Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Incretin Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Network Meta-Analysis

Saad Masood
Allama Iqbal Medical College
Hamna Ibrar
Allama Iqbal Medical College
Muhammad Asfandyar Nadir
Allama Iqbal Medical College
Musa Masood
Allama Iqbal Medical College
Asna Moghis
Allama Iqbal Medical College
Abdul Wasay
Allama Iqbal Medical College
Muhammad Hamza Khalid
Allama Iqbal Medical College
Muhammad Ans Asif
Lahore Medical and Dental College
Muhammad Ahsan Asif
Allama Iqbal Medical College
Arooba Suhaib
University College of Medicine and Dentistry
Muhammad Sohaib
HCA Healthcare
Muhammad Ali Butt
butt0275@umn.edu

University of Minnesota
Ming Valerie Lin
Lahey Hospital and Medical Center

Research Article

Keywords: MASLD, incretin receptor agonists, hepatic fibrosis, hepatic steatosis, glucagon-like peptide-1, semaglutide

Posted Date: November 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11486609/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Incretin Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Network Meta-Analysis

Abstract

Background

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is rapidly emerging as a leading cause of cirrhosis and liver-related mortality. Incretin-based therapies have shown compelling metabolic benefits, however, their comparative efficacy remains unclear.

Aims

We compared incretin agonists across liver fat reduction, weight loss, histological, and non-invasive fibrosis biomarker outcomes in MASLD using a network meta-analysis.

Methods

Five databases were searched for randomized controlled trials. Primary outcomes included MRI-PDFF reduction, MASH resolution, and ≥1-stage fibrosis improvement; secondary outcomes were weight change and Enhanced Liver Fibrosis (ELF) score. A random-effects network meta-analysis estimated treatment effects and ranked interventions using P-scores. Indirect comparisons relied on transitivity, while inconsistency could not be assessed.

Results

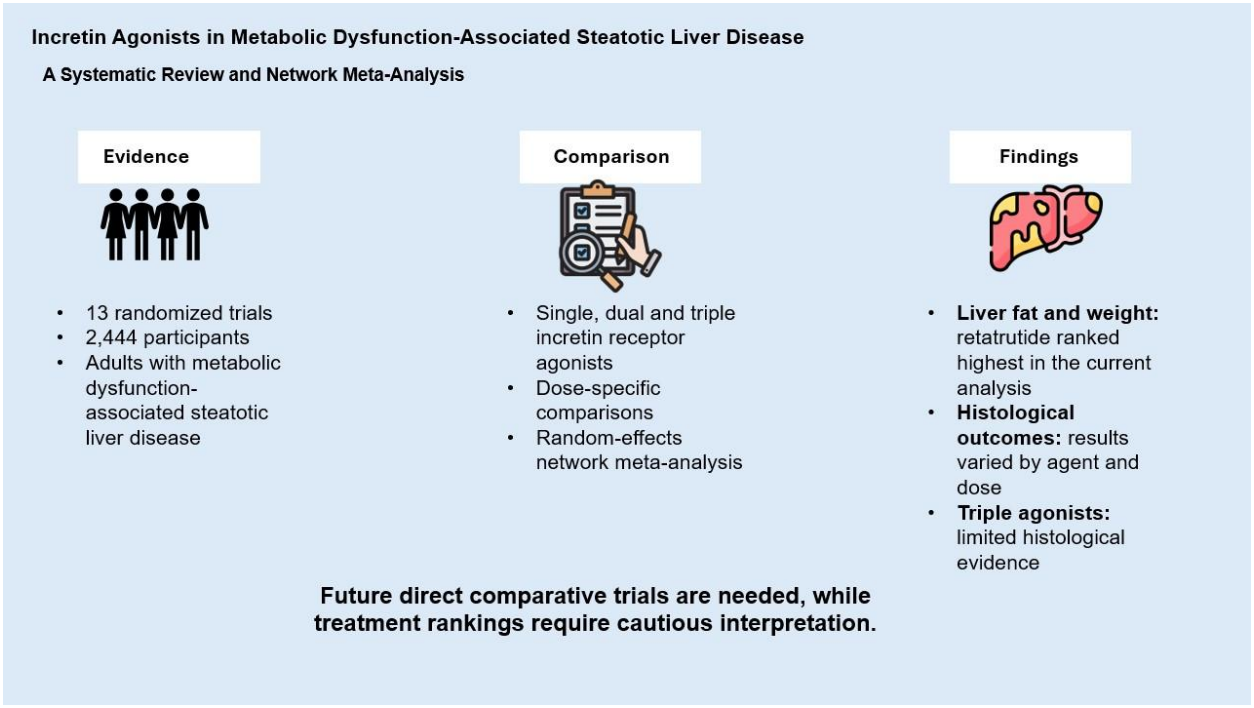
Thirteen trials involving 2,444 participants were included. Retatrutide 12 mg showed the greatest reduction in liver fat versus placebo (MD −82.70 percentage points; 95% CI −95.41 to −69.99), followed by 8 mg and 4 mg. Among dual agonists, survodutide 6 mg ranked highest for liver fat reduction. Retatrutide 8 mg and 12 mg also led the rankings for weight loss and achieving ≥30% liver fat reduction. Survodutide 4.8 mg ranked highest for MASH resolution (OR 10.67), while tirzepatide 5 mg ranked highest for fibrosis improvement (OR 3.01) and ELF score reduction (MD −0.66).

