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# Incretin and Glucagon Signalling in MASLD and MASH: Integrating Metabolic Pathways With Disease Progression

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## ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) arises from dysregulated interactions between nutrient delivery, adipose tissue lipid handling and liver lipid metabolism, which collectively coalesce to drive inflammatory signalling leading to metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis. Recent clinical success of incretin- and glucagon-based therapies in both diabetes and obesity has intensified interest into how these hormonal pathways modify liver disease progression. In this review, we integrate preclinical and clinical data to examine how glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon engage key pathogenic nodes, including the gut–liver and adipose–liver axes, hepatic lipid synthesis and oxidation, mitochondrial function and nonparenchymal inflammatory responses. GLP-1-based therapies consistently improve steatosis and steatohepatitis through reductions in nutrient flux to the liver, improved adipose tissue insulin sensitivity and weight-independent anti-inflammatory effects, despite limited direct action in hepatocytes. GIP signalling appears to modulate adipose tissue lipid handling and expandability, thereby limiting fatty acid spillover to the liver, although its role in hepatic inflammation remains incompletely defined. In contrast, glucagon receptor activation directly targets hepatocytes to enhance oxidative metabolism and reduce hepatocellular stress. Across studies, improvements in fibrosis appear secondary to sustained reductions in metabolic and inflammatory injury suggesting the addition of anti-fibrotic combination therapies may exert further benefits. Looking ahead, a key challenge will be defining how these hormonal pathways interact within distinct metabolic states and how this greater mechanistic understanding can be leveraged to rationally combine therapies and expand the proportion of patients who respond across the MASLD spectrum.

## 1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has increased markedly over the past two decades and now affects an estimated 38% of adults worldwide, paralleling the rise in obesity [1]. MASLD is tightly linked to the development of type 2 diabetes (T2D), in part through its contribution to hepatic insulin resistance [2]. In addition to its metabolic consequences, MASLD is strongly associated with chronic kidney disease and atherosclerotic cardiovascular disease, the latter representing the leading cause of mortality in this population [3]. In a subset of individuals, MASLD progresses to metabolic dysfunction-associated steatohepatitis (MASH), characterised by hepatocellular injury, inflammation and fibrosis, which can ultimately lead to cirrhosis and hepatocellular carcinoma [2]. Crosstalk between hepatic immune cells and stellate cells plays a central role in determining whether fibrosis progresses or regresses [4, 5]. Reflecting its growing burden, MASH is now among the leading indications for liver transplantation in North America and Europe.

**Plain Language Summary**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked with obesity, type 2 diabetes, and cardiovascular disease. In some individuals it progresses to metabolic dysfunction-associated steatohepatitis (MASH), a more severe condition characterized by liver inflammation and fibrosis that can lead to cirrhosis and liver cancer. In this review we discuss how MASLD develops through disruptions in metabolic communication between several organs including increased lipid delivery from adipose tissue, enhanced fat production within the liver, and altered nutrient signaling from the gut to promote the accumulation of lipotoxic metabolites that trigger inflammation and liver injury. We then discuss how the incretin hormones, Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as well as glucagon coordinate nutrient handling across these tissues to reduce body weight, improve insulin sensitivity and stimulate liver fat metabolism to exert beneficial effects. Finally we discuss drugs that engage these pathways individually or in combination, improve MASLD, and highlight remaining challenges, including understanding which patients benefit most and how these agents may be combined with therapies that directly target liver fibrosis.

Hepatic lipid homeostasis depends on tightly regulated interactions between gut-derived nutrient delivery, adipose tissue lipid mobilisation, hepatic de novo lipogenesis and mitochondrial oxidative capacity [5]. Accordingly, MASLD is best viewed as a multisystem disorder arising from dysregulated communication between the gut, adipose tissue and liver (Figure 1). Excess nutrient flux from the gastrointestinal tract, together with microbial-derived signals, increases hepatic substrate availability and promotes de novo lipogenesis (DNL). In parallel, insulin resistance drives adipose tissue lipolysis, increasing spillover of circulating non-esterified fatty acids (NEFAs) to the liver, which further augments hepatic lipid synthesis from glucose, fructose and amino acids [6–13]. Together, these processes increase hepatocellular lipid burden and when combined with diminished mitochondrial function and fatty acid oxidation can create an environment that promotes inflammation and fibrogenesis.

The clinical success of incretin- and glucagon-based therapies in diabetes and obesity has intensified interest in how modulation of nutrient flux, adipose tissue biology, hepatic lipid metabolism and inflammatory signalling can be leveraged to treat MASH. Over the past two decades, evidence has established that glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon signal through distinct receptors with unique expression patterns and biological actions that map directly onto the dysregulated gut–liver and adipose–liver axes and inflammatory pathways that drive MASLD pathogenesis. This review integrates mechanistic and clinical evidence to explain how these diverse but overlapping pathways modify steatosis and steatohepatitis, and why engaging complementary mechanisms may be required to more fully address progressive disease.

## 2 | Incretin and Glucagon Signalling Across Key Metabolic Nodes in MASLD

### 2.1 | Overview of GLP1, GIP and Glucagon

The physiology of GLP1 [14], GIP [15] and glucagon [16] have been comprehensively reviewed elsewhere and are therefore summarised only briefly here. These peptide hormones all act through Gsα-coupled receptor signalling; however, their biological effects differ largely due to distinct patterns of secretion (feeding vs. fasting) and cellular receptor expression. GLP1 is released from intestinal L cells in response to nutrient ingestion and is rapidly inactivated by dipeptidyl peptidase-4 (DPP4), resulting in a circulating half-life of less than 2 min [14, 17–19]. Plasma DPP4 is elevated in individuals with MASLD [20] and while inhibiting DPP4 in hepatocytes using siRNA reduces liver fibrosis independent of changes in blood glucose [21], germline deletion of DPP4 leads to greater liver inflammation and fibrosis [22], suggesting that maintaining DPP4 activity in other cell types is important. The GLP1 receptor (GLP1R) is expressed on pancreatic β cells and central neural circuits involved in regulating appetite, and is also detected at low abundance in hepatic non-parenchymal compartments, including liver sinusoidal endothelial cells and select immune populations [14, 17–19]. GIP is secreted from intestinal K cells following ingestion of fat and carbohydrate. The GIP receptor (GIPR) is found on pancreatic α and β cells, endothelial cells within adipose tissue and select immune and neuronal populations [15, 23–25]. Glucagon is secreted from pancreatic α cells in response to hypoglycaemia and amino acids [26–28]. It acts primarily in hepatocytes, where the glucagon receptor (GCGR) is highly expressed and stimulates glycogenolysis, gluconeogenesis and fatty acid oxidation, thereby maintaining fuel availability during fasting [29–33]. Notably, GLP1, GIPR or the GCGR are not detected on hepatic stellate cells, the primary effector cell type driving liver fibrosis [34]. Taken together, the cellular expression patterns and physiological actions of GLP1, GIP and glucagon link these hormones to several processes relevant to MASLD, including the gut–liver and adipose–liver axes as well as hepatic lipid metabolism and inflammation as will be discussed in detail in the following sections.

