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NARRATIVE REVIEWS

Charles J. Kahi, Section Editor

The Emerging Role of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis

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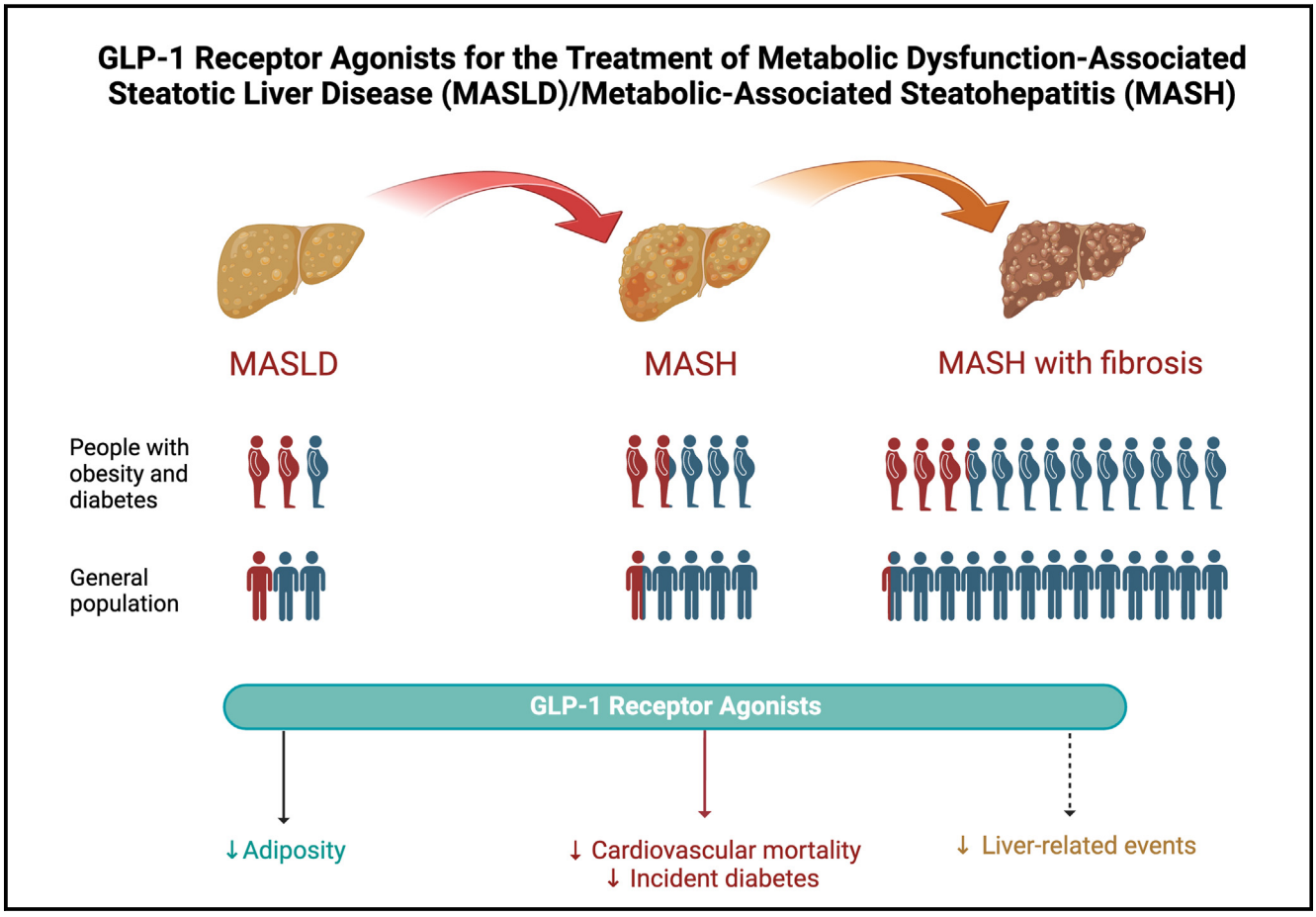

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects 1 in 3–4 adult individuals and can progress to metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis. Insulin resistance plays a central role in MASLD/MASH pathophysiology with higher rates of MASLD (2 in 3) and MASH with fibrosis (1 in 5) in adults with obesity and diabetes. This review summarizes the role of glucagon-like peptide-1 receptor agonists in treating MASLD/MASH. Although not approved by the Food and Drug Administration for the treatment of MASLD, this class of medication is available to treat obesity and type 2

*Authors share co-first authorship. §Authors share co-senior authorship.

Abbreviations used in this paper: **CV, cardiovascular; CVD, cardiovascular disease; FIB-4, Fibrosis 4 index score; GLP-1, glucagon-like peptide-1; IR, insulin resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; RA, receptor agonists; RCT, randomized controlled trial; SC, subcutaneous; T2D, type 2 diabetes.**

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diabetes and has been shown to reverse steatohepatitis, reduce cardiovascular risk, and is safe to use across the spectrum of MASLD with or without fibrosis.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease; GLP-1; Steatosis; Cirrhosis.

