***Recent Advances in Clinical Practice – Invited Review***

**Recent Advances in Incretin-Based Therapy for MASLD: From Single to Dual or Triple Incretin Receptor Agonists**

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**Abbreviation List**

CKD, chronic kidney disease

CVD, cardiovascular disease

eGFR, estimated glomerular filtration rate

GIP, glucose-dependent insulinotropic polypeptide

GLP-1, glucagon-like peptide 1

GLP-1RAs, glucagon-like peptide 1 receptor agonists

MRI-PDFF, magnetic resonance imaging-proton density fat fraction

MASLD, metabolic dysfunction-associated steatotic liver disease

MASH, Metabolic dysfunction-associated steatohepatitis

MetS, Metabolic syndrome

RCT, randomized clinical trial

T2DM, type 2 diabetes mellitus

**Key Messages**

* Incretins are derived from the glucagon superfamily and are produced by enteroendocrine cells in the ileum and colon in response to food ingestion.
* The first GLP-1RA (exenatide) was licensed for the treatment of hyperglycemia in T2DM in 2005.
* Incretin and glucagon receptor agonists can be combined in single peptides to have powerful effects in many organ systems and benefit cardiometabolic diseases.
* Phase 2 clinical trials show that GLP-1RAs and other incretin receptor co-agonists have beneficial effects on histological liver endpoints in MASLD/MASH.
* Retrospective cohort studies highlight incretin-based agents as a promising treatment option for preventing long-term liver clinical outcomes in people with MASLD.

**Abstract**

Clinically effective pharmacological treatment(s) for metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form metabolic dysfunction-associated steatohepatitis (MASH) represent a largely unmet need in medicine. Since glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been licensed for the treatment of type 2 diabetes mellitus and obesity, they were one of the first drug classes to be examined in individuals with MASLD/MASH. Successful phase 2 randomized clinical trials with these agents have resulted in progression to phase 3 clinical trials (principally testing the long-term efficacy of subcutaneous semaglutide). Over the last few years, in addition to GLP-1RAs, newer agents with glucose-dependent insulinotropic peptide (GIP) and/or glucagon receptor agonist functions have been tested, with increasing evidence from phase 2 randomized clinical trials of histological improvements in MASLD/MASH, as well as benefits on MASLD-related extrahepatic complications. Based on this background of evidence, single, dual or triple incretin receptor agonists are becoming an attractive and promising treatment option for MASLD or MASH, particularly in individuals with coexisting obesity or type 2 diabetes mellitus. In this narrative review, we examine the rapidly expanding body of clinical evidence supporting a role of incretin-based pharmacotherapies in delaying or reversing MASH progression. We also discuss the biology of incretins and the putative hepatoprotective mechanisms of incretin-based pharmacotherapies for managing MASLD or MASH.

**Introduction**

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly named non-alcoholic fatty liver disease, is increasingly recognized as a public health problem, affecting up to ~30-35% of the global adult population [1, 2, 3]. The clinical burden of MASLD is not only due to liver-related complications but also to an increased incidence of extrahepatic diseases, such as cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and certain types of extra-hepatic cancers (mainly non-liver gastrointestinal cancers) [4, 5, 6, 7].

Currently, there is a pressing need for drugs to treat MASLD and its more progressive form, metabolic dysfunction-associated steatohepatitis (MASH). In March 2024, resmetirom, a liver-directed, thyroid hormone receptor beta-selective agonist, was the first drug conditionally approved by the FDA for treating adults with non-cirrhotic MASH and moderate to advanced fibrosis [8, 9].

Nearly two decades have passed since the licensing of exenatide as the first glucagon-like peptide 1 receptor agonist (GLP-1RA) for treating T2DM in 2005. The last five years have proven to be very exciting for clinicians because of the realization that GLP-1RAs are important agents for treating not only T2DM but also obesity and their related cardiovascular and renal complications [10, 11, 12]. The incretin-based therapies include long-acting hormone receptor agonists targeting the GLP-1 receptor, dual agonists of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, dual agonists of the GLP-1 and glucagon receptors, and more recently, triple agonists of the GLP-1, GIP and glucagon receptors. Based on this evidence, incretin-based pharmacotherapy is becoming an attractive and promising therapeutic option for MASLD or MASH, particularly in individuals with coexisting T2DM or obesity.

In this narrative review, we examine the evolving evidence for the role of incretin-based pharmacotherapy, alone or as part of combination therapies, in delaying or reversing MASH progression. We also discuss the biology of incretins and the putative hepatoprotective mechanisms of GLP-1RAs and other dual or triple incretin-based drugs for treating MASLD or MASH.

**Biology of Incretins and the Entero-insular Axis**

An incretin is a gut-secreted hormone derived from proglucagon-derived peptides and produced from the enteroendocrine cells in the epithelium of the ileum and colon that stimulates pancreatic insulin secretion in response to food ingestion. There are two main incretin hormones in humans: GIP, produced by the K cells in the upper small intestine and GLP-1, produced by the L cells in the small intestine and colon. In healthy individuals, the term “incretin effect” describes the phenomenon whereby orally ingested glucose stimulates insulin secretion more potently than intravenous injection of the same amount of glucose. GIP and GLP-1 potentiate insulin secretion from the pancreatic beta cells at plasma glucose concentrations greater than 4.0 mmol/L [13, 14]. The concept of incretins being restricted to only GLP-1 and GIP is probably too narrow, and other gastrointestinal hormones likely interact with GLP-1 and GIP to modify their actions in response to food ingestion. Such peptides/hormones include cholecystokinin, gastrin, glucagon, PYY and xenin, all displaying satiating qualities while also improving pancreatic beta-cell function or survival, therefore making these molecules attractive candidates for amplifying the actions of GLP-1 and GIP [15]. However, of all these molecules, glucagon receptor agonism is the most advanced in clinical trials as a potential adjunctive therapy to GLP-1 and GIP receptor agonism. For such reasons, we have focused only on the biology of GLP-1, GIP, and glucagon receptor agonism relevant to treating MASLD or MASH.