### 2.2 | The Gut-Liver Axis

The gut–liver axis contributes to the development of MASLD by modulating nutrient load, microbial metabolites and inflammatory signals delivered to the liver [35]. In rodents fed a diet high in fructose, there are increases in intestinal permeability that result in greater portal exposure to lipopolysaccharide and other microbial products that activate Kupffer cells and augment hepatic inflammation [36], however, whether this occurs in humans remains unclear [37]. Fructose also increases microbial production of acetate [38], which promotes the proliferation and activation of fibrosis-inducing hepatic stellate cells [39]. In individuals with MASH, the gut microbiome is also an important source of ethanol, which promotes hepatocyte toxicity [40] and generates D-lactate, which fuels liver inflammation and fibrosis in mice [41]. When combined with impaired gut-barrier function common with obesity [42] or induced by food additives [43],

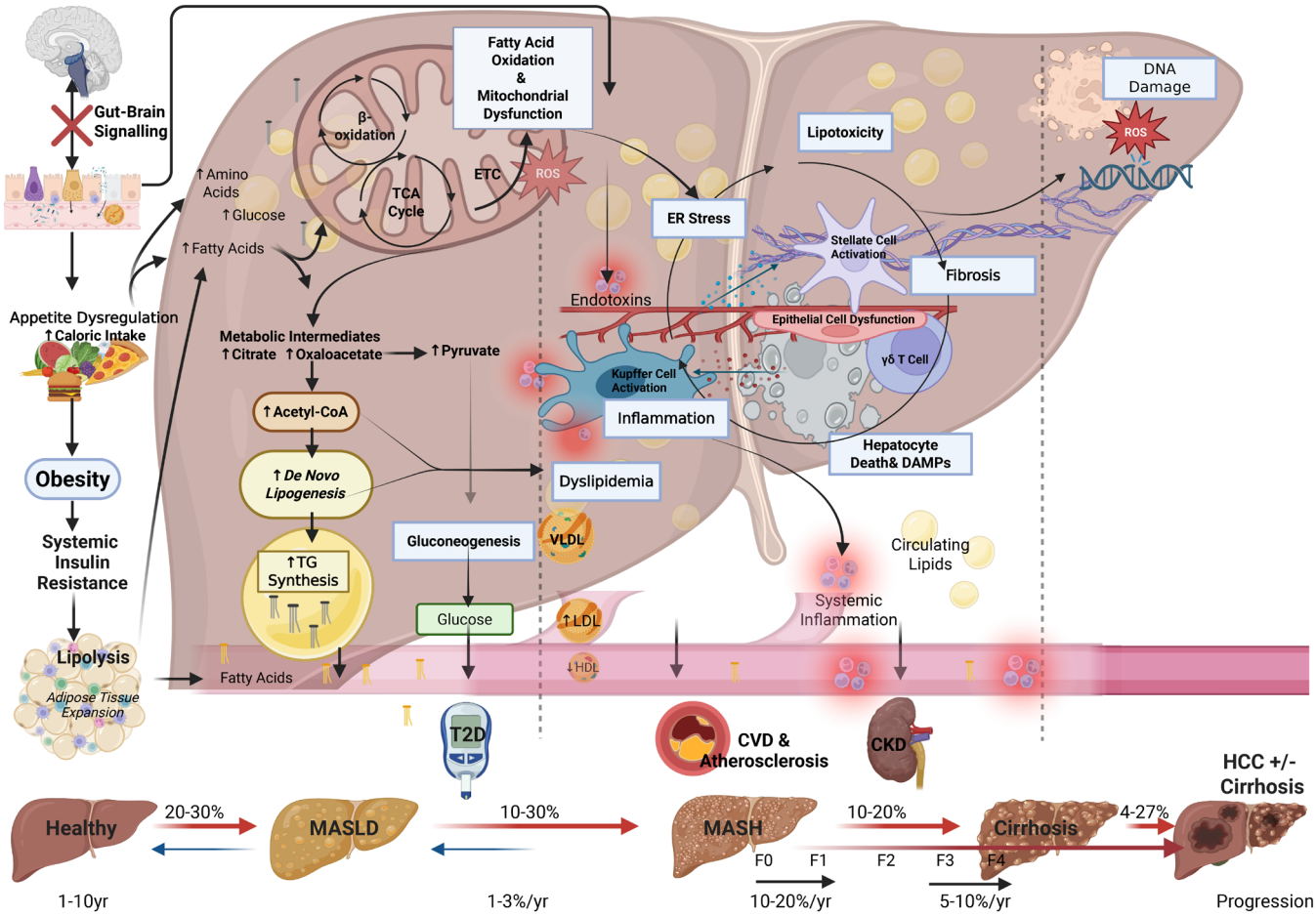


**FIGURE 1** | Integrated pathophysiology of MASLD progression. This schematic depicts the multi-organ and intrahepatic mechanisms driving progression from metabolic dysfunction-associated steatotic liver disease (MASLD) to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis and hepatocellular carcinoma (HCC). It highlights stages of liver disease progression at which risk of extrahepatic metabolic complications, including type 2 diabetes (T2D), cardiovascular disease (CVD) and chronic kidney disease (CKD), is increased. Excess caloric intake and gut–brain axis perturbations promote obesity, systemic insulin resistance, and adipose tissue expansion, increasing free fatty acid flux to the liver. In hepatocytes, increased glucose and amino acid availability fuels mitochondrial metabolism, expanding acetyl-CoA pools and driving de novo lipogenesis, triglyceride (TG) synthesis, and very-low-density lipoprotein (VLDL) secretion. Nutrient overload induces oxidative and ER stress, impairing mitochondrial fatty acid handling. Lipotoxicity, oxidative stress, and gut-derived endotoxin activate hepatic immune and stellate cells, promoting inflammation, hepatocyte injury and fibrosis. The lower panel illustrates approximate timelines and probabilities of disease progression. Created in BioRender. Tsakirdis, E. (2026) https://BioRender.com/1ah379w.

these findings suggest that altered gut-derived substrates such as acetate and ethanol play a central role in promoting hepatic steatosis, inflammation and activation of fibrosis [44, 45].

Compared to GLP1, neither GIP nor glucagon have been implicated as major regulators of the gut-liver axis. GLP1 suppresses nutrient transfer along the gut–liver axis by altering afferent and efferent signals. Afferent signals trigger satiety while efferent signals slow gastric emptying through the central and vagal pathway, delaying nutrient entry into the small intestine [14]. In the pancreas, GLP1 enhances glucose-dependent insulin secretion and reduces glucagon in the setting of hyperglycemia [14] (Figure 2). Calorically matched neuron and vagal specific GLP1R knockout models have delineated the importance of both peripheral and central actions in slowing gastric emptying [14]. GLP1 also suppresses intestinal chylomicron secretion independently of meal size by regulating enterocyte lipid handling [46–48]. Collectively this limits post-prandial glucose, fructose, amino acid and lipid delivery to the liver [2].

