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ABOUT COVER

Peer Reviewer of *World Journal of Hepatology*, Raquel Rocha, MD, Associate Professor, Department of Sciences of Nutrition, School of Nutrition, Federal University of Bahia, Salvador 41701-035, BA, Brazil.
raquelrocha2@yahoo.com.br

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REVIEW

Role of incretins and glucagon receptor agonists in metabolic dysfunction-associated steatotic liver disease: Opportunities and challenges

Chencheng Xie, Naim Alkhouri, Mohamed A Elfeki

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Chencheng Xie, Mohamed A Elfeki, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, SD 57105, United States

Chencheng Xie, Department of Hepatology, Avera Mckennan University Hospital and Transplant Institute, Sioux Falls, SD 57105, United States

Naim Alkhouri, Department of Hepatology, Arizona Liver Health, Chandler, AZ 85712, United States

Mohamed A Elfeki, Department of Hepatology, Avera McKennan University Hospital and Transplant Institute, Sioux Falls, SD 57105, United States

Corresponding author: Mohamed A Elfeki, MD, MSc, Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, 1315 S Cliff Ave, Plaza 3, Suite 1200, Sioux Falls, SD 57105, United States. m_elfiky@hotmail.com

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease worldwide, paralleling the rising pandemic of obesity and type 2 diabetes. Due to the growing global health burden and complex pathogenesis of MASLD, a multifaceted and innovative therapeutic approach is needed. Incretin receptor agonists, which were initially developed for diabetes management, have emerged as promising candidates for MASLD treatment. This review describes the pathophysiological mechanisms and action sites of three major classes of incretin/glucagon receptor agonists: glucagon-like peptide-1 receptor agonists, glucose-dependent insulinotropic polypeptide receptor agonists, and glucagon receptor agonists. Incretins and glucagon directly or indirectly impact various organs, including the liver, brain, pancreas, gastrointestinal tract, and adipose tissue. Thus, these agents significantly improve glycemic control and weight management and mitigate MASLD pathogenesis. Importantly, this study provides a summary of clinical trials analyzing the effectiveness and safety of incretin receptor agonists in MASLD management and provides an in-depth analysis highlighting their beneficial effects on improving liver function, hepatic steatosis, and intrahepatic inflammation. There are emerging challenges associated with the use of these medications in the real world, particularly adverse events, drug-drug interactions, and barriers to access,

which are discussed in detail. Additionally, this review highlights the evolving role of incretin receptor agonists in MASLD management and suggests future research directions.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Metabolic dysfunction-associated steatohepatitis; Glucagon-like peptide-1; Glucose-dependent inulinotropic polypeptide; Glucagon; Incretin; Receptor agonist

Core Tip: In this review, we highlight the evolving role of incretin and glucagon receptor agonists in metabolic dysfunction-associated steatotic liver disease. These agents showed promising potential for improving hepatic steatosis and metabolic dysfunction-associated steatohepatitis (MASH) with a clear benefit for associated cardiometabolic risk factors. However, its role in MASH-associated fibrosis remains unclear. Barriers to access due to limited supplies, cost, and lack of insurance coverage could be overcome through patent and regulatory reforms on drug-device combinations, which may allow for generic competitors of these agents to be available for patients at affordable prices.

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INTRODUCTION

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly increasing. MASLD has become the most common chronic liver disease worldwide, affecting more than 30% of the global population, and is associated with the pandemic of obesity and type II diabetes mellitus (T2DM)[1,2]. MASLD and its severe phenotype metabolic dysfunction-associated steatohepatitis (MASH) can progress to hepatic fibrosis and cirrhosis and increase the risk of hepatocellular carcinoma[3]. Moreover, MASLD is associated with an increased risk of cardiovascular diseases, chronic kidney disease, and extrahepatic malignancies[4-6].

Given the growing global disease burden of MASLD, there is an unmet clinical need for therapeutic intervention. Regular physical activity and dietary modifications are essential in managing MASLD at various stages of disease progression. However, implementation of a healthy lifestyle that maintains a sustainable and significant weight loss to alleviate MASH and hepatic fibrosis is challenging, and only a small portion (approximately 20%) of the MASLD population achieves at least 10% total body weight loss and sustains it for at least one year[7]. Bariatric surgery can maintain significant long-term weight loss, resolve MASH, and result in fibrosis regression. However, due to its surgical risk, it cannot be considered a first-line treatment[8,9]. Thus, pharmacological interventions are becoming a rising research focus.

The pathogenesis of MASLD is complex and regulated by multiple factors, including genetic, environmental, microbiome, and lifestyle factors. T2DM and obesity are two well-known risk factors linked to MASLD[3]. T2DM is characterized by insulin resistance and relative insulin deficiency. Insulin resistance increases the breakdown of fats in adipose tissue, leading to an excessive influx of free fatty acids into the liver. Moreover, insulin resistance is linked to increased hepatic de novo lipogenesis, which results in further fat accumulation in the liver. Intrahepatic fat accumulation promotes oxidative stress, mitochondrial dysfunction, and inflammation, which can progress to hepatic inflammation[10-13]. Obesity contributes to MASLD *via* a complex crosstalk network. It shares many similarities with T2DM, as it is primarily impacted by insulin resistance and adipocyte dysfunction. Moreover, obesity is affected by the hallmark process of lipolysis, excess circulating free fatty acids and increased de novo lipogenesis. Furthermore, it subsequently triggers inflammatory processes *via* mitochondrial defects, endoplasmic reticulum stress, and oxidative stress, contributing to fibrogenesis and cirrhosis[14].

Given the close pathogenic link between MASLD and T2DM/obesity, incretins have emerged as a promising therapeutic option for treating MASLD. Incretins are gut-derived peptide hormones secreted after meals and regulate insulin secretion in response to fluctuations in glucose levels. Incretin-based therapy was initially developed for diabetes management and achieved great success in glycemic control. It also shows significant potential in addressing obesity. Recently, these agents have also been shown to provide considerable cardiovascular and renal health benefits[15,16]. There are two well-studied incretins, glucagon-like peptide-1 receptor (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and both can regulate glucagon secretion[17,18]. Although glucagon (GC) is not considered a kind of incretin, its agonism shares many similarities and synergistic effects with incretin agonism according to liver studies[19]. This review focuses on glucagon-like peptide-1 receptor agonists (GLP-1RAs), glucose-dependent insulinotropic polypeptide receptor agonists (GIPRAs), and glucagon receptor agonists (GCGRAs). There are emerging studies on dual or triple receptor agonists (RAs) that could boost the advantages and offset the disadvantages of certain incretins. These agents have been gaining increasing attention as novel agents that can better control hyperglycemia and reduce body weight, and they might benefit MASLD patients due to their potential to target multiple pathways[20].

This narrative review of incretins and glucagon RAs highlights the underlying mechanisms of action, provides a summary of clinical data from recently published trials, reveals potential safety concerns, highlights challenges in accessing incretins, and explores future perspectives on this emerging topic.

PATHOPHYSIOLOGICAL MECHANISMS AND SITES OF ACTION OF INCRETINS/GLUCAGON

GLP-1RAs

GLP-1 is secreted by specific enteroendocrine cells (L cells) predominantly located in the lower intestine and colon[17]. GLP-1 can be secreted at a low continuous basal level during fasting and is secreted in a bolus fashion after a meal, with an increase of approximately two to three times its baseline[21,22]. It stimulates glucose-dependent insulin release and inhibits glucagon secretion from pancreatic α-cells, improving glycemic control[17].

It is a consensus that hepatocytes and other types of liver cells, such as Kupffer cells and stellate cells, do not express the typical GLP-1 receptor, suggesting that the effects of GLP-1 on the liver in MSALD patients are mainly indirect[21,22]. GLP-1 can regulate portal and peripheral plasma insulin and glucagon concentrations to maintain glucose homeostasis[23]. In the diet-induced MASLD mouse model, GLP-1RAs decrease insulin resistance, hepatocyte lipotoxicity, and intrahepatic inflammation by improving mitochondrial function[24].

The GLP-1 receptor is distributed in various organs and tissues, including the pancreas, brain, adipose tissue, and gastrointestinal tract. Thus, GLP-1 exerts a broader range of physiological effects beyond its effects on glycemic regulation and direct and indirect effects on various types of organs and tissues (Figure 1) to influence MASLD[25].