Conclusion

Retatrutide showed the greatest liver fat and weight reductions, while survodutide and tirzepatide ranked highest for MASH resolution and fibrosis improvement, respectively. Limited histologic evidence for triple agonists warrants further clinical trials.

Keywords: MASLD; incretin receptor agonists; hepatic fibrosis; hepatic steatosis; glucagon-like peptide-1; semaglutide

Graphical Abstract



Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is a global health concern affecting approximately 16% of the global population[1, 2]. It can be progressive in nature and encompasses a wide spectrum ranging from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH)[3].

As a leading cause of cirrhosis and hepatocellular carcinoma, MASLD is closely associated with metabolic syndrome, particularly obesity and type 2 diabetes mellitus (T2DM). These conditions share key pathophysiological mechanisms, including systemic insulin resistance and lipotoxicity [4].

Within its pathophysiological framework, incretin receptor and glucagon receptor (GR) systems play a crucial role in modulating metabolic homeostasis. Glucagon-like peptide-1 (GLP-1) receptors suppress appetite centrally and enhance glucose-dependent insulin secretion; glucose-dependent insulinotropic polypeptide (GIP) receptors improve adipose tissue insulin sensitivity and limit excess lipid spillover; and GRs directly stimulate hepatic fatty acid oxidation and lipid export [3–5].

Until recently, the management of MASLD was largely limited to lifestyle modification and, in selected cases, bariatric surgery. However, a major shift in pharmacological treatment occurred in March 2024 with the FDA approval of resmetirom, a thyroid hormone receptor-β agonist [6]. While this marked a significant milestone, there remains a need for therapies that target the multi-organ drivers of the disease, including obesity and concomitant T2DM.

Incretin-based therapies improve glycemic control, weight reduction, and hepatic fat content [7]. Semaglutide, a GLP-1 receptor agonist, demonstrated significant MASH resolution along with liver fibrosis regression in the phase 3 ESSENCE trial, findings that led to FDA approval as the second pharmacologic therapy for MASH in August 2025 [8]. Newer dual and triple receptor agonists target complementary metabolic pathways [5, 7].

Understanding whether weight loss directly translates into histological improvement, and whether specific receptor profiles confer unique antifibrotic benefits, is essential for personalizing MASLD treatment. This systematic review and network meta-analysis aims to address this gap by evaluating the relative efficacy of single, dual, and triple incretin receptor agonists on radiological and histological outcomes in patients with MASLD.

Methods

Literature review and Search Strategy

This systematic review and network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. We searched PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Google Scholar and Embase for relevant articles from inception through December 2025. The complete search strategy is provided in Online Resource 1 (Online Resource 1, Table S1). As this study is a review of existing literature, institutional review board approval was not required. This study was not registered with PROSPERO.

Eligibility Criteria

The inclusion criteria were as follows: (1) human studies only; (2) adults aged ≥18 years; (3) randomized controlled trials, with conference abstracts included only if they reported relevant data from ongoing clinical trials; (4) use of any dose of incretin analogs/agonists; and (5) patients with histologically confirmed MASLD or patients who met the inclusion criteria of 6.4% or greater liver fat content assessed by MRI-PDFF.