GLP1 further influences the gut-liver axis by improving intestinal barrier integrity and microbial driven inflammatory signalling, although the extent to which these effects are mediated by direct GLP1R action or are secondary to reductions in food intake, weight loss and transit time remain uncertain [49]. Preclinical studies show that GLP1R activation increases epithelial tight junction proteins and reduces intestinal permeability in diet induced obesity, findings associated with lower portal endotoxin exposure and hepatic inflammatory signalling [50], findings consistent with improved gut-barrier integrity with GLP-1 agonism in both mice and humans [51, 52]. In pre-clinical models, GLP1 agonism increases gut microbiome species linked to improvements in insulin sensitivity independent of weight loss [53] and faecal transfer can replicate many of the beneficial effects [54, 55]. A trial in people with T2D examining the effects of semaglutide on intestinal barrier function (NCT04979130) and its pre-specified secondary analysis comparing intestinal microbiota is expected to provide more definitive insight on these parameters.

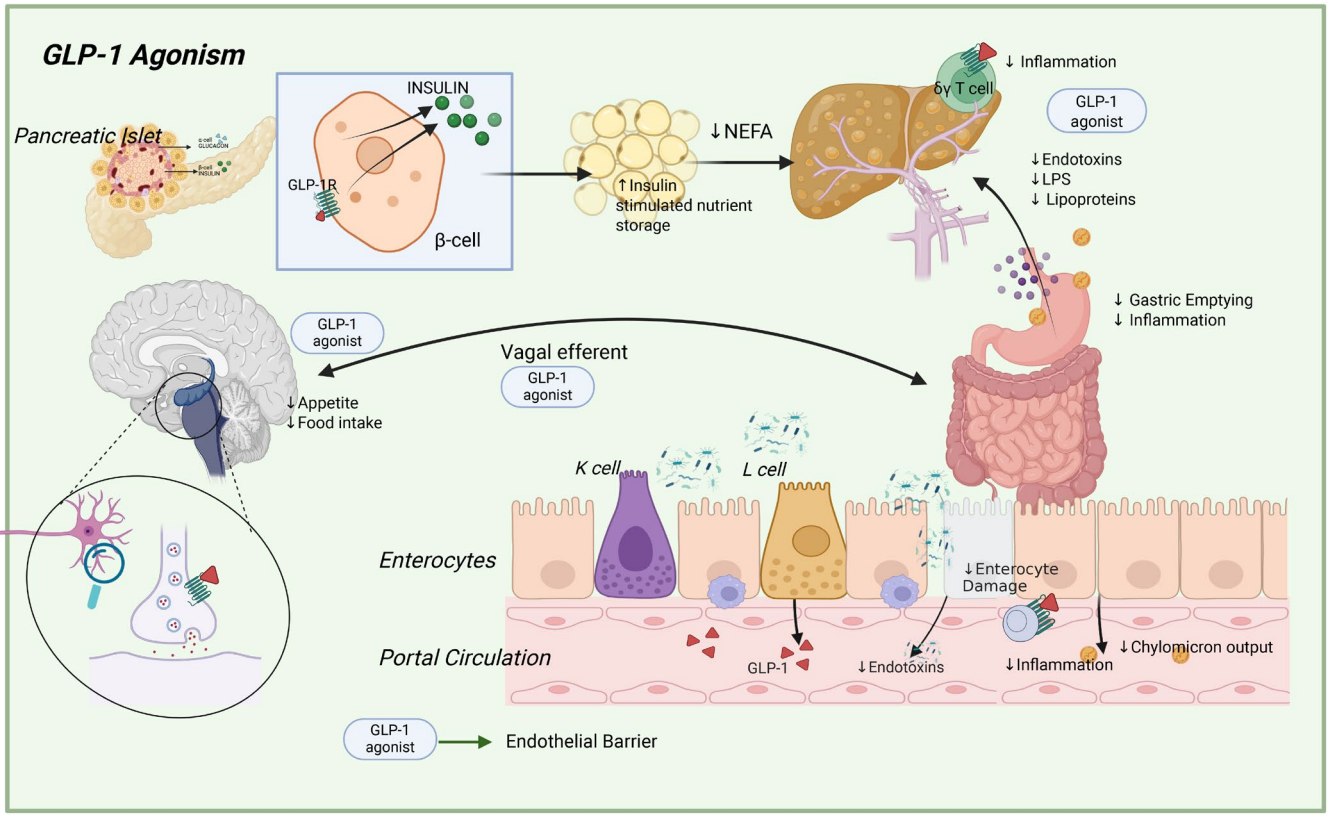


**FIGURE 2** | GLP-1 receptor agonism. GLP-1 receptor (GLP-1R) agonism improves metabolic homeostasis through coordinated actions on the central nervous system, gastrointestinal tract, and liver. Central appetite suppression and delayed gastric emptying occur through GLP-1 binding to it's GLP1R expressed in regions of the brain including the hypothalamus, brainstem, and vagal afferent neurons. This not only reduces appetite and food intake but also suppresses post-prandial glycemic and lipoprotein excursions while delaying gastric emptying. GLP-1 binding intestinal lymphocyte populations reduces inflammation and improves epithelial integrity, reduces enterocyte injury, and endotoxin translocation. Thereby decreasing portal delivery of inflammatory and lipotoxic substrates to the liver. Despite minimal GLP-1R expression in adipocytes, GLP-1 reduces circulating non-esterified fatty acids (NEFAs) from adipose tissue, reflecting improved glycaemic control and enhanced insulin-mediated suppression of adipose lipolysis in response to GLP-1 binding to GLP-1R in pancreatic β-cells. Ultimately, reduced lipid and inflammatory cytokines alleviate hepatic drivers of MASLD. Created in BioRender. Tsakirdis, E. (2026) https://BioRender.com/p3wgixi.

### 2.3 | Adipose-Liver Crosstalk

White adipose tissue contributes to hepatic lipid accumulation through increased release of NEFAs and dysregulated adipokine secretion [56] (Figure 1). In obesity and T2D, insulin's ability to suppress adipose lipolysis is impaired, leading to chronically elevated NEFA concentrations that increase hepatic fatty acid uptake and triglyceride synthesis [57–61]. Visceral adipose tissue is particularly important due to its direct drainage into the portal circulation and its enrichment in inflammatory cytokines and adipokines that exacerbate hepatic insulin resistance [62, 63]. Human studies demonstrate that elevated portal NEFA flux correlates strongly with intrahepatic lipid content and impairs insulin-mediated suppression of hepatic glucose production [57, 58, 64]. The clinical relevance of targeting adipose and systemic lipid handling is underscored by observations that PPARγ agonists such as pioglitazone reduce adipose tissue lipolysis and increase NEFA clearance into adipose tissue, improving MASLD, despite increasing subcutaneous adiposity [65–68]. Thus, supporting the concept that reducing lipid flux from the adipose tissue can be metabolically beneficial, even in the absence of weight loss.

GLP1 does not appear to act directly on adipocytes, as GLP1R expression in adipose tissue is extremely low (Figure 2). Instead, reductions in circulating NEFA following GLP1 agonism likely reflect improved insulin-mediated suppression of lipolysis [13, 61, 69, 70], potentially due to reductions in adipocyte size, improved perfusion, increased adiponectin and decreased macrophage infiltration [71–73]. Despite the absence of a direct adipocyte receptor-mediated mechanism, the combined metabolic effects of GLP1 to lower NEFA flux to the liver, early in treatment and progressively improve adipose tissue insulin sensitivity as weight decreases reduces hepatic exposure to lipotoxic substrates and pro-inflammatory cytokines [74–78].