Metabolic dysfunction-associated liver disease (MASLD), formerly nonalcoholic fatty liver disease,[1] is a multisystemic disease defined by the presence of hepatic steatosis in ≥5% of hepatocytes, in addition to at least ≥1 of 5 cardiometabolic risk factors (overweight/obesity, hypertension, hyperglycemia, dyslipidemia with either low plasma high-density lipoprotein cholesterol or high triglycerides, or treatment for these conditions) and absence of other causes of steatosis (medications, excessive alcohol use, viral hepatitis or other liver diseases).[2,3] A new category, metabolic and alcohol-related liver disease, is used to describe people with MASLD who consume greater amounts of alcohol (140–350 g/wk and 210–420 g/week for females and males, respectively).[1] MASLD encompasses a range of chronic liver conditions, from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH; characterized by the presence of inflammation and cellular injury [ballooning]), with or without the presence of liver fibrosis, which can lead to cirrhosis, and/or hepatocellular carcinoma.[4]

MASLD is the most common cause of chronic liver disease worldwide.[5] A recent modeling study projects that the incidence of MASLD and MASH will increase by 21% and 63%, respectively, by 2030.[6] It is estimated that approximately 20%–30% of people with MASLD may develop MASH.[6] When compared with the general population, people with type 2 diabetes (T2D) have a higher prevalence of MASLD, 60%–70% vs 25%–30%, and MASH, 37% vs 5%–14%, respectively.[4,5,7,8] MASLD is linked to similar risk factors as other conditions contributing to metabolic syndrome (eg, glucose intolerance, high triglycerides, reduced high-density lipoprotein cholesterol, waist circumference, and hypertension) suggesting a bidirectional association.[9] Higher burden of metabolic traits leads to an incremental increase in the risk of MASLD progression.[10] In addition, MASLD is linked to an increased risk of cardiovascular disease (CVD),[11] whereas CVD, conversely, is the leading cause of mortality in people with MASLD (∼25%), likely because of shared cardiometabolic risk factors.[12] Obesity and T2D are the most impactful risk factors for development of MASLD and share common pathophysiologic pathways.[2,3]

Metabolic Dysfunction-Associated Steatotic Liver Disease Pathogenesis and Fibrosis Risk Stratification

People with MASLD have several metabolic defects, including elevated fasting insulin levels, decreased posthepatic insulin clearance, impaired suppression of endogenous insulin release, impaired glucose disposal, and abnormal lipid oxidation. The primary driving forces for ectopic fat accumulation for individuals predisposed to MASLD are imbalances between energy intake and disposal and insulin resistance (IR) in the muscles, adipose tissue, and liver.[13–15] These defects lead to increased lipolysis, which, along with impaired glucose disposal, leads to increased fasting glucose and free fatty acid concentrations and stimulation of insulin secretion, augmented by decreased clearance of insulin by the liver.[14] To protect the body from increased free fatty acids, adipose tissue attempts storage via increased hypertrophy and hyperplasia. Ultimately, this adaptation leads to activation of macrophage and common inflammatory pathways, such as adipocyte Toll-like receptor-4 receptors, secretion of C-reactive protein, increased reactive oxygen species generation,[16] inhibited insulin signaling via tumor necrosis factor-α,[17] and activation of the Janus kinase/signal transducer and activator of transcription pathway.[18]

The impaired lipolysis in an insulin-resistant environment causes the liver's metabolic capacity to be exceeded by unchecked transport of fatty acids and glucose-dependent increased de novo lipogenesis. Ultimately, exogenous fat accumulation, including hepatic steatosis, occurs because of impaired fatty acid oxidation and adipose tissue IR. As a result, lipotoxic lipids are produced, resulting in cellular stress, inflammation, tissue regeneration, and fibrogenesis.

Additionally, adipokine secretion is affected, including a decrease in adiponectin, which is thought to be protective against IR and inflammation. This decrease in adiponectin leads to the progression of MASLD via increased steatosis and fibrosis and contributes to a higher risk of T2D in MASLD.[19] Lipotoxicity is further propagated by increased proinflammatory and prophagocytic macrophages, a highly inflammatory status that promotes steatohepatitis and fibrosis.[20]

The mechanisms implicated in the progression from MASLD to steatohepatitis and liver fibrosis (Figure 1) are complex and involve the previously mentioned metabolic and inflammatory and immunologic changes, in addition to microbiome-related variables[9] and environmental and social factors (eg, alcohol and dietary fat).[3] Certain genetic variants (*PNPLA3*, *TM6SF2*, *HSD17B13*, *CIDEB*, *MARC1*) may worsen the interaction with environmental factors, alter clinical phenotype, and accelerate disease progression.[21] Impaired mitochondrial adaptation to chronic lipotoxicity and compromised mitochondrial fatty acid oxidation are thought to also be implicated in the progression of MASLD to MASH.[22–25] Peripheral and adipose tissue IR are associated with the severity of steatohepatitis and liver fibrosis in people with MASLD.[13,26] This could explain why people with T2D have a high prevalence of steatosis and moderate-to-advanced fibrosis.[8,27–30]

