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Tirzepatide in metabolic dysfunction-associated steatotic liver disease and steatohepatitis: a novel star on the horizon?

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Academic Editor: Fernando Albericio, University of KwaZulu-Natal, South Africa, Universidad de Barcelona, Spain
Received: July 10, 2025 **Accepted:** August 18, 2025 **Published:** September 4, 2025

Cite this article: Lonardo A, Weiskirchen R. Tirzepatide in metabolic dysfunction-associated steatotic liver disease and steatohepatitis: a novel star on the horizon? Explor Drug Sci. 2025;3:1008128. https://doi.org/10.37349/eds.2025.1008128

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its more rapidly progressive variant steatohepatitis (MASH) are widespread chronic liver conditions linked to obesity and other common metabolic disorders. The emergence of tirzepatide, a dual incretin receptor agonist targeting both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, presents major therapeutic potential for MASLD. This review article explores the mechanisms of action of tirzepatide, highlighting its ability to improve glycemic control, promote weight loss, and potentially ameliorate hepatic steatosis and fibrosis. Recent studies suggest that tirzepatide may offer significant benefits in managing MASLD/MASH by modulating metabolic pathways and enhancing liver health. However, further research is needed to fully understand its long-term impact on MASLD/MASH progression and outcomes across diverse patient populations.

Keywords

metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), dual incretin receptor antagonist, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), type 2 diabetes mellitus, obesity, tirzepatide

Introduction

Burden of obesity-associated metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to under the umbrella of non-alcoholic fatty liver disease (NAFLD), is now recognized as the most prevalent chronic liver

disease condition globally, closely linked to the rising rates of obesity [1, 2]. At the core of MASLD is hepatic steatosis, an excessive accumulation of fat in liver cells that can progress to more severe conditions like liver inflammation, fibrosis, cirrhosis, and even hepatocellular carcinoma. Obesity increases these risks by causing insulin resistance (IR), increasing the influx of free fatty acids into the liver, and promoting chronic low-grade inflammation [3]. The impact on the quality of life for affected individuals is substantial, as MASLD is also associated with metabolic comorbidities like type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension. From a public health perspective, the increase in healthcare expenses associated with MASLD and its complications is significant, underscoring the urgent need for effective treatment strategies that tackle both the liver-specific issues and the broader metabolic risks faced by affected individuals [2].

Presentation of tirzepatide

Tirzepatide is a synthetic dual incretin receptor agonist (molecular mass ~4.8 kDa, water-soluble) that has recently emerged as a novel therapeutic strategy for metabolic disorders by targeting both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors (GLP-1R), leading to marked improvements in glycemic control and body weight in clinical trials for T2DM [4] (Table 1, Figure 1).

Table 1. Characteristics of tirzepatide[1].

Drug name	Tirzepatide
Alternate names	LY-3298176, twincretin
Trade names	Mounjaro, Zepbound
CAS-No.	2023788-19-2
Chemical class	Synthetic peptide (39 amino acids) with a C20 fatty acid diacid moiety attached, dual GIP/GLP-1 receptor agonist
Drug class	Antidiabetic agent (incretin-based therapy), GLP-1 receptor agonist
Molecular formula	$C_{225}H_{348}N_{48}O_{68}$
Molecular mass	4,813.527 g/mol
Appearance	Generally, a white to off-white powder (lyophilized peptide)
Melting point	Not well-defined (peptide typically denatures rather than exhibiting a true melting point)
pKa	Not well-defined (multiple ionizable amino acid residues)
Half-life	5 days (varies slightly by individual and given concentration)
AUC brain/AUC plasma ratio	No publicly disclosed/unknown
B/P ratio	No publicly disclosed/unknown
Solubility in water	Soluble (typical for peptide therapeutics)
Soluble in DMSO	Yes, though actual solubility values are not extensively documented
Bioavailability	Information for subcutaneous administration suggests effective absorption; precise percentage not widely reported; the drug is highly bound to plasma albumin (99%)
Application	Treatment of type 2 diabetes mellitus and body weight reduction (investigational and off-label research for obesity and MASLD), administered subcutaneously once weekly
Dosage	1.5–15 mg (for reduction of fasting serum glucose and body weight); the initial dosage for treatment initiation is 2.5 mg once weekly
Maximum observed drug concentration (Cmax, ng/mL)[2]	26.0 ng/mL (29) at dosage 0.25 mg to 874 ng/mL (19) at dosage 8.0 mg
Time of Cmax (h)[3]	24 (24, 72) at 5 mg; high individual variation at different concentrations
Apparent total body clearance of drug following subcutaneous administration (L/h)[2]	0.0416 (22)–0.0553 (15)
Apparent volume of distribution of drug during terminal phase following subcutaneous administration (L)[2]	6.76 (18)–9.80 (7)
Side effects	Dose-dependent gastrointestinal discomfort (vomiting, nausea, decreased appetite, diarrhoea, and abdominal distension), sinus tachycardia, acute kidney injury, likely secondary to dehydration from gastrointestinal losses, hypersensitivity reactions, pancreatitis, and hypoglycemia

1: Part of the information was taken from [5, 6]; 2: data are given as geometric mean (coefficient of variability CV%); 3: Median (minimum, maximum). AUC: area under the curve; B/P ratio: blood/plasma ratio; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; MASLD: metabolic dysfunction-associated steatotic liver disease.

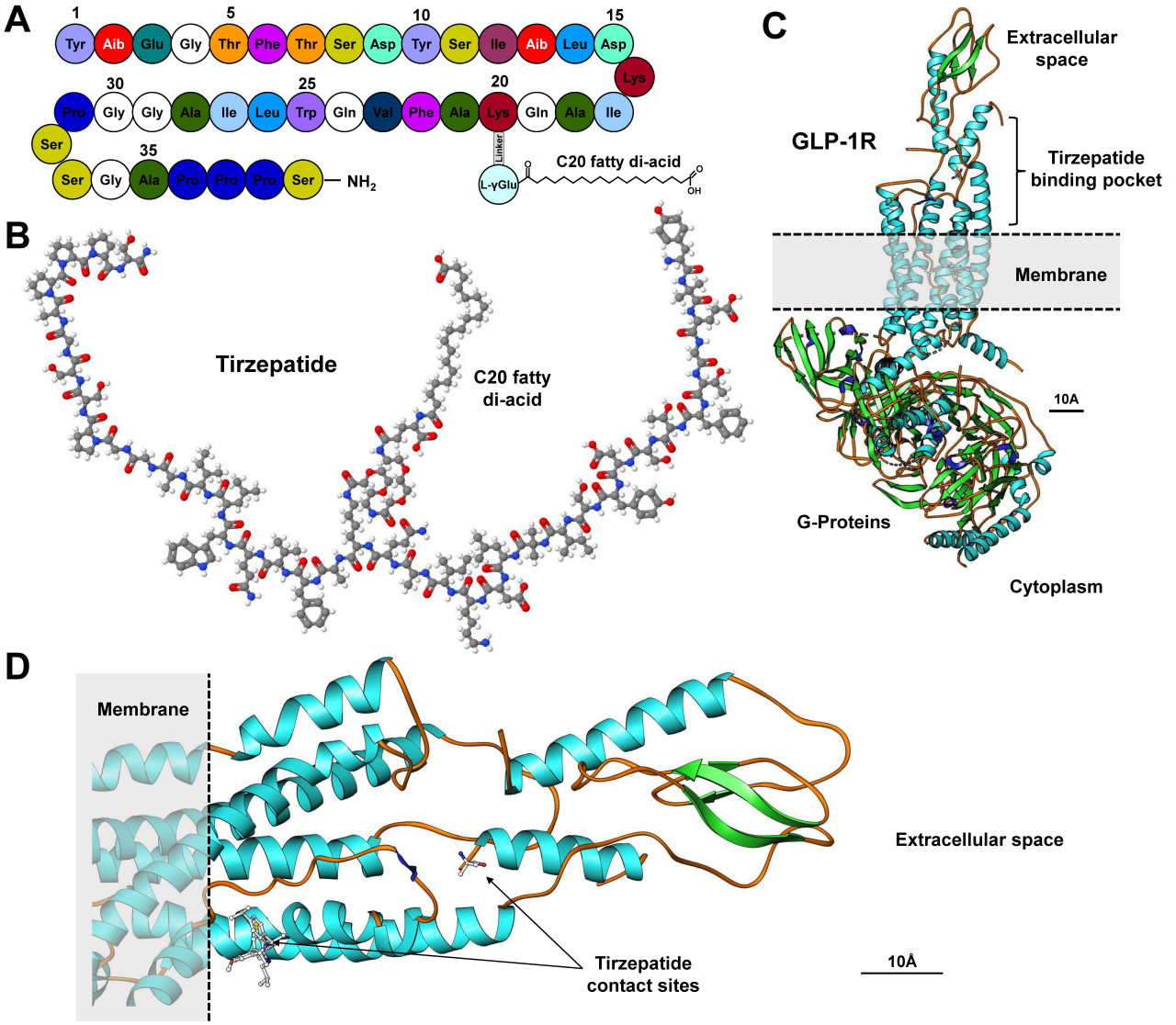

Figure 1. Tirzepatide structure and function. (**A**) Tirzepatide is a synthetic peptide of 39 amino acids carrying a C20 fatty di-acid moiety that is connected via a linker to lysine at position 20. The peptide contains two non-natural amino acids (α-amino isobutyric acids, Aib) at positions 2 and 13; (**B**) chemical structure of tirzepatide showing the peptide sequence and the location of the C20 fatty-di-acid moiety. The structure coordinates were taken from the PubChem database (PubChem CID: 172874756, https://pubchem.ncbi.nlm.nih.gov/compound/172874756#section=2D-Structure) [7] and the image was generated with Jmol (version 14.2.15_2015.07.09); (**C**) 3D representation of the structure of the GLP-1R/tirzepatide complex. Tirzepatide binds to the extracellular domain of GLP-1R, leading to recruitment of different G-proteins; (**D**) rough depiction of the binding sites of tirzepatide within the extracellular domain of the GLP-1R. The structure coordinates of the receptor-drug complex were taken from the RCSB Protein Data Bank (PDB ID: 7RBT DOI Citation: B. Sun, B.K. Kobilka, K.W. Sloop, D. Feng, T.S. Kobilka, cryo-EM structure of human Gastric inhibitory polypeptide receptor GIPR bound to tirzepatide (2022) https://doi.org/10.2210/pdb7rbt/pdb) [8] and the image was generated with Ribbons (Ribbons XP Version 3.0). Details about the structure are given elsewhere [9]. GLP-1R: glucagon-like peptide-1 receptor.

This dual agonism of tirzepatide represents a promising approach to obesogenic and metabolic pathways. As interest in addressing the multifaceted pathophysiology of MASLD expands, the potential of tirzepatide to improve insulin sensitivity, promote weight loss, and modify hepatic inflammation makes it an attractive candidate for further investigation. Recent experimental studies, first case reports, and clinical trials suggest that these benefits may extend to ameliorating hepatic fat accumulation, reducing fibrosis, and modulating gut microbiota may hold promise to mitigate the progression of MASLD and its more rapidly evolutive variant metabolic dysfunction-associated steatohepatitis (MASH) [10–12].

Aims of the review

This review aims to clarify the relationship between tirzepatide and MASLD, focusing on its mechanistic basis and preliminary data on clinical outcomes. First, we will provide a comprehensive overview of the

mechanism by which tirzepatide exerts its metabolic effects, exploring its dual receptor activity and downstream signaling pathways. We will then discuss the current evidence, detailing how the ability of tirzepatide to reduce weight, improve insulin sensitivity, and potentially possess anti-inflammatory properties could lead to therapeutic benefits for MASLD. Finally, we will identify gaps in the existing literature and emphasize the need for further clinical trials to understand the long-term impact of tirzepatide on MASLD disease progression and outcomes in various patient populations.

Mechanism of action of tirzepatide in the context of metabolic dysfunction

Tirzepatide is a new dual incretin receptor agonist designed to activate both the GIP receptor (GIPR) and the GLP-1R [9]. This dual action has attracted significant attention, especially in the context of conditions like T2DM, obesity, and, consequently, MASLD [13]. In the following, we will discuss mechanistic aspects of tirzepatide, with a focus on its receptor targets, intracellular signaling cascades, effects on metabolic organs, and how these changes may work synergistically together to alleviate the pathophysiological processes underlying MASLD.

Mechanistic insights and biological pathways

Incretin hormones such as GIP and GLP-1 are secreted by enteroendocrine cells in response to oral nutrient intake. The 42-amino acid peptide hormone GIP is primarily released by K-cells in the duodenum and proximal jejunum, while GLP-1 is secreted by L-cells located predominantly in the distal ileum and colon [14, 15]. Both hormones play critical roles in glucose homeostasis, affecting insulin secretion, suppressing glucagon, regulating gastric emptying, and controlling appetite through central nervous system signals. There are two clinically important incretin receptors, the GIPR and the GLP-1R [16, 17]. The GIPR is a G-protein-coupled receptor (GPCR) that, upon binding GIP, initiates a signaling cascade predominantly through the stimulatory G-protein [16]. Activation of adenylate cyclase leads to increased cyclic adenosine monophosphate (cAMP) levels, which in turn activate protein kinase A (PKA) and downstream targets [16]. The overall effect promotes glucose-dependent insulin secretion in pancreatic β-cells and may have additional effects on lipolysis and adipocyte function. Like the GIPR, GLP-1R is also a GPCR primarily coupled to Gs, leading to elevated cAMP levels and PKA-mediated signaling. The downstream effects in pancreatic β-cells include enhanced insulin synthesis and secretion, while in α-cells, GLP-1R activation reduces glucagon secretion. Peripheral actions include delayed gastric emptying, reduced appetite, and a variety of cardioprotective and anti-atherogenic effects [16].

Tirzepatide is specifically designed with structural elements to bind to both GIPR and GLP-1R. While many existing drugs for T2DM and obesity target the GLP-1R alone, the ability of tirzepatide to act on both incretin receptors seems to provide synergistic or at least additive benefits [18]. This is in terms of enhanced insulin secretion by stimulating both GIPR and GLP-1R on β-cells. Tirzepatide augments insulin release in a glucose-dependent manner, reducing the risk of hypoglycemia commonly associated with non-glucose-dependent insulin secretagogues, such as sulfonylureas and meglitinides [19]. Furthermore, in states of hyperglycemia, activation of GLP-1R in α-cells due to tirzepatide helps curb excessive glucagon secretion, further improving glycemic control. Therefore, the net effect of tirzepatide in T2DM is a reduction in inappropriately high glucagon levels, likely due to the predominant GLP-1R-mediated suppression. Moreover, tirzepatide can lead to a mean reduction in body weight, as both GIP and GLP-1 play roles in modulating appetite and satiety [20]. However, GLP-1R agonism is most famously associated with central appetite suppression and delayed gastric emptying, and the effects of tirzepatide on weight reduction are multifactorial. These encompass central appetite regulation, changes in gut motility, and improved insulin sensitivity [21].

Upon binding to their respective GPCRs, GIP and GLP-1 trigger a cascade of intracellular events. In the first step, there is a Gs-mediated increase in cAMP, leading to PKA-dependent phosphorylation of key transcription factors such as cAMP response element-binding protein (CREB) [22]. This process subsequently simulates regulatory genes responsible for β-cell growth, insulin biosynthesis, and mitochondrial function in various tissues. Additionally, increased cAMP also modulates the flow of

intracellular calcium through secondary messenger systems, which is a prerequisite for insulin granule exocytosis in β-cells. By facilitating calcium-dependent vesicle release, tirzepatide can enhance insulin output in T2DM. In addition to the cAMP axis, incretin hormone receptor activation can engage the extracellular signal-regulated kinase (ERK1/2) and phosphoinositide 3-kinase (PI3K)/Akt routes, pathways integral to cell survival, proliferation, and receptor cross-talk [22], further potentiating the beneficial effects of incretin agonists on β-cell health and peripheral insulin sensitivity.

The pancreas is perhaps the most direct target of the dual agonism of tirzepatide, affecting both endocrine and, to a lesser extent, exocrine function. Chronic exposure to GLP-1R agonists (GLP-1RAs) can promote β-cell proliferation and protect cells from apoptosis, possibly mediated by anti-inflammatory signals and an improved metabolic environment [23]. GIP has also been implicated in β-cell maintenance, although debates remain regarding its long-term effects. The combined effect of tirzepatide therapy may support better β-cell mass maintenance over time. Its glucose-dependent effect on insulin release implies a reduction of the risk of hypoglycemia with tirzepatide, while providing more robust glycemic control with reductions in glycated hemoglobin (HbA1c) levels compared to traditional secretagogues [24, 25]. Moreover, the potent effects of tirzepatide on GLP-1R activity in hyperglycemic states also contribute to preventing hyperglycemic surges postprandially through fine-tuning of glucagon levels.

Appetite suppression and reduced food intake are primarily driven by GLP-1RAs through three synergistic mechanisms. Firstly, the hypothalamus integrates peripheral signals of nutrient status. Incretin hormones that cross or signal through the blood-brain barrier can impact neuron populations that regulate feeding behavior, such as the pro-opiomelanocortin (POMC) neurons and the neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons [26, 27]. Secondly, incretin-based therapies may influence dopaminergic reward pathways, leading to a reduction in food-related cravings [28], which is particularly relevant for managing obesity. Thirdly, by slowing gastric emptying, tirzepatide promotes an earlier sense of fullness and sustained release of nutrients into the intestines, further enhancing satiety and improving postprandial glucose control [21].

An intriguing biological aspect of tirzepatide activity is its potential influence on adipose tissue metabolism. GIP signaling in adipocytes has historically been linked to both anabolic and catabolic pathways, making the net effect somewhat context dependent. Under certain metabolic states, GIP can promote fat storage by enhancing insulin-mediated lipogenesis in adipocytes [29]. Paradoxically, in an environment where metabolic dysfunction is being actively corrected (e.g., through improved insulin sensitivity, reduced inflammation, or calorie deficit), the net effect of improved glucose handling might facilitate more efficient fuel partitioning, thereby reducing ectopic fat accumulation in the liver. However, some animal studies regarding GIP analogs and GLP-1RAs have hinted at possible “browning” of white adipose tissue, increasing energy expenditure and thermogenesis [30]. Although this mechanism is not fully elucidated in humans, the interplay between GIP and GLP-1 in tirzepatide could theoretically promote a metabolically healthier adipose tissue phenotype. Other studies have shown that incretin therapies may influence the profile of adipokines (e.g., leptin, adiponectin) that modulate steatogenesis, insulin sensitivity, and inflammation [31].

Clinical and pathophysiological context

MASLD is characterized by hepatic steatosis, which results from an imbalance between the influx of free fatty acids, hepatic de novo lipogenesis, and export of triglycerides [1, 2, 32]. Tirzepatide may help correct this imbalance through several interconnected mechanisms. First, by improving glycemic control and insulin sensitivity, tirzepatide addresses key contributors to hepatic lipid accumulation. Chronically elevated insulin levels upregulate lipogenesis while IR in peripheral tissues increases circulating free fatty acids [33]. Through its glucose-dependent insulin-stimulating effects and its capacity to enhance peripheral insulin responsiveness, tirzepatide reduces the hepatic fat load. Second, by promoting weight reduction, tirzepatide alleviates the systemic inflammation and excessive free fatty acid flux that accompany excess adiposity, giving the liver an opportunity to reduce ectopic fat deposition [10]. Third, although direct anti-inflammatory effects of tirzepatide have not been as extensively documented as those observed with GLP-1

agonists alone, its dual incretin receptor activation is widely hypothesized to modulate generation of reactive oxygen species pro-inflammatory cytokine production [21]. Finally, tirzepatide may influence key transcription factors involved in lipid metabolism, such as SREBP-1c and PPAR-α/γ, and by improving systemic insulin sensitivity and promoting weight loss, it could push hepatocytes toward a less lipogenic gene expression profile [34]. Collectively, these direct and indirect effects on the liver position tirzepatide as a promising therapy for mitigating the development and progression of MASLD.

Although not a direct hepatic mechanism, improvements in cardiovascular and renal function under tirzepatide therapy can promote better overall metabolic homeostasis, offering additional benefits for MASLD. On the cardiovascular front, evidence from GLP-1RAs suggests a reduction in major adverse cardiovascular events, particularly in patients with T2DM at high cardiovascular risk [35]. By addressing cardiac dysfunction and atherosclerosis, tirzepatide may indirectly benefit the liver by enhancing nutrient utilization and oxygen delivery to peripheral tissues. Regarding renal protection, the ability of tirzepatide to lower blood pressure, reduce inflammation, and improve glycemic control helps in preserving kidney function [36]. A healthier renal profile allows for more efficient excretion of metabolic byproducts, contributing to a stable internal environment that reduces the risk factors exacerbating hepatic steatosis and inflammation. This cardiovascular and renal crosstalk is crucial for the broader improvements in metabolic health that could ultimately support liver function in patients with MASLD.

While the mechanistic rationale for tirzepatide in MASLD is compelling, several limitations and uncertainties remain. One consideration is the variable patient response to GIP, given the complex involvement of GIPRs in metabolic processes that can sometimes promote anabolic pathways in adipose tissue. The net effect on hepatic steatosis may thus depend on an individual's metabolic milieu and genetic predisposition. Additionally, although tirzepatide has shown robust benefits for glycemic control and weight management, most clinical evidence has been derived from T2DM-focused studies with relatively limited long-term data on direct hepatoprotective outcomes, such as inflammation, fibrosis markers, or histological changes in the liver. Lastly, common side effects of incretin-based therapies, including nausea, vomiting, or diarrhea, could theoretically affect nutrient absorption and hepatic metabolism, and require more thorough investigation to elucidate their implications for liver health in diverse patient populations.

Given the overlap in pathophysiology among T2DM, obesity, and MASLD, it is logical that a treatment with proven efficacy in glycemic control and weight reduction would be explored for hepatic benefits. Future research is likely to include head-to-head comparisons of tirzepatide with established GLP-1RAs, focusing on liver-specific outcomes, such as MRI-PDFF measurements or histological findings from liver biopsies. Investigations into combination therapies will also be key, as MASLD encompasses lipotoxicity, oxidative stress, inflammation, and fibrosis; pairing tirzepatide with other agents targeting these pathways may offer complementary or synergistic effects. Another priority will be the development of reliable non-invasive biomarkers to track changes in liver fat content and fibrosis, which could include circulating markers like cytokeratin-18 fragments or scoring systems like fibrosis-4 (FIB-4) score and enhanced liver fibrosis (ELF) test, in addition to imaging-based assessments in patients with MASLD [37, 38]. These endeavors will help clinicians better personalize tirzepatide-based treatments and more accurately monitor their impact on disease progression.

MASLD results from a confluence of metabolic derangements that drive lipid overaccumulation and hepatic injury. The capacity of tirzepatide to address IR, obesity, and dysregulated nutrient handling makes tirzepatide particularly pertinent. Its dual incretin receptor agonism confers significant weight and glycemic improvements, targeting two main factors that hasten MASLD progression. Additionally, while direct evidence regarding tirzepatide's anti-inflammatory and hepatoprotective actions is emerging, the broader metabolic benefits and known anti-inflammatory potential of incretin-based therapies suggest a plausible mechanism by which tirzepatide might reduce hepatic injury and fibrosis. This is especially relevant to patients with MASLD who frequently present with coexisting T2DM or prediabetes. By simultaneously addressing both glycemic control and hepatic steatosis, tirzepatide therapy may reduce the need for multiple medications, simplifying disease management and improving overall patient outcomes.

Clinical studies on the effects of tirzepatide on liver health

Efficacy

Given the multifaceted biological, epidemiological, and clinical association of MASLD and MASH with obesity and diabetes, which has been extensively reviewed elsewhere [1, 39, 40], studies have assessed the efficacy profile of tirzepatide on MASLD and MASH. The number of such original and meta-analytical studies is limited so far, as shown in Table 2 [10, 40–47].

Table 2. Clinical studies investigating the impact of tirzepatide on MASLD/MASH, listed in chronological order.

Author, year [ref.]	Method	Results	Conclusion
Gastaldelli et al., 2022 [40]	296 individuals with an FLI ≥ 60 out of 502 T2DM subjects enrolled in the SURPASS-3 trial were submitted to MRI scanning and were randomised (1:1:1:1) in the main study to s.c. tirzepatide (5 mg, 10 mg, or 15 mg) once weekly or s.c. insulin degludec once daily, using an interactive web-response system, and were stratified by country, HbA1c, and concomitant oral anti-diabetic drugs.	At week 52, the absolute decrease in LFC was significantly greater for the pooled 10 mg and 15 mg tirzepatide groups (–8.09%, SE 0.57) vs. the insulin degludec group (–3.38%, SE 0.83). The estimated treatment difference versus insulin degludec was –4.71% (95% CI –6.72 to –2.70; $p < 0.0001$). Among individuals randomized to tirzepatide, the decreased LFC was significantly correlated ($p \leq 0.0006$) with baseline LFC (ρ = –0.71), reductions in VAT (ρ = 0.29), reductions in ASAT (ρ = 0.33), and reductions in BW (ρ = 0.34).	In this subpopulation of T2DM patients in the SURPASS-3 study, the use of tirzepatide compared to insulin degludec was associated with significantly reduced LFC, VAT, and ASAT.
Loomba et al., 2024 [10]	Phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving 190 participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis who were randomized to once-weekly s.c. tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary endpoint was MASH resolution without worsening of fibrosis at 52 weeks. The secondary endpoint was a decrease of ≥ 1 fibrosis stage without worsening of MASH.	At week 52, liver biopsies of 157 among 190 randomized participants could be evaluated, with missing values imputed under the assumption that they would follow the pattern of results in the placebo group. The proportion of enrollees who exhibited MASH resolution without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% CI, 17 to 50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI, 29 to 62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI, 37 to 69) ($p <$ 0.001 for all three comparisons). The fraction of individuals showing an improvement of ≥ 1 fibrosis stage without MASH worsening was 30% vs. 55% in the placebo group, vs. the 5-mg tirzepatide group, respectively (difference vs. placebo, 25 percentage points; 95% CI, 5 to 46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI, 1 to 42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI, 1 to 42). The most common adverse events in the tirzepatide groups were GI events, and most were mild or moderate.	Tirzepatide treatment for 52 weeks is more effective than placebo in resolving MASH without worsening fibrosis.
Sawamura et al., 2024 [41]	Retrospective analysis at months 3 and 6 after the switch of data from 40 T2DM patients who received a prescription change from dulaglutide to tirzepatide.	Six months after the treatment switch, average reductions of 1.2% and 3.6 kg were observed in HbA1c and BW, respectively. The change in HbA1c was negatively correlated with the baseline HbA1c value. However, BW reduction was observed regardless of baseline features. Moreover, AST, ALT, and GGT values decreased 6 months after the switch. The FIB-4 did not improve during the study period.	Among T2DM patients, switching from dulaglutide to tirzepatide treatment has beneficial effects on blood glucose level, BW, and liver enzymes.
Ferch et al., 2025 [42]	Report of two cases living with AS who were treated with tirzepatide. SLD was assessed with MRI.	The first subject, with 18 months on treatment, experienced weight loss of –28 kg (113.6 kg to 83 kg, –26.9%); HbA1c decreased by –0.4% (6.7% to 6.3%), with considerable reductions in daily insulin doses. SLD resolved from a previous fat fraction of 20%. The second individual was followed up for 9 months and showed a weight reduction of –9.5 kg (132 kg to 122.5 kg; –7.2%) with a reduction of LFC from 21% to 11% after ~3 months of therapy.	In the rare, genetic, multi-systemic disorder AS, tirzepatide treatment is associated with a significant reduction in BW, IR, and LFC.
Sattar et al., 2025 [43]	Post-hoc, sub-study analysis of 296 individuals in whom thigh muscle fat infiltration, muscle volume, and muscle volume *Z* score were	At week 52 compared to the baseline value, significant reductions were observed in muscle fat infiltration for the pooled and individual tirzepatide dose groups (for pooled tirzepatide, mean change –0.36 percentage points [95% CI –0.48 to –0.25, $p < 0.0001$], muscle volume [–0.64 L	Tirzepatide (but not insulin degludec) treatment was associated with potentially favorable

Table 2. Clinical studies investigating the impact of tirzepatide on MASLD/MASH, listed in chronological order. (*continued*)

Author, year [ref.]	Method	Results	Conclusion
	assessed by MRI at baseline and week 52 out of 502 T2DM participants enrolled in the SURPASS-3 trial who were randomly assigned (1:1:1:1) to receive s.c. (5, 10, or 15 mg) tirzepatide once weekly, or daily s.c.insulin degludec.	(95% CI –0.74 to –0.54, $p < 0.0001$)], and muscle volume *Z* score [–0.22 (95% CI –0.29 to –0.15), $p < 0.0001$], which occurred in the context of significant BW reduction. Conversely, treatment with insulin degludec was associated with increased BW and muscle volume.	changes in muscle fat infiltration and reductions in muscle volume.
Okuma et al., 2025 [44]	Retrospective study of a cohort of 54 Japanese with T2DM and MASLD submitted to a treatment switching from a GLP-1RA to tirzepatide.	Six months after the treatment switch, BW, HbA1c, FLI, FIB-4, and hsCRP levels were observed. MRA disclosed age, T2DM duration, and pre-switch HbA1c levels independently predicted BW loss while pre-switch age predicted a decrease in FLI.	Switching from GLP-1RAs to tirzepatide among Japanese T2DM subjects with MASLD is effective, and predictors of BW loss and FLI decrease after switching to tirzepatide are identifiable.
Oe et al., 2025 [45]	Case study.	A 50-year-old man with a 16-year history of poorly controlled T2DM diabetes had elevated liver enzymes and histologically proven MASH. Liraglutide was administered for 3 years but his liver function and glycemic control deteriorated gradually, and a second liver biopsy found cirrhosis. At this point, liraglutide was switched to tirzepatide. Over 6 months of tirzepatide administration, the patient's HbA1c and liver enzymes decreased. A third biopsy performed at this point showed markedly improved histology, including ameliorated liver fibrosis.	Severe MASH improved after switching from GLP-1RA treatment to tirzepatide.
Souza et al., 2025 [46]	Network meta-analysis of 29 RCTs totaling 9,324 cases.	Tirzepatide was significantly superior to placebo at achieving the regression of liver fibrosis without MASH worsening and MASH resolution without worsening of liver fibrosis.	By providing updated data on MASH drug therapies for fibrosis regression and resolution, this study may inform clinical practice and trial design.
Wang et al., 2025 [47]	Systematic review and meta-analysis of 25 RCTs totaling 2,600 patients.	GLP-1RAs treatment for a median of 24 weeks induced a significant reduction in LFC by 5.21%. Moreover, significant histological improvements in steatosis, hepatocellular ballooning, and lobular inflammation were observed, with stronger evidence for tirzepatide compared to semaglutide and liraglutide.	In MASLD and MASH, tirzepatide treatment is associated with decreased LFC and improved liver histology without worsening fibrosis.

ALT: alanine aminotransferase; AS: Alström syndrome; ASAT: abdominal subcutaneous adipose tissue; AST: aspartate aminotransferase; BW: body weight; CI: confidence interval; FIB-4: fibrosis-4 index; FLI: fatty liver index; GGT: γ-glutamyl transpeptidase; HbA1c: glycated hemoglobin; GI: gastrointestinal; GLP-1RA: glucagon-like peptide 1 receptor agonist; hsCRP: high-sensitivity C-reactive protein; IR: insulin resistance; LFC: liver fat content; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; MRA: multiple regression analysis; MRI: magnetic resonance imaging; RCTs: randomized controlled trials; s.c.: subcutaneous; SE: standard error; SLD: steatotic liver disease; T2DM: type 2 diabetes mellitus; VAT: visceral adipose tissue.

Regardless of how it is achieved, whether through lifestyle changes, endoscopic procedures, or metabolic/bariatric surgery, weight loss provides clear benefits on MASH histology [48]. For patients with "diabesity", the introduction of GLP-1RAs has marked a shift in treatment approaches. The advantages of using GLP-1RAs go beyond their anti-obesity and glucose-lowering effects, encompassing a reduced risk of major adverse cardio-nephro-vascular and hepatic outcomes by lowering arterial hypertension and overall improving metabolic function [49, 50]. Early placebo-controlled randomized controlled trials (RCTs) of GLP-1RAs in patients with obesity and T2DM indirectly indicated positive effects on the liver, as evidenced by improvements in surrogate indices, particularly liver enzymes [51]. Tirzepatide differs from GLP-1RAs

in that, in addition to agonizing the GLP-1R, this drug also acts as a GIPR agonist, providing direct effects on white adipose tissue that may further benefit MASH histology beyond glycemic control and weight loss [52].

In this context, the seminal SYNERGY-NASH trial has shown that, by week 52, tirzepatide administration was more effective than placebo in achieving histologic MASH improvement without exacerbating fibrosis, an endpoint supported by the Food and Drug Administration [10]. Among individuals with biopsy-proven MASH and F2 or F3 liver fibrosis, subcutaneous weekly tirzepatide administration was superior to placebo in terms of MASH resolution without worsening liver fibrosis [10]. Additionally, the use of tirzepatide was linked to reductions in body weight, improved liver enzymes, and decreased intrahepatic fat content, hepatitis, and liver fibrosis as assessed noninvasively [10]. Overall, tirzepatide was found to be safe and well-tolerated, with only minor reports of gastrointestinal adverse effects [10]. Interestingly, serious events and adverse events resulting in trial discontinuation were similar across all four study arms, including the placebo arm.

It is reasonable to speculate that MASH resolution could lead to regression of liver fibrosis, a significant factor in major adverse liver outcomes (MALO) such as ascites, hepatic encephalopathy, variceal bleeding, liver transplantation or liver-related mortality. However, current studies have not extended the trial duration long enough to evaluate the effect of tirzepatide on MALO and lack sufficient power to detect any differences in liver fibrosis improvement compared to placebo administration [10]. The trial authors acknowledge that assessing fibrosis improvement will likely require studies longer than 52 weeks. Additionally, it remains to be seen if there is a limit to the amount of fibrosis regression achievable with GLP-1RAs (or weight loss alone). Patients with F4 fibrosis (cirrhosis) and those without fibrosis or with early-stage liver fibrosis (F0 and F1, respectively) were excluded by study design, suggesting the need for further studies. With these limitations in mind, the meta-analytic review by Wang et al. [47] based on 25 RCTs found that GLP-1RAs treatment induced significant histological improvements in steatosis, hepatocellular ballooning, and lobular inflammation but non-significantly improved fibrosis, with the evidence for tirzepatide being more robust than that for semaglutide and liraglutide. Clearly, additional sufficiently sized and long-term studies are requested incorporating not only robust histological endpoints but also clinically significant outcomes.

Methodological concerns and safety profile

It has been noted that there is a lack of placebo-controlled randomized trials with liver histology outcomes. This is because studies have mainly focused on extra-hepatic outcomes, such as body weight loss and metabolic compensation of T2DM. As a result, some studies have assessed liver health using surrogate biomarkers like liver enzymes or imaging techniques to measure intrahepatic liver fat content. Importantly, given the sexually dimorphic nature of MASLD [53] that could potentially affect therapy response [54–56], there have been no male-to-female comparative studies conducted to determine if one sex responds better to tirzepatide. Most studies on tirzepatide have been designed and conducted by the manufacturer, while independent investigations conducted in “real-world” scenarios by investigators are often underpowered due to low enrollment numbers. Regarding safety, a systematic assessment of tirzepatide has found limited side effects, mostly related to the gastrointestinal tract and of mild-to-moderate severity. However, there have been reports of liver toxicity [57, 58] that highlight the need for additional studies in the post-marketing period as more individuals are exposed to the drug, increasing the likelihood of identifying liver safety concerns.

Tirzepatide, marketed as Mounjaro for T2DM, was first approved in the USA in May 2022 for use in adult patients as an adjunct to diet and exercise [59]. In November 2023, it was approved for chronic weight management in adults with obesity or overweight and weight-related conditions under the brand name Zepbound [59]. However, tirzepatide is not yet approved for the treatment of MASH and clinical trials to evaluate its efficacy and safety for MASH are underway, and the manufacturer is collaborating with regulatory authorities regarding potential future approval for this indication of use. This implies that the true safety profile of tirzepatide among MASLD subjects is incompletely characterized, even though individuals living with obesity, overweight or T2DM often have MASLD. A recent pharmacovigilance study

based on the Food and Drug Administration's Adverse Event Reporting System (FAERS) database offers an accurate analysis based on real-world data [60]. These authors analyzed adverse drug events (ADEs) reports from the 2nd quarter of 2022 to the 4th quarter of 2023 using the reporting odds ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) methods. Importantly, this study specifically addressed sex-specific differences and reporting biases. Data have shown that among 25,212 tirzepatide-related ADE reports, common ADEs included nausea and vomiting while previously unreported ADEs included eructation, gastroesophageal reflux disease, hemorrhage at the site of drug injection, and hyperglycemia. Women reported more injection-site reactions, while men experienced more gastrointestinal complaints [60].

In this regard, alarming reports of drug-induced liver injury due to tirzepatide [57, 58] and major changes in thiopurine metabolites in tirzepatide-treated subjects with inflammatory bowel disease [61] are of specific significance for gastroenterological practice. These reports fully support the notion that close monitoring and further research are needed to ensure the safe use of tirzepatide, particularly among MASLD and MASH subjects.

Tirzepatide in the context of currently available therapeutic options in MASLD and MASH arena

At the time of writing, no direct head-to-head studies have compared tirzepatide to resmetirom and semaglutide, two of the best-studied drugs against MASH.

Resmetirom, the first and only FDA-approved agent against MASH, is an orally active, liver-selective agonist of the thyroid hormone receptor [62]. Resmetirom has proven efficacy in reducing liver fat content, liver enzyme levels, improving surrogate biomarkers of liver fibrogenesis, decreasing liver stiffness, and eliciting a favorable cardiometabolic profile [63]. Based on available data, resmetirom has a good safety and tolerability profile, with mild nausea and diarrhea occurring more often with the active drug than placebo [64].

Semaglutide, a synthetic analogue of GLP-1, may be administered weekly subcutaneously or daily orally [65]. This drug promotes significant weight and waist circumference reduction versus placebo by regulating glucose metabolism and gut motility. Semaglutide has been shown to resolve nonalcoholic steatohepatitis in many cases and lowers cardiovascular risk for patients with established atherosclerotic cardiovascular disease by reducing blood pressure, fasting glucose, C-reactive protein, and lipid levels. These effects are associated with decreased risk of kidney outcomes and cardiovascular-related mortality, as well as potential improvement in mental health and quality of life [66]. Common side effects are mild gastrointestinal issues and hypoglycaemia. Stopping semaglutide often leads to weight regain [49].

Compared to GLP-1 RAs, tirzepatide has shown superior glycemic control and weight loss [67]. Its ability to reduce hepatic fat and visceral adipose tissue further underscores its potential advantage in treating MASH over GLP-1 RAs [40].

A key research question is whether tirzepatide has any indication in MASLD/MASH non-diabetic individuals. It is important to note that tirzepatide is currently approved for use only in patients with T2DM and, therefore, its utility in non-diabetic MASLD/MASH individuals remains to be investigated. Further analysis of available drugs in the MASH arena is beyond the scope of this review and has been extensively covered elsewhere [68–70]. In conclusion, additional research will clarify the advantages and disadvantages of different drugs in MASH resolution, fibrosis regression, weight loss, lipid and glucose homeostasis, and safety profiles. These studies will clearly position tirzepatide in the complex context of drugs being investigated for possible use in MASH.

Conclusions

Tirzepatide operates through a dual mechanism of incretin receptor activation, utilizing both GIP and GLP-1 pathways. This mechanism results in improved insulin secretion, better glucagon regulation, and significant

weight loss, all of which help alleviate the metabolic strain on the liver. Central appetite suppression delayed gastric emptying, and potential remodeling of adipose tissue contribute to an overall improvement in metabolic health, which is expected to benefit patients with MASLD. However, the net effect of tirzepatide on MASLD may conceivably vary based on each patient's metabolic milieu, sex, reproductive status, lifestyle habits, and genetic predisposition, particularly due to the complex involvement of GIPRs in metabolic processes that can sometimes promote anabolic pathways in adipose tissue. This variability in patient response may limit the predictability of treatment outcomes. For example, a consistent line of research has shown that MASLD, sex, and reproductive status may affect the course of hepatic and extra-hepatic outcomes differently [71–74]. Collectively, these data call for sex-specific analysis of data in MASLD trials [54, 55]. Additionally, many existing publications report on manufacturer-sponsored investigations calling for investigator-driven studies and data derived from real-world practices.

While there are still questions about the long-term hepatic outcomes that require further research, the underlying mechanism of tirzepatide strongly supports its potential as a therapeutic agent for MASLD. The synergy of GIPR and GLP-1R signaling within the pancreas, adipose tissue, central nervous system, and potentially the liver provides a robust framework for how tirzepatide could help reduce the progression or outcome of MASLD. Nevertheless, rigorous clinical trials specifically targeting liver outcomes remain essential before incorporating this antidiabetic drug in routine MASLD management and clinical practice.

Given the complexity of its dual mechanism of action as a GIP and GLP-1RA, tirzepatide, hence defined as "twincretin" [75], is a key innovation in the MASLD armory [76]. Based on the 62% MASH response rate of the SYNERGY-NASH trial, tirzepatide is expected to be a new pillar of MASLD treatment, but its added value beyond semaglutide needs to be further validated. The intricate associations of liver histology with hepatic and extrahepatic outcomes dictate the necessity to adopt a holistic approach to MASH treatment [55]. To this end, large-scale studies need to be developed to permit stratification based on liver, determinants, extra-hepatic, and parameters (LDE classification) [77] or similar integrated categorization systems. Importantly, future studies on tirzepatide should specifically focus on sex differences, the role of reproductive status, and other major disease modifiers on treatment response [54, 55, 78, 79].

Studies with longer duration and larger sample sizes are necessary to further clarify the efficacy of tirzepatide (and other drug agents under investigation for MASLD) on fibrosis regression and risk reduction of robust clinical outcomes, such as MALO, and major adverse cardio-nephro-vascular outcomes in the context of an integrated view of cardiometabolic health [80]. Additionally, future studies will be required to assess the efficacy and safety of tirzepatide among individuals with MASH and F0 fibrosis as well as among those with MASH-cirrhosis. Given the high prevalence of MASLD globally, active investigation to identify and effectively triage the patient population that is more likely to benefit from long-term MASH therapy with tirzepatide as opposed to resmetirom [62] remains a key and yet unanswered research question. Finally, data regarding the safety profile of tirzepatide among MASLD subjects needs to be fully defined, as this drug is not approved for the treatment of MASLD.

Abbreviations

ADEs: adverse drug events

cAMP: cyclic adenosine monophosphate

GIP: glucose-dependent insulinotropic polypeptide

GIPR: glucose-dependent insulinotropic polypeptid receptor

GLP-1: glucagon-like peptide-1

GLP-1R: glucagon-like peptide-1 receptor

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

GPCR: G-protein-coupled receptor

IR: insulin resistance

MALO: major adverse liver outcomes

MASH: metabolic dysfunction-associated steatohepatitis

MASLD: metabolic dysfunction-associated steatotic liver disease

PKA: protein kinase A

RCTs: randomized controlled trials

T2DM: type 2 diabetes mellitus

Declarations

Acknowledgments

Authors used RWTHgpt software in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Author contributions

AL and RW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. Both authors read and approved the submitted version.

Conflicts of interest

Amedeo Lonardo and Ralf Weiskirchen, who serve as Guest Editor and Associate Editor of Exploration of Drug Science, had no involvement in the decision-making or review process of this manuscript.

Ethical approval

Not applicable.

Consent to publication

Not applicable.

Consent to participate

Not applicable

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

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