*GLP-1 receptor agonism*

GLP-1 is derived from proglucagon, which is cleaved in a tissue-specific manner into either glucagon or GLP-1, and GLP-1 then undergoes post-translational modifications to become fully active. GLP-1 (and GIP) have a short half-life *in vivo* due to their rapid metabolism by the key enzyme di-peptidyl peptidase (DPP-IV). Consequently, to circumvent the actions of DPP-IV and prolong the half-life *in vivo*, GLP-1RAs are modified peptides that DPP-IV does not metabolize. GLP-1RAs act in the pancreas to increase insulin secretion mainly via their effects on GLP-1 receptors expressed in beta cells. GLP-1RAs also increase insulin gene expression [16] and induce beta-cell proliferation [17]. GLP-1 receptors are also expressed in other organs, suggesting that GLP-1RAs produce other disease-related benefits. For example, evidence suggests that GLP-1 receptor agonism has neuroprotective [18], anti-inflammatory [19], cardioprotective [20], and metabolic benefits [21].

GLP-1 has various physiological actions in multiple tissues [22], many of which could also benefit MASLD/MASH. For example, in the stomach, GLP-1 decreases gastric emptying and gastric motility, which can lead to feelings of fullness during a meal and potentially reduce food intake. GLP-1 decreases intestinal motility, and in the brain, GLP-1 controls food intake and regulates intestinal transit and gastric emptying. Several effects have also been described in the pancreas, including increased insulin secretion, glucose transporter and beta cell survival, and decreased glucagon secretion and apoptosis [22]. Weight loss can be considerable in patients treated with GLP-1RAs [11, 12].

GLP-1 receptors are not expressed in human hepatocytes. A phase 3 randomized clinical trial with semaglutide is underway in patients with MASH and liver fibrosis (NCT04822181), and although GLP-1RA-induced weight loss is undoubtedly beneficial for ameliorating MASH, preclinical experiments show that there are populations of hepatic endothelial cells and T cells expressing GLP-1 receptors [23] that may benefit liver disease in MASLD/MASH.

Although the heart, blood vessels, liver and kidneys all contain populations of cells expressing GLP-1 receptors, it is plausible that a key mechanism that may unify beneficial effects of GLP-1 receptor agonism across multiple organs are effects mediated via reductions in levels of inflammation [24] (that often occurs at low levels in individuals with cardiometabolic diseases). This notion is supported by evidence showing that specific intestinal lymphocytes and T cells express GLP-1 receptors within the immune system [24]. Alpha-1 adrenergic, delta-opioid, and kappa-opioid receptor signaling are critical for transduction of the systemic GLP-1 receptor anti-inflammatory-mediated effects, suggesting that there may be a gut-brain linked GLP-1 receptor axis for suppression of systemic low-grade inflammation [25]. The anti-inflammatory and immunomodulatory effects are described in more detail below in the section focusing on the potential anti-inflammatory and immunomodulatory benefits of these agents for treating MASLD/MASH.

*GIP and glucagon receptor agonism*

GIP is formed by post-translational processing of the precursor protein pro-GIP at residue 65 by proprotein convertase subtilisin/kexin type 1 in intestinal K cells, which gives rise to the established 42-amino-acid form of GIP [GIP(1-42)]. GIP signaling increases insulin secretion by acting via binding to the GIP receptor to potentiate glucose-dependent insulin secretion through cyclic adenosine 3′,5′-monophosphate (cAMP) protein kinase A (PKA) and exchange protein (directly activated by cAMP 2 [Epac2] signaling) [26]. In contrast to GLP-1, it is less certain how GIP acts in the brain to affect appetite, and GIP also has potentially important effects in adipose tissue that are unique to this incretin by producing a stimulatory effect on lipoprotein lipase and pre-adipocyte differentiation [27], thereby having an impact that may be of clinical relevance in MASLD. Recently, Regmi et al. investigated how long-acting GIP receptor agonists regulate fasted and fed adipocyte functions [28]. These authors reported that GIP receptor agonism enhanced insulin signaling, augmented glucose uptake, and increased the conversion of glucose to glycerol in a cooperative manner with insulin; however, in the absence of insulin, GIP receptor agonists increased lipolysis [28].

Glucagon is a hormone produced by the alpha cells of the pancreatic islets. Glucagon agonism would seem counter-intuitive in people with abnormal glucose tolerance with MASLD since it has been known for many decades that glucagon antagonizes insulin actions as a counter-regulatory hormone. However, when combined with incretin receptor agonism (and with GLP-1 receptor agonism in particular), the effects of glucagon receptor agonism in vivo seem neutral, with no harmful effects on glucose metabolism. Relevant to its potential benefit in MASLD, glucagon signals directly via its specific receptor and may have several effects [13, 14] potentially relevant to MASLD. In the liver, glucagon receptor agonism increases hepatic glycogenolysis and gluconeogenesis. In the gastrointestinal tract, glucagon receptor agonism increases gall bladder contraction, decreases gastric emptying and motility, and reduces appetite in the brain. In the pancreas, glucagon receptor agonism increases insulin secretion, and in the heart, it increases cardiac output, cardioprotection, and myocardial contractility [13, 29]. In the adipose tissue, glucagon receptor agonism increases lipolysis, thermogenesis and energy expenditure [13, 29], all of which can facilitate weight loss. The effects of incretin receptor and glucagon receptor agonism relevant to MASLD are shown in the schematic **Figure 1**.