In people with MASLD, the presence and stage of fibrosis is the best histologic indicator of hepatic and

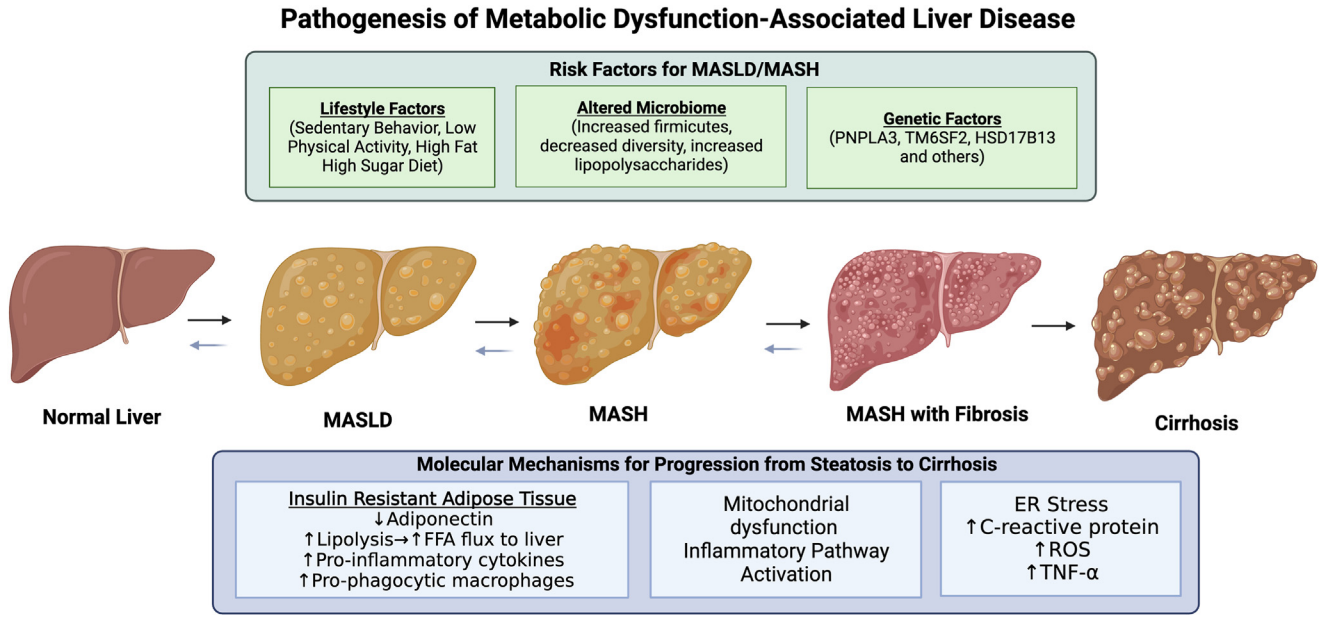

Figure 1. The pathogenesis of MASLD involves several metabolic defects from energy imbalance leading to insulin resistance, increased lipolysis, and activation of inflammatory pathways, to mitochondrial dysfunction, endoplasmic reticulum stress, and increasing reactive oxygen species. These metabolic defects lead to disease progression from normal liver to steatosis, steatohepatitis, fibrosis, and, ultimately, cirrhosis. Created with BioRender.com. ER, endoplasmic reticulum; FFA, free fatty acid; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

overall outcomes, including hepatic decompensation, hepatocellular carcinoma, and liver-related mortality. On average, MASH progresses 1 stage of fibrosis every 7 years.[31] MASH is the major contributor to fibrosis progression; changes in steatohepatitis status positively impact fibrosis stage such that improvement in MASH leads to fibrosis regression and vice versa.[32] The risk of MASH with advanced fibrosis in people with T2D has been demonstrated in several studies; it is estimated that 14%–17% of people with T2D have MASH with advanced fibrosis (compared with 0.9%–2% in the general population), and 6%–7% have cirrhosis.[3,27,28,30,33] The risk of fibrosis in T2D is even higher in the presence of older age, obesity, dyslipidemia, and for those needing insulin treatment.[8,29,30,33]