In contrast to GLP1, there is growing evidence suggesting a potentially important role for GIP in mediating adipose-liver cross talk. In clinical studies, elevations in GIP following an oral glucose tolerance test are tightly linked to reductions in MASLD [79, 80]. GIP acts predominantly in adipose tissue primarily through receptors on endothelial cells, pericytes, stromal vascular cells and myeloid populations rather than mature adipocytes [81–83] (Figure 3). Studies in humans illustrate that endothelial GIPR activation increases adipose perfusion and

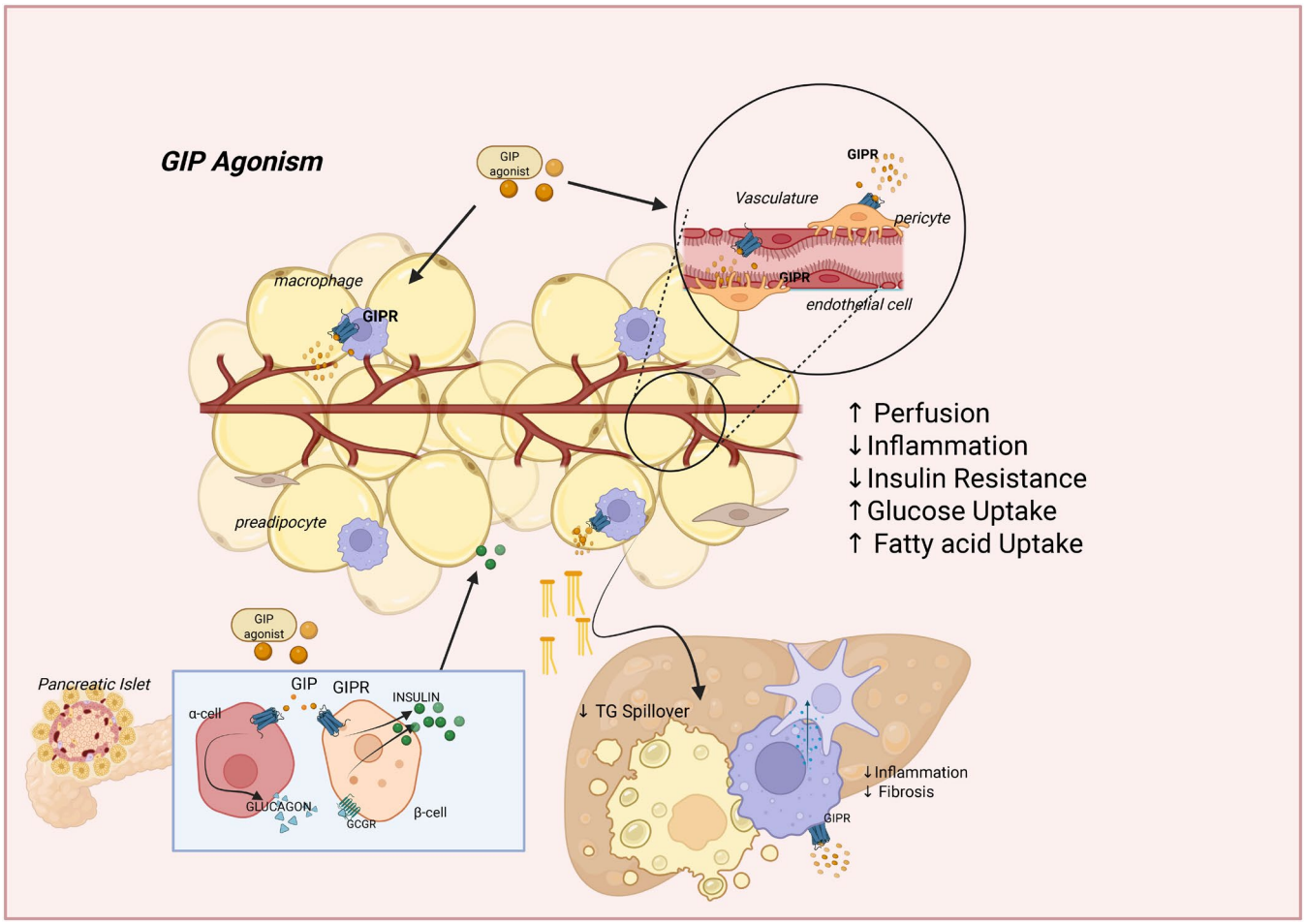


**FIGURE 3** | GIP agonism. Glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonism in adipose tissue occurs primarily through endothelial cells, pericytes and myeloid populations. Endothelial GIPR activation increases adipose tissue perfusion, enhancing postprandial fatty acid delivery and uptake into adipose depots; this coupled with incretin signalling in pancreatic α and β cells reduces triglyceride spillover into the circulation and limits hepatic lipid exposure. In parallel, signalling in myeloid cells suppresses macrophage recruitment and inflammatory chemokine production, improving adipose insulin sensitivity and fed-state suppression of lipolysis. Created in BioRender. Tsakirdis, E. (2026) https://BioRender.com/6evxbld.

enhances delivery of dietary fatty acids to adipose depots; improving postprandial lipid uptake and reducing the fraction of triglyceride-derived substrates that spill over into the circulation [84, 85]. In parallel, GIPR signalling in stromal vascular cells promotes adipocyte differentiation and depot expandability, increasing the capacity to safely store lipid during caloric excess; thus, limiting ectopic deposition in the liver and muscle [86]. Preclinical studies also support a role for adipose GIPR activation in enhancing thermogenesis and lipid sequestration via increased lipoprotein lipase (LPL); however, to date direct evidence for these adipose-specific effects in humans is limited [15, 82, 86–89]. Beyond benefits on adipose lipid handling, single-nucleus RNA-sequencing has found that genetic deletion of GIPR in adipocytes reduces the recruitment of macrophages and T cells to adipose tissue, leading to reductions in adipose tissue inflammation and insulin resistance which would be expected to enhance the suppression of adipose tissue lipolysis [81]. Collectively, these coordinated actions position GIP as a key regulator of adipose tissue expandability, lipid buffering capacity, inflammation and insulin resistance which may have important downstream implications for reducing lipid spillover and MASLD (Figure 3).

In contrast to GLP-1 and GIP, the actions of glucagon on adipose tissue appear to differ between rodents and humans. In mice, elevated glucagon promotes adipose tissue lipolysis, increasing circulating NEFAs, whereas simultaneously enhancing thermogenesis and energy expenditure in brown and beige adipocytes [31, 32, 90] (Figure 4). Through coordinated increases in fatty acid oxidation, these responses may limit net lipid spillover to the liver despite increased lipolytic flux [8, 91]. In humans, however, glucagon does not appear to directly stimulate adipose tissue lipolysis or fatty acid oxidation [92, 93], consistent with substantially lower glucagon receptor (GCGR) expression in human adipocytes compared with rodents. Collectively, these data suggest that in individuals with MASLD, GCGR-mediated benefits are unlikely to be driven by direct adipocyte actions, but instead reflect effects on hepatocyte metabolism or indirect inter-organ signalling.