The exclusion criteria were: (1) Studies primarily involving hepatic steatosis attributable to causes other than metabolic associated dysfunction, including alcohol-associated, viral, genetic metabolic disorders, or medication-induced liver disease; (2) review articles, letters to the editor, meta-analyses, case reports, and case series; (3) studies in which incretin agonists were administered with an additional non-incretin glucose-lowering or MASLD-directed intervention that differed between randomized groups; and (4) prospective or retrospective observational studies.

Study Screening and Data Extraction

Initial screening of titles and abstracts was independently performed by two authors (S.M. and A.M.). Subsequently, the same authors reviewed full-text articles to determine eligibility based on predefined inclusion and exclusion criteria. No filters or limitations were applied during the search process, and only human studies published in peer-reviewed journals were considered. No language restrictions were imposed.

Disagreements were resolved by consensus or by consultation with a third author (M.M.). Data extraction was performed independently by two authors (M.H.K. and H.I.) using Google Sheets and was subsequently cross-checked by a third author (A.W.) to ensure accuracy.

Study Endpoints

The primary outcomes included histological endpoints such as MASH resolution without worsening of fibrosis, fibrosis improvement by ≥1 stage, quantitative liver fat reduction assessed by MRI-proton density fat fraction (MRI-PDFF), and ≥30% relative reduction in MRI-PDFF.

Secondary outcomes included change from baseline in body weight and change from baseline in enhanced liver fibrosis (ELF) score.

Quality Assessment of Included Studies

The methodological quality of included studies was assessed using the Cochrane Risk of Bias tool. For randomized controlled trials, the revised Cochrane Risk of Bias tool (RoB 2) was applied. This tool evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain was rated as low risk, some concerns, or high risk of bias, and an overall judgment was assigned based on domain-level assessments [10].

Statistical Analysis

All outcomes were pooled with 95% confidence intervals (CIs) using a random-effects model. Odds ratios (ORs) with 95% CIs were calculated for dichotomous outcomes, while mean differences (MDs) were used for continuous outcomes. Statistical significance was defined as $P < 0.05$. All analyses were conducted in R (version 4.5.1) using the "netmeta" and "meta" packages.

Between-study heterogeneity was assessed using the I^2 statistic and τ^2, with I^2 values >50% indicating substantial heterogeneity and >75% indicating considerable heterogeneity [11]. Treatment ranking was performed using P-scores, with higher values indicating greater efficacy.

The network geometry was examined for each outcome. Assessment of statistical inconsistency using the design-by-treatment interaction model and node-splitting approach was not feasible due to the absence of closed loops (degrees of freedom = 0). Therefore, the validity of network estimates relies on the transitivity assumption across included trials.

Results

Eligible Studies

The search identified 9,120 records; 3,141 duplicates were removed, leaving 5,979 records for screening. Of 34 reports assessed for eligibility, 21 were excluded and 13 randomized controlled trials were included (Figure 1). These included two conference abstracts (GLORY-1 and AbdulMalek 2020) as well. The trials evaluated single, dual, and triple incretin receptor agonists at different doses.

Characteristics of Included Studies

The included trials enrolled 2,444 participants: 1,646 assigned to intervention groups and 798 to comparator groups. Baseline and study characteristics are summarized in Tables 1 and 2. Comparators included placebo, standard care, and semaglutide.

Quality Assessment of Included Studies

To assess the quality of the included studies, two authors (M.H.K and M.M.) independently evaluated each study using the Cochrane RoB 2 tool. Most included studies were judged to have

a low risk of bias. Kuchay et al. (2020) and Romero-Gómez et al. (2023) raised some concerns regarding deviations from intended interventions because both trials used open-label designs. Kuchay et al. also raised concerns regarding missing outcome data because 12 of 64 randomized participants were excluded from the per-protocol MRI-PDFF analysis owing to unavailable week-24 data (Online Resource 1, Figs. S2 and S3).