Individuals considered at high risk for MASLD/MASH-related fibrosis (people with steatosis on imaging or elevated aminotransferases, T2D, obesity with $\geq$2 metabolic risk factors) should be risk-stratified for liver fibrosis to prevent progression and related complications (Figure 2).[34] The first step involves a noninvasive, nonproprietary test, such as the Fibrosis-4 (FIB-4) score (calculated using age in years, aspartate aminotransferase, alanine aminotransferase, and platelet count; calculator available at https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis), recommended mainly because of no additional cost and ease of use. This is followed by a tier-2 test, such as an imaging modality measuring liver stiffness (vibration-controlled transient elastography is preferred over magnetic resonance elastography because of low cost) or a proprietary biomarker panel, such as Enhanced Liver Fibrosis, in those with a positive FIB-4 (cutoff $\geq$1.3 or $>$2.0 if age is older than 65).[2,3] This approach allows risk stratification of people for liver fibrosis groups and emphasizes the need for more aggressive interventions in those with intermediate or high risk, including the need for specialty referral. Current guidelines endorse this approach, and the need to screen those with T2D should be emphasized.[2,3,34]

Understanding mechanisms of MASH incidence and progression is critical to developing future therapies. Current investigative therapeutic approaches are based on targeting the underlying dysfunction in the metabolic, inflammatory, and fibrotic pathways in MASH.

The Role of Glucagon-Like Peptide-1 Receptor Agonists in the Treatment of Metabolic Dysfunction-Associated Steatohepatitis

The Pleiotropic Effects of Glucagon-Like Peptide-1 Receptor Agonists and How They Address the Metabolic Components in Metabolic Dysfunction-Associated Steatohepatitis

Given the overlap of MASH with diabetes and obesity, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have been pursued as a potential treatment option. Although GLP-1 RAs are approved for T2D and/or obesity, they are not yet specifically approved for treating MASLD or MASH (Figure 3). However, their mechanisms of action target common metabolic defects and lipotoxicity.