## 2.4 | Liver Lipid Metabolism

In hepatocytes, increased substrate supply from the gut and adipose tissue interacts with intrinsic pathways that regulate DNL

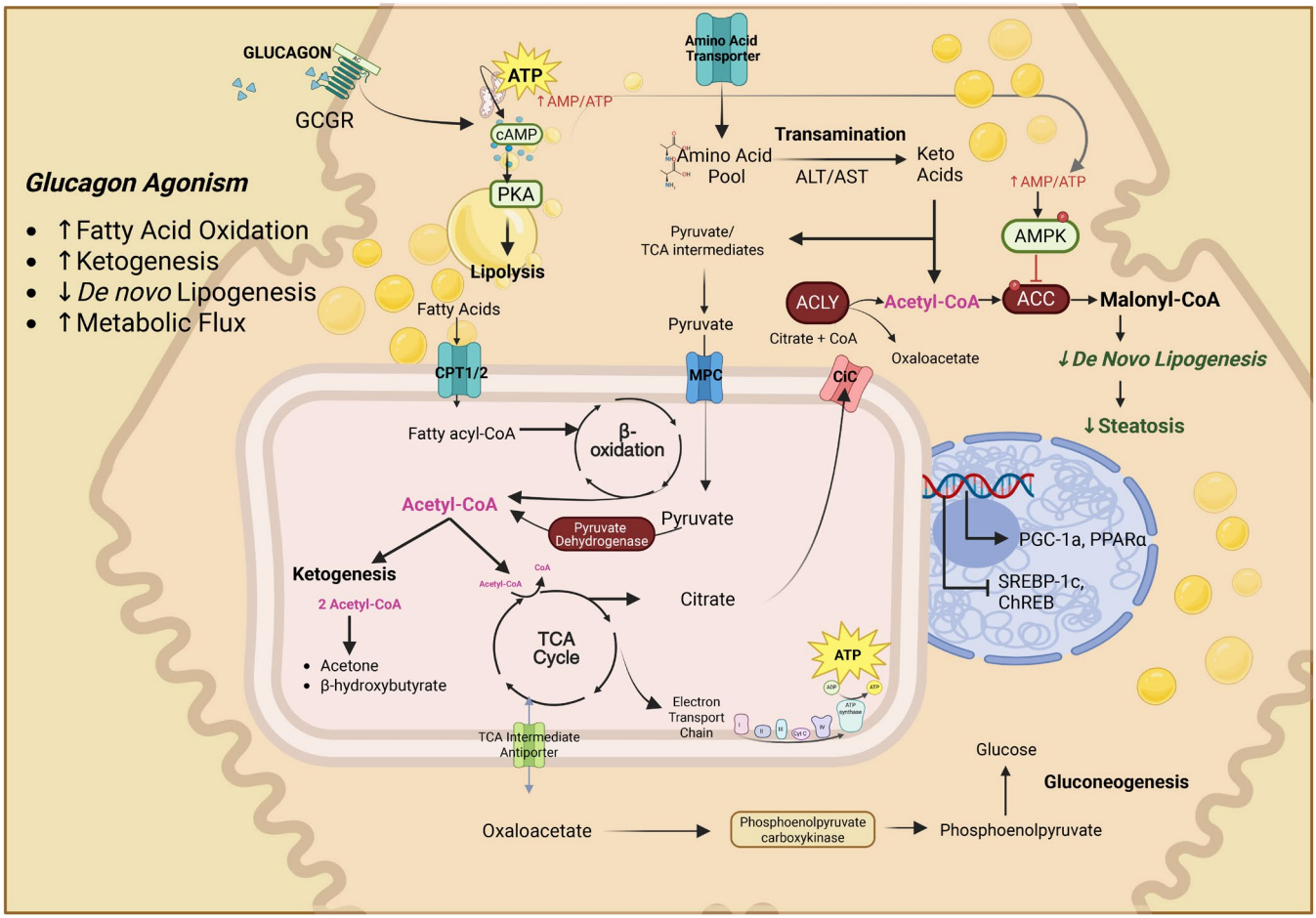


**FIGURE 4** | Hepatic metabolic effects of glucagon receptor (GCGR) agonism. GCGR agonism shifts hepatic metabolism towards fatty acid oxidation and ketogenesis. Glucagon signalling promotes lipid mobilisation and increases mitochondrial β-oxidation and amino acid catabolism, expanding the hepatic acetyl-CoA pool. Acetyl-CoA is oxidised via the tricarboxylic acid (TCA) cycle or diverted into ketone body production, whereas TCA-derived intermediates support gluconeogenesis. Sustained GCGR activation increases cAMP and AMP-activated protein kinase (AMPK) activity, suppressing acetyl-CoA carboxylase (ACC) and de novo lipogenesis, whereas inducing oxidative and ketogenic gene programs. Collectively, these actions reduce hepatic lipid burden and metabolic stress relevant to MASLD progression. Abbreviations: cAMP: cyclic AMP, PKA: Protein Kinase A, CPT: Carnitine Palmitoyltransferase, MPC: Mitochondrial Pyruvate Carrier, CiC: Citrate Carrier, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PGC-1a: Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha, PPARa: Peroxisome Proliferator-Activated Receptor alpha, SREBP1c: Sterol Regulatory Element-Binding Protein 1c, ChREB: Carbohydrate-Responsive Element-Binding Protein. Created in BioRender. Tsakirdis, E. (2026) https://BioRender.com/8evgl9e.

and fatty acid oxidation [2, 4] (Figure 1). In humans, most excess carbohydrate is initially directed towards glycogen storage; however, once glycogen stores are replete, continued carbohydrate and amino acid flux increases acetyl-CoA availability and supports DNL, with carbohydrates and protein together contributing substantially to hepatic lipogenic carbon pools in MASLD. DNL is consistently elevated in MASLD and correlates inversely with hepatic insulin sensitivity [11, 57, 94]. Clinically, individuals with MASLD have a reduced capacity to inhibit DNL even under fasting conditions [95].

High intake of fructose and glucose increases hepatic acetyl CoA availability through enhanced glycolytic and tricarboxylic acid cycle flux, driving DNL and promoting triglyceride synthesis [96]. Fructose metabolism is particularly lipogenic because it bypasses key glycolytic control points through ketohexokinase to increase the production of lipogenic triose phosphates and citrate [97, 98]. Stable isotope studies in combination with ketohexokinase inhibitors have established that fructose contributes disproportionately to lipogenic carbon pools in individuals with MASLD even in the absence of a high-fructose diet [11, 12, 99]. Fructose and, to a lesser extent, glucose are also metabolised by the gut microbiome to generate acetate [38] and ethanol [40, 100] which are converted to acetyl-CoA by acetate CoA-synthetase 2 (ACSS2), whereas amino acid catabolism contributes to elevations in DNL through reductive carboxylation [101]. Inhibition of lipogenic enzymes ACSS2, ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) all decrease MASH in rodents [7, 39, 102–107]. Clinical studies with ACC and FAS inhibitors validate the importance of the DNL pathway for driving steatosis but also highlight challenges with directly targeting this pathway, as these agents increase circulating triglycerides and, at least for ACC inhibitors, also fail to reduce liver fibrosis [108–110]. This lack of antifibrotic efficacy may reflect a central role for acetate-derived acetyl-CoA-directed cholesterol synthesis in hepatic stellate cell

activation [39]. Collectively, these data support a central role for increased hepatic fatty acid and cholesterol synthesis in driving MASLD.

Although increased fatty acid and cholesterol synthesis is a primary driver of MASLD, defects in mitochondrial function become increasingly evident with progression to MASH and advanced disease. Specifically, studies using magnetic resonance spectroscopy and high-resolution respirometry demonstrate reduced hepatic oxidative phosphorylation, diminished β-oxidation capacity and impaired tricarboxylic acid cycle flux in individuals with MASH compared with those with MASLD, with more pronounced defects observed in the presence of T2D [111–113]. As mitochondrial function declines, incomplete β oxidation leads to accumulation of saturated fatty acids, ceramides, free cholesterol and metabolic intermediates such as succinate that drive inflammation and liver fibrosis [24, 112]. Consistent with these observations, recent studies in individuals with MASLD demonstrate that the degree of liver injury correlates positively with increases in ketogenesis [25] suggesting that elevations in fatty acid oxidation in the presence of mitochondrial dysfunction may have adverse effects [114]. Specifically, mitochondria physically associated with lipid droplets support polyunsaturated fatty acid (PUFA) elongation [115] which may serve a protective role in buffering excess lipid flux [116, 117]. In this context, the common human PNPLA3 I148M variant leads to accumulation of the mutant PNPLA3 protein on lipid droplets and rewires hepatic lipid metabolism, resulting in mitochondrial dysfunction, altered fatty acid handling and activation of stress pathways that promote hepatocyte injury and cell death [118].

A critical regulator of both liver fatty acid oxidation as well as fatty acid and cholesterol synthesis is the AMP-activated protein kinase (AMPK) [119]. AMPK activators inhibit both fatty acid and cholesterol synthesis through phosphorylation of ACC and HMG-CoA reductase, respectively [120] and importantly do not result in elevations in circulating triglycerides in clinical trials in people with MASLD [121–123]. This is likely because in addition to suppressing DNL, AMPK phosphorylates many proteins critical for increasing fatty acid oxidation and maintaining mitochondrial homeostasis, including those critical for promoting mitochondrial biogenesis and mitophagy [124]. Consistent with these findings, mitochondrial uncouplers activate AMPK and reduce MASLD in preclinical models and early clinical trials [125, 126]. The recent approval of the selective thyroid hormone receptor β (THRβ) agonist resmetirom for the treatment of MASLD also provides compelling clinical evidence that enhancing hepatic oxidative metabolism can improve steatosis, steatohepatitis and fibrosis, although the precise mechanisms underlying these effects remain incompletely defined [127–129].

In contrast to GLP-1 and GIP, which do not act directly on hepatocytes, glucagon has a clear and direct effect on hepatic lipid metabolism. Hepatocytes have high expression of the GCGR, which, upon glucagon binding, leads to increases in hepatic cAMP and ATP turnover, which raises AMP and ADP, activating AMPK under fasting conditions [28, 130]. AMPK-dependent phosphorylation of ACC reduces malonyl CoA levels, reducing DNL and enhancing fatty acid oxidation [28, 131]. Glucagon also suppresses expression of SREBP1c and ChREBP target genes in several experimental models, reducing transcription of lipogenic enzymes, including ACC, FAS and ACLY, while simultaneously increasing the expression of PPARα and PGC1α, genes that stimulate fatty acid oxidation and ketogenesis [32, 132] (Figure 5). Consistent with these mechanisms, $Gcgr^{-/-}$ mice exhibit increased *Acly* and *Fas* expression, elevated lipogenesis, impaired β-oxidation and reduced capacity to maintain hepatic energy homeostasis during fasting [28, 131]. Glucagon also activates mitophagy, supporting enhanced mitochondrial quality [133]. Collectively, this enhances the capacity of the liver to safely oxidise fatty acids while simultaneously suppressing fatty acid and cholesterol synthesis, key drivers of liver inflammation and fibrosis.

### 2.5 | Liver Inflammation

Lipotoxic metabolites including saturated fatty acids, free cholesterol, ceramides and mitochondrial reactive oxygen species promote activation of innate immune pathways that are important for driving the progression from MASLD to MASH. This includes activation of the NLRP3 inflammasome and the release of proinflammatory cytokines from Kupffer cells and B-cells that further trigger the recruitment of monocyte-derived macrophages to the liver [4, 134–140]. These immune responses contribute to hepatocyte apoptosis and necrosis, increasing the release of damage-associated molecular patterns such as mitochondrial DNA and ATP. Crosstalk between hepatocytes, macrophages and hepatic stellate cells promotes stellate cell activation and extracellular matrix deposition. Although many attempts to directly target inflammatory or fibrotic pathways have shown success in preclinical models, to date many of these agents have failed to produce meaningful histologic improvements in clinical trials [136]. This underscores the importance of targeting upstream metabolic dysregulation to reduce downstream inflammatory injury and stellate cell activation that drive steatohepatitis and fibrosis.

In addition to reducing upstream drivers of steatosis, GLP1 appears to exert anti-inflammatory effects in the liver through actions on non-parenchymal immune and endothelial cells that express GLP1R, as well as through central pathways that modify autonomic inputs regulating hepatic immune tone [78] (Figure 2). Although GLP1R is not expressed on hepatocytes, it is found in liver sinusoidal endothelial cells and intrahepatic lymphocyte populations including gamma delta T cells [141, 142] where GLP1 signalling reduces NF-κB activation, cytokine production and oxidative stress responses [74, 141, 143] in models of diet-induced obesity [78, 141]. In endothelial cells, GLP1R activation improves barrier function, limiting the exposure of resident immune cells and stellate cells to circulating inflammatory mediators [144, 145]. In addition to its potentially direct actions on the liver, central GLP1R activation may also be important for suppressing inflammation as observed with TLR agonists [74]. Although the relative contribution of central versus peripheral pathways remains incompletely defined, their integrated actions likely contribute to the anti-inflammatory effects of GLP1 therapy observed in MASLD [17, 143]. When combined with GLP1-mediated reductions in meal size and nutrient delivery to the circulation, this reduction in inflammatory signalling supports a coordinated model

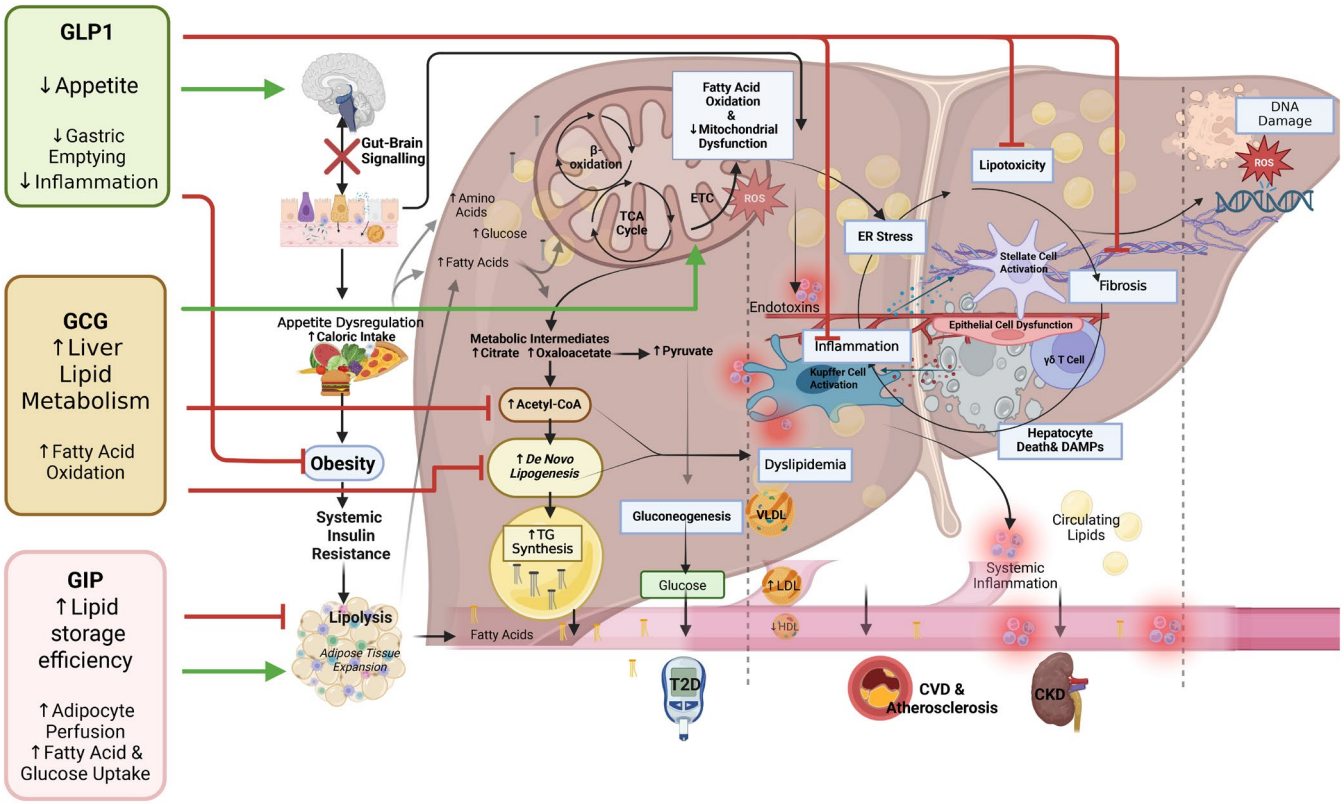


**FIGURE 5** | Integrated benefits of GLP-1, GIP, Glucagon, agonists in MASLD-MASH pathogenesis. Here we build on the integrated pathophysiology of MASLD progression presented in Figure 1. Incretin-based therapies and complementary metabolic agonists target distinct but interconnected pathways across the gut–adipose–liver axis to promote resolution of MASLD and MASH. GLP-1 receptor agonism acts centrally and within the brain-gut axis tract to reduce appetite, slow gastric emptying, improve epithelial barrier integrity, and limit endotoxin and chylomicron delivery to the liver, thereby reducing hepatic nutrient overload and inflammatory signals. GIP receptor agonism predominantly targets adipose tissue via endothelial, stromal vascular and mesothelial cells to enhance perfusion, improve insulin sensitivity, increase glucose and fatty acid uptake, expand lipid storage capacity and reduce triglyceride spillover into the circulation. Glucagon receptor agonism exerts direct hepatic effects, activating fatty acid oxidation and mitochondrial function while suppressing de novo lipogenesis and fibrosis while delivering broader cardiometabolic and renal benefits, supporting combination and multi-agonist strategies for durable MASH resolution. Created in BioRender. Tsakirdis, E. (2026) https://BioRender.com/ws1af0a.

in which GLP1 lowers hepatic inflammatory tone without directly targeting hepatocytes [17, 143].

Building on this framework, attention has increasingly turned to whether GIP and glucagon may also engage immune compartments relevant to MASH. In this context, the GIPR is of particular interest because it has been detected in haematopoietic and immune cell lineages, including myeloid progenitors and macrophages [146]. These observations suggest that GIP may influence myelopoiesis as well as the recruitment and activation of hepatic macrophages, processes that are central to steatohepatitis progression as recently described for the gut-derived hormone serotonin [138]. Although speculative, it is possible that GCGR induced activation of AMPK in hepatocytes may also reduce inflammation through similar mechanisms involving reductions in myelopoiesis and subsequent recruitment of pro-fibrotic macrophages [138]. Future studies using deep sequencing and loss of function approaches will need to more carefully define the cell types in which GIPR and GCGR are functionally expressed, the conditions under which these pathways exert pro- or anti-inflammatory effects, and how signals originating in the gut integrate with hepatic immune and metabolic responses during MASH [147].

Collectively, these findings indicate that GLP1, GIP and glucagon engage distinct biological pathways that converge on several upstream drivers of MASLD but do so through markedly different mechanisms (Figure 5). GLP1 primarily alters hepatic substrate exposure by slowing nutrient delivery from the gut, reducing chylomicron output, improving gut barrier integrity and decreasing adipose-derived NEFA and inflammatory signals, whereas also acting directly in non-parenchymal hepatic immune and endothelial cells to reduce inflammatory activation. GIP acts mainly within adipose tissue through endothelial, stromal vascular and myeloid receptors to improve lipid uptake, expandability and local immune tone, changes that lower NEFA spillover and reduce the lipid and cytokine burden reaching the liver during nutrient excess. Glucagon acts directly in hepatocytes to increase fatty acid oxidation, activate AMPK-dependent regulation of malonyl CoA, enhance mitochondrial function and reduce accumulation of lipid-derived metabolites that drive inflammatory and fibrogenic responses. Across these pathways, GLP1 and GIP modify hepatic stress primarily by altering the quality and quantity of substrates and inflammatory signals arriving at the liver, whereas glucagon changes the liver's intrinsic capacity to process lipids under conditions of increased metabolic demand. These mechanisms address complementary

components of MASLD pathophysiology, including nutrient flux, adipose dysfunction, lipogenesis, mitochondrial overload and inflammatory activation, and provide a framework for interpreting the metabolic and histologic responses observed with incretin and glucagon-based therapies.

## 3 | Therapeutic Targeting of Incretin and Glucagon Pathways in MASH

This section provides a high-level overview of major clinical studies evaluating GLP1-, GIP- and glucagon-based therapies in MASH, with emphasis on how metabolic and histologic outcomes align with the mechanistic pathways outlined above. Rather than detailing drug-specific efficacy, safety or trial design, which are reviewed elsewhere [4, 17, 148, 149], the focus is on mechanistic interpretation of clinical responses and how distinct receptor profiles may translate into differential effects on nutrient flux, adipose biology, hepatic lipid metabolism, mitochondrial function and inflammatory and fibrogenic pathways.

### 3.1 | GLP-1 Receptor Agonists

Semaglutide is a long-acting, GLP-1 receptor agonist approved for once-weekly treatment of T2D (up to 2.0 mg) and obesity (2.4 mg) in the United States and European Union [150]. In dietary and genetic mouse models of steatohepatitis, semaglutide reduced hepatic triglyceride content, inflammatory infiltrates and expression of inflammatory and fibrogenic gene programs [151, 152]. In the initial phase two MASH trial, semaglutide produced high rates of MASH resolution without worsening fibrosis, although the treatment duration and maximum dose provided (0.4 mg) were likely insufficient to meaningfully change fibrosis stage [151, 153]. In the phase three ESSENCE trial in patients with biopsy confirmed MASH and F2 to F3 fibrosis, semaglutide 2.4 mg achieved MASH resolution without worsening fibrosis in approximately 63% of patients compared with 34% on placebo and improved fibrosis by at least one stage in approximately 37% compared with 22% on placebo [152]. A proportion of patients achieved both resolution and fibrosis improvement, but many did not meet either endpoint, indicating heterogeneity in treatment response [152]. In individuals with PNPLA3 mutations, semaglutide leads to greater reductions in ALT, a marker of hepatocellular damage, than those without these risk alleles, despite similar reductions in body mass [154]. Proteomic analyses have revealed that semaglutide reduces circulating markers of innate immune activation and tissue injury even after adjusting for weight loss, indicating that reductions in hepatic inflammation are not explained solely by decreased adiposity [155, 156]. These findings are consistent with earlier observations using liraglutide in the LEAN trial [157] and with smaller phase two imaging studies of dulaglutide [158] and exenatide [159] that demonstrated reductions in liver fat and aminotransferases. The ESSENCE trial (NCT04822181) remains ongoing to assess long term clinical outcomes, including all cause mortality, cardiovascular events and liver related endpoints, which will be essential to determine the full therapeutic impact of semaglutide in MASH [152]. In 2025, the FDA granted approval for Semaglutide (2.4 mg) in adults with MASH.

### 3.2 | GLP-1/GIPR Agonists

Tirzepatitide is a dual GLP1 and GIPR agonist that in preclinical models, lowered body mass and reduced MASH more than GLP1 agonism alone [89], effects that were associated with activation of brown adipose tissue [160]. In clinical trials liver fat reductions occur early and in parallel with improvements in glycemia and markers of adipose insulin sensitivity, but current data do not distinguish whether this reflects direct physiological actions of GIP on adipose tissue or the magnitude of weight loss and systemic metabolic improvement [72, 161, 162]. In the SURPASS-3 MRI substudy, tirzepatide led to dose-dependent reductions in liver fat content compared with active comparator therapy [163]. More recently, the phase 2 SYNERGY-NASH trial demonstrated that tirzepatide achieved high rates of histologic resolution of steatohepatitis without worsening fibrosis, as well as meaningful improvements in fibrosis stage in patients with biopsy-confirmed F2–F3 MASH [72], with post hoc analysis suggesting greater reductions in MASH, but not fibrosis, in individuals with PNPLA3 CC-mutations (AASLD 2024 Abstract 5014). SYNERGY-NASH remains ongoing (NCT04166773) to assess long term outcomes.

### 3.3 | Dual GLP-1/Glucagon Receptor Agonists

Dual GLP1 and glucagon receptor agonists produce a metabolic profile distinct from selective GLP1 agonists, with studies in preclinical models finding increases in energy expenditure and body mass, hepatic fat, inflammation and markers of hepatocellular stress, but the degree to which these effects depend on glucagon induced changes in hepatic fatty acid oxidation versus weight loss alone remains unresolved [148, 164]. In clinical studies, survodutide demonstrated reductions in liver fat and improvements in both steatohepatitis and fibrosis in a 48-week phase two biopsy trial [165]. Other dual agonists, including cotadutide [166], efinopegdutide [167] and pemvidutide [168], have also shown reductions in liver fat and improvements in non-invasive markers of hepatic inflammation in early clinical studies, but histologic data remain limited. Clarifying whether glucagon receptor engagement contributes directly to improvements in hepatic inflammatory or fibrogenic pathways, or primarily amplifies weight loss and systemic metabolic improvements, is a key unanswered question for this class [149].

### 3.4 | Triple GLP-1/GIP/Glucagon Receptor Agonists

Triple agonists that activate GLP1, GIP and glucagon receptors produce large metabolic effects in obesity and diabetes, and early evidence suggests potentially important relevance for MASH based on the magnitude of weight loss and reductions in liver fat [148]. In preclinical dietary MASH models, triple agonists reduced hepatic triglyceride content and inflammatory gene expression more than single or dual agonists [4, 17]. Retatrutide, the most clinically advanced triple agonist, has produced marked reductions in liver fat by MRI PDFF in phase two obesity studies, together with improvements in aminotransferases and non-invasive markers of hepatic injury [169]. Because these changes occur alongside profound weight loss, current data cannot

distinguish whether liver-specific improvements are mediated by receptor-specific actions or reflect the magnitude of weight reduction and associated improvements in insulin sensitivity and lipid flux [170]. Determining whether triple agonists have hepatic effects that extend beyond those attributable to large weight loss remains an important question for future trials.

## 4 | Conclusion

A central theme emerging from the data reviewed here is that responsiveness to incretin- and glucagon-based therapies is likely to vary across MASLD and MASH subtypes and disease stages. In patients with obesity, T2D and early to intermediate fibrosis, where steatosis and inflammatory injury remain prominent, therapies that reduce nutrient delivery to the liver, adipose tissue lipid flux and hepatocellular metabolic stress can meaningfully improve steatohepatitis and may permit fibrosis remodelling. In contrast, in lean MASLD, in patients without diabetes, or in those with advanced fibrosis and relatively little steatosis, it is currently unknown whether further reductions in liver fat will be sufficient to reverse established scarring. In these settings, incretin- and glucagon-based therapies are likely to function best as foundational metabolic treatments and may require combination with agents that act more directly on fibrogenic pathways. Emerging genetic and experimental data further suggest that disease biology may influence therapeutic responsiveness, with preliminary studies indicating enhanced metabolic benefit in individuals carrying PNPLA3 risk variants, consistent with greater dependence on pathways regulating lipid handling and mitochondrial stress. Together, these observations support a rationale for combination strategies that pair incretin- or glucagon-based therapies with agents such as THRβ agonists [127], FGF21 analogues [171, 172] or inhibitors of acetyl-CoA-generating pathways [39] to address advanced or 'burnt-out' MASH where defects in mitochondrial function and activation of hepatic stellate cells predominate.

Taken together, the studies discussed in this review support a model in which GLP1, GIP and glucagon-based therapies improve MASLD and MASH primarily by modifying upstream metabolic and inflammatory drivers of disease. In addition, GLP1 receptor signalling is now well established to exert anti-inflammatory effects beyond weight loss; however, the contributions of GIPR and GCGR signalling to hepatic immune regulation remain less well defined but biologically plausible. Across clinical studies, improvements in steatosis and steatohepatitis consistently track with reduced nutrient flux to the liver, altered adipose tissue lipid handling, improved hepatocellular metabolic function and modulation of inflammatory tone. A key challenge moving forward will be to define how these pathways interact across disease stages and patient subtypes, and how metabolic improvements can be translated into durable antifibrotic benefit across the full spectrum of MASLD and MASH.


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### Conflicts of Interest

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The authors have nothing to report.

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