Nervous system: GLP-1 receptors are found in various parts of the brain, such as the hypothalamus, hindbrain, and amygdala, and are crucial for controlling appetite. In preclinical and clinical studies, activation of central GLP-1 receptors by GLP-1RAs has been shown to reduce appetite, satiety, food intake, and weight[17,26-30]. In mouse models, this effect is mediated by the modulation of key appetite-regulating pathways. GLP-1RAs can inhibit the activity of neuropeptide Y (NPY) and agouti-related peptide (AgRP)-expressing neurons in the arcuate nucleus located in the hypothalamus. Moreover, GLP-1RAs stimulate neurons to express proopiomelanocortin and cocaine- and amphetamine-regulated transcripts, which indirectly inhibit NPY-AgRP neurons. These collective effects lead to the release of inhibitory signals to the parabrachial nucleus, suppressing appetite, increasing postprandial satiety, and contributing to weight loss[28,29]. A human model study also indicated that GLP-1 receptors are expressed on neurons in the human hypothalamus, medulla, and parietal cortex and that GLP-1RAs decrease appetite and responses to desirable foods by suppressing brain activation in T2DM patients[30]. Outside the central nervous system, GLP-1 receptors located in vagal afferent nerves could facilitate food termination by sending anorexigenic signals to parabrachial nucleus neurons. Moreover, activation of GLP-1 receptor vagal afferents increases glucose tolerance, and its inhibition causes hyperglycemia, which is independent of food intake[31]. GLP-1 also influences food intake by regulating taste sensation, as GLP-1 receptor expression on adjacent taste nerve fibers[32] and GLP-1 receptor knockout mice exhibit reduced responses to sweeteners, suggesting that GLP-1 plays a critical role in maintaining sweet taste sensitivity[33]. The effective regulation of appetite through mechanisms such as those mediated by GLP-1 receptors is vital in managing MASLD, as it directly influences food intake and body weight, both of which are key factors in the progression and treatment of this disease.

Pancreas: In addition to their direct effects on pancreatic α-cells to inhibit glucagon secretion, GLP-1RAs enhance insulin secretion from pancreatic β-cells. Importantly, this effect is glucose dependent and occurs when glucose levels are elevated, thereby lowering the risk of hypoglycemia[17,34]. In MASLD, increased insulin secretion may help address the underlying insulin resistance associated with this disease, potentially reducing hepatic glucose production and liver fat accumulation.

Gastrointestinal tract: GLP-1RAs exert an essential influence on gastrointestinal motility. Hypoglycemia can induce the acceleration of gastric emptying, which is an essential physiological response to increase the rate of carbohydrate absorption; however, this accelerated gastric emptying effect can be attenuated by the administration of exogenous GLP-1 [35]. This delay in gastric emptying leads to a more gradual and sustained postprandial glucose response, and the effects of GLP-1 on lowering postprandial glycemia are strongly correlated with its impact on gastric emptying[36]. In addition to gastric emptying, GLP-1RA also inhibits small intestinal motility, flow, and transit, subsequently affecting glucose absorption in humans[37]. GLP-1RA slows gastric emptying, likely through the vagus nerve, and this effect can be aborted after vagal denervation in animals. A human study also indicated that GLP-1 did not impact gastric volume during fasting or postprandial periods in patients with vagal neuropathy[38]. Slower gastric emptying and intestinal motility contribute to feelings of fullness and satiety, potentially resulting in reduced food intake.

Adipose tissue: Adipose tissue is essential for lipid metabolism. Dysregulation of lipolysis in fat cells can result in an increase in the efflux of free fatty acids into the blood, increased de novo lipogenesis, decreased fatty oxidation, and reduced lipid export from the liver. These effects are essential for liver fat accumulation and the development of inflammation, which are hallmarks of MASLD[19,39,40]. The GLP1 receptor is present in adipose tissue and can stimulate lipolysis in adipocytes in a receptor-dependent fashion *via* adenylate cyclase/cAMP signaling[41]. Furthermore, GLP-1 stimulates thermogenesis and overall energy expenditure in brown adipose tissue[42,43]. A meta-analysis studying the effect of GLP-1RAs on fat distribution in patients with T2DM showed that treatment with GLP-1RAs led to significant reductions in both visceral and subcutaneous adipose tissue. These findings indicate that GLP-1RAs play a critical role in fat distribution and can reduce adipose tissue mass in patients with T2DM[44].

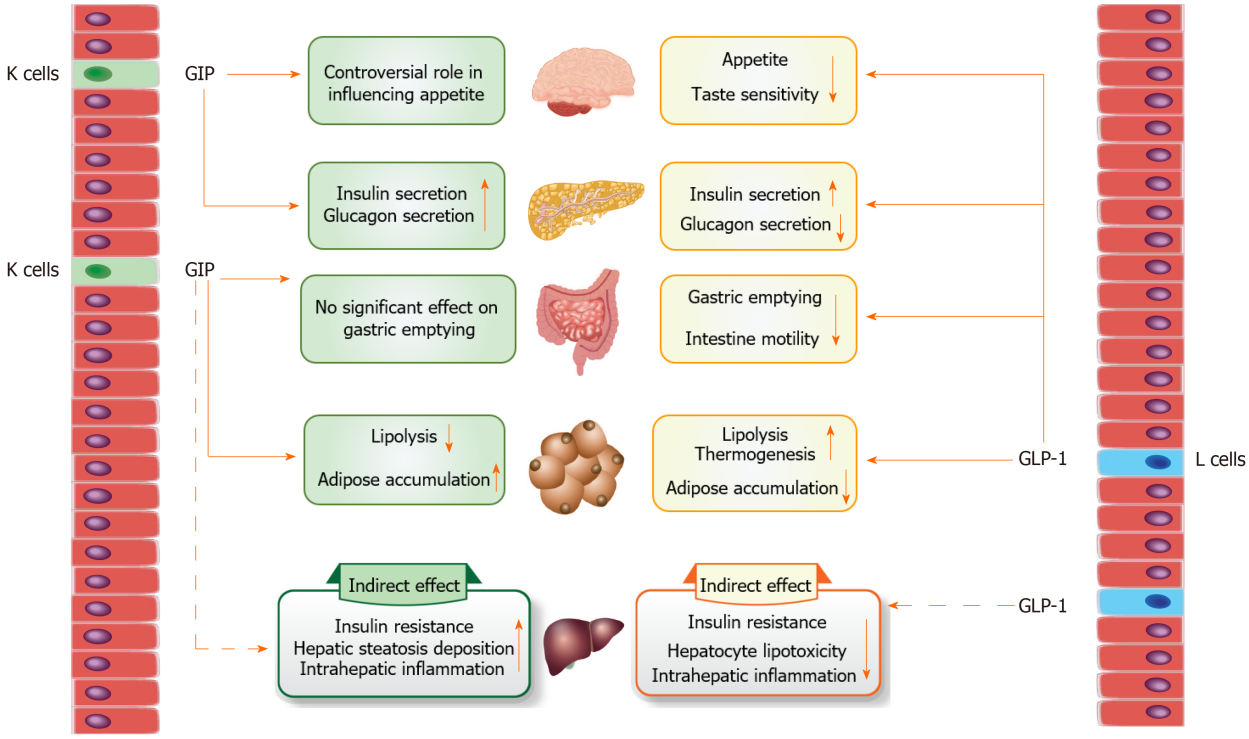

Figure 1 A schematic illustration showing how glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide act on multiple organs to mitigate metabolic dysfunction-associated steatotic liver disease. GLP-1: Glucagon-like peptide 1; GIP: Glucose-dependent insulinotropic polypeptide.

GIPRAs

GIP is an incretin hormone secreted by K cells in the upper small intestine in reaction to the intake of nutrients[34]. Like GLP-1, GIP plays a pivotal role in glucose homeostasis by enhancing glucose-dependent insulin secretion from pancreatic β-cells through binding to the GIP receptor and activating cAMP and its related pathway[45]. There is no robust evidence for the presence of GIP receptors in liver cells, suggesting that GIP affects MASLD mainly *via* indirect effects[21,22]. Inhibition of GIP signaling could reduce insulin resistance, liver weight, hepatic steatosis deposition, and the levels of the inflammatory cytokine interleukin-6[46]. While GIP primarily targets the pancreas, it is present in multiple organs (Figure 1) and exerts additional effects on metabolic regulation, making GIPRA a promising candidate for MASLD management.

Brain: Emerging evidence suggests that GIP receptors are expressed in the central nervous system, particularly in the hypothalamus, and are involved in appetite regulation[47]. The role of GIP in the hypothalamus in relation to hunger and satiety is less clear than that of GLP-1. Although GLP-1 has an established mechanism and a clear role in influencing food intake, the impact of GIP on appetite regulation has not been determined. Multiple studies with inconsistent results highlight the need for more focused research to fully understand the neurological functions of GIP, particularly its potential effects on appetite and satiety regulation. In rodent models, both GIP receptor antagonism and agonism can positively impact body weight while decreasing food intake. However, additional studies are needed to determine the cause of this phenomenon[48]. One possible theory is that GIP receptors can achieve inactivation or downregulation *via* internalization. After receptor activation, the status can switch to receptor desensitization. Thus, agonists may act as functional antagonists under certain circumstances[48,49]. The compensatory relationship between GLP-1 and GIP might also play a role in the paradoxical agonist-antagonist phenomenon[48]. However, GIP did not exert any acute effects on appetite or food intake in a human study[50].