**Effects of Incretin-Based Therapies for MASLD or MASH – Randomized Clinical Trial Results**

Over the past few years, an increasing number of randomized controlled trials (RCTs) have examined the possible hepatoprotective effects of incretin-based pharmacotherapies for MASLD or MASH.

*GLP-1RAs*

In 2021, our group performed a comprehensive meta-analysis of RCTs examining the efficacy of GLP-1RAs for treating MASLD or MASH, irrespective of T2DM status [30]. This meta-analysis incorporated eleven active-controlled or placebo-controlled phase 2 RCTs (including a total of 936 middle-aged overweight or obese participants, about 70% of whom had T2DM) that used liraglutide (n=6 RCTs), exenatide (n=3 RCTs), dulaglutide (n=1 RCT), or semaglutide (n=1 RCT) to specifically treat MASLD or MASH, as assessed by magnetic resonance-based techniques (n=9 RCTs) or liver biopsy (n=2 RCTs). Compared with placebo or reference therapy, treatment with GLP-1RAs for a median of 26 weeks (interquartile range: 24-27 weeks) was associated with significant reductions in the absolute percentage of liver fat content, as assessed by magnetic resonance-based techniques (pooled weighted mean difference: -3.92%; 95%Cl -6.3 to -1.6) and serum liver enzymes levels. Notably, this meta-analysis also showed that in the two placebo-controlled phase 2 RCTs with histological liver endpoints, GLP-1RAs (subcutaneous liraglutide 1.8 mg/day for 48 weeks or semaglutide at daily doses of 0.1 mg, 0.2 mg, or 0.4 mg for 72 weeks) resulted in a greater resolution of MASH without worsening of fibrosis than did placebo (pooled random-effects odds ratio 4.06, 95%Cl 2.5-6.6). Conversely, there was no difference in the percentage of participants with improvement in ≥1 stage of fibrosis without worsening of MASH (pooled random-effects odds ratio 1.50; 95%CI 0.98-2.3; p=0.060) [30]. GLP-1RAs also led to significant reductions in body weight (by ~4 kg) and hemoglobin A1c (by ~0.5%) and improved plasma lipid profile [30]. GLP-1RA use was well tolerated in these RCTs, with adverse event rates not exceeding those of either placebo or reference therapy, except for a higher frequency of transient, mild-to-moderate gastrointestinal events.

After the publication of this meta-analysis in 2021, other phase 2 RCTs have examined the hepatoprotective effects of subcutaneous semaglutide, showing significant reductions in liver fat content (as measured by magnetic resonance imaging-proton density fat fraction [MRI-PDFF]) in individuals with obesity and MASLD [31, 32].

Interestingly, in 2023, Loomba et al. also investigated the safety and efficacy of semaglutide in patients with MASH-related compensated cirrhosis. In this phase 2b placebo-controlled RCT involving 71 obese patients with biopsy-confirmed MASH-related cirrhosis, the authors found that once-weekly subcutaneous semaglutide 2.4 mg for 48 weeks did not significantly improve liver fibrosis or achievement of MASH resolution versus placebo [33]. However, compared to placebo, semaglutide led to significant reductions in serum liver enzymes, liver fat content (but not liver stiffness), and circulating levels of the exploratory hepatic collagen biomarker pro-collagen 3 peptide [33].

Recently, retrospective cohort studies have explored the association between the use of GLP-1RAs and the risk of developing major adverse liver-related outcomes in patients with T2DM. Using a propensity score matching approach, these retrospective cohort studies reported that patients who initiated GLP-1RAs had a significantly lower risk of developing incident cirrhosis, hepatic decompensation events, or hepatocellular carcinoma compared with those who initiated dipeptidyl peptidase-4 inhibitors or other glucose-lowering medications [34, 35, 36, 37, 38, 39, 40].

Collectively, these findings, mainly derived from phase 2 RCTs, suggest that GLP-1RAs (especially subcutaneous semaglutide, which was tested in the largest and longest phase 2 RCT published to date [41]) exert hepatoprotective effects on MASH and the evidence to date suggests that the benefit of these agents probably occurs earlier in the spectrum of liver disease with MASLD. That said, phase 3 placebo-controlled RCTs of GLP-1RAs in individuals with MASH and liver fibrosis are needed to answer questions regarding their impact on MASH resolution, fibrosis improvement, and long-term liver-related clinical outcomes. One phase 3 placebo-controlled RCT, i.e., the ESSENCE trial (NCT04822181), in approximately 1,200 individuals with biopsy-proven MASH and liver fibrosis is ongoing to investigate the effects of subcutaneous semaglutide (at a dose of 2.4 mg weekly) on liver histological endpoints (over 72 weeks) and liver-related clinical events (over 240 weeks).

