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Review Article

Current Status of Glucagon-like Peptide-1 Receptor Agonists in Metabolic Dysfunction-associated Steatotic Liver Disease: A Clinical Perspective

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently a pressing public health issue associated with adverse outcomes such as cirrhosis, malignancy, transplantation, and mortality. Lifestyle modifications constitute the most effective and fundamental management approach, but they often pose challenges in sustaining long-term clinical benefits. Hence, there is a critical need to enhance our understanding through pharmacological management, which unfortunately remains limited. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a leading treatment in the fields of diabetes and obesity, with recent preclinical and clinical studies indicating significant benefits in the management and treatment of MASLD. Our article begins by reviewing the beneficial therapeutic components of GLP-1RAs in MASLD. Subsequently, from a clinical research perspective, we concluded with the liver outcomes of current primary GLP-1RAs and co-agonists. Finally, we presented our insights on clinical concerns such as appropriate trial endpoints, management of comorbidities, and future developments. In conclusion, the benefits of GLP-1RAs in MASLD are promising, and background therapy involving metabolic modulation may represent one of the future therapeutic paradigms.

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Introduction

Nonalcoholic fatty liver disease has been used to describe hepatic steatosis without significant alcohol intake. However, in response to the growing understanding of the disease and its associated stigma, metabolic dysfunction-associated fatty liver disease was proposed by an international consensus panel in 2020.[1] Later, the American Association for the Study of Liver Diseases led the adoption of a new multisociety Delphi consensus in 2023, proposing metabolic dysfunction-associated steatotic liver disease (MASLD) as another replacement term for nonalcoholic fatty liver disease.[2] Metabolic dysfunction-associated fatty liver disease and MASLD remain controversial but are not considered superior to each other. This review will use the term MASLD, defined as the presence of hepatic steatosis with no other discernible cause, in conjunction with at least one cardiometabolic risk factor (CMRF), such as type 2 diabetes mellitus (T2DM), obesity, hypertension, or dyslipidemia.[2] The spectrum of MASLD encompasses metabolic dysfunction-associated steatotic liver, metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, and cirrhosis, representing a significant global public health threat. Recent epidemiological data indicate an overall incidence of MASLD ranging from 46.1 to 46.9 new cases per 1,000 person-years, with a prevalence estimated at 30.05% to 32.4%.[3–5] Regional prevalence varies significantly due to ethnic, genetic, and lifestyle factors, with the lowest rates observed in Western Europe and the highest in Latin America, ranging from 25.1% to 44.3%.[4] The burden of MASLD is projected to increase exponentially, with anticipated rises of 21% and 63% in cases of MASLD and MASH, respectively. Furthermore, MASLD-related mortality and the total number of advanced liver diseases are expected to double.[6,7]

Despite the current severe disease burden, effective medical management options for MASLD remain limited. Primary measures still rely on lifestyle improvements through diet and exercise. The first targeted therapy for MASLD, a selective thyroid hormone receptor-β agonist called resmetirom, was approved by the U.S. Food and Drug Administration (FDA) in March 2024 and is recommended in the latest European Association for the Study of the Liver guidelines for MASLD with locally approved F2/F3 fibrosis.[8] Based on data from the MAESTRO-NASH trial, resmetirom demonstrated histological benefits with a number needed to treat of five for the resolution of MASH and 8.5 for fibrosis regression,[9] thus posing significant economic challenges. Moreover, evidence on the long-term efficacy and safety of prolonged use, as well as combination therapy with other drugs, remains insufficient.[8] There is an urgent need to expand therapeutic options for MASLD.

Glucagon-like peptide-1 (GLP-1) is one of two known in-

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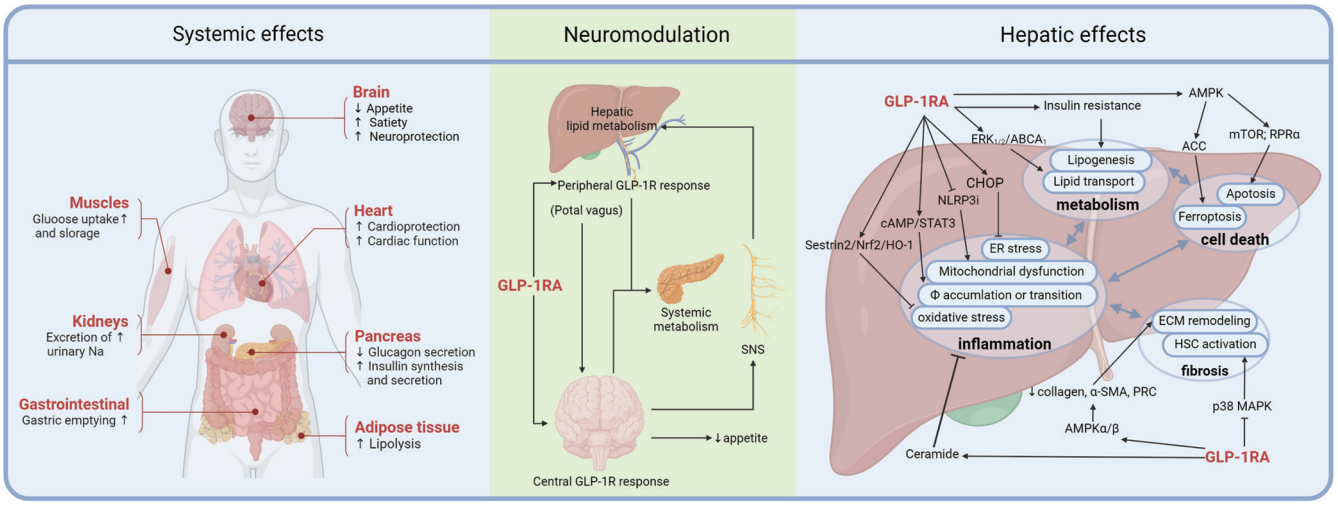

Fig. 1. Systemic, neuromodulatory, and hepatic effects of GLP-1RA. GLP-1RA, GLP-1 receptor agonist; SNS, sympathetic nervous system; ER, endoplasmic reticulum; CHOP, C/EBP homologous protein; NLRP3i, NLRP3 inflammasome; PRC, Picrosirius red content; Φ, macrophages. ↓, decrease; ↑, increase. Image created with BioRender.com.

cretins, contributing to the regulation of glucose metabolism, pancreatic function, appetite, inflammation, and cardiovascular pathophysiology.[10] GLP-1 receptor agonists (GLP-1RAs), or incretin mimetics, are currently among the most promising drugs for adjusting metabolic function, playing significant roles in the management of T2DM, and some have been approved for obesity management. They are actively being studied in clinical research for other conditions, such as metabolic disorders related to skeletal muscle preservation,[11] MASLD,[12] and neurological disorders like Parkinson's disease.[13] Regarding the application of GLP-1RAs in MASLD, current understanding suggests they can serve as additional pharmaceutical options in lifestyle management for patients with complications like obesity and T2DM. However, there is no prioritized recommendation between glucose-lowering agents or weight-loss drugs, apart from avoiding sulfonylureas that can cause weight gain.[8,14,15] Although most approved GLP-1RAs and co-agonists have not yielded satisfactory results in histological endpoint clinical trials, the future of managing and treating MASLD holds promise.