Pancreas: GIP acts on beta cells in the pancreas and regulates postprandial insulin secretion. GIP increases pancreatic insulin secretion by binding to the GIP receptor to potentiate glucose-dependent insulin secretion by activating cAMP and its related downstream signaling pathway[45]. By facilitating insulin release, GIPRAs may help address hyperglycemia and insulin resistance, both of which are central features of MASLD. The insulinotropic effect of GIP is lost in patients with T2DM; thus, restoring GIP deficiency with GIPRA could be a potentially interesting focus of future studies[51]. However, in contrast to GLP-1, which suppresses glucagon secretion, GIP acts on alpha cells to facilitate glucagon release, which represents an essential aspect of its regulatory impact on glucose hemostasis[18].

Gastrointestinal tract: Administration of exogenous GIP does not significantly affect human gastric emptying[52]. Urva *et al*[53] showed that GIPRA alone does not affect gastric emptying, and increasing doses of GIPRAs to GLP-1RAs did not slow gastric emptying. These findings indicate that GLP-1, but not GIP, is the primary factor involved in reducing gastric emptying in a mouse model. In human studies, the gastric emptying delays observed with both dual GLP-1RA/GIPRA

and solely GLP-1RA were comparable. This finding suggested that the delay is primarily caused by GLP-1RA, and GIP agonism does not contribute significantly to this effect[53].

Adipose tissue: GIP is proposed to influence fat deposition in adipose tissue, and it also affects fat deposition in nonadipose tissues, such as liver tissue. GIP reduces adipokine secretion and increases white adipose tissue storage capacity[19]. The study also revealed that GIP receptors in adipocytes and GIP itself might increase fat accumulation in subcutaneous adipose tissue. This occurs through the activation of lipoprotein lipase, which helps breakdown chylomicron triglycerides and inhibits lipolysis triggered by catecholamines and glucagon[54]. A large-scale population study suggested that higher GIP levels were associated with more visceral abdominal fat and a greater waist-to-hip ratio, independent of the plasma insulin concentration[55]. The direct effect of GIP agonism as a therapy for liver fat deposition remains uncertain, and additional in-depth research is needed to fully understand its effects and mechanisms.

GCGRAs

Glucagon, which is produced mainly by alpha cells in the pancreas and, to some extent, in the small intestine, is crucial for regulating key metabolic processes. Glucagon acts on beta cells in the pancreas and stimulates insulin secretion to maintain glucose hemostasis. Dysregulated glucagon secretion occurs in patients with MASLD or associated comorbidities, which has triggered research interest in the role of glucagon in MASLD[56-58].

In contrast to GIP and GLP-1, which are believed not to act on the liver directly, glucagon receptors are predominantly located in the liver and are also present in other types of organs and tissues, such as the brain and adipose tissue. This widespread distribution underlines the multifaceted role of these receptors in MASLD (Figure 2)[19,59].

In the liver, glucagon significantly lowers hepatic glycogen levels while increasing gluconeogenesis[60]. Chronic dosing with glucagon may increase hepatic insulin sensitivity by augmenting insulin activity[61]. Glucagon stimulates beta-oxidation of fatty acids and inhibits hepatic fat synthesis, which could reduce fatty acid storage. It also increases mitochondrial turnover, decreases oxidative stress, and decreases the activation of stellate cells. These effects could subsequently reduce intrahepatic fatty acid storage and inflammation/fibrosis[19,62].

Dysregulation of glucagon signaling is implicated in MASLD, suggesting that GCGRA is an attractive therapeutic option. These agents, which target the glucagon receptor in various organs and tissues, offer an approach to address the complex pathophysiology of MASLD.

Brain: Glucagon can cross the blood-brain barrier and bind to receptors in many brain areas, including the hypothalamus [63,64]. Administering glucagon significantly suppressed satiety in animal studies, and administering antibodies against glucagon could stimulate appetite[65,66]. It is postulated that the hepatic branch of the vagus nerve transmits satiety signals to the hypothalamus. This liver-brain axis theory is supported by evidence that the satiety effect induced by glucagon administration into the portal vein is aborted after hepatic vagotomy and that damaging terminal fields of vagal afferent neurons blocks the glucagon-induced suppression of food intake[65,67]. In a small-scale human study, it was found that coadministration of low dosages of glucagon and GLP-1 could suppress appetite, which supports the concept that GLP-1 and glucagon dual agonism might have synergistic effects on diet suppression and weight control[68]. The GCGRA may influence neural circuits governing food intake, potentially reducing appetite and caloric intake. By suppressing excessive caloric intake, GCGRA could contribute to weight loss, which is an essential aspect of MASLD treatment.

Adipose tissue: Glucagon receptors have been shown to exist in solubilized membranes of human adipose tissue. Thus, the function of glucagon in adipose tissue has drawn increasing research attention, highlighting a potentially key role in metabolic processes and energy regulation within this tissue type[69].

In animal models, glucagon can increase energy expenditure by inducing thermogenesis through the stimulation of brown adipose tissue[70]. Administration of glucagon alone in healthy human volunteers significantly increased resting energy expenditure[71].

Many experiments have indicated that glucagon can stimulate lipolysis in adipocytes in rodents[72,73]. However, infusion of physiological concentrations of glucagon into human volunteers did not significantly impact lipolysis in human white adipose tissue but increased lipolysis in other species. Additionally, glucagon has been shown to inhibit the proliferation of human white adipose stem cells, but the concentration required for this effect is high, leading to questions about its physiological relevance[74].

From dual to triple receptor agonism: The evolution of incretin therapy

A notable concern with GCGRAs is their potential to cause significant hyperglycemia. This is particularly relevant in MASLD patients, many of whom also have T2DM. Consequently, using GCGRA monotherapy may not be a safe and effective treatment strategy for MASH. However, when GCGRAs are combined with GLP-1RAs, this approach mitigates the risk of glucagon-induced hyperglycemia while preserving the beneficial anti-inflammatory and antifibrotic effects of glucagon. This combination therapy could, therefore, offer a more suitable treatment option for MASLD patients with T2DM[19].

The dual GLP-1RA/GCGRA combination has been shown to increase gluconeogenesis and glycogenolysis while reducing intrahepatic lipids in mice. Compared with GLP-1 mono-selective receptor agonists, dual agonists significantly reduce liver triglyceride, diacylglycerol, and cholesterol ester levels; inflammation; and fibrosis in mouse models[75]. Kannt *et al*[76] utilized C57BL/6J mice fed a MASLD diet and noted that neither GCGRA nor GIPRA alone influenced body weight, liver lipids, or histology. However, the combination of dual GLP-1RA/GCGRA or GLP-1RA/GIPRA provided additional health benefits compared with monotherapy regarding weight loss, liver triglyceride reduction, and