Primary Outcomes

1. **Mean Reduction in Liver Fat Content % (MRI-PDFF)**
   Relative percentage change from baseline in MRI-PDFF was analyzed across 17 interventions (Online Resource 1, Fig. S5), with negative MDs indicating greater reductions in hepatic fat compared with placebo. Retatrutide 12 mg and 8 mg produced the greatest reductions, with MDs of −82.70 (95% CI −95.41 to −69.99) and −81.70 (−94.60 to −68.80), respectively. Significant reductions were also observed with Retatrutide 4 mg, Survodutide 6 mg and 4.8 mg, Efocipegtrutide 0.06 and 0.02 mg/kg, Tirzepatide 15, 10, and 5 mg, Survodutide 2.4 mg, Pemvidutide 1.8 and 1.2 mg, Retatrutide 1 mg, and Dulaglutide 1.5 mg (Figure 2). Retatrutide 12 and 8 mg ranked highest (P-scores 0.9718 and 0.9607), followed by Retatrutide 4 mg (0.7389) and Survodutide 6 mg (0.7275). Efocipegtrutide 0.01 mg/kg ranked lowest (P-score 0.0924; Online Resource 1, Fig. S6). Detailed analyses and league tables are provided in Online Resource 1 file.
2. **>30% Reduction in Liver Fat Content (MRI-PDFF)**
   The achievement of >30% relative reduction in MRI-PDFF was assessed across 14 interventions (Online Resource 1, Fig. S7). Retatrutide 8 mg and 12 mg showed the largest effects, with ORs of 315.00 (95% CI 11.87–8358.05) and 279.00 (10.47–7434.87), respectively. Mazdutide 6 mg, Retatrutide 4 and 1 mg, Pemvidutide 1.8 and 1.2 mg, Efinopegdutide 10 mg, Survodutide 4.8, 2.4, and 6 mg, Mazdutide 4 mg, and Semaglutide were also significantly more effective than placebo (Online Resource 1, Fig. S3). Retatrutide 8 and 12 mg ranked highest (P-scores 0.9243 and 0.9150), followed by Mazdutide 6 mg (0.7763) and Retatrutide 4 mg (0.6784). Cotadutide 600 μg ranked lowest among active treatments (P-score 0.1347) and did not significantly differ from placebo (OR 3.38, 95% CI 0.76–14.98; Online Resource 1, Fig. S8).
3. **MASH Resolution (without worsening of fibrosis)**
   MASH resolution was analyzed across 13 interventions at varying doses (Online Resource 1, Fig. S9). Survodutide 4.8 mg demonstrated the greatest benefit, with an OR of 10.67 (95% CI 4.70–24.21), followed by Liraglutide 1.8 mg, Survodutide 2.4 and 6 mg, Pemvidutide 1.2 and 1.8 mg, Semaglutide 0.4, 2.4, 0.1, and 0.2 mg, and Tirzepatide 15 mg, all of which were significantly more effective than placebo (Figure 3). Tirzepatide 10 and 5 mg did not significantly improve MASH resolution. Survodutide 4.8 mg ranked highest (P-score 0.9461), followed by Liraglutide 1.8 mg (0.7101), Survodutide 2.4 mg

(0.7076), and Pemvidutide 1.2 mg (0.6941). Tirzepatide 5 mg ranked lowest among active treatments (P-score 0.0793; Online Resource 1, Fig. S10).

4. **Fibrosis Improvement (≥1 Stage without Worsening of MASH)**
   Fibrosis improvement was assessed across 13 interventions (Online Resource 1, Fig. S11). Tirzepatide 5 mg demonstrated the greatest effect (OR 3.01, 95% CI 1.29–7.02), followed by Tirzepatide 10 and 15 mg and Semaglutide 2.4 mg, all of which significantly improved fibrosis compared with placebo (Figure 4). Tirzepatide 5 mg ranked highest (P-score 0.8251), followed by 10 mg (0.7301), 15 mg (0.7045), and Survodutide 4.8 mg (0.6220). Semaglutide 0.2 mg ranked lowest among active treatments (P-score 0.1744). Several other interventions, including Liraglutide 1.8 mg and Survodutide 4.8 mg, did not significantly differ from placebo (Online Resource 1, Fig. S12).