In this article, we will conclude with the potential pharmacological mechanisms of GLP-1 treatment for MASLD, including clinical insights into GLP-1RAs and co-agonist drugs. Ultimately, we will discuss the challenges and future prospects of GLP-1RA management and treatment of MASLD.

Therapeutic role of GLP-1RA in MASLD

Improvement of MASLD by GLP-1RA is multidimensional, encompassing three main aspects: its effects on overall metabolic status, neuroregulatory functions, and its controversial direct effects on the liver (Fig. 1).

Systematic metabolic benefits

In circulation, GLP-1 is primarily produced by intestinal L cells and pancreatic α cells (its activity remains controversial), stimulated by the digestion of food or bile acids. The overall physiological effects include promoting insulin secretion, inhibiting glucagon release, delaying gastric emptying, and influencing appetite.[16] GLP-1RAs achieve sustained pharmacological effects by resisting degradation by DPP-4 in the body, consequently contributing to hyperglycemia and insulin resistance related to glucose metabolism,[17,18] lipid profile alterations, changes in fat composition, visceral fat accumulation, and obesity related to lipid metabolism,[19–21] which constitute the systemic metabolic characteristics of interest in MASLD management.

Glucose is a substrate for lipogenesis, and either dietary intake of glucose and fructose or hyperglycemia due to T2DM-associated insulin resistance can lead to hepatic *de novo* lipogenesis.[22] The relationship between insulin resistance and MASLD has not been fully elucidated, but potential mechanisms that promote MASLD/MASH include influencing hepatic lipid synthesis and catabolism, as well as impairing mitochondrial fatty acid β-oxidation function.[23] Retrospective cohort studies indicate that T2DM significantly increases the risk of cardiovascular events, malignant tumors, and liver-related outcomes in MASLD patients.[24] Another study reported that even within the normal range, elevated HbA1c is associated with MASLD progression.[25] Another systemic benefit of GLP-1RA is its improvement of lipid metabolism. Macrocharacterization consists of visceral fat and body weight, which can mutually promote insulin resistance by promoting lipogenesis and inflammation that affect the progression of MASLD.[26] Lifestyle-induced weight loss of 7–10% can improve MASH with fewer risk factors, and more than 10% can be beneficial for fibrosis.[27]

Interestingly, a meta-analysis discussed the efficacy of different types of drugs, including anti-fibrotic, anti-metabolic, and anti-apoptotic agents, on MASH and fibrosis. Overall, anti-metabolic drugs performed the best in both aspects, with odds ratios of 2.15 and 1.35, while anti-fibrotic drugs showed ratios of 0.86 and 1.11.[28] The overall metabolic improvement is indeed beneficial for MASLD.

Neuromodulation

There is substantial evidence demonstrating that liver neuroregulation influences hepatic metabolism, immunity, and regeneration processes. Neurostructural damage and functional disruptions can interact with components such as steatosis, fibrosis, and inflammation, collectively forming the neuroregulatory phenotype of MASLD.[29] In terms of the nervous system, GLP-1 receptor (GLP-1R) expression is enriched in central nervous system (CNS) regions, including the

hypothalamus, which regulates appetite, and the brainstem, which primarily secretes brain-derived GLP-1, as well as in the peripheral vagus nerve.[30,31] On one hand, neuro-signals mediated by GLP-1 activation regulate food intake by controlling appetite and satiety and modulate endocrine organs like the pancreas, thus affecting overall metabolism.[32] On the other hand, local hepatic lipid metabolism is regulated by sympathetic neural signals through the brain-liver axis, while glucose metabolism receives CNS regulation, although the signaling pathways remain unclear.[32,33]

Under physiological conditions, besides the paracrine secretion pathway in the gastrointestinal tract, most endogenous GLP-1 in circulation is locally deactivated by DPP-4 and the liver,[34] making it difficult to directly enter the CNS through the blood-brain barrier. Activation of the peripheral nervous system likely occurs primarily through stimulation of the hepatic vagal nerve in the portal area. Brain-derived GLP-1 pathways are generally not activated unless metabolic balance is disrupted, such as under stress conditions. Additionally, the central and peripheral nervous pathways activated by GLP-1 are independent and synergistic.[30,35] At therapeutic doses, whether GLP-1RA can directly affect the CNS depends on the drug's properties. For instance, exenatide can cross the blood-brain barrier, while semaglutide (SEMA) has a limited ability to do so.[36] Generally, drugs with smaller molecular weights are considered to have more potential in this regard.[32]

Direct hepatic effect

The direct hepatic effects of GLP-1RA have not been fully elucidated. Preclinical experiments have shown that GLP-1RA can ameliorate inflammation by modulating processes such as endoplasmic reticulum stress,[37] mitochondrial dysfunction,[38] oxidative stress,[39] and macrophage function.[40] GLP-1RA can also influence hepatic stellate cell activation and extracellular matrix adjustment.[41,42] In addition, lipid metabolism, inflammation, fibrosis, and cell death interact with each other, and the respective roles of GLP-1RA therein collectively comprise its therapeutic pathway in MASLD. However, controversy exists regarding whether these effects are mediated through the direct effects of GLP-1RA targeting intrahepatic cells.

One concern is the lack of conclusive evidence for GLP-1R expression in the liver. Some studies have reported GLP-1R expression identified through immunohistochemistry in human liver tissue or liver cell lines,[43,44] but RNA sequencing has not detected GLP-1R in human liver tissue, including the non-parenchymal Kupffer or stellate cells.[45] A review based on recent data using next-generation antibodies suggests that GLP-1R is not expressed in the human liver, regardless of its structural integrity.[46] On the other hand, some experiments seem to confirm direct hepatic effects of GLP-1RA. One study reported the presence of GLP-1R on the membrane of human liver cells, which undergoes endocytosis following GLP-1RA stimulation and acts by regulating downstream molecules of insulin signaling.[47] However, whether these potential hepatic effects are fully or partially mediated through GLP-1 signaling remains uncertain. There is a viewpoint suggesting that observed potential direct effects on liver cells may involve mechanisms independent of GLP-1 signaling entirely.[46]

The mainstream view holds that the canonical GLP-1 receptor is not expressed in the human liver, and any hepatic effects are likely mediated through extrahepatic mechanisms rather than direct action.[12] Canonical GLP-1 receptor signaling involves coupling GLP-1R with Gαs, a subtype of Gα subunit, but GLP-1R can also initiate diverse signaling patterns through non-Gαs pathways.[48] Given the structural absence of GLP-1R identified in human liver tissue, this appears to be a compromise.