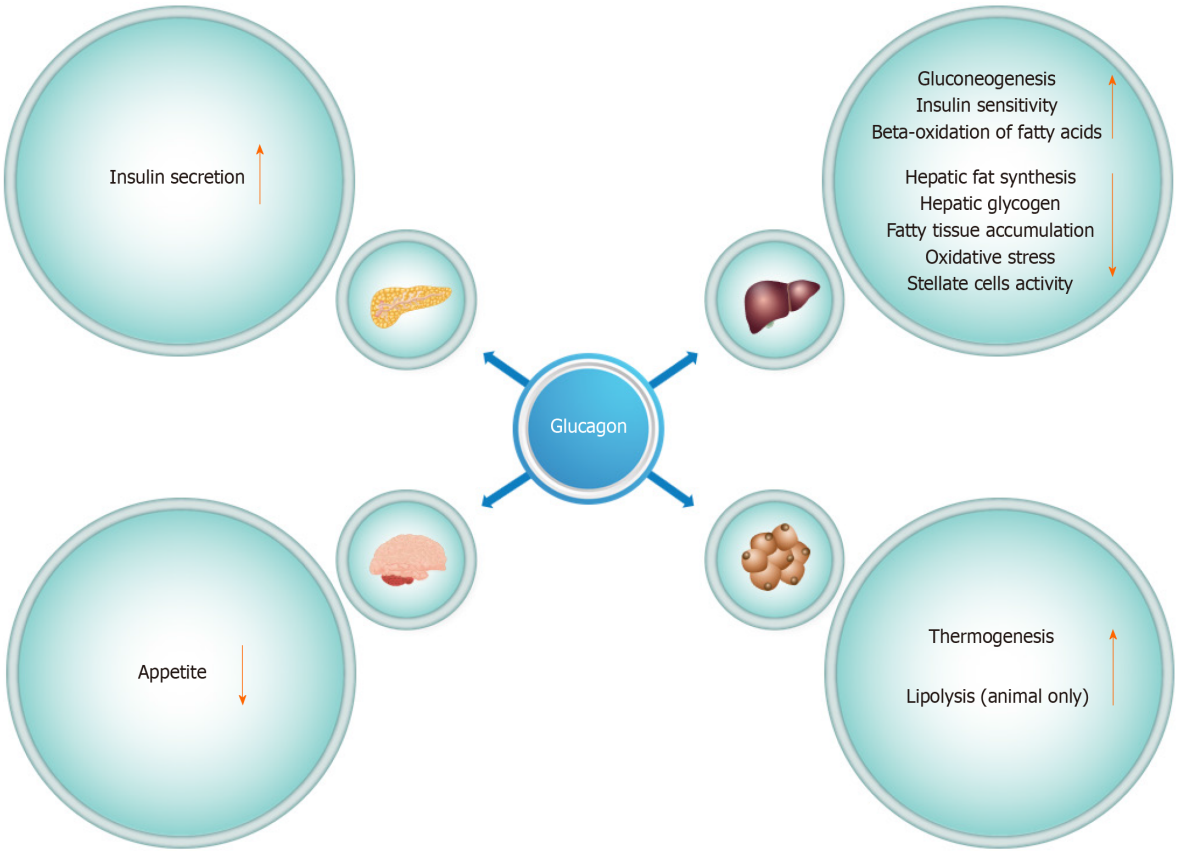

Figure 2 A simplified schematic illustrating how glucagon acts on multiple organs to mitigate metabolic dysfunction-associated steatotic liver disease.

MASLD activity score improvement[76]. Nestor *et al*[77] used a different dual GLP-1RA/GCGRA agent and concluded that the dual agonist significantly reduced steatosis in the MASH mouse model[77].

Although the role of GIP in satiety suppression and weight reduction is under debate, the coadministration of GLP-1RA and GIPRA has produced promising results. Combining GIPRA with GLP-1RA significantly increases weight loss, glycemic control, and lipid profile management compared with mono GLP-1RA alone[21,78].

Dual GLP-1 and GIPRA outperform single selective GLP-1RA in achieving better glycemic control and weight loss. These unimolecular dual incretins synergize to reduce fat mass, and the selective GIP agonist does not significantly reduce body weight. Compared with selective mono-agonists, dual RAs also demonstrate superior antihyperglycemic and insulinotropic efficacy. Its effectiveness extends across various species, including rodents, primates, and humans. These dual RAs have also been engineered for less frequent dosing and minimized side effects, offering a more physiological approach to managing conditions such as impaired glucose tolerance[62,79-81].

Adding GLP-1 and GIP components to glucagon appears to mitigate the diabetogenic effect of glucagon, and the synergistic effect between GLP-1 and GIP could provide superior health potential. Therefore, managing MASLD and its related comorbidities is a promising endeavor for triple RAs. In rodent models of obesity, compared with existing mono-receptor agonists or dual coagonists, balanced unimolecular triple agonists have been shown to have superior effects on body weight reduction, glycemic control, and hepatic steatosis regression[82]. A triple combination of selective mono-agonists significantly reduced the MASH histological activity score compared to that of high-dose liraglutide at the exact extent of body weight loss[76].

Over time, we can expect the development and evolution of multiagonist agents. These agents are anticipated to be part of a new class of drugs that are ingeniously designed to merge the amino acid sequences of crucial metabolic hormones. This innovative approach aims to create a single, more potent entity with prolonged efficacy.

CLINICAL TRIALS AND THERAPEUTIC EFFECTS OF INCRETINS AND GLUCAGON RAS

The evolving role of GLP-1RAs in MASLD or MASH has been investigated in multiple randomized controlled trials (RCTs) that enrolled patients with or without T2DM. The key phase II RCTs that evaluated GLP-1RAs, dual GLP-1RA/GIPRAs, or dual GLP-1RA/GCGRAs for the specific treatment of individuals with MASLD or MASH are summarized in Table 1. In all these RCTs, the diagnosis of MASLD or MASH was established either by magnetic resonance imaging-based techniques, such as magnetic resonance proton density fat fraction (MRI-PDFF) and magnetic resonance spectroscopy (MRS), or based on liver biopsy histology evidence. The minimum enrollment of each trial must be more

than 15 individuals per treatment group. To our knowledge, there were no published RCTs on GLP-1/GIP/GCG triple receptor agonists for MASLD/MASH in humans at the time of writing. However, the results of ongoing clinical trials investigating the effect of triple agonists on biopsy-confirmed MASH are urgently needed[83]. The effect of incretin and glucagon RAs on MASH is postulated to be related to indirect beneficial effects on weight loss and insulin resistance, as well as reductions in metabolic dysfunction, lipotoxic effects, and inflammation. In a phase II RCT by Newsome *et al*[84], semaglutide significantly improved MASH without worsening fibrosis but did not improve fibrosis. The lack of improvement in fibrosis in this trial was an unexpected finding despite a notable benefit with respect to MASH resolution and dose-dependent weight loss. The reason for these unexpected findings is unclear but could be explained by the relatively short duration of follow-up and lack of statistical power. Similarly, in a phase II RCT by Loomba *et al*[85], semaglutide failed to meet the primary endpoint of fibrosis improvement without worsening MASH among patients with compensated liver cirrhosis. However, semaglutide reduced liver enzyme levels, liver steatosis, and the levels of the exploratory hepatic collagen biomarker pro-collagen 3 peptide. The effect of semaglutide on advanced fibrosis improvement and liver-related outcomes remains to be investigated, and the results of this ongoing large clinical trial are expected in Q3 of 2029 (NCT04822181).

GLP-1RAs

Currently, 13 published placebo or active-controlled phase II RCTs have investigated the use of liraglutide (n = 6), exenatide (n = 2), semaglutide (n = 4), or dulaglutide (n = 1) in the treatment of MASLD or MASH (Table 1). A total of 584 individuals were enrolled in the intervention arm, and 528 were enrolled in the placebo or active control arm. The mean age was 52 years, and the mean follow-up duration was 36 wk. Only one RCT, by Loomba *et al*[85], investigated the effect of semaglutide on biopsy-proven MASH-related cirrhosis compared to that of a placebo. The researchers found that, compared with placebo, semaglutide did not improve liver fibrosis [11% *vs* 29%, OR: 0.28 (95%CI 0.06-1.24); P = 0.087]. Similarly, no notable differences were observed between the treatment groups in terms of the percentage of patients who achieved MASH resolution [34% *vs* 21%, OR: 1.97 (95%CI 0.56-7.91); P = 0.29]. However, despite the lack of a significant difference in liver stiffness between the semaglutide group and the placebo group, semaglutide significantly reduced liver enzyme levels, the hepatic collagen biomarker pro-collagen-3 peptide levels, and steatosis. Those who achieved substantial weight loss by semaglutide had lower levels of VLDL cholesterol and triglycerides, and those with T2DM had lower levels of HbA1c. Semaglutide did not cause any new or significant safety concerns, and the main adverse events were transient, mild to moderate gastrointestinal-related AEs[85].

Notably, in a proof-of-concept phase II trial, Alkhouri and colleagues demonstrated that, in comparison with semaglutide monotherapy, the combination of semaglutide and firsocostat (an acetyl-coenzyme A carboxylase inhibitor that reduces hepatic de novo lipogenesis) with and without cilofexor (a farnesoid X receptor agonist that inhibits lipogenesis, gluconeogenesis, and bile acid synthesis) resulted in more significant improvements in liver fat content (LFC) measured by MRI-PDFF, with a mean of absolute changes ranging from -9.8% to -12.6% *vs* -8.6% (P < 0.05). However, the reduction in LFC was comparable between the triple and double combinations[86]. Of the remaining 11 trials, GLP-1RAs demonstrated significant improvement in LFC as evaluated by MRS or MRI-PDFF compared to placebo or active control in 6 trials[87-92], and two other phase II trials with biopsy-confirmed MASH, liraglutide, and semaglutide resulted in promising outcomes with MASH resolution compared to placebo (P < 0.05)[84,93]. In contrast, three small trials of liraglutide and exenatide failed to show a significant reduction in liver fat content measured by MRS compared to that of the active control or placebo[94-96]. Remarkably, GLP-1RAs were relatively safe and had limited major serious adverse effects (AEs); the most frequently reported AEs were mild to moderate gastrointestinal-related AEs that occasionally led to medication discontinuation. The details of these trials are summarized in Table 1.