*Dual GLP-1/glucagon receptor agonists*

Cotadutide is a GLP-1/glucagon receptor co-agonist that has significantly improved body weight, hemoglobin A1c, and non-invasive hepatic fibrosis biomarkers in patients living with obesity and T2DM [42, 43]. In a phase 2a placebo-controlled RCT, Shankar et al. examined the efficacy and safety of once-daily subcutaneous injections of cotadutide (600 μg or 300 μg) or placebo in 74 obese participants with biopsy-proven MASH and liver fibrosis [44]. These authors reported that treatment with cotadutide for 19 weeks improved hepatic fat content (as measured by MRI-PDFF), serum liver enzyme levels, and non-invasive fibrosis scores, with adverse events mainly mild to moderate and gastrointestinal (treatment discontinuation rates due to adverse events were ~17% and 8% and 4% with cotadutide 600 μg, 300 μg, and placebo, respectively). A phase 2b/3 placebo-controlled RCT is currently ongoing to investigate the efficacy of cotadutide on MASH resolution and liver fibrosis improvement over 84 weeks in approximately 1,800 adults with biopsy-confirmed MASH and liver fibrosis (NCT05364931). Two other small phase 2a active-controlled or placebo-controlled RCTs have tested the efficacy of other GLP-1/glucagon receptor co-agonists, i.e., efinopegdutide 10 mg once weekly for 24 weeks [45], or pemvidutide at weekly dosages of 1.2 mg, 1.8 mg, or 2.4 mg for 12 weeks [46], on liver fat content in 145 (for efinopegdutide) or 94 (for pemvidutide) individuals with overweight/obesity and MASLD. Both trials showed that efinopegdutide or pemvidutide yielded significant reductions in liver fat content (as measured by MRI-PDFF), markers of hepatic inflammation, and body weight.

Interestingly, in a recent phase 2b multicenter, placebo-controlled RCT involving 293 obese middle-aged individuals (~40% with T2DM) with biopsy-proven MASH and liver fibrosis (stages F1–F3), Sanyal et al. investigated the efficacy of survodutide, another GLP-1/glucagon receptor co-agonist, on histological liver endpoints [47]. Participants were randomly assigned to once-weekly subcutaneous injections of 2.4 mg, 4.8 mg or 6 mg of survodutide or placebo over 48 weeks. A significant improvement (reduction) in MASH with no worsening of fibrosis occurred in 47% of participants in the survodutide 2.4-mg group, 62% of those in the 4.8-mg group, and 43% of those in the 6-mg group, as compared with 14% of those in the placebo group. A significant decrease in liver fat content (measured by MRI-PDFF) by at least 30% also occurred in 63% of the participants in the survodutide 2.4-mg group, 67% of those in the 4.8-mg group, 57% of those in the 6-mg group, and 14% of those in the placebo group. Improvement in ≥1 stage of fibrosis with no worsening of MASH occurred in 34%, 36%, 32%, and 18%, respectively (multiple comparison tests did not formally test the p-value for between-group differences). Participants in the survodutide groups lost ~10% to 13% of their body weight and had lower concentrations of triglycerides and hemoglobin A1c and lower blood pressure than placebo. Rates of adverse events were more frequent with survodutide than placebo and included nausea (66% vs. 23%), diarrhea (49% vs. 23%), and vomiting (41% vs. 4%). Survodutide also significantly increased heart rate compared to placebo. The percentage of participants who discontinued survodutide was high. Discontinuation of survodutide and placebo due to adverse events occurred in 20% and 3% of participants, respectively [47].

A small, non-randomized, open-label phase 1 clinical trial also assessed the pharmacokinetics and safety of survodutide in 41 patients with MASH-related compensated or decompensated cirrhosis [48]. Results indicated that survodutide was well tolerated in these patients and improved metabolic and hepatic disease markers, including liver fat content, liver fibrosis biomarkers and body weight [48]. Based on this pilot study, further investigation of survodutide for MASH-related cirrhosis is warranted.

*Dual GLP-1/GIP receptor agonists*

A substudy of the open-label, phase 3 SURPASS-3 trial examined the effect of tirzepatide (i.e., a GLP-1/GIP receptor co-agonist) versus insulin degludec for 52 weeks on liver fat content and abdominal adipose tissue (as measured by MRI-PDFF) in patients with T2DM [49]. This trial included 296 overweight or obese individuals with T2DM randomly assigned to once-weekly subcutaneous tirzepatide (tirzepatide 5 mg, n=71; tirzepatide 10 mg, n=79; and tirzepatide 15 mg) or once daily insulin deglutec (n=72). From an overall mean baseline liver fat content of 15.7% (on MRI-PDFF), the absolute reduction in liver fat content at week 52 was significantly higher for the pooled tirzepatide 10 mg and 15 mg groups than the insulin degludec group (-8.1% vs. -3.4%). All tirzepatide doses significantly reduced body weight (~8-10 kg) and abdominal visceral fat depots from baseline at week 52, whereas insulin degludec increased these adiposity measures [49].

Recently, in the phase 2b SYNERGY-NASH trial, Loomba et al. [50] assessed the efficacy of tirzepatide in 190 obese patients with biopsy-proven MASH and moderate or severe liver fibrosis (58% of whom had T2DM). Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide at doses of 5 mg, 10 mg or 15 mg, or a placebo for 52 weeks. MASH resolution with no worsening of fibrosis (i.e., the primary endpoint) was achieved in 44% of the patients in the 5-mg group, 56% in the 10-mg group and 62% in the 15-mg group, compared with 10% in the placebo group (p<0.001 for all three groups versus placebo). Secondary endpoints were also met, including improvement in ≥1 stage of fibrosis in 55% of patients in the 5-mg group, 51% in the 10-mg and 15-mg groups, versus 30% in the placebo group. Participants who received tirzepatide had a mean reduction in body weight of up to 16% (with the 15-mg dose). Furthermore, tirzepatide improved plasma lipids and hemoglobin A1c compared to placebo. The most common adverse events were gastrointestinal events, most of which were mild or moderate in severity. Less than 5% of the adverse events reported during the trial led to the discontinuation of tirzepatide or placebo [50].