Further clarification on the hepatic benefits of GLP-1RA is urgently needed, as these insights could contribute to explaining the pharmacological actions in MASLD and the formulation of clinical strategies.

Status of GLP-1RA drug in developing MASLD indication

Generally, targeted drugs include single GLP-1R agonists and co-agonists, as well as combination formulations, innovative oral peptide preparations, and non-peptide small molecule agonists. GLP-1-targeted therapies have seen continuous updates over the past decades. Here, we primarily discuss GLP-1RAs that are currently approved and under consideration for MASLD, along with some co-agonist strategies showing promising results. Critical clinical trial outcomes and ongoing registered trials are summarized in Tables 1 and 2, respectively.[49–53]

Liraglutide

Liraglutide, developed by Novo Nordisk in Denmark, is currently the most widely used daily formulation of GLP-1RA, with a half-life of 13 h. The FDA approved liraglutide (Victoza) at doses of 0.6 mg, 1.2 mg, and 1.8 mg daily for T2DM patients with unsatisfactory diet or exercise control, and 2.4 mg and 3 mg as a chronic weight management drug.[54]

The LEAN trial first evaluated the anti-steatotic effects of liraglutide in patients with MASH. Compared to placebo, after 48 weeks of treatment with liraglutide 1.8 mg daily, the treatment group showed significant histological improvement [risk ratio = 4.3, 95% confidence interval (CI) = 1.0–17.7], including resolution of MASH and absence of liver fibrosis progression.[49] Treatment with liraglutide 0.9 mg daily and 1.2 mg daily after 96 weeks and six months, respectively, both demonstrated reductions in hepatic steatosis, and the 0.9 mg treatment group underwent histological assessment revealing improvement in hepatitis.[55,56] Furthermore, a trial conducted in patients without T2DM indicated that liraglutide 3 mg daily provided benefits comparable to those of structured lifestyle changes in improving liver enzymes, insulin resistance, and weight, which are considered effective and fundamental measures for managing and improving MASLD/MASH.[15,57] Notably, liraglutide exhibits relatively clear antifibrotic effects among GLP-1RAs, although statistically significant improvements in fibrosis were not observed in clinical trials.[49,58]

Considering that GLP-1RA's beneficial effects on MASLD may relate to improving systemic metabolism rather than direct hepatic effects, comparing hepatic benefits among different antidiabetic medications is meaningful. Compared to sulfonylureas and metformin, liraglutide demonstrates advantages in glycemic control (assessed by HbA1c levels) and reduction of liver fat content (LFC) in patients with MASLD and T2DM, with a more significant difference observed over sulfonylureas.[59] In MASLD patients with inadequate glycemic control on metformin, sitagliptin (a DPP-4 inhibitor) and liraglutide 1.8 mg daily showed no significant differences in improving LFC assessed by MRI-PDFF, visceral adipose tissue, and weight reduction; however, both were significantly better than insulin glargine.[60] Additionally, there were no statistically significant differences in glycemic control between the two medications, and neither demonstrated significant benefits for liver fibrosis.[60]

Currently, there is no discussion regarding the differential efficacy of different doses of liraglutide in the treatment

Table 1. Available histological data of candidate drugs

Drug	Study design	Population	Arms	Outcomes		Safety	Registration number
				Resolution of MASH	Improvement of fibrosis		
Liraglutide[49]	Phase 2 RDBPC 48w	52 patients with MASLD	1:1 liraglutide QW SQ 1.8 mg/placebo	39%:9% (RR = 4.3 [1.0–17.7])	Significantly less progression of fibrosis; Decrease in fibrosis score with no statistical difference	mild to moderate gastrointestinal response (81%)	NCT01237119
Semaglutide[50,51]	Phase 2 RDBPC 72w	320 patients with MASH and F1-3 fibrosis	1:1:1:1 semaglutide QD SQ 0.1 mg/0.2 mg/0.4 mg/placebo	40%:36%:59%:17% (0.4 mg RR = 6.87 [2.6–17.6])	49%:32%:43%:33% No statistical difference	gastrointestinal response (60–70%, not dose-dependent) no AP, rare SHE, and tumor correlation unknown	NCT02970942
	Phase 2 RDBPC 48w	71 patients with MASH and cirrhosis	2:1 semaglutide QW SQ 2.4 mg/placebo	34%:21% No statistical difference	11%:29% No statistical difference	mild to moderate gastrointestinal response (77%) more liver events but hepatic function remained stable	NCT03987451
Tirzepatide[52]	Phase 2 RDBPC 52w	190 patients with MASH and F2-3 fibrosis	1:1:1:1 tirzepatide QW SQ 5 mg/10 mg/15 mg/placebo	44%:56%:62%:10% (15 mg RD = 53 [37–69])	55%:51%:51%:30% (15 mg RD = 21 [1–42])	mild to moderate gastrointestinal response	NCT04166773
Survodutide[53]	Phase 2 RDBPC 48w	293 patients with MASH and F2-3 fibrosis	1:1:1:1 Survodutide QW SQ 2.4 mg/4.8 mg/6.0 mg/placebo	47%:62%:43%:14%	34%:36%:32%:18% No statistical difference	mainly gastrointestinal response (overall related incidence, 82%)	NCT04771273

Histologic improvements in outcomes follow the definitions below: regression of NASH is defined as a decrease of at least two points in the NASH Activity Score (NAS); resolution of NASH is defined as a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis; improvement in liver fibrosis is defined as a ≥1 decrease in the NASH CRN fibrosis scale. RDBPC, randomized double-blind placebo control; SQ, subcutaneous injection; RR, risk ratio; RD, risk difference; AP, acute pancreatitis; SHE, severe hypoglycemic episode.

Table 2. Representative ongoing clinical trials involving GLP-1RA

Drug	Registration number	Status	Study design	Estimated sample size	Population	Duration (weeks)	Interventions (control)	Primary outcome measures	Estimated completion time
Semaglutide	NCT04822181	Recruiting	Phase 3, RDBPC	1,200	MASH	240	Semaglutide target dose once weekly SQ	Resolution of MASH at week 72; Improvement of fibrosis at week 72; Cirrhosis-free survival at week 240	April 25, 2029
Semaglutide	NCT05813249	Recruiting	Phase 4, open, non-randomized	180	T2DM with MASLD	48	Semaglutide PO; Semaglutide SQ; Tocopherol and/or actos	Improvement of severity of hepatic steatosis evaluated by CAP	August 15, 2024
Dulaglutide	NCT03648554	Not yet recruiting	Phase 4, open, randomized, controlled	93	T2DM with MASH	52	Dulaglutide 1.5 mg/w SQ (reinforced dietary monitoring)	Resolution of MASH	March 30, 2024
Survodutide	NCT06309992	Recruiting	Phase 3, RDBPC	160	MASH with	48	Survodutide SQ	LFC and body weight change	March 9, 2026
Efinopegdutide	NCT05877547	Recruiting	Phase 2b, RDBPC	300	MASLD/ MASH	52	Efinopegdutide SQ, (Placebo) (Semaglutide SQ, dose-escalation)	Resolution of MASH; Safety assessment evaluated by percentage of AE and related withdraw	December 5, 2025
Cotadutide	2021-005484-53	Ongoing	Phase 2b/3, RDBPC	1860	MASH with fibrosis	84	Cotadutide SQ	Regression of MASH at week 48 and 84; Improvement of fibrosis at week 84	April 19, 2024