GLP-1/GIP dual RAs

In a substudy of the open-label phase III SURPASS-3 trial, Gastaldelli and colleagues examined the effect of 52 wk of subcutaneous tirzepatide once per week *vs* once-daily insulin degludec on LFC measured by MRI-PDFF in patients with MASLD and T2DM. By the end of the 52 wk of therapy, the absolute reduction in LFC was significantly greater in the pooled 10 mg and 15 mg tirzepatide groups (-8.1%) than in the insulin degludec group (-3.4%), with an estimated treatment difference in LFC of -4.7% [95%CI -6.72 to -2.70; P < 0.0001]. At week 52, the proportion of individuals with at least a 30% relative decrease in LFC was greater in the tirzepatide group (67%-81%) than in the insulin degludec group (32%)[97]. Tirzepatide was associated with a substantial weight loss of 8 to 11 kg and a notable reduction in abdominal visceral fat depots. In contrast, insulin degludec increased the expression of both metabolic parameters[97]. This study demonstrated that tirzepatide benefits patients with MASLD and T2DM. However, the lack of liver biopsy did not allow for an evaluation of the effects of tirzepatide on individual histological features of MASH. Gastrointestinal AEs were mild to moderate and more frequently reported in the tirzepatide group than in the insulin degludec group.

GLP-1/GCG dual RAs

A recent phase II open-label active comparator RCT investigated the effects of GLP-1RA/GCGRA (efinopontinide) compared to a selective GLP-1RA (semaglutide) on LFC evaluated by MRI-PDFF in patients with MASLD with or without T2DM. The main finding was that the mean relative reduction in LFC was 72.7% in the efinopegdutide group *vs* 42.3% in the semaglutide group. The mean relative reduction in LFC at week 24 in the efinopegdutide group compared to the semaglutide group was 30.4% (95%CI 22.1-38.7; P <0.001). Moreover, a more significant proportion of participants achieved a normal LFC (< 5%) at week 24 in the efinopegdutide group (66.7%) than in the semaglutide group (17.8%)[98]. Overall, mild to moderate gastrointestinal AEs were more frequently reported in patients taking efinopegdutide than in those receiving semaglutide.

AES AND DRUG-DRUG INTERACTIONS

GLP-1RAs and dual GLP-1RA/GIPRAs for treating T2DM and, more recently, for weight loss have become more frequently encountered in clinical practice. This was attributed to the potent class effect for better diabetes control[99-101], the up to 20% reduction in total body weight[102,103], and a notable improvement in metabolic syndrome and cardiac risk, even in patients without diabetes[104]. The most commonly reported adverse events associated with these incretin RAs are gastrointestinal symptoms, which include nausea, vomiting, gastroparesis, constipation, diarrhea, and bowel obstruction. There are limited data on head-to-head comparisons between the different available incretin RAs regarding gastrointestinal AEs and gastric emptying as primary outcomes.

A recent retrospective study that used extensive health claims data captured 93% of all outpatient prescriptions and physician diagnoses in the United States through the international classification of diagnoses, ninth or tenth revision, and examined gastrointestinal AEs associated with GLP-1RAs for weight loss in a clinical setting. This study revealed that, compared with patients receiving bupropion-naltrexone, patients receiving GLP-1RAs had an increased risk of pancreatitis [adjusted HR, 9.09 (95%CI, 1.25-66)], bowel obstruction [HR, 4.22 (95%CI, 1.02-17.40)], and gastroparesis [HR, 3.67 (95%CI, 1.15-11.90)], but there was no significant difference in the risk of biliary disease [HR, 1.50 (95%CI, 0.89-2.50)] [105]. In the SUSTAIN 10 trial, in a head-to-head comparison of subcutaneous semaglutide *vs* liraglutide, gastrointestinal AEs were reported in 36.7% *vs* 29.3% of the patients in the semaglutide and liraglutide groups, respectively[106]. Nonetheless, gastrointestinal AEs are highly prevalent with oral GLP-1RAs[107]. Oral semaglutide at 25 and 50 mg per day were associated with nausea in 27% and vomiting in 18% of patients. Moreover, in patients with obesity without T2DM treated with 50 mg oral semaglutide, 52% of patients developed nausea, 24% developed vomiting, 28% developed constipation, and 27% developed diarrhea[108,109]. The experimental oral non-peptide GLP-1RAs danuglipron and orforglipron induced significant gastrointestinal AEs, mainly nausea, which occurred primarily during dose escalation [110,111]. A longitudinal assessment of gastrointestinal AEs during a 68-wk trial of once-weekly subcutaneous semaglutide in adults with overweight or obesity revealed that gastrointestinal AEs developed at any time up to 68 wk, with a median duration of nausea occurring for 8 d and vomiting for 2 d. Moreover, the AEs led to discontinuation of medication in 10% to 17% of the study participants across different dose cohorts at any time after randomization[111].

Multiple cases of depression, suicidal ideation, and self-injury among patients using liraglutide and semaglutide were recently reported to the European Medicines Agency for review. Importantly, patients with a medical history of depression or suicidal ideation were excluded from clinical trials of semaglutide and liraglutide. According to the pharmaceutical company drug label for liraglutide, 0.3% of those who received the drug in clinical trials reported suicidal ideation, whereas 0.1% reported suicidal ideation in patients receiving placebo. Therefore, clinicians need to exercise caution in prescribing these medications to patients with depression or suicidal ideation[112]. Additionally, close monitoring for symptoms of depression or the development of suicidal ideation is required for patients on GLP-1RAs.

Medullary thyroid cancer is a potential risk factor according to rodent studies, but because cancer is a latent disease, it will take many years to gather data on people. A personal or family history of medullary thyroid cancer is a contraindication for both GLP-1RA and GLP-1RA/GIPRA[112].

GASTROINTESTINAL AES AND CLINICAL PRACTICE IMPLICATIONS

The most common side effects of incretin RAs are gastrointestinal related (nausea, vomiting, diarrhea, constipation, or bowel obstruction). Multiple studies have shown that AEs are dose dependent and primarily occur during the dose escalation period[113]. They usually tend to abate with long-term use. However, the mechanism of such improvement is unclear[114]. In the PIONEER-7 trial, individuals were allowed to adjust doses of oral semaglutide according to efficacy and tolerability. Nine percent of the study participants stopped the drug due to gastrointestinal AEs, which were documented in some patients after the first exposure at an initial dose of 3 mg per day. Individual variability in the onset of these AEs could be related to pharmacokinetics, such as the T-max of each drug[115,116]. In the STEP-1 trial, the researchers showed that gastrointestinal AEs may occur at any time during the 68-wk study after maximal dose-up titration has been implemented[103]. Therefore, a tailored individualized approach is recommended to place patients on the maximum tolerated dose, providing medication benefits with the least possible side effects. This can be accomplished by following the recommendations of the regulating agencies, starting with lower doses and adopting a slower titration strategy to induce tolerance before exposure to higher doses. Such a slow titration strategy may help minimize the risks of potential side effects. Generally, patients need to be educated about the expected effect of early satiation and nausea they may experience while eating after they feel full[114]. It is also recommended that patients who develop gastrointestinal AEs implement dietary modifications, such as eating frequent small meals and decreasing fat and nondigestible fiber consumption, similar to patients with gastroparesis[117]. In some instances, when a patient continues to experience persistent side effects, a dose de-escalation approach to the lowest tolerable dose may help reduce symptoms. It is comprehensible that these medications may exacerbate symptoms of diabetic gastroparesis. Therefore, alternative weight loss therapeutics, such as naltrexone-bupropion or phentermine-topiramate, should be considered for these patient subgroups.

INCRETIN RAS AND PERIOPERATIVE MANAGEMENT

Recently, there have been growing concerns regarding the risks of GLP-1RA administration relative to perioperative management. These risks stem from increased residual gastric content in patients receiving GLP-1RAs, increasing the risk for aspiration[118,119]. Given the short half-life, the older universal recommendation was to hold these medications the same day of the procedure. However, in light of the development of longer-acting GLP-1RAs that carry different AE profiles, including gastric stasis, the preoperative management of these medications has been challenging[120,121]. There are limited data on the perioperative and postoperative outcomes associated with treatment with GLP-1RA. A single-center small observational study evaluated point-of-care gastric ultrasound data from patients taking semaglutide to treat obesity after a 10-hour fast. The study investigated whether these patients had a "full stomach," defined as clear fluid content (1.5 mL/kg, or solids), compared with patients not taking GLP-1RAs. In the lateral and supine positions, 90% and 70%, respectively, of the semaglutide group had solids identified, compared with 10% of controls[119]. A recent retrospective cohort study investigated the effect of GLP-1RAs on the quality of bowel preparation for patients undergoing colonoscopy for colon cancer screening. These findings revealed that the percentage of patients with poor bowel preparation was significantly greater in the GLP-1RA group than in the control group (15.5% *vs* 6.6%, $P = 0.01$). Notably, a greater proportion of patients in the GLP-1RA group required a repeat colonoscopy due to poor bowel preparation than did those in the control group (18.9% *vs* 11.1%, $P = 0.041$)[122].