*Triple GLP-1/GIP/Glucagon receptor agonists*

In a phase 2a placebo-controlled RCT, Sanyal et al. [51] investigated the efficacy of retatrutide, a novel triple GLP-1/GIP/glucagon receptor co-agonist, in 98 obese individuals with MASLD (assessed by MRI-PDFF≥10%). Patients were randomly assigned to receive a placebo (n=19) or subcutaneous retatrutide 1 mg (n=20), 4 mg (n=19), 8 mg (n=22), or 12 mg (n=18) once per week for 48 weeks. The trial was completed by 11 patients in the placebo group and by 18, 15, 17 and 15 patients in the treatment groups, respectively. At 24 weeks, normal liver fat content (MRI-PDFF <5%) was achieved by 27% (1 mg), 52% (4 mg), 79% (8 mg), 86% (12 mg) and 0% (placebo) of participants. At 48 weeks, the mean relative reduction in liver fat content was −51% (1 mg), −59% (4 mg), −82% (8 mg), −86% (12 mg), and −4.6% (placebo) (p<0.001 for all groups versus placebo). Retatrutide also markedly reduced body weight and improved insulin sensitivity, plasma lipids (principally decreasing plasma triglycerides, very low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol), and adipocyte hormones (principally increasing plasma adiponectin, and reducing circulating leptin and fibroblast growth factor-21 levels). Adverse effects were mainly associated with transient and mild-to-moderate gastrointestinal events, which were higher in the 8 mg and 12 mg dose groups [51].

Although, to date, there are no head-to-head clinical trials comparing the hepatic effects of incretin receptor agonists, we have summarized in **Figure 2** the results of recently published phase 2 placebo-controlled RCTs (with a follow-up length of at least 48 weeks) that have examined the hepatoprotective effects of subcutaneous semaglutide [41], survodutide [47], or tirzepatide [50] on resolution/improvement of MASH and ≥1 stage fibrosis improvement in patients with MASH and liver fibrosis. We have not included the recent phase-2 RCT’s retatrutide data because this trial had no histological liver endpoints [51]. We have also summarized the principal multinational, placebo-controlled phase 2 RCTs (with a follow-up length ≥48 weeks) assessing the efficacy of GLP-1RAs and other (dual or triple) incretin receptor agonists for the treatment of MASLD or MASH in **Supplementary** **Table 1**. The findings need to be further validated in phase 3 placebo-controlled RCTs with longer follow-ups (enrolling more participants with lean MASLD/MASH and different ethnicities other than White individuals), and studies are also warranted to investigate the long-term risk of major adverse liver outcomes in individuals treated with incretin-based therapies.

**Putative Hepatoprotective Effects of Incretin-Based Drugs Focusing on Potential Anti-inflammatory and Immunomodulatory Benefits in the Treatment of MASLD/MASH**

It has been recognized in the past decade that incretin-based agonists act in a pleiotropic manner, beneficially affecting various biological systems, including the immune system. Whereas mechanisms might be rather diverse and somewhat indirect as GLP-1 receptors are not expressed by all cells in the human body, knowledge in this area has increased substantially in recent years [52, 53, 54].

*Anti-inflammatory and immunomodulatory effects: basic mechanisms*

Pivotal studies have revealed that understanding why GLP-1RAs reduce adverse cardiovascular and kidney outcomes; it might be partly due to reductions in systemic low-grade inflammation [27]. An intact gut-brain axis could be mandatory for GLP-1RAs to achieve anti-inflammatory activities as suppression of tumor necrosis factor (TNF)-alpha in various models of T-cell mediated inflammation was not dependent on hematopoietic or endothelial GLP-1 receptors, but required neuronal GLP-1 receptors [27]. These authors showed that impaired TNF-alpha production, driven by GLP-1 receptors, was dependent on alpha-1 adrenergic, delta-opioid and kappa-opioid receptor signaling. This evidence highlighted the importance of brain-immune interactions in mediating the beneficial effects of GLP-1RAs. Early studies reported almost 20 years ago that GLP-1RAs protected pancreatic beta cells from proinflammatory cytokine-induced toxicity by reducing cytokine-induced phosphorylation of protein kinase B [55]. Further studies revealed that exendin-4, an early available GLP-1RA, protected isolated human, rat and mouse pancreatic islets from the toxicity of interleukin (IL)-1 by potent inhibition of the JNK pathway [56]. Suppression of proinflammatory cytokines and thus anti-inflammatory action by GLP-1RAs appeared soon as a general concept since GLP-1 receptor agonism blocked interferon (IFN)-gamma-induced nitric oxide synthesis through suppressing TNF-alpha synthesis by pancreatic beta cells [57]. However, not only suppression of proinflammatory cytokines but also the induction of anti-inflammatory mediators, such as certain adipokines, demonstrated key effects of GLP-1 receptor agonism [58]. Exendin-4 increased the secretion of adiponectin from 3T3-L1 adipocytes while the synthesis of proinflammatory cytokines was suppressed [59]. Similar findings were later described in patients with T2DM treated with liraglutide [60]. The induction of other anti-inflammatory cytokines, such as IL-10, by human macrophages further supported the evidence for a strong anti-inflammatory action of GLP-1RAs [61]. Effects in macrophages include the preferential polarization towards M2 macrophages (anti-inflammatory macrophages with a preferential synthesis of IL-10), and such effects may contribute to the overall anti-inflammatory effects of GLP-1RAs [62]. It is currently not known which immune cells express GLP-1 receptors, but besides T cells, macrophages may express GLP-1 receptors as suggested by various studies, including that by Bruen et al., who showed an atherosclerosis-protective effect of liraglutide that was accompanied by an M2 macrophage phenotype [63]. Anti-inflammatory effects of GLP-1RAs also extend towards endothelial cells as liraglutide inhibited protein kinase C-alpha (PKC-), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and NF-kappa B (NF-B) signaling in these cells [64]. GLP-1RAs may also activate and up-regulate adenosine monophosphate kinase (AMPK), which is crucial for metabolic improvements [65]. GIP-receptor deficiency in myeloid cells was associated with weight gain, greater insulin resistance, hepatic steatosis and impaired energy expenditure, and this process was paralleled by the downregulation of S100A8 expression, an important proinflammatory mediator in adipose tissue [66]. Therefore, one might assume that both incretin receptor agonists can similarly affect immune pathways (**Figure 3**).