Hepatic diagnosis is determined by histologic evidence, and the outcomes share the same histological endpoint definitions as in Table 1. RDBPC, randomized double-blind placebo control; T2DM, type 2 diabetes mellitus; SQ, subcutaneous injection; CAP, controlled attenuation parameter; PO, oral intake; LFC, liver fat content; AE, adverse event.

of MASLD. Current understanding suggests that anti-obesity drugs cannot be used alone for diabetes management in obese patients with diabetes; they need to be used in combination with other hypoglycemic drugs or insulin, thereby posing a risk of hypoglycemia related to the type of combined drug and dose.[61] In clinical trials of liraglutide for MASLD, the dose setting is still mainly based on the diabetes condition. Clinical experience targeting T2DM has shown that the 3 mg dose is more effective than the 1.8 mg dose in managing T2DM in combination with other hypoglycemic drugs and improving weight. Although gastrointestinal adverse events (AEs), such as nausea, are more common in the 3 mg treatment group, other AEs such as hypoglycemic episodes and pancreatitis did not show dose dependency.[62] Another study demonstrated that the obesity control dose of liraglutide can significantly reduce the risk of progression to diabetes in patients with prediabetes.[63] Considering that T2DM and MASLD can reciprocally cause and affect each other, and given liraglutide's potential therapeutic characteristics for MASLD, which may be beneficial for anti-fibrosis, more aggressive use of higher doses may bring greater clinical benefits in some groups, such as those with higher-grade fibrosis with or without T2DM.

SEMA

SEMA, a weekly GLP-1RA developed by Novo Nordisk, enhances its affinity for albumin by incorporating two amino acids into human GLP-1, resulting in resistance to degradation in the body.[64]

SEMA has demonstrated clear clinical improvements in MASLD/MASH and allows use beyond the instructions, particularly in patients with T2DM and obesity.[15] Phase II trials targeting MASH have shown that treatment with SEMA 0.4 mg daily for 72 weeks resulted in more patients with liver fibrosis stage F2/F3 achieving improvement in MASH without progression of liver fibrosis (odds ratio = 6.87, 95% CI = 2.60–17.63) compared to placebo.[50] Moreover, SEMA has significant benefits in improving clinical symptoms and quality of life for patients as well.[65,66] A network meta-analysis ranked SEMA 0.4 mg first in the resolution of MASH among alternative treatments [surface under the cumulative ranking (SUCRA) = 0.89], higher than liraglutide (SUCRA = 0.84) and resmetirom (SUCRA = 0.44).[67]

Due to effective management of weight, metabolism, and LFC, it is expected to yield clinical benefits in liver fibrosis. However, current data from SEMA clinical trials indicate that therapeutic effects on liver fibrosis are unclear, with potential benefits possibly involving the delay of fibrosis progression.[50] *In vitro* experiments suggest that SEMA may participate in regulating the fibrosis process by improving factors such as inflammatory or metabolic triggers of fibrosis, like IL-6 and free fatty acids, as well as fibrotic structural features.[68–70] However, in patients with cirrhotic conditions (fibrosis stage 4), there is no difference in MASH regression compared to placebo treatment after SEMA 2.4 mg weekly.[51] The insufficient trial duration and the weakened ability of higher-grade fibrosis to change, secondary to factors like weight loss, are considered the primary reasons for the lack of positive outcomes.[71] Differences in pathological mechanisms between fibrosis and cirrhosis are also assumed to contribute to these outcomes.[72] Interestingly, a meta-analysis reported that SEMA significantly reduces liver stiffness (mean difference = −3.08 kPa; 95% CI: −3.39, −2.77), although subgroup analysis based on formulation and dosage was not conducted.[73] Currently, a Phase III trial (NCT04822181) investigating SEMA's effect on improving liver fibrosis is ongoing and is expected to conclude on April 25, 2029.

The oral SEMA formulation was approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. A Japanese study discussed the safety and efficacy of oral SEMA 14 mg in patients with MASLD and T2DM.[74] Besides the expected improvements in metabolism and hepatic steatosis, liver fibrosis markers, including the fibrosis-4 index, ferritin, and type IV collagen 7s, were observed to decrease after 24 weeks of treatment. However, there was no significant change in liver stiffness. Enhancing understanding of SEMA's oral formulation in MASLD is necessary, as it may improve compliance and thus lead to better clinical outcomes. A tocopherol and/or actos-controlled clinical trial (NCT05813249) concluded on April 2, 2024, assessing the effects of oral and subcutaneous SEMS on hepatic steatosis and fibrosis improvement in MASLD with T2DM. Relevant data from this trial have not yet been published.

Exenatide

Exendin-4 is a hormone extracted from the venom of the lizard Heloderma suspectum, exhibiting biological effects similar to human GLP-1. Exenatide, a synthetic version of exendin-4 produced industrially, was the first GLP-1RA approved for the market [exenatide twice daily (EX-BID)], followed by a long-acting formulation that improved the delivery system [exenatide once a week (EX-QW)].[75]

A comparative study conducted in China over 24 weeks evaluated the treatment of MASLD and T2DM in patients not receiving additional glucose control medications.[76] EX-BID demonstrated superior outcomes compared to insulin glargine in liver-related indicators such as LFC, FIB-4 index, and liver enzymes, as well as metabolic indicators like postprandial glucose and LDL-C. A meta-analysis based on low-quality data reported that EX-BID was the most effective method for reducing LFC compared to liraglutide and long-acting formulations like EX-QW.[77] However, there is currently no histological evaluation data confirming these findings for EX-BID; other investigations have shown that LFC reduction associated with metabolic disorder improvement and a relative decrease of 30% combined with an improvement in ALT may be predictive of a more active histological response.[78,79] A retrospective study conducted in Turkey reported that treatment with EX-BID led to significant decreases in NFS and APRI scores, although FIB-4 showed a completely opposite trend.[80] The small sample size (n = 50) may have contributed to this discrepancy. Another notable issue is the heterogeneity of metabolism, which could be crucial in treating MASLD. T2DM patients combined with MASLD appear to respond better to EX-BID or EX-QW compared to those without MASLD, resulting in greater benefits in terms of LFC and cardiometabolic improvement.[81,82] Additionally, EX-BID has been shown to increase adiponectin levels, potentially offering cardiovascular benefits.[81]

Unlike long-acting formulations, there is a general consensus that EX-BID is used as an add-on therapy to oral antidiabetic medications or insulin, which is why its efficacy is usually compared to insulin glargine. This strategy is more flexible and may offer potential additional benefits. A six-year study in the United States indicated that combination therapy with pioglitazone/exenatide (twice daily)/metformin effectively reduced the incidence of high-stage liver fibrosis (7% vs. 26%) and steatosis (31% vs. 69%) compared to single medications such as metformin, glipizide, or insulin.[83] Interestingly, EX-QW appears not to have a significant additive effect. In the DURATION-8 trial, dapagliflozin as monotherapy and in combination with EX-QW showed trends favoring improvements in LFC, glucose and lipid metabolism, and liver fibrosis scores at the end of the study, but no sig-

nificant statistical differences were observed.[84] Similar results were found in trials evaluating hepatic lipid changes in patients with T2DM.[82] The effects of short-acting agents on MASLD are likely multifactorial, and these issues will be further discussed in the section on lixisenatide.