However, no studies have yet been conducted to examine the effect of GLP-1RAs in gastrointestinal-related surgeries. The Society of Perioperative Assessment and Quality Improvement developed a consensus recommendation suggesting continuing GLP-1RAs before the day of surgery unless patients experienced gastrointestinal AEs or were undergoing gastrointestinal-related surgery. In such a clinical scenario, longer-acting GLP-1RAs should be held 7 d prior to surgery, and closer monitoring of antidiabetic medications should be performed in patients with T2DM. Otherwise, patients were instructed to take GLP-1RAs in the morning after surgery[121]. The half-life of most long-acting GLP-1RAs is approximately 5 d, and it would be rational to recommend holding these medications for approximately 4 wk prior to the elective procedure (which is equivalent to 5-6 times the half-life of these medications). In the context of obesity, such a recommendation may be applicable without significant clinical consequences. However, in patients with T2DM, it is imperative to ensure that alternative antidiabetic treatments, such as biguanide (*e.g.*, metformin) or sodium-glucose cotransporter-2 (SGLT2) inhibitors (*e.g.*, empagliflozin), are used and, if indicated, that insulin supplementation be managed under the guidance of endocrinologists or primary care physicians. Moreover, in urgent or emergency surgery settings, it should be presumed that patients receiving GLP-1RAs have gastric stasis and appropriate measures should be implemented to prevent aspiration. For example, bedside ultrasound should be used to assess residual gastric contents [123,124]. Furthermore, intravenous erythromycin may be considered to fasten gastric emptying[125,126]. The standard erythromycin dose is 3 mg/kg IV infused over 45 minutes[127].

BARRIERS TO ACCESSING AND PRESCRIBING INCRETIN RAS IN CLINICAL PRACTICE

Currently, Medicare does not provide coverage of GLP-1RAs for the diagnosis of obesity alone without T2DM, while Medicaid and commercial insurance coverage vary substantially[128]. The annual out-of-pocket cost of semaglutide and liraglutide for chronic weight management is roughly $16,000, and for tirzepatide (a duaL GLP-1RA/GIPRA recently FDA approved for obesity), it is expected to be $12700[129]. This costly annual out-of-pocket pay, in addition to lack of insurance coverage, creates disturbing trends. For example, there are emerging versions of compounded semaglutide that patients can purchase online or overseas at a lower cost. However, the FDA issued a warning about reports of adverse events associated with the use of compounded semaglutide. Furthermore, the agency expressed concerns that some products may not contain the same active ingredient as FDA-approved products. In fact, the agency issued warning letters to companies involved in the online sale of unapproved and misbranded semaglutide and tirzepatide drugs[112].

Clearly, there is an imbalance in the supply and demand of GLP-1RAs[112]. In a recent retrospective cohort study, researchers found that during the first year of availability of GLP-1RAs, the mean monthly growth rate for Ozempic, Wegovy, Rybelsus, and Saxenda exceeded 85%. Additionally, the Mounjaro and Wegovy populations demonstrated monthly user growth rates greater than 200% and 100%, respectively[130]. Despite this noticeable growth in the demand and limited supply of GLP-1RAs, no generic competitors for these products have yet emerged in the market. A recent analysis by Alhiary *et al*[131] evaluated the patent and regulatory system strategies used by manufacturers of the brand name GLP-1RAs to extend market exclusivity. This study revealed that brand name manufacturers obtained a median of 19.5 patents per GLP-1RA and secured a median of 18.3 years of expected protection. Interestingly, more than half of these patents were obtained on delivery devices rather than on active ingredients[131]. These long periods of GLP-1RA market exclusivity highlight the need for patent and regulatory reforms on drug-device combinations.

CLINICAL TRIALS EVALUATING INCRETIN AND GLUCAGON RAS FOR MASLD AND FUTURE PERSPEC-TIVES

Semaglutide is currently being evaluated in a phase III double-blind placebo-controlled RCT in patients with biopsy-confirmed MASH; the primary outcomes investigated were the histological resolution of MASH after 72 wk of treatment and the time to the first liver-related clinical event after 240 wk of treatment (NCT04822181; Table 2). This pivotal trial is

Table 1 The main phase II and phase III randomized controlled trials investigating glucagon-like peptide 1 receptor agonist, glucagon-like peptide 1 receptor agonist/glucose-dependent insulinotropic polypeptide receptor agonist, or glucagon-like peptide 1 receptor agonist/glucagon receptor agonist in metabolic dysfunction-associated steatotic liver disease or metabolic dysfunction-associated steatohepatitis

Ref. (trial phase)	Intervention (*n*)	Comparator (*n*)	Participants	Duration	Primary hepatic outcome measures	Major adverse events
GLP-1 RAs (*n* = 13 trials)						
Armstrong *et al*[93] (2016) (phase II)	Liraglutide 1.8 mg/d (26)	Placebo (26)	Biopsy-confirmed MASH with or without T2DM	48 wk	Liraglutide use was associated with greater histological MASH resolution (39%) than placebo use (9%, $P = 0.019$). Fibrosis progression occurred in 9% of the liraglutide group *vs* 36% in placebo ($P = 0.04$)	Moderate gastrointestinal AEs in the liraglutide group (81%) *vs* placebo group (65%)
Dutour *et al* [87] (2016) (phase II)	Exenatide 5-10 μg twice a day (22)	Placebo (22)	T2DM and 95% with MASLD (assessed by MRS)	26 wk	LFC was reduced with exenatide (-23.8% [SD 9.5] more than placebo (+12.5% [9.6]; $P = 0.007$)	Not reported
Yan *et al*[88] (2019) (phase II)	Liraglutide 1.8 mg/d (24)	Insulin glargine 0.2 IU/kg/d (24) or Satigliptin 100 mg/d (27)	T2DM and MASLD (assessed by MRI-PDFF)	26 wk	In the liraglutide and sitagliptin groups, LFC decreased from baseline to week 26 (liraglutide: from 15.4% [SD 5.6] to 12.5% [6.4], $P < 0.001$; sitagliptin: from 15.5% [5.6] to 11.7% [5.0]; $P = 0.001$). Delta MRI-PDFF was greater with liraglutide than sitagliptin, but was not significantly different between the two groups (-4.0 *vs* -3.8; $P = 0.911$). MRI-PDFF did not change significantly from baseline in the insulin glargine group	Not reported
Khoo *et al* [95] (2019) (phase II)	Liraglutide 3 mg/d (15)	Lifestyle modifications (diet and exercise) (15)	Obesity and MASLD without T2DM (assessed by MRS)	26 wk	Both treatment groups showed similar reduction in LFC at 26 wk (-8.1% [SD 13.2] *vs* -7.0% [7.1]) $P = 0.78$	Nausea, abdominal discomfort, and diarrhea in the liraglutide group
Liu *et al*[96] (2020) (phase II)	Exenatide 5-10 μg twice a day (38)	Insulin glargine 0.1-0.3 IU/kg per day (38)	T2DM and MASLD (assessed by MRS)	24 wk	LFC was not significantly reduced after exenatide treatment (change in LFC: -17.6% [SD 12.9]) compared with insulin glargine (change in LFC -10.49 [SD 11.38]) $P = 0.1248$	Similar between the two groups
Binzino *et al* [94] (2020) (phase II)	Liraglutide 1.8 mg/d (23)	Placebo (26)	T2DM and MASLD (assessed by MRS)	26 wk	Reduction in LFC was not different between the two groups (liraglutide: from 18.1% [SD 11.2] to 12.0% [7.7]; placebo: from 18.4% [9.4] to 14.7% [10.0%]; estimated treatment effect -2.1% [95% CI -5.3 to 1.0]) $P = 0.17$	No serious AEs were reported
Kuchay *et al* [89] (2020) (phase II)	Dulaglutide 1.5 mg/wk (32)	Standard of care for T2DM (32)	T2DM and MASLD (assessed by MRI-PDFF)	26 wk	Dulaglutide resulted in a control-corrected absolute reduction in LFC -3.5% (95% CI -6.6 to -0.4; $P = 0.025$) and relative reduction of -26.4% (-44.2 to -8.6; $P = 0.004$) compared with placebo; absolute changes in liver stiffness on VCTE (-1.31 kPa [-2.99 to 0.37]; $P = 0.12$) with no difference between two treatment groups	No serious AEs were reported
Guo *et al*[90] (2020) (phase II)	Liraglutide 1.8 mg/wk (32)	Insulin glargine once a day (32); Placebo (32)	T2DM and MASLD (assessed by MRS) treated with metformin	26 wk	Liraglutide resulted in a control-corrected absolute reduction in LFC of -6.3% ($P < 0.05$) and relative reduction of -24% ($P < 0.05$); reduction in liver fat content was greater with liraglutide (-6.3%) than with insulin glargine (-3.4%) with no difference between the two treatment groups ($P > 0.05$)	No serious AEs; mild-to-moderate gastrointestinal AEs were reported in the liraglutide group
Zhang *et al*	Liraglutide 1.2	Pioglitazone 30 mg a day	T2DM and MASLD	24 wk	Liraglutide resulted in a control-corrected absolute reduction in	No serious AEs; mild-to-moderate gastrointestinal AEs were