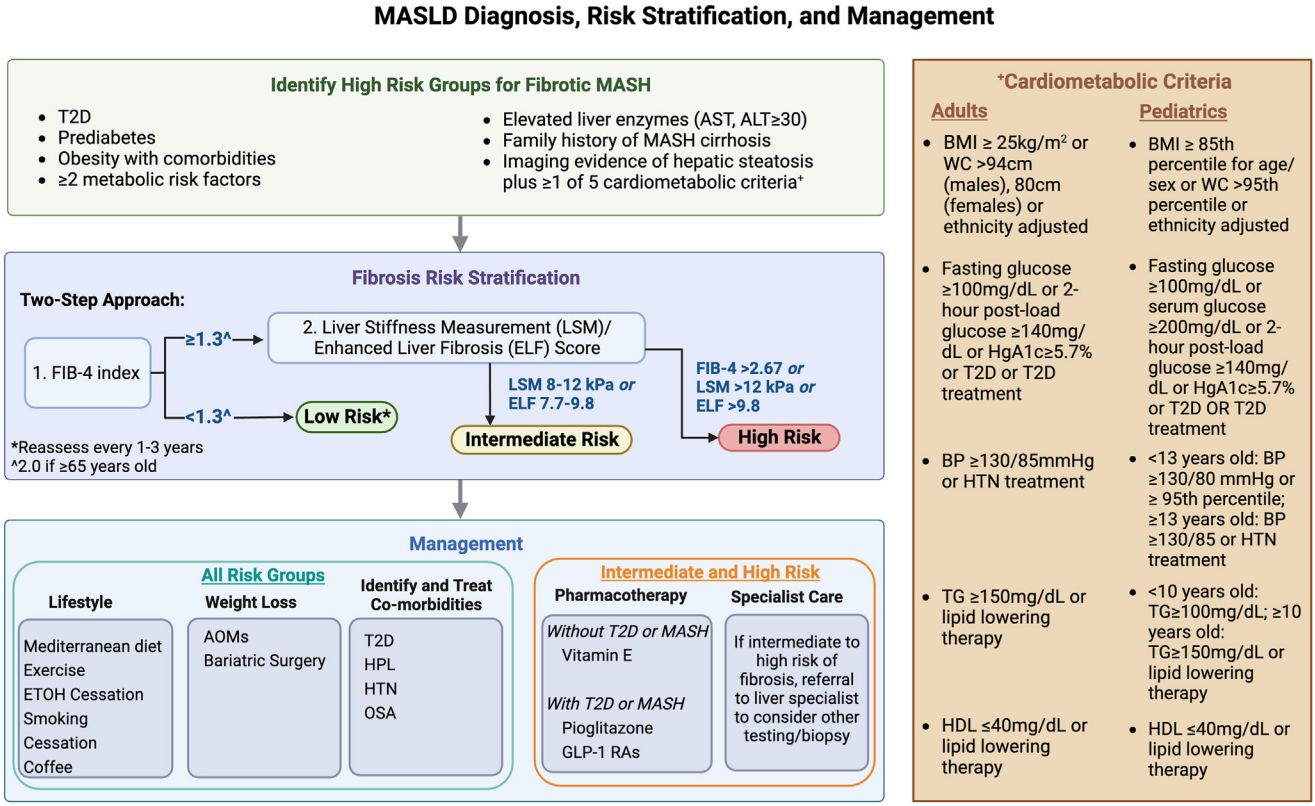

Figure 2. MASLD/MASH risk stratification involves screening high-risk groups with a 2-step approach with further work-up dependent on fibrosis stage. Comorbidities and fibrosis stage impact treatment options. *Fibrosis risk status should be reassessed every 1–2 years in T2D or ≥2 metabolic risk factors and every 3 years in the low-risk category. The intermediate and high-risk categories should prompt referral to specialist for additional testing or liver biopsy. Patients with MASH and fibrosis should be followed by a specialist (ie, for cirrhosis management). In patients older than age 65, a FIB-4 cutoff of >2.0 should be used. Created with BioRender.com. BMI, body mass index; BP, blood pressure; ELF, enhanced liver fibrosis; HDL, high-density lipoprotein; HgA1c, hemoglobin A1c; HPL, hyperlipidemia; HTN, hypertension; LSM, liver stiffness measurement; OSA, obstructive sleep apnea; TG, triglycerides; WC, waist circumference.

GLP-1 is an incretin, a hormone naturally released by the gastrointestinal system in response to nutrient intake.[35] Incretins increase insulin secretion and lower blood glucose levels. GLP-1 slows gastric emptying and suppresses glucagon. These effects remain in those with T2D despite metabolic dysregulation, although GLP-1 levels are lower.[35] People with T2D who received intravenous GLP-1 had increased insulin secretion, decreased glucagon, and plasma glucose that approached normal.[36] GLP-1 also decreased free fatty acids and appetite and improved IR and β-cell function, leading to weight loss.[37] However, because of the short half-life of GLP-1 (<2 minutes), GLP-1 RAs were developed to deliver these effects and overcome the problem of rapid clearance.[35,38]

GLP-1 RAs have been shown to improve CV risk factors, including decreased blood pressure, improved lipid profiles, and decreased weight.[39] Additionally, CV outcome trials demonstrated that subcutaneous (SC) liraglutide (LEADER),[40] dulaglutide (REWIND),[41] albiglutide (HARMONY),[42] and semaglutide (SUSTAIN-6)[43] reduced major adverse CV events, particularly in those with a history of past atherosclerotic CVD.[44,45] These agents have shown efficacy in glycemic control, control of CV risk factors, and prevention of CVD in people with T2D (Table 1).

Because of the effects of GLP-1 RAs on appetite, satiety, and weight, the efficacy of these medications has also been studied in people with overweight/obesity. SC daily liraglutide (up to 3 mg) and weekly semaglutide (up to 2.4 mg) have been approved as weight loss therapies.[46,47]

Although GLP-1 receptors are not expressed on hepatocytes,[48] GLP-1 RAs have been shown to affect the liver indirectly via their effect on hepatic IR, peripheral plasma insulin and glucose, and improvement in lipotoxicity.[49] Specifically, weight loss and increased insulin secretion from treatment with GLP-1 RAs directly lead to reduced free fatty acids and decreased intrahepatic triglycerides. The increase in insulin and decrease in glucagon by GLP-1 RAs leads to a reduction in de novo lipogenesis and triglyceride secretion, decreases in gluconeogenesis, and increases in glucose uptake, ultimately leading to improvement in hepatic parameters.[50] They have also been shown to reduce adipose tissue IR, leading to decreased lipolysis, decreased inflammatory markers, and increased adiponectin.[51] The pleiotropic effects of GLP-1 RA and their application in MASLD/MASH are illustrated in Figure 4.

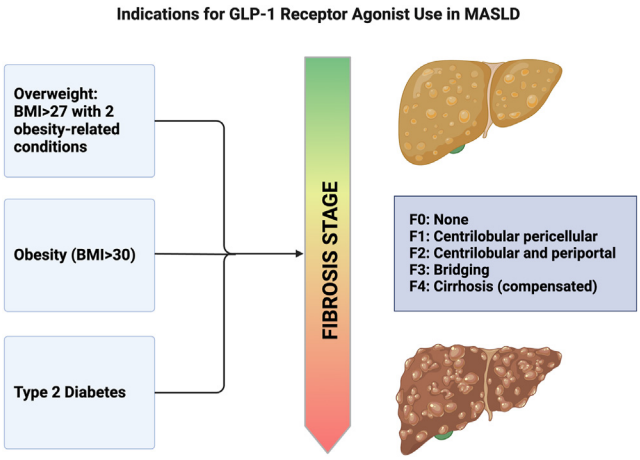

Figure 3. Indications for GLP-1 RA use include T2D, overweight or obesity, and MASLD with any fibrosis stage, excluding decompensated cirrhosis. Obesity-related conditions include dysglycemia, dyslipidemia, hypertension, cardiovascular disease, MASLD, polycystic ovarian syndrome, obstructive sleep apnea, or any other medical condition exacerbated by obesity.[81] Created with BioRender.com. BMI, body mass index.

Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonist in Metabolic Dysfunction-Associated Steatotic Liver Disease/Metabolic Dysfunction-Associated Steatohepatitis

GLP-1 RAs have been shown to improve steatohepatitis, decrease fibrosis progression, and reduce the risk of related complications. In 1 small study of people with T2D and MASLD, exenatide 10 μg twice daily (n = 19) and liraglutide 1.2 mg daily (n = 6) showed a 42% reduction in liver fat.[52] Treatment with dulaglutide 1.5 mg weekly demonstrated a 2.6-fold greater reduction in liver fat content compared with placebo in an open-label study.[53] Liraglutide has also been shown to reduce liver fat content by 19%–32% on imaging in randomized controlled trials (RCT) and open-label studies.[49] In a meta-analysis of the LEAD program, liraglutide improved liver enzymes and showed a positive trend for hepatic steatosis after 26 weeks of treatment.[54] In the LEAN trial, a 48-week phase 2 RCT, 39% of people on liraglutide had resolution of MASH by liver histology, compared with 9% in the placebo group (n = 45 with paired liver biopsies).[55] Similarly, in a larger phase 2 RCT (n = 320; 65% with T2D) with paired liver biopsies at 72 weeks, 36%–59% of people with MASH and liver fibrosis (stages F1-F3) achieved MASH resolution without worsening fibrosis on SC semaglutide compared with only 17% of those on placebo.[56] MASH resolution was achieved in a dose-dependent manner (0.1 mg/day, 40%; 0.2 mg/day, 36%; 0.4 mg/day, 59%) and was proportional to the amount of weight loss, which was also higher in the 0.4-mg group (0.1 mg, 5%; 0.2 mg, 9%; 0.4 mg, 13%; placebo, 1%). Higher incidences of nausea (30%–40%), vomiting (15%–22%), constipation (16%–22%), and gallbladder-related disorders (5%–7%) were seen in semaglutide arms versus 11%, 12%, 14%, and 2%, respectively, in placebo group. Despite evidence of fibrosis improvement in treatment groups (43% in the 0.4-mg group), this was not statistically significant when compared with placebo (33%), largely because of high rates of fibrosis improvement with placebo.[56] However, the rates of fibrosis progression were highest with placebo (18.8%) and lowest in the people receiving 0.4 mg/day semaglutide (4.9%), with intermediate rates on the lower doses (7.7%–10%).[56] High-dose SC semaglutide (2.4 mg) administered weekly was also recently investigated in a small phase 2 RCT (n = 71) in people with MASH and compensated cirrhosis (75% had T2D).[57] Although treatment with semaglutide was not found to improve fibrosis or lead to MASH resolution at the end of the 48-week trial, it was safe and provided cardiovascular (CV) benefits through weight reduction and improved lipids and glycemic control. In a population-

Table 1. GLP-1 RAs with Cardiovascular Benefit in Cardiovascular Outcome Trials[40–43]

GLP-1 RA	Study (*y*)	Median follow-up (*y*)	3p-MACE[a] (95% CI)	HbA_{1c}[b] (95% CI)	Weight change (95% CI)
Liraglutide	LEADER (2016)	3.8	HR, 0.87 (0.78 to 0.97)	-0.4% (-0.45 to -0.34)	-2.3 kg (-2.5 to -2.0)
Semaglutide	SUSTAIN-6 (2016)	2.1	HR, 0.74 (0.58 to 0.95)	-1.05% (-1.19 to -0.91)	-4.35 kg (-4.94 to -3.75)
Albiglutide[c]	HARMONY (2018)	1.5	HR, 0.78 (0.68 to 0.9)	-0.52 (-0.58 to -0.45)	-0.83 kg (-1.06 to -0.60)
Dulaglutide	REWIND (2019)	5.4	HR, 0.88 (0.79 to 0.99)	-0.61% (-0.58 to -0.65)	-1.46 kg (-1.67 to -1.25)

3p-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; RA, receptor agonist.
[a]Composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.
[b]HbA_{1c} and weight changes are compared with placebo.
[c]Production discontinued July 2017.