Dulaglutide

Dulaglutide, developed by Eli Lilly, achieves its long-acting effect by being linked to a human IgG4-Fc heavy chain, which helps resist degradation by DPP-4.[85] Dulaglutide 1.5 mg has demonstrated non-inferiority in diabetes control compared to liraglutide 1.8 mg, and comparable weight reduction efficacy to oral SEMA (Orforglipron) 3 mg.[86,87]

Differing from the effects observed in T2DM, the therapeutic efficacy of dulaglutide for MASLD is not particularly compelling based on current statistics. A small retrospective study in Japan reported that dulaglutide 0.75 mg improved liver enzymes, glucose metabolism, and liver stiffness in patients with MASLD and T2DM after 12 weeks; however, it also resulted in an undesired elevation in the controlled attenuation parameter (evaluating LFC).[88] Interestingly, one patient underwent histological evaluation before and after treatment, showing a complete histological improvement from a NAS score of 6 and fibrosis stage 1 to normal histology after treatment. A prospective clinical trial conducted in India reported a significant decrease in LFC, but liver enzymes, liver stiffness, and pancreatic fat did not show statistically significant differences after 24 weeks of treatment with dulaglutide 1.5 mg in patients with MASLD and T2DM.[89] Glucose levels were balanced between groups by other glucose-lowering medications, suggesting a potential mismatch in liver benefits. However, it is noteworthy that a 26-week treatment of dulaglutide 1.5 mg or tirzepatide 5 mg showed comparable outcomes in improvements of MASH and liver fibrosis biomarkers, including liver enzymes, keratin-18, procollagen III, and adiponectin.[90] A recent clinical trial assessing the histological benefits of tirzepatide for MASH reported that tirzepatide 5 mg achieved at least one-stage improvement in fibrosis for 55% of patients without worsening MASH, and 43.6% of patients experienced MASH resolution with no worsening fibrosis.[52] Therefore, the potential benefits of dulaglutide for MASLD may be promising. Clinical trial data from NCT03648554 evaluating dulaglutide based on histological assessment have not been published, and further clinical trials are needed to comprehensively assess the liver benefits of dulaglutide.

Lixisenatide and beinaglutide

Lixisenatide and beinaglutide, including EX-BID as discussed earlier, are classified as short-acting GLP-1RAs based on pharmacokinetic characteristics such as clearance half-life and concentration-time distribution.[91] In essence, long-acting formulations can achieve sustained therapeutic drug concentrations in the body, whereas short-acting formulations produce transient concentration peaks shortly after injection.

Lixisenatide is a daily GLP-1RA developed by Zealand Pharma, which prolongs its half-life through structure-inducing probe technology based on exendin-4/exenatide.[92] Data from diabetes trials indicate that lixisenatide can improve liver transaminases, especially ALT.[93] Another study compared the efficacy of lixisenatide, dapagliflozin, sitagliptin, or pioglitazone, combined with basal metformin use over 72 weeks in patients with MASLD and T2DM.[94] The lixisenatide group demonstrated significant advantages in both glycemic control and liver fibrosis prediction indicators, such as the AST to platelet ratio index.

Beinaglutide is another short-acting recombinant human GLP-1RA that closely resembles human GLP-1(6-37), approved in China for the indications of type 2 diabetes mellitus and weight loss. In the context of patients with MASLD and diabetes, only one clinical study evaluated the benefits of beinaglutide treatment over 24 weeks compared to recommended standard lifestyle management for T2DM. Beinaglutide demonstrated significant advantages in weight reduction, but no significant differences were observed between the two groups in terms of improvements in liver stiffness, HbA1c control, liver enzymes, and blood lipids.[95]

Short-acting GLP-1RAs are generally less studied in MASLD. EX-BID stands out unexpectedly. On one hand, exenatide is a prototypical GLP-1RA known for its potent effects on weight reduction and lowering LFC, instilling confidence in its use for MASLD. On the other hand, limitations in available GLP-1RA choices have led to selection biases, particularly in the early 2010s and in regions where access to other GLP-1RAs was relatively delayed.[76,81,96,97] The main factor contributing to the lack of greater investment in lixisenatide and other short-acting agents for MASLD may be their influence on metabolic function, including pharmacokinetic differences induced by a single-dose method and their effects on gastric emptying,[91] which could limit their effectiveness in improving glycolipid metabolism.[98] Indeed, different temporal patterns of GLP-1RAs tend to correspond to different clinical characteristics.[99] Short-acting GLP-1RAs, regarded as postprandial GLP-1, are typically used as add-on therapy for T2DM. However, in terms of MASLD, short-acting agents still hold potential clinical advantages. From a management perspective, with the necessity of glucose-lowering medications like metformin or basal insulin in populations with T2DM complications,[61] combination products with routine injections or basal insulin may offer compliance advantages, simpler titration strategies (adjusting to maximum maintenance dose only once), and lighter economic burdens. From a therapeutic benefit standpoint, impaired GLP-1 secretion mediated by blood glucose has been observed in MASLD patients.[100] Short-acting GLP-1RAs mimicking physiological processes may provide a gentler and more personalized treatment strategy.[101] Therefore, the long-term liver benefits of short-acting agents warrant further attention in personalized medicine.

Co-agonist strategy

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptor (GCGR) are currently the primary targets alongside GLP-1R for combined stimulation. GIP, another type of incretin, contributes to improving white adipose tissue function by increasing fat storage and reducing visceral ectopic deposition. It also directly contributes to insulin sensitization and expands the therapeutic domain of GLP-1RA by targeting the CNS to reduce nausea.[102] The latter, glucagon, is a basic glucose-regulating hormone with catabolic and thermogenic actions, but it also increases glucose levels and the risk of gluconeogenesis.[103] Moreover, GCGR is expressed in the liver and shows direct hepatic benefits, including a reduction in lipid content and an increase in metabolic expenditure.[45] Currently, the strategy of multiple receptor stimulation is actively expanding indications in metabolic disorders, particularly in MASLD, and some medications have reported more potent therapeutic efficacy compared to single GLP-1RA.