[91] (2020) (phase II)	mg/wk (30)	(30)	(assessed by MRS) treated with metformin		LFC of -4.0% (95% CI -6.6 to -0.4; $P < 0.05$) and relative reduction of -17% ($P < 0.05$); this reduction in LFC was greater with liraglutide than pioglitazone	reported in the liraglutide group
Newsome *et al*[84] (2021) (phase II)	Semaglutide 0.1 mg/d (80); 0.2 mg/d (78); 0.4 mg/d (82)	Placebo (80)	Biopsy-proven MASH and liver fibrosis with or without T2DM	72 wk	Among patients with stage F2 or F3 fibrosis, the percentage of patients with MASH resolution and no worsening of fibrosis was 40% in the 0.1 mg group, 36% in the 0.2 mg group, 59% in the 0.4 mg group, and 17% in placebo ($P < 0.001$ for semaglutide 0.4 mg *vs* placebo); fibrosis stage improvement occurred in 43% of the 0.4 mg group and in 33% of the placebo group ($P = 0.48$)	No serious AEs; nausea, constipation, and vomiting was higher in the 0.4 mg group than in the placebo group
Flint *et al*[92] (2021) (phase II)	Semaglutide 0.4 mg/d (34)	Placebo (33)	MASLD (assessed by MRI-PDFF and MRE) with or without T2DM	72 wk	Semaglutide significantly reduced LFC compared with placebo and more patients had a ≥ 30% reduction in LFC with semaglutide at 24, 48, and 72 wk (with an estimated treated ratio of 0.50 at week 72 with $P < 0.0001$); changes in liver stiffness were not different between the two groups	Gastrointestinal AEs (diarrhea and nausea) were more frequently reported in the semaglutide group than the placebo group
Alkhouri *et al*[86] (2022) (phase II)	Semaglutide 2.4 mg/wk (21)	Semaglutide 2.4 mg/wk plus cilofexor 30 mg/d (22) or Semaglutide 2.4 mg/wk plus cilofexor 100 mg/d (22) or Semaglutide 2.4 mg/wk plus firsocostat 20 mg/d (22) or Semaglutide 2.4 mg plus cilofexor 30 mg/d plus firsocostat 20 mg/d (21)	MASH with mild to moderate fibrosis (assessed by either liver biopsy or MRI-PDFF ≥ 10% and VCTE measured liver stiffness ≥ 7 kPa) with or without T2DM	24 wk	Combination treatments *vs* semaglutide monotherapy resulted in greater improvements in LFC (least-squares mean of absolute changes: ranging from -9.8% to -12.6% *vs* -8.6%; the difference was significant only between the semaglutide and semaglutide plus firsocostat groups) and in noninvasive tests of liver fibrosis	Treatment was well tolerated; the incidence of AEs was similar across the groups (73-90%), and most commonly reported AEs were gastrointestinal, including nausea, diarrhea, and constipation
Loomba *et al*[85] (2023) (phase II)	Semaglutide 2.4 mg/wk (47)	Placebo (24)	Biopsy-proven compensated MASH cirrhosis with or without T2DM	48 wk	Semaglutide, compared to placebo, resulted in no improvement in liver fibrosis (11% *vs* 29%, OR: 0.28 [95%CI 0.06-1.24]); $P = 0.087$ and no significant difference between treatments for MASH resolution (34% *vs* 21%, OR: 1.97 [95%CI 0.56-7.91]); $P = 0.29$	
GLP-1RA/GIPRA ($n = 1$ trial)						
Gastaldelli *et al*[97] (2022) (substudy of phase III)	Tirzepatide 5 mg/wk (71); 10 mg/wk (79); 15 mg/wk (72)	Insulin degludec once a day (74)	T2DM and MASLD (assessed by MRI-PDFF) treated with metformin and/or SGLT2 inhibitors	52 wk	The absolute reduction in LFC at week 52 was significantly higher for the pooled tirzepatide 10 mg and 15 mg groups (-8.1%) *vs* the insulin degludec group (-3.4%); the estimated treatment difference *vs* insulin degludec was -4.7% (95%CI -6.7 to -2.7; $P < 0.0001$); those with at least a 30% relative decrease in LFC at week 52 were higher in each tirzepatide group (ranging from approximately 67% to 81% for tirzepatide doses) *vs* the insulin degludec group (32%)	
GLP-1RA/GCGRA ($n = 1$)						
Romero-Gómez *et al*[98] (2023) (phase II)	Efinopegdutide 10 mg/wk (72)	Semaglutide 1 mg/wk (73)	MASLD (assessed by MRI-PDFF) with or without T2DM	24 wk	The mean relative reduction in LFC was 72.7% with efinopegdutide and 42.3% with semaglutide. The difference in mean relative reduction from baseline in LFC at week 24 in the efinopegdutide group compared to the semaglutide group was 30.4% (95%CI 22.1-38.7; $P < 0.001$)	Overall, gastrointestinal AEs were more frequently reported in the efinopegdutide group compared to semaglutide

Post hoc analyses of randomized controlled trials investigating the effects of incretin receptor agonists (RAs) (*e.g.*, cotadutide) on plasma aminotransferase concentrations in patients with type 2 diabetes mellitus or studies that used liver ultrasound or blood biomarkers or scores for testing the effects of incretin RAs on metabolic dysfunction-associated steatotic liver disease were excluded. AEs: Adverse effects; GLP-1: Glucagon-like peptide 1; GIP: Glucose-dependent insulinotropic polypeptide; GCG: Glucagon; LFC: Liver fat content; MRS: Magnetic resonance spectroscopy; MRI-PDFF: MRI-proton density fat fraction; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; RAs: Receptor agonists; RCT: Randomized controlled trial; SGLT2: Sodium-glucose cotransporter 2; T2DM: Type 2 diabetes mellitus; VCTE: Vibration-controlled transient elastography.

Table 2 The main ongoing randomized controlled trials assessing the efficacy and safety of incretin receptor agonists in metabolic dysfunction-associated steatotic liver disease

Clinical trial registration number	Trial acronym	Status	Study participants	Interventions	Study characteristics	Estimated sample size, *n*	Primary hepatic outcome measures	Estimated completion date
GLP-1 RAs								
NCT04822181	ESSENCE	Recruiting	MASH on liver biopsy	Semaglutide *vs* placebo	Phase III double-blind, placebo-controlled trial	1200	Histological resolution of MASH with no worsening of liver fibrosis after 72 wk of treatment Improvement in liver fibrosis and no worsening of MASH after 72 wk of treatment Time to first liver-related clinical events (composite endpoint) after 240 wk of treatment	July, 2029
NCT05016882	N/A	Active not recruiting	MASH on liver biopsy	Semaglutide Plus NNC0194-0499[1] *vs* placebo	Phase II, randomized, double-blind, active and placebo-controlled, double-dummy, parallel-group, multinational trial	672	Improvement in liver fibrosis and no worsening of MASH after 52 wk of treatment	March, 2025
NCT04971785	N/A	Active not recruiting	MASH-related compensated cirrhosis on liver biopsy	Semaglutide plus cilofexor or fisocostat	Phase II, randomized, double-blind, double-dummy, placebo-controlled trial	440	Percentage of participants who achieve ≥ 1 stage improvement in liver fibrosis without worsening of MASH after 72 wk of treatment Histological resolution of MASH after 72 wk of treatment	December, 2024
NCT04639414	COMBATT2NASH	Recruiting	T2DM with MASH on liver biopsy	Semaglutide plus empagliflozine *vs* placebo and empagliflozine *vs* placebo	Phase IV, randomized, double-blind placebo-controlled trial	192	Histological resolution of MASH without worsening of fibrosis after 48 wk of treatment	December, 2023
NCT05140694	N/A	Not yet recruiting	T2DM with MASLD on transient elastography with CAP	Dulaglutide *vs* empagliflozin *vs* empagliflozin plus dulaglutide	Phase IV, randomized, active-comparator controlled, parallel grouped trial	135	Changes in CAP score after 24 wk of treatment	December, 2025
NCT03648554	REALIST	Not yet recruiting	T2DM with MASH on liver biopsy	Dulaglutide *vs* placebo	Phase IV, multicenter, open, prospective, randomized, controlled dietary	93	Histological resolution of MASH with no worsening of fibrosis after 52 wk of treatment	March, 2024