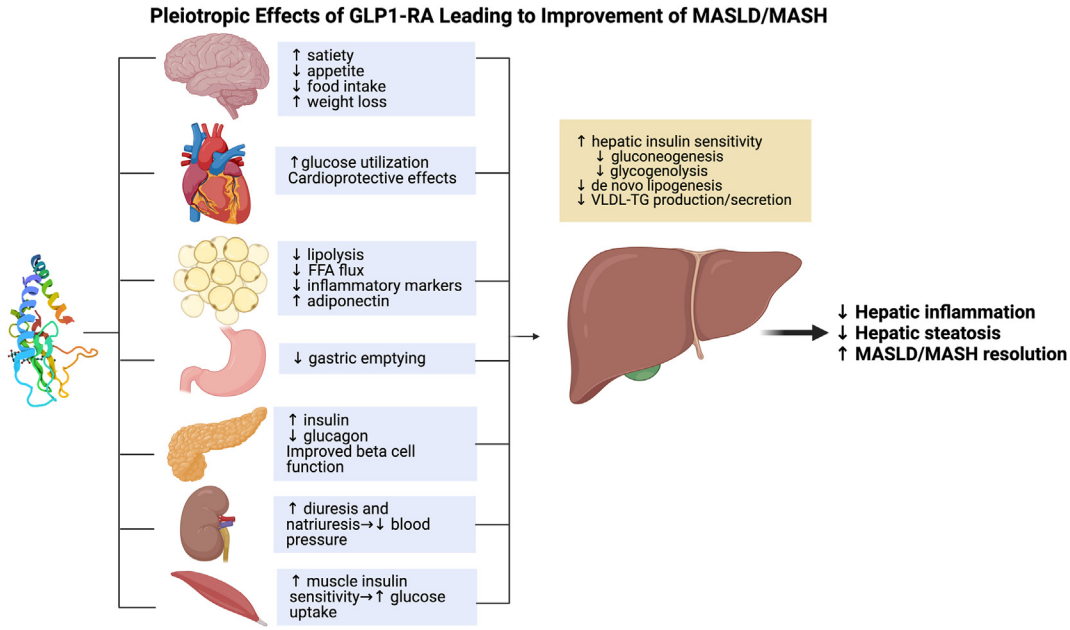

Figure 4. Direct effects of GLP-1 RAs that contribute to proposed indirect effects on the liver, leading to a reduction in inflammation, steatosis, and resolution of MASLD/MASH. Created with BioRender.com. FFA, free fatty acid; VLDL-TG, very-low-density lipoprotein triglyceride.

based cohort study from Taiwan, use of GLP-1 RAs in patients with T2D and liver cirrhosis lowered the risk for death, CVD, and hepatic decompensation.[58] These effects on the liver are related to significant body weight reduction, improved glycemic control in people with T2D, and improved IR.

Additional interventional trials using GLP-1 RAs in MASH/MASLD have recently completed or are ongoing. Some of these studies evaluate effects of GLP-1 RAs compared with other interventions in MASLD, such as diet (NCT03648554), empagliflozin (NCT05946148, NCT05140694), pioglitazone or vitamin E (NCT05813249), or metabolic surgery (NCT06138821, NCT02654665). The combination of semaglutide with a fibroblast growth factor 21 analog (NCT05766709) is also being investigated. A larger, phase 3 RCT of SC semaglutide (2.4 mg weekly for 240 weeks) for the treatment of noncirrhotic MASH is currently underway (NCT04822181) with plans to enroll 1200 participants to assess the effects of semaglutide on histology as the primary outcome and CV outcomes (time to major adverse CV events) as a major secondary outcome.[59] Additionally, the impact of SC semaglutide on histologic improvement, liver fat content reduction, and change in hepatic gene expression on liver biopsies in people with MASLD and MASH is currently being studied (NCT03884075).[60] Larger and longer RCTs are needed to further demonstrate the long-term effects of semaglutide on MASH and to explore its effects on liver fibrosis.

Tirzepatide, a dual agonist to GLP-1 and glucose-dependent insulinotropic polypeptide receptors, has shown efficacy and superiority compared with once-weekly 1 mg SC semaglutide in glycemic control and weight loss for people with overweight/obesity and T2D.[61] The SURPASS 3 trial in T2D found that participants who received tirzepatide 5, 10, or 15 mg/week had significantly larger reductions in glycated hemoglobin, lost weight, improved liver enzymes, reduced liver fat (∼6%–8% from baseline, an approximate 46% relative reduction), and visceral adipose tissue when compared with insulin degludec.[62] Administration of tirzepatide 15 mg also demonstrated a 20.9% weight loss in participants with overweight/obesity without T2D.[63] Studies are ongoing to assess the effects of tirzepatide on liver fat content, liver histology, and fibrosis in people with MASH (NCT04166773).[64]

GLP-1/glucagon receptor coagonists are also in development. In preclinical studies, cotadutide reduced liver fat, de novo lipogenesis, and induced MASH resolution.[65] In a phase 2b trial in people with T2D, cotadutide decreased glycated hemoglobin (hemoglobin A_{1c}) and body weight and improved liver parameters.[66] Pemvidutide, another balanced GLP-1/glucagon receptor coagonist, was superior to placebo in achieving meaningful weight loss (mean weight loss of 10.7% at 24 weeks) in people with obesity.[67] In a phase 2 study of MASLD, pemvidutide 1.8 mg induced a significant liver fat content reduction of 68.5% ($P < .001$), with 94.4% achieving a 30% reduction in liver fat ($P < .0001$), which is likely to correlate with improvement in steatohepatitis.[68] Clinical trials with survodutide in people with T2D (NCT06066528), overweight and obesity (NCT06066515), and efinopegdutide in people with nonalcoholic fatty liver disease (NCT04944992) and precirrhotic nonalcoholic steatohepatitis (NCT05877547) are also ongoing.