Importantly, GLP-1 receptor agonism affects various leukocyte populations, including T-cell populations. GLP-1 receptor signaling regulates lymphocyte proliferation, and GLP1r-/- mice exhibit lower numbers of peripheral regulatory T cells [19]. GLP-1RAs might broadly affect immunity, as suggested by another study. Xu et al. showed that exenatide influences FoxO1, a critical transcription factor of regulatory T cells, and restores Th17/Treg balance in *db/db* mice, thus proposing that exenatide might protect pancreatic islet inflammation by inhibition of Th17 cell infiltration [67]. The role of GLP-1 receptors in T cell function is complex as a recent experimental study showed that GLP-1 receptors are mainly expressed in a subset of T lymphocytes (particularly in those apoptotic anergic) and act as a T cell-negative costimulatory molecule, and GLP-1 receptor antagonism triggered anti-tumor immunity when tested in a preclinical mouse model of colorectal cancer [68]. Notably, the effects of dual or triple incretin agonists on the immune system are less well-studied, and respective studies are urgently awaited.

*Anti-inflammatory effects: preclinical models*

Numerous studies have investigated potential anti-inflammatory and immunomodulatory effects for GLP-1RAs in preclinical models. In one early study, AC3174, an exenatide analogue, improved hepatic steatosis and inflammation in *ob/ob* mice exposed to a high trans-fat diet [69]. GLP-1r-/- mice were protected from liver disease after a high trans-fat diet, supporting the notion that the GLP-1 receptor pathway might protect from metabolic liver diseases [69]. Liraglutide administration prevented liver pathology in ApoE and adiponectin knockout mice fed a high-fat diet (HFD) [69]. The beneficial effects of liraglutide were accompanied by suppression of TNF-alpha, NF-B and JNK phosphorylation, whereas adiponectin and AMPK phosphorylation were increased [70]. A beneficial effect of semaglutide on MASLD in *db/db* mice was paralleled by favorable effects on the intestinal barrier and gut microbiota [71]. In another animal MASLD study where liver disease was induced by the consumption of a trans-fat, fructose and cholesterol-enriched diet, the dual GLP-1/glucagon receptor agonist NN1177 showed more pronounced beneficial effects on hepatic steatosis, inflammation and fibrosis compared to semaglutide, whereas the metabolic effects controlled by the glucagon receptor showed a bell-shaped curve [72]. GLP-1 receptors are not expressed on hepatocytes, but preclinical studies show expression on hepatic endothelial cells and T cells, suggesting that the hepatoprotective effects of GLP-1RAs on MASLD/MASH might be mediated either indirectly or via interaction with these cells in the liver [23, 73]. Importantly, administration of recombinant adenovirus producing GLP-1 improved adipose tissue macrophage infiltration in *ob/ob* mice, paralleled by suppression of adipose tissue monocyte chemoattractant protein-1 (MCP-1), TNF and IL-6 mRNA expression and NF-B and JNK activation [74]. In line with a potential anti-inflammatory effect *in vivo*, GLP-1RAs have also improved atherosclerosis, frequently observed in MASLD. Both liraglutide and semaglutide decreased atherosclerosis in ApoE-/- and LDL-receptor-/- mice and this effect occurred in parallel to a decrease in the expression of proinflammatory mediators and reduced leukocyte infiltration in affected vessels [75]. Human endarterectomy samples treated with liraglutide also exhibited decreased secretion of MCP-1, TNF-alpha and IL-1 from human macrophages in ex-vivo studies paralleled with beneficial effects again in ApoE-/- mice [76] (**Figure 3**). Liraglutide in these studies also induced the important anti-inflammatory cytokine IL-10. Dual GLP-1/GIP receptor agonists might be more effective for improving atherosclerosis since male APO\*3-Leiden.CETP mice receiving a GIP receptor agonist (GIPFA-085) and a GLP-1RA (GLP-140) attenuated atherosclerotic lesions more potently than each agonist itself, accompanied by a decrease of systemic low-grade inflammation [77]. Gut intraepithelial lymphocytes (IEL) are essential for the GLP-1RA effects on gut microbiota; conversely, IELs play a key role in controlling local and systemic T cell-mediated types of inflammation, whereas endotoxin-driven inflammation was not [78].