Tirzepatide is an approved GLP-1R/GIP dual agonist developed by Eli Lilly, garnering significant attention alongside SEMA in the field of T2DM and weight loss. A phase 2 trial (SYNERGY-NASH) first demonstrated *in vivo* that GLP-1RA

can achieve histological reversal of hepatic fibrosis in MASLD.[52] Patients with MASH and F2/F3 stage fibrosis were treated with tirzepatide at doses of 5 mg, 10 mg, and 15 mg for 52 weeks, of which 58% of patients had T2DM. Regression of MASH showed dose dependency, with the 15 mg dose exhibiting the best response at 62% (vs. placebo 10%, risk difference = 53, 95% CI = 17–50). There was no significant difference between treatment groups in the improvement of liver fibrosis; the 5 mg dose of tirzepatide showed the best performance, with 55% of patients responding (vs. placebo 30%, risk difference = 25, 95% CI = 5–46). Safety profiles were favorable, with no significant differences in the incidence and profile of AEs between tirzepatide and placebo. Rough estimates based on the number needed to treat suggest tirzepatide is superior to resmetirom in both MASH regression and fibrosis improvement (1.9 vs. 5 and 4.8 vs. 8.5, respectively), and it shows a slight advantage in MASH regression over SEMA (1.9 vs. 2.4).[9,50] A phase 3 trial is not yet registered but is anticipated to commence soon.

Survodutide (BI 456906) is a GLP-1R/GCGR dual agonist developed by Boehringer Ingelheim, with outcomes of a phase 2 trial in MASLD and a phase 1 trial in cirrhosis published almost simultaneously with tirzepatide. In patients with MASH and F1-F3 stage fibrosis treated with survodutide for 48 weeks across doses ranging from 2.4 to 6.0 mg, regression of MASH without fibrosis progression did not show a dose-dependent trend, with the best response observed at 4.8 mg (62% vs. placebo 14%). Improvement in fibrosis was also assessed, showing a dose-dependent trend, with 34% of patients achieving at least a 1-stage improvement in fibrosis without MASH progression in the 6 mg group (vs. placebo 22%), although this did not reach statistical significance.[53] Survodutide is generally well tolerated in patients with compensated or decompensated cirrhosis, of which more than 80% are diagnosed with MASLD. It showed potential benefits in patients assessed at Child-Pugh A/B stages, including reducing liver volume and weight, and possibly improving liver stiffness and fibrosis (95% CI spans a wide range).[104]

Cotadutide by AstraZeneca and efinopegdutide by Merck Sharp & Dohme are other GLP-1R/GCGR dual agonists. Currently, there are limited clinical trials evaluating the efficacy of these two drugs in MASLD. Cotadutide has shown greater promotion of liver glycogen and fat consumption compared to liraglutide.[105] However, exploration of the MASLD indication was terminated in the U.S. based on strategic pipeline considerations (NCT05517226), although it is still ongoing in the EU (2021-005484-53). As for efinopegdutide, a 10 mg dosage demonstrated stronger reduction in LFC compared to SEMA 1 mg, despite a relatively higher safety risk.[106] Two additional clinical trials are being conducted to gather more data on adverse effects in different situations of liver injury, and a phase 2 trial investigating treatment effects for MASH with fibrosis based on histological assessment is ongoing (NCT05877547).

Problems in GLP-1RA development

Cost-effective and reliable trial endpoints for MASLD medication

Assessing long-term liver benefits in clinical trials has remained a complex issue. Clinical outcomes such as cirrhosis progression, liver transplant, and all-cause mortality are recognized as solid endpoints for evaluating drug efficacy in MASLD. It is estimated that clinical trials evaluating liver-related events in patients with MASLD and compensated or decompensated cirrhosis would require a minimum recruitment of 2,886 patients with at least four years of follow-up and 1,602 patients with at least two years of follow-up, respectively.[107] This poses a significant challenge for both the pharmaceutical industry and research activities. To date, no prospective clinical study of drug treatment has completed a comprehensive assessment of clinical benefits in MASLD. The interpretation of clinical outcomes in some retrospective studies remains problematic. In patients with T2DM and chronic liver disease attributed to MASLD, the risk of major adverse liver outcomes after GLP-1RA treatment over 10 years fails to decrease (15.8% vs. 11.2%, hazard ratio = 1.41, 95% CI = 0.53–2.23).[108] Another retrospective study reported that in a population with T2DM and previously diagnosed MASLD/MASH, GLP-1RA is associated with a decreased incidence of hepatocellular carcinoma (HCC) and a reduced risk of hepatic decompensation events compared with other antidiabetic agents.[109] These controversial findings may be attributed to issues of dosing strategy, statistical bias,[110] and the clinical stage of MASLD.

Short-term predictive indicators that are strongly correlated with clinical outcomes in MASLD are highly anticipated, but reliable surrogate endpoints are currently lacking.[111] The only acceptable alternative endpoint in drug development, histological evidence, consists of the resolution of steatohepatitis and no worsening of liver fibrosis, or improvement in liver fibrosis of at least one stage without worsening of steatohepatitis.[112] However, histological assessments are recognized to have variability in pathological readings and an unignorable placebo response. For instance, in phase 2 trials of SEMA 2.4 g, a substantial reduction in placebo response was observed in composite endpoints of MASH and fibrosis.[51,113] Based on indications for the drug industry released by the FDA in 2019, candidate drugs achieving histological outcomes can be conditionally approved, and there remains a necessity to refine the assessment of clinical outcomes in the future.[112] However, in recent years, the FDA has introduced the patient-focused drug development initiative, where patient-reported outcomes such as improvements in quality of life and healthy life years in MASH patients following treatment can serve as trial endpoints, potentially influencing final approval based on these data.[114] This may represent a pivotal shift, particularly for GLP-1RA, as it is based on metabolic improvement and has already been explored in some trials for exploratory research.[49,66]

Metabolic benefits of GLP-1RA in the management of weight-related MASLD

MASLD is highly correlated with other metabolic disorders and may even be a mutual cause, compounded by a wide range of disease development stages, making its management highly complex. GLP-1RA appears advantageous in this regard. The metabolic benefits of GLP-1RAs are summarized in Table 3.[115–133] It is noteworthy that these data primarily derive from clinical trials in T2DM or obesity, and given the heterogeneity of metabolic disorders, caution should be exercised. T2DM is the most significant and extensively studied comorbidity in MASLD, as reviewed recently.[134] Here, we specifically focus on the understanding of GLP-1RA in another critical metabolic disorder: obesity.