In phase 2 trials, the triple GLP-1/glucose-dependent insulinotropic polypeptide/glucagon receptor coagonist retatrutide 12 mg induced dose-dependent and

substantial weight loss in people with T2D (-17% at 36 weeks vs -3% for placebo) or obesity (-24% at 48 weeks vs -2.1% for placebo), along with beneficial effects on blood pressure, lipids, and IR.[69,70] Among those with MASLD and ≥10% liver fat (n = 98), retatrutide normalized liver fat in 90% of participants after 48 weeks of treatment.[71]

Recent Guidelines and Consensus Statements Incorporating Glucagon-Like Peptide-1 Receptor Agonist for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis

Given the above, although GLP-1 RAs are not approved solely for treating MASLD/MASH, major society guidelines and consensus statements have incorporated GLP-1 RAs in treatment pathways. The American Association of Clinical Endocrinologists 2022 Clinical Practice Guidelines for MASLD recommended GLP-1 RAs for persons with T2D and biopsy-proven MASH and those at high risk of MASH to offer CV benefit (grade A evidence).[2] The 2023 American Association for the Study of Liver Diseases Practice Guidance recommends the use of semaglutide for people with MASH and T2D or obesity given its CV benefit and improvement in measures for associated comorbidities.[3] Therefore, GLP-1 RAs have a role in guideline-directed therapy of people with MASLD and MASH.

Practical Considerations for the Use of Glucagon-Like Peptide-1 Receptor Agonist in Metabolic Dysfunction-Associated Steatohepatitis

With increasing indications for use, there are practical considerations for using GLP-1 RAs in MASH. In general, treatment with GLP-1 RAs is well-tolerated. The most common side effects of GLP-1 RA are gastrointestinal, including nausea, vomiting, diarrhea, and constipation.[72,73] These effects are typically mild to moderate (>70% are nonserious) and dose-dependent; they are usually managed by slow dose up-titration, reducing food intake, and ensuring adequate hydration. Gallstones can arise and are likely related to rapid weight loss. Pancreatitis is rare; routine monitoring of lipase in clinical practice is generally not recommended in asymptomatic patients. A large meta-analysis that included data from large CV outcome trials found that the risk of pancreatitis and pancreatic cancer with long-term use of these agents was not higher than in comparator arms.[74] Use of GLP-1 RA is contraindicated in the setting of medullary thyroid cancer or multiple endocrine neoplasia type 2 because of the potential for C-cell hyperplasia observed in preclinical studies. A recent population-based case-control study in people with T2D reported an increased risk of medullary and differentiated thyroid cancer with GLP-1 RA exposure over 1–3 years;[75] these findings are not observed in more rigorous conducted RCTs,[76] and are likely caused by several biases, including detection bias seen with observational studies.[77] A meta-analysis of 45 trials with GLP-1 RAs[78] and a large population-based cohort study[79] did not show significant effects on thyroid cancer occurrence. Further studies are needed to investigate this association with long-term use of GLP-1 RAs.

The identification of people who would benefit from pharmacotherapy is primarily based on the presence of comorbidities and disease severity. People with MASLD/MASH with overweight/obesity with or without T2D would benefit from the initiation of GLP-1 RAs. Because T2D increases the risk of hepatic fibrosis,[3] effective weight management and glycemic control, such as with GLP-1 RAs, may prevent and slow the progression to fibrosis. None of these therapies should be used in the setting of decompensated cirrhosis. Other limitations of available treatments include a lack of long-term data beyond 2 years; limited data in those with MASH cirrhosis; and, with the exception of pioglitazone, high costs and poor insurance coverage.[80]

Conclusions

Significant advancements have been made in understanding the pathophysiology of MASLD/MASH. Although there is currently no Food and Drug Administration–approved pharmacologic treatment for MASLD/MASH, physicians have tools that can be used to identify and alter the disease progression. Although lifestyle corrections, such as caloric restriction and physical activity to achieve a 7%–10% weight loss, should be promoted,[3] these are hard to sustain long-term. GLP-1 RAs have emerged as a promising therapy for MASLD and MASH by targeting metabolic and inflammatory pathway defects shared by T2D, obesity, and MASLD. These agents can be used across the spectrum of MASLD, alone or in combination with other agents, such as pioglitazone or SGLT2 inhibitors. GLP-1 RAs have been shown to result in high proportions of MASH resolution and are recommended as first-line therapy for biopsy-proven MASH, regardless of the presence or absence of T2D.[55,56] Additionally, they improve IR, confer CVD risk reduction, and promote weight loss.[55,61–63,65,67]

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