GLP-1RAs have also exerted beneficial effects in other preclinical models beyond metabolic liver inflammation or atherosclerosis, further supporting the supposition that these drugs have clinically relevant anti-inflammatory effects. The expression of GLP-1 receptors was increased in intestinal IELs, characterized by cAMP induction after exendin-4 exposure and suppression of proinflammatory cytokines [24]. In accordance with a potential role for GLP-1 receptors in gut biology, Glp-1r-/- mice exhibited intestinal dysbiosis and increased sensitivity towards dextran sodium sulfate (DSS) toxicity [24]. Administration of GLP-1RAs improves DSS colitis, and this is accompanied by not only affecting dysbiosis but also modulating group 3 innate lymphoid cells and IL-22 production by these cells, thereby proposing a role for this pathway in intestinal inflammation [79]. Liraglutide may protect mice from T-cell-dependent glomerulonephritis by inhibiting T-cell proliferation and blocking glycolysis in T cells [80]. These experimental findings are interesting as they suggest a potentially profound impact of GLP-1RAs on models of inflammation involving T-cell-mediated processes. Finally, GLP-1RAs have also demonstrated beneficial effects in various models of lung inflammation, including sepsis-induced lung injury [81, 82]. Mechanistically, these studies showed that GLP-1RAs could reduce apoptosis and exert anti-inflammatory effects in organs far beyond the heart, kidney, blood vessels, or liver.

*Anti-inflammatory and immunomodulatory effects: clinical evidence*

GLP-1 receptor signalling protects the heart, vasculature, and potentially the liver, especially in the context of MASLD/MASH [83, 84]. Not many clinical studies have investigated the effects of GLP-1RAs on inflammatory pathways. Exenatide, one of the first GLP-1RA used in clinical medicine, decreased expression of reactive oxygen species, NF-B, TNF-alpha, IL-1, toll-like receptor (TLR)-2, TLR3, JNK-1 and suppressor of cytokine signalling (SOCS)-3 in mononuclear cells isolated from patients with T2DM after 12 weeks of therapy [85]. Furthermore, in this study, circulating levels of MCP-1, amyloid A, and IL-6 were decreased after exenatide therapy. In another study of patients with T2DM, an 8-week treatment with liraglutide revealed significant reductions in serum TNF-alpha, IL-1, and the inflammatory macrophage protein soluble CD163, whereas serum levels of the anti-inflammatory adipokine adiponectin increased significantly [86]. There is an urgent need for more carefully designed clinical studies with GLP-1RAs to examine the effects on immune pathways, as it seems likely that the clinical benefits of GLP-1RAs, especially on adverse cardiovascular and renal outcomes, are associated with interference in inflammatory and immune pathways.

Despite proven evidence that GLP-1 receptors are expressed on specific immune and endothelial cells, there remain many questions about how the beneficial effects of GLP-1RAs are exerted and how GLP-1RAs, especially dual or triple incretin receptor agonists, interact with the immune system. The pleiotropic effects of incretin receptor agonists are exciting, and prolonged use of these agents will enable a broader view of their effects on immunity and related clinical effects [53, 54].

**Conclusions**

Evidence from randomized clinical trials shows that treatment with GLP-1RAs or other (dual or triple) incretin receptor co-agonists has beneficial effects on histological liver endpoints in MASLD/MASH, and new phase 2 and phase 3 RCTs are ongoing. Real-world retrospective cohort studies also provide evidence supporting the notion that incretin-based agents are a promising therapeutic option for preventing long-term liver-related clinical outcomes, such as cirrhosis, hepatic decompensation events and hepatocellular carcinoma. Accumulating experimental data indicate that incretin receptor agonists have beneficial effects not only on liver disease but also on MetS traits, T2DM, CKD, CVD and low-grade inflammation relevant to a diagnosis of MASLD [87, 88]. Indeed, incretins might also affect hepatokines, which appear of crucial importance in the crosstalk between a steatotic or inflamed liver and other organs [87]. Collectively, these insights advocate for the integration of incretin-based therapy, either alone or as part of combination therapies (e.g., with resmetirom and/or peroxisome proliferator-activated receptor agonists), into therapeutic strategies for the management of MASLD/MASH as a multisystem disease. The multi-organ benefits of these agents underline their potential for improving the care of patients with MASLD.

**Figure Legends**

**Figure 1. Biology of endogenous GLP-1 and GIP, and effects of incretin and glucagon receptor agonists in MASLD or MASH.**