					reinforcement trial			
GLP-1RA/GIPRA								
NCT04166773	SYNERGY-NASH	Active, not recruiting	MASH on liver biopsy with or without T2DM	Tirzepatide *vs* placebo	Phase IIb, randomized, double-blind, placebo-controlled trial	196	Histological resolution of MASH with no worsening of fibrosis after 52 wk of treatment	February, 2024
Dual GLP-1RA/GCGRAs								
NCT05364931	PROXYMO-ADV	Active, not recruiting	MASH with fibrosis on liver biopsy	Cotudatide *vs* placebo	Phase IIb/III randomized double-blind, placebo-controlled trial	1860	Histological resolution of MASH with no worsening of fibrosis after 48 wk of treatment Histological resolution of MASH with no worsening of fibrosis and improvement in liver fibrosis by at least one stage without worsening of MASH after 84 wk of treatment	April, 2024
NCT05006885	N/A	Completed	MASLD on MRI-PDFF	Pemvidutide *vs* placebo	Phase I	95	Percentage of change in LFC by MRI-PDFF from baseline to day 85	August, 2022
NCT04771273	N/A	Completed	MASH on liver biopsy	Survodutide (BI456906) *vs* placebo	Phase IIb, multicenter, double-blind, parallel-group, randomized trial	240	Percentage of patients with histological improvement in MSAH (defined as NAS reduction of two or more points) after 48 wk of treatment	December, 2023
Triple GLP-1RA/GIPRA/GCGRA								
NCT04505436	N/A	Recruiting	MASH on liver biopsy	Efocipegtrutide (HM15211) *vs* placebo	Phase IIb, adaptive, randomized, double-blind, placebo-controlled, parallel-group trial	240	Histological resolution of MASH with no worsening of liver fibrosis after 52 wk of treatment	November, 2025

[1]NNC01940499 is a new subcutaneously administered FGF21 analog. The last search on https://clinicalstrial.gov/ was completed on December 21, 2023.

CAP: Controlled attenuation parameter; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide 1; GCG: Glucagon; MRI-PDFF: MRI-proton density fat fraction; MASLD: Metabolic dysfunction-associated steatotic liver disease; NAS: NAFLD activity score; MASH: Metabolic dysfunction-associated steatohepatitis.

well powered and has a sufficient follow-up duration, which will help provide answers regarding the effect of semaglutide on primary outcomes. Moreover, there are two ongoing placebo-controlled RCTs evaluating the effect of the combination of semaglutide with a fibroblast growth factor 21 (FGF21) analog and with cilofexor or firsocostat on liver fibrosis improvement and MASH resolution *vs* placebo (NCT05016882/NCT04971785; Table 2). COMBATT2NASH is a phase 4 placebo-controlled double-blind RCT studying the effect of semaglutide plus empagliflozin *vs* empagliflozin monotherapy *vs* placebo on MASH resolution with no worsening of liver fibrosis (NCT04639414; Table 2). Additionally, the REALIST trial is a phase 4 placebo-controlled RCT examining the effect of dulaglutide on MASH compared to that of the placebo (NCT03448554; Table 2).

SYNERGY-NASH is a phase 2b, double-blind, placebo-controlled RCT evaluating the effect of tirzepatide (a dual GLP-1RA/GIPRA) on MASH resolution after 52 wk of treatment (NCT04166773; Table 2). Cotudatide is a dual GLP-1RA/GGCRA currently being investigated in a phase 2b/3 placebo-controlled RCT to evaluate its effect in 1860 patients with biopsy-confirmed MASH and fibrosis (NCT05364931; Table 2). Cotadutide significantly reduced body weight and improved glycemic control, serum liver enzyme levels, and noninvasive fibrosis biomarker levels in individuals with T2DM and obesity[132]. Moreover, cotadutide improved the histological features of MASH and fibrosis in mice[75], and verified data regarding the efficacy of MASH histological resolution in human trials are awaited. Harrison and colleagues

presented data on dual GLP-1RA/GCGRA pemvidutide from a proof-of-concept trial and demonstrated a marked reduction in LFC (with 94% of participants achieving more than 30% relative reduction in just 12 wk of treatment with the 1.8 mg weekly dose) and normalization of LFC (< 5%) in 56% of participants. Unfortunately, almost one-quarter of patients discontinued pemvidutide due to adverse events that were mainly gastrointestinal (NCT05006885; Table 2). Another dual GLP-1RA/GCGRA agent is survodutide (BI 456906), which has greater potency against GLP-1 than glucagon. This agent has shown promising results in inducing rapid weight loss and improving insulin sensitivity[133]. A phase II RCT evaluated survodutide use in patients with MASH and fibrosis and has completed enrollment. The results are anticipated in Q1 2024 (NCT04771273; Table 2).

In a recent phase 2, double-blind, randomized, placebo-controlled 48-wk trial (NCT04881760), the use of retatrutide (a novel triple GLP-1RA/GIPRA/GCGRA) in overweight or obese adults resulted in substantial weight loss of -22.8% and -24.2%, respectively, with the 8 mg and 12 mg dose regimens, respectively[134]. Data from the subgroup analysis of this study were presented at the American Association for the Study of Liver Disease Conference in 2023, which evaluated the effects of retatrutide on 98 individuals with LFC > 10%, as measured by MRI-PDFF. The investigators found that the mean relative LFC changes from baseline at 24 wk were -81.4% and -82.4% with the 8 mg and 12 mg dose regimens, respectively, compared to 4.6% with the placebo, with $P < 0.001$. Notably, at 48 wk, LFC < 5% was achieved in 89% and 93%, respectively, of the 8 mg and 12 mg dose regimens, respectively, *vs* 0% in the placebo group ($P < 0.001$)[135]. Similarly, efocipegtrutide (HM15211) is another novel triple GLP-1RA/GIPRA/GCGRA agent that is currently being investigated in phase 2b trials, an adaptive, randomized, double-blind, placebo-controlled, parallel-group trial in patients with biopsy-confirmed MASH. The primary outcome of this trial was histological resolution of MASH with no worsening of liver fibrosis after 52 wk of treatment (NCT04505436)[83].

CONCLUSION

MASLD and its aggressive MASH phenotype are heterogeneous multisystem diseases that require multidisciplinary management plans and a holistic approach. GLP-1RAs showed promising potential for improving hepatic steatosis and MASH mainly through substantial weight loss, in addition to providing clear improvement in associated cardiometabolic risk factors. However, the role of GLP-1RAs in MASH-associated fibrosis remains unclear. Barriers to access such as limited supplies, cost, and lack of insurance coverage, particularly for nondiabetic MASLD patients with obesity, could be mitigated through patent and regulatory reforms on drug-device combinations, which may allow for generic competitors of these agents to be available for patients at affordable prices. Notably, emerging evidence suggests that the newer dual GLP-1RA/GIPRAs, dual GLP-1RA/GCGRAs, and triple GLP-1RA/GIPRA/GCGRAs have substantial effects on weight loss and consequently play critically important roles in the MASH therapeutic armamentarium. However, these findings remain to be confirmed by ongoing clinical trials[21]. Importantly, given the multiple complex mechanistic pathophysiologies of MASH, it is postulated that the combination of incretin RAs with different agents that exert effects on MASH through different mechanisms of action, such as liver-directed thyroid hormone receptor beta-selective agonists (Resmetirom; NCT04197479), farnesoid X RAs or acetyl-CoA carboxylase inhibitors (NCT04971785); an FGF-21 analog (NCT05016882); SGLT2 inhibitors (NCT04639414 and NCT05140694); or a pan peroxisome proliferator-activated receptor agonist (lanifibranor; NCT03008070), might prove to be the best therapeutic strategy for treating MASLD. The extrahepatic effects of MASLD, which include T2DM, chronic kidney disease, diastolic dysfunction, and some extrahepatic cancers (mainly colorectal and breast cancers), have become more evident. Thus, incretin RAs, which act not only on the liver but also on extrahepatic organs negatively impacted by MASLD, could be a promising therapeutic strategy that may lead to improved disease outcomes and prolonged survival beyond its effect on the liver.

FOOTNOTES

Author contributions: Xie C conceptualized of the design of the review article, performed the literature review, wrote the initial draft of the introduction and pathophysiology sections, created the figures, and critically revised the manuscript for important intellectual content; Alkhouri N revised the manuscript critically and added important intellectual content; Elfeki MA conceptualized the design of the review article, performed the literature search and review, wrote the initial draft of the following sections: clinical trials and therapeutic effects of incretin and glucagon RAs, adverse effects, clinical practice implications, barriers to access, perioperative management, clinical trials and future perspective sections, created the tables, and revised the manuscript critically for important intellectual content.

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Country/Territory of origin: United States

ORCID number: Naim Alkhouri 0000-0001-9872-2391; Mohamed A Elfeki 0000-0002-5623-2770.

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