Secondary Outcomes

1. **Mean Reduction in Weight (%)**
   Percentage change in body weight was analyzed across 13 interventions, with negative MDs indicating greater weight loss compared with placebo (Online Resource 1, Fig. S13). Retatrutide 8 and 12 mg produced the greatest weight reductions, with MDs of −17.80 (95% CI −20.51 to −15.09) and −17.50 (−20.21 to −14.79), respectively. Efinopegdutide 10 mg, Survodutide 6 and 4.8 mg, Retatrutide 4 and 1 mg, Semaglutide, Survodutide 2.4 mg, Pemvidutide 1.8 and 1.2 mg, and Liraglutide 1.8 mg also significantly reduced body weight compared with placebo (Online Resource 1, Fig. S4). Retatrutide 8 and 12 mg ranked highest (P-scores 0.9659 and 0.9546), followed by Efinopegdutide 10 mg (0.7630) and Survodutide 6 mg (0.7393). In contrast, Dulaglutide 1.5 mg ranked lowest (P-score 0.0003) and was associated with increased weight compared with placebo (MD 2.30, 95% CI 0.63–3.97; Online Resource 1, Fig. S14).
2. **Reduction in Mean ELF Score**
   Change in ELF score was assessed across 11 interventions, with negative MDs indicating greater reductions compared with placebo (Online Resource 1, Fig. S15). Tirzepatide 5 mg produced the greatest reduction (MD −0.66, 95% CI −0.99 to −0.33), followed by Tirzepatide 10 and 15 mg, Pemvidutide 1.2 and 1.8 mg, Semaglutide ≥1 mg, 0.4, 0.2, and 0.1 mg, and Efinopegdutide 10 mg, all of which significantly reduced ELF scores compared with placebo (Online Resource 1, Fig. S16). Tirzepatide 5 mg ranked highest (P-score 0.7430), followed by Pemvidutide 1.2 mg (0.7101), Tirzepatide 10 mg (0.6951), and Semaglutide ≥1 mg (0.6748). Semaglutide 0.1 mg ranked lowest among active treatments (P-score 0.2257; Online Resource 1, Fig. S17).

Discussion

In this network meta-analysis, we aimed to assess the comparative efficacy of single, dual, and triple incretin receptor agonists within two main domains: radiological reduction in hepatic fat

content measured by MRI-PDFF, and histological MASH resolution without worsening of hepatic fibrosis and improvement in hepatic fibrosis without worsening of MASH assessed by liver biopsy. Incretin receptor agonists improve MASLD by targeting core metabolic drivers, including insulin resistance, excess hepatic fat accumulation, and lipotoxicity. While all incretin-based therapies promote weight loss and improve glycemic control, differences in receptor targeting may translate into varying hepatic outcomes [12–23]. Single GLP-1 receptor agonists primarily act through appetite suppression, delayed gastric emptying, and improved insulin sensitivity, leading to reductions in hepatic steatosis and inflammation [12]. Dual receptor agonists combine GLP-1/GIP or GLP-1/GR activation, producing synergistic metabolic effects that may confer greater efficacy than single-receptor therapies [24, 25]. GIP receptor agonism may also preserve pancreatic β-cell function through anti-apoptotic effects [26], while GIP and GR activation increase glucagon secretion and may reduce hypoglycemia risk and improve tolerability [24, 27]. GIP agonists have less pronounced effects on gastric emptying [28] and may improve lipid handling through effects on lipoprotein lipase activity and adipose tissue regulation [29]. Adding GR agonism to GLP-1/GIP receptor activation in triple receptor agonists may further enhance energy expenditure and lipid oxidation, augmenting reductions in adiposity and hepatic steatosis [30, 31]. These mechanistic advantages are reflected in our findings, where dual and triple receptor agonists demonstrated strong efficacy across endpoints.

Triple receptor agonists, particularly retatrutide, were most effective for MRI-PDFF score reduction and achieving ≥30% reduction in hepatic fat, with a positive dose-response relationship. Retatrutide 8 mg and 12 mg produced greater hepatic fat reduction than 4 mg, in line with the greater weight reduction seen at higher doses. For MASH resolution without worsening fibrosis, survodutide and tirzepatide were the most effective dual agonists. Survodutide showed a positive dose-response pattern, with 4.8 mg associated with greater MASH resolution than 2.4 mg. In contrast, tirzepatide showed an inverse dose-response pattern for fibrosis improvement, with 5 mg performing better than 10 mg. This finding is consistent with the SYNERGY-NASH trial and may reflect temporal and biological factors underlying fibrosis regression. MASH resolution and fibrosis improvement do not occur synchronously, and fibrosis improvement may lag behind metabolic and histologic changes. Given the 52-week duration of SYNERGY-NASH, dose-related differences may not have been fully captured. A potential ceiling effect in fibrosis regression with weight reduction may further attenuate a clear dose-response relationship [32]. Semaglutide 0.2 mg daily showed the least fibrosis improvement, likely reflecting subtherapeutic exposure, whereas semaglutide 2.4 mg weekly significantly improved fibrosis without worsening MASH. Liraglutide 1.8 mg did not show significant fibrosis improvement. These findings emphasize the importance of dose selection, as lower doses may underestimate the therapeutic potential of GLP-1 receptor agonists. The effect of triple receptor agonists, such as retatrutide, on fibrosis improvement could not be assessed due to the lack of histological data. Based on our findings, dual receptor agonists consistently demonstrated superior antifibrotic outcomes compared to single receptor agonists. This superior