Endogenous GLP-1 and GIP are secreted from neuroendocrine (K and L) cells in the small intestine in response to dietary food ingestion. Both GLP-1 and GIP are rapidly inactivated by the ubiquitously expressed enzyme dipeptidyl peptidase 4 (DPP-4), and the inactivation of GIP occurs at a slower rate than GLP-1, giving GIP a half-life of 5 to 7 minutes, compared with approximately 2 minutes for GLP-1. Modifying these peptides has allowed the generation of agonists that DPP-4 does not metabolize. The incretin receptor agonists have potent direct and indirect effects in several other tissues and organs, affecting MASLD/MASH beyond their incretin effect in the pancreas. In the pancreas, GLP-1 and GLP-1RAs are potent inhibitors of glucagon secretion (which is also strictly glucose-dependent), possibly mediated by a direct effect on the pancreatic α-cells. However, this inhibitory effect is also likely to occur via the paracrine effects of increased levels of somatostatin (not shown) and insulin from neighboring δ-cells and β-cells, respectively. GLP-1 signalling is key in influencing appetite, satiety and calorie intake via actions in the arcuate nucleus within the hypothalamus, area postrema, and nucleus tractus solitarii, resulting in decreased calorie intake and weight loss. Weight loss is principally due to the loss of adipose tissue, and this reduces the flux of adipose tissue-derived long-chain fatty acids (LCFAs) and glycerol to the liver. (LCFAs from adipose tissue are a powerful stimulus and substrate for triglyceride lipogenesis and glycerol is a substrate for hepatic gluconeogenesis). Thus, weight loss facilitated by incretin effects has a powerful effect on the liver, facilitating a reduction in hepatic lipid accumulation and thereby improving insulin sensitivity and decreasing associated metabolic syndrome (MetS) traits as key components of MASLD. In contrast to GLP-1, GIP has anti-apoptotic functions mediated mainly by activating cyclic AMP response element-binding protein and suppressing p38 mitogen-activated protein kinase and c-Jun N-terminal kinase. GIP expression has also been detected in the brain, including the hippocampus, thalamus, cerebellum, brainstem, and cortex in rats and the hypothalamus in men. However, it is controversial whether GIP has any clinically relevant effects on appetite, and both positive and negative effects of GIP on appetite have been described. Nutrient intake is also a potent stimulant of GIP release, and GIP stimulates glucagon secretion from the pancreas. GIP also directly induces energy accumulation in adipocytes by increasing lipoprotein lipase activity, stimulating hepatic lipogenesis, and enhancing plasma membrane glucose transporter-4 expression and glucose uptake. Unlike GLP-1, GIP increases the anabolic action of insulin in adipose tissue, facilitating lipogenesis and pre-adipocyte differentiation. Thus, GLP-1 and GIP both act indirectly to benefit the liver in MASLD and dual agonist incretin pharmacotherapy has a powerful therapeutic effect to induce weight loss, improve glycemic control and plasma lipids and, therefore, benefit the MetS traits besides liver disease. In contrast to incretin receptors, glucagon receptors are highly expressed in the liver and several other tissues and organs. In the liver, glucagon receptor agonism potentially reduces lipid content, increases glycogen flux, and improves mitochondrial turnover and function. In the pancreas, glucagon receptor agonism increases insulin secretion, and in the heart, it increases cardiac output, cardioprotection, and myocardial contractility. Glucagon receptor agonism also increases thermogenesis and energy expenditure, and in the adipose tissue, glucagon receptor agonism increases lipolysis. Consequently, the direct and indirect effects of incretin receptor agonists and glucagon receptor agonists have many beneficial effects on liver disease in MASLD/MASH, but also MetS traits linked to MASLD (including central obesity, atherogenic dyslipidemia, dysglycemia, increased blood pressure and hypertension). These effects benefit not only MASLD/MASH but also the common non-communicable diseases that are now known to be associated with MASLD, such as T2DM, cardiovascular disease (CVD), congestive heart failure, chronic kidney disease (CKD), and certain common extrahepatic cancers (mainly non-liver gastrointestinal cancers). (Figure made with BioRender).

**Figure 2**. **Hepatoprotective effects of incretin-based pharmacotherapies for MASH and liver fibrosis.**

The results are derived from recent phase 2 placebo-controlled randomized controlled trials (with a follow-up length of at least 48 weeks) that examined the effects of subcutaneous semaglutide [41], survodutide [47], or tirzepatide [59] on histological liver endpoints, i.e., resolution/improvement in MASH and liver fibrosis, in patients with biopsy-confirmed MASH and liver fibrosis.

**Figure 3. Pleiotropic immunomodulatory and anti-inflammatory effects of incretins.**

Intestinal incretins, such as GLP-1 or GIP, are mainly produced by neuroendocrine cells from the small intestine dependent on food ingestion. The beneficial effects of incretin-based therapies in various metabolic disorders might include their immunomodulatory and anti-inflammatory properties on various organ systems. (1) Brain: beneficial anti-inflammatory effects may require primarily effects of GLP-1RAs on the brain as neuronal GLP-1 receptors seem crucial for their anti-inflammatory effects. (2) Liver: hepatocytes do not express GLP-1 receptors but beneficial effects of incretin-based therapies in MASLD/MASH could involve effects mediated via interaction with endothelial cells (EC) or T cells in the liver as GLP-1RAs suppress protein kinase C-alpha (PKC-), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, or NF-kappa B (NF-B) expression in these cell types. (3) Immune system: incretins may exert significant effects on various immune system cell types, and these effects are primarily anti-inflammatory. GLP-1RAs suppress the synthesis of pro-inflammatory cytokines (for example, TNF, IFN-gamma, IL-1) and induce anti-inflammatory cytokines, such as IL-10 and M2 macrophages. (4) Pancreas: incretins may affect pancreatic islet inflammation by suppressing c-jun N-terminal kinases (JNKs) expression and Th17 cell pancreatic infiltration. (5) Adipose tissue: incretins may influence adipose tissue biology and secretion of various adipokines. Importantly, they upregulate adiponectin synthesis and suppress the production of leptin and monocyte chemoattractant-protein-1 (MCP-1). (6) Colon: incretins may beneficially modulate colonic inflammation by suppressing IL-22 synthesis and by affecting the biology of innate lymphoid cell type 3 (ILC3) cells. Most studies on immune processes have been performed with GLP-1RAs, whereas experimental data using GIP and glucagon agonists are awaited. (Figure made with BioRender).

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