RAs as a standard treatment modality for metabolic liver disease.

Disclosure

Author contributions:

All authors contributed to the article.
Conceptualization: MB;
Methodology: MB;
Software: TS, ABi, IC;
Check: JG, HB;
Formal analysis: MK, KN;
Investigation: MB, TS, PK;
Resources: IC, MK, HB;
Data curation: IC, JG, TS;
Writing-rough preparation: MB, IC, KN;
Writing - review and editing: MB, MK, IC, JG, HB, TS, PK, ABi, KN, ABr;
Visualization, KN, ABr;
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