Overweight, including obesity (BMI ≥ 25 kg/m^2; 23 in partial Asian regions), is a manifestation of metabolic disorders and can constitute one of the diagnostic criteria for MASLD.[2] The relationship between obesity and MASLD is tightly intertwined. An estimated 51.3% of MASLD patients are obese, and the percentage rises to 81.8% in MASH,[22] with approximately 10–20% categorized as lean MASLD.[135] It is noteworthy that MASLD patients exhibit diverse clinical character-

Table 3. Extra-hepatic effects of leading GLP-1RAs

Drug	Glucose metabolism[115]			Lipid metabolism (Serum lipid profile)[115]	Weight (kg) and BMI[115]	Cardiovascular benefits[116–122]	Renal benefits[122–127]
	HbA1c (%)	FBG (mmol/L)	Insulin effects[128–133]				
Liraglutide	−1.04	−1.46	Improve insulin sensitivity slightly and beta cell function significantly.	Fail to improve.	−1.33 Improve BMI as well	Reduce cardiovascular mortality (HR = 0.87 [0.78–0.97]) and risk factors like overweight, SBP in T2DM. Fail to improve incidence of retinopathy events.	Reduce composite renal outcomes in T2DM (HR = 0.78 [0.67–0.92]).
Semaglutide	−1.40	−1.99	Improve insulin resistance and beta cell function significantly.	Decrease LDL (−0.16 mmol/L) and total cholesterol (−0.48 mmol/L)	−3.13 Improve BMI as well	Reduce composite cardiovascular outcomes in obesity without T2DM (HR = 0.80 [0.72–0.90]), and MACE in T2DM (HR = 0.82 [0.68–0.98]).	Reduce composite renal outcomes in obesity without T2DM (HR = 0.78 [0.63–0.96]), and in T2DM (HR = 0.79 [0.66–0.94]).
Exenatide	−0.81	−0.90	Improve beta cell function. No effect on insulin sensitivity.	Fail to improve.	−0.62	Fail to reduce MACE in T2DM, but reduction observed in age ≥ 65 years subgroup (HR = 0.80 [0.71–0.91]).	Reduce composite renal outcomes (HR = 0.85 [0.73–0.98]).
Dulaglutide	−1.09	−1.49	Improves insulin resistance, similar to liraglutide.	Fail to improve.	−0.73	Reduce composite cardiovascular outcomes in age ≥ 50 years T2DM (HR = 0.88 [0.79–0.99]).	Reduce composite renal outcomes in age ≥ 50 years T2DM (HR = 0.85 [0.77–0.93]).
Lixisenatide	−0.61	−0.61	Improves beta cell function slightly in add-on therapy.	Fail to improve.	−0.62	Fail to reduce cardiovascular mortality and MACE in T2DM with recent an ACS attack.	Fail to reduce renal adverse events in the same pool.
Tirzepatide	−2.10	−3.12	Improve insulin resistance and beta cell function significantly, better than dulaglutide and semaglutide.	Decrease triglycerides (−0.89 mmol/L)	−8.47 Improve BMI as well	Assessment ongoing (NCT05556512, NCT04255433). Possibly reduce MACE (HR = 0.80 [0.57–1.11]).	Lack evidence.

Unless otherwise stated, composite cardiovascular outcomes consist of cardiovascular death and MACE; composite renal outcomes consist of new macroalbuminuria, eGFR decline, renal replacement therapy, and death. MD, mean difference (compared to placebo); FBG, fasting blood glucose; BMI, body mass index; SMI, skeletal muscle index; MACE, major adverse cardiovascular events; ACS, acute coronary syndrome; HR, hazard ratio.

istics, including biochemical markers, histology, and clinical outcomes due to varying body types,[136,137] which can lead to different treatment benefits.[138] Recommended treatments for MASLD, including lean MASLD, still emphasize lifestyle interventions such as diet and exercise for weight loss.[139]

GLP-1RA presents two considerations regarding weight-related factors in MASLD. Firstly, whether overweight or obese patients can achieve greater benefits at higher doses or anti-obesity doses with acceptable risks of side effects. Based on data from semaglutide and tirzepatide, the improvement in MASH with GLP-1RA appears to be dose-dependent,[50,52] but there are no additional data to explain this. With the recent confirmation of the therapeutic role of GLP-1RA in MASLD, a broader dosage spectrum is needed to respond to individualized treatments with different metabolic profiles. Secondly, whether lean MASLD patients can benefit from GLP-1RA-related weight loss. Despite reasons to believe that GLP-1RA maintains similar glycemic regulation capabilities in patients of different body weights,[140] its comprehensive metabolic capability and resulting hepatic outcomes have not been thoroughly evaluated. Expert reviews differ on whether lean MASLD patients should aim for weight loss.[15,139] The latest guidance from the European Association for the Study of the Liver recommends a 3–5% weight reduction even in normal-weight patients, though solid histological evidence supporting this is lacking.[8] Therefore, given the increasing burden of lean MASLD in some populations and the benefits of GLP-1RA in weight management, more clinical attention is warranted.

Potential benefits of GLP-1RA in complex liver-related etiologies

MASLD is no longer considered a diagnosis of exclusion based on current understanding and thus can coexist with other liver conditions. A global retrospective study reported that a single hepatic cause of MASLD resulted in HCC in only 12% of cases, while a combination of other hepatic causes was found in 39%.[141] Management of multiple liver etiologies of MASLD is therefore an important aspect of avoiding adverse clinical outcomes. A recent review summarized the interaction between hepatitis B virus or hepatitis C virus (HCV) infection and MASLD.[142] We discuss here the potential benefits of GLP-1RA for these patients.

The impact of MASLD on long-term hepatic outcomes, such as liver fibrosis and HCC in co-infection with hepatitis B virus, is controversial and may depend on disease severity and the presence of metabolic syndrome.[142,143] Early simple steatosis and abnormal lipid metabolism in MASLD may be protective factors.[144,145] It is worth considering the combined outcomes from the full effect of GLP-1RA on hepatic steatosis and metabolic syndromes such as T2DM and dyslipidemia. Thus, individualized regimens should be anticipated for groups with different metabolic profiles and clinical stages.

MASLD and chronic HCV infection share similar pathological features, such as insulin resistance and risk factors such as T2DM.[142] Both conditions appear to synergistically contribute to liver disease progression and poor prognosis. HCV infection increases the risk of advanced fibrosis,[146] and MASLD increases the risk of HCC through the mediation of CMRFs.[147] Notably, viral clearance of HCV infection may increase the risk of cardiovascular events.[148] One retrospective cohort did not find an increased risk of developing atherosclerotic cardiovascular disease; however, the trial only assessed carotid plaque.[149] Thus, the potential of GLP-1RA for MASLD with co-existing HCV prognosis is promising, and early initiation seems necessary in this population.

Interestingly, the process of HCV infection and replication is associated with lipid synthesis and insulin resistance.[150] Although metabolic adjustments based on GLP-1RA, such as improvements in insulin resistance, do not provide additional benefits beyond direct antiviral therapy for HCV,[142] the direct antiviral benefits of GLP-1RA against HCV remain in question. Few *in vitro* trials have explored this issue,[151] but no additional data are available to clarify it.

MASLD associated with increased alcohol consumption (20–50 g/day for females and 30–60 g/day for males) is defined as MetALD,[2] and individuals in this population may have previously been diagnosed with alcohol-related liver disease (ALD). Currently, the respective contributions of alcohol and metabolic factors to liver disease are not elucidated in this population.[8] The applicability of GLP-1RA to this additional group of patients is intriguing; however, no clinical data based on alcohol intake are available. Exendin-4 (exenatide) has been shown to be effective in a mouse model of ALD, ameliorating hepatic steatosis and improving metabolic markers such as insulin resistance and lipid levels.[152] A recent study reported that the histologic features of fibrosis in ALD combined with metabolic syndrome are similar to those of MASLD, especially in the diabetic group.[153] Therefore, GLP-1RA may be effective in MetALD and may provide benefits for the metabolic components of ALD. The influence of low alcohol intake on MASLD remains controversial.[142] It appears that the risk of fibrosis increases with higher alcohol intake or among individuals with metabolic syndrome.[154] Improvement in T2DM with GLP-1RA seems beneficial for reducing fibrosis risk.[155] However, whether this can be extrapolated to other CMRFs, and whether there is a pharmacoeconomic imperative, needs further clarification.

GLP-1RA for the treatment of pediatric MASLD

MASLD is highly prevalent in children and adolescents, with an estimated overall global prevalence of 7.4%, rising to 52.49% in the context of obesity.[156] A recent expert consensus discussed but did not reach agreement on the potential therapeutic role of GLP-1RA in pediatric MASLD,[157] which may be attributed to considerations of safety and efficacy. GLP-1RA is safe for use in children and adolescents over the age of 10 years, and some formulations have been approved for pediatric T2DM or obesity.[158,159] However, there is a lack of safety data for younger age groups, and earlier studies reported a prevalence of 0.7–3.3% in this population.[160] Similar disease characteristics exist between children and adults with MASLD, but there are differences in epidemiology, histology, and clinical diagnosis.[157] These differences necessitate a re-examination of clinical experiences in adults for application to children. Currently, histologic improvement remains the primary criterion for evaluating effective outcomes in MASLD, but invasive tests are often not accepted in the pediatric population. Future studies need to rely on more reliable non-invasive predictors to assess the effectiveness of GLP-1RA therapy. Moreover, pediatric MASLD is associated with T2DM, cardiovascular metabolism, and renal risk,[157] indicating that GLP-1RA can act as a metabolic modifier, thereby improving prognosis, especially in patients who have difficulty adhering to lifestyle changes.

In conclusion, GLP-1RA is a promising candidate drug therapy for pediatric MASLD, and patients may benefit from metabolic improvement even if the liver disease ameliorating effects are not yet clear.

Safety considerations for GLP-1RA use

Based on current data from clinical trials in MASLD and longer-term cohorts in T2DM and obesity, GLP-1RA is generally considered safe. Gastrointestinal symptoms are the most common side effects, particularly nausea, vomiting, and di-

arrhea. Major trials conducted in patients with MASLD have reported prevalence rates of 42–46%, 19–38%, and 15–19% for these symptoms, respectively.[49–52] The proportion of subjects withdrawing from trials due to gastrointestinal symptoms is about 5%. Tolerance can generally be built up by titrating the dose in steps and increasing the duration of use. Some other serious adverse effects of note include thyroid C-cell tumors, acute pancreatitis (AP), pancreatic tumors, and renal impairment, which have raised concerns in preclinical studies or post-marketing reports.[161] However, these problems have not been shown to have a clear causal relationship with GLP-1RA in the general population, and there is a lack of data specific to the MASLD population, especially in individuals without co-existing T2DM.

Among these serious adverse effects, AP has raised additional concerns, as MASLD clearly increases the risk of incidence and severity.[162,163] Some trials have reported elevated pancreatic enzyme levels,[50,53] and further clarification is needed as to whether this indicates low-grade pancreatic inflammation.[164] Notably, larger doses or longer durations of GLP-1RA therapy have been associated with an increased risk of cholelithiasis,[165] a primary risk factor for AP. Long-term follow-up assessments are necessary. On the other hand, patients with MASLD and a history of AP are expected to gain greater benefits from GLP-1RA. GLP-1RA interventions may reduce the incidence of recurrent AP, particularly SEMA and tirzepatide.[166] In fact, only a portion (37.5%) of recurrent AP cases exposed to GLP-1RA may be attributable to pharmacologic factors.[167] Careful use of GLP-1RA in MASLD patients, with or without a history of AP, may be beneficial, but more prospective studies are needed to confirm this.

Feature of GLP-1RA

As emphasized, MASLD encompasses a wide range of diseases with distinctive clinical features. There is no clear consensus on when to initiate drug management for MALFD. Based on current data predicting liver outcomes by fibrosis stage, patients with stages F2-F4 are considered likely to benefit from antifibrotic medication, often seen as a signal to initiate drug intervention.[168] Indeed, liver biopsies confirm that the prevalence of clinically significant fibrosis in MASLD and MASH patients is only 20.27% and 35.14%, respectively,[169] with lower proportions in patients with normal or lean body weight,[170] suggesting that antifibrotic treatment may not be necessary for a larger proportion of patients. A prospective trial assessing clinical outcomes across different stages of fibrosis in MASLD showed parallel increases in liver adverse outcomes and all-cause mortality with fibrosis severity; however, no significant difference was observed in cardiovascular event rates across stages.[111] Lifestyle management is integral throughout MASLD, with some perspectives advocating for initiation as long as metabolic risk factors are present.[8] Concerningly, lifestyle improvements are often difficult to sustain, underscoring the potential benefits of early initiation and background therapy with GLP-1RA due to its benefits on metabolic disorders (Table 3) and chronic liver disease.[108] Some have proposed a substantial model of "induction" therapy consisting of targeted therapy with drugs that have specific mechanisms of action, followed by metabolism-regulating drugs to maintain long-term benefits.[113] This could be the paradigm in which GLP-1RAs are indicated for MASLD with complications. Moreover, existing data indicate that single-target GLP-1RAs such as SEMA and liraglutide show promising capabilities for fibrosis improvement, and the initial success of the dual agonist tirzepatide suggests potential benefits of dose titration therapy in the monotherapy management of MASLD.

Conclusions

MASLD is one of the pressing public health issues; yet, unfortunately, there is a scarcity of available pharmacological management options. GLP-1RAs have transformed the treatment landscape for diabetes and obesity, making them promising candidates for MASLD. GLP-1RAs contribute to metabolic adjustments in MASLD by controlling fat deposition, inflammation, and potentially fibrosis. However, more evidence is needed to clarify their systemic effects and controversial direct hepatic benefits. GLP-1RAs and co-agonists have shown promising outcomes in the clinical management of MASLD. In the future, GLP-1RAs and co-agonists may serve as supplements for personalized therapies targeting metabolic control, anti-inflammation, and even anti-fibrosis effects. Moreover, their potential as monotherapy for sequential control of MASLD warrants further investigation.

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Conflict of interest

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