efficacy likely reflects the complementary effects of multi-receptor activation; however, the relative contribution of each pathway to fibrosis regression remains uncertain and warrants further investigation. Findings of this outcome are in line with the secondary outcome of improvement in ELF scores, where again progressively lower doses of Tirzepatide were associated with a marked reduction in ELF scores due to reasons mentioned above.

The most striking findings of our analysis were the remarkable efficacy of novel triple incretin receptor agonists, specifically retatrutide, in reducing hepatic fat content on MRI-PDFF and substantial weight loss. Although histologic outcomes remain as the gold standard, they were not assessed in the retatrutide phase 2a sub-study, which primarily evaluated hepatic fat content using MRI-PDFF. Thus, these radiological and metabolic improvements are encouraging noninvasive signals but require confirmation in dedicated MASH trials with histologic endpoints. Although triple incretin agonists markedly reduced weight and liver fat on imaging, they did not consistently outperform dual agonists in our analysis. These benefits may emerge before histologic changes become measurable. Limited histologic data for triple agonists and more established evidence for dual agonists may also explain the latter's stronger results in fibrosis and MASH outcomes [33–35]. Higher doses of retatrutide and survodutide led to greater liver fat reduction and MASH resolution, respectively, possibly through stronger receptor engagement and metabolic effects. In contrast, tirzepatide showed an inverse dose-response pattern for fibrosis improvement, potentially reflecting the delayed fibrosis regression and ceiling effect discussed above [32].

This study has several notable strengths. To our knowledge, this is the first network meta-analysis to compare single, dual, and triple incretin agonists by dose across multiple liver outcomes. Unlike earlier analyses, it enables dose-specific rankings and clarifies the added benefits of different degrees of receptor agonism. These findings may help clinicians weigh benefits against costs and adverse effects, while cautioning against stopping treatment prematurely during dose escalation, when efficacy may be underestimated. However, several limitations warrant consideration. Some triple agonist data came from conference abstracts, supplemented by trial registries, because full peer-reviewed reports were unavailable. All networks were placebo-centered and lacked closed loops, limiting head-to-head evidence and preventing formal assessment of inconsistency. Furthermore, the validity of indirect comparisons relies on the assumption of transitivity across included trials. Finally, safety was not systematically assessed, and evidence for newer agents, particularly triple agonists, remains limited.

Future research should focus on large, long-term trials of triple incretin agonists to better understand their benefits and role in treating MASLD and MASH. Studies should also clarify why some agents, such as tirzepatide, show weaker responses at higher doses, and whether this reflects biology, treatment duration, or gaps in the evidence. More comprehensive safety data is

needed to understand tolerability and long-term risks before widespread use. Finally, head-to-head trials of single, dual, and triple agonists would provide more reliable comparisons and help guide treatment choices.

In conclusion, incretin receptor agonists represent a promising therapeutic class for the management of MASLD and MASH. Dual receptor agonists, particularly tirzepatide and survodutide, show notable efficacy in improving MASH activity and fibrosis-related endpoints, while triple incretin agonists such as retatrutide appear especially effective in reducing hepatic fat content and promoting weight loss. Further research is required to better define the role of triple receptor agonists, to characterize adverse effect profiles, and to facilitate direct comparative studies across different incretin-based therapies.

References

1. Kim S, Oh J, Shin JI, et al (2026) Global burden of metabolic dysfunction-associated steatotic liver disease, 1990–2023, and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2023. The Lancet Gastroenterology & Hepatology 11:463–494. https://doi.org/10.1016/s2468-1253(26)00011-7

2. Rinella ME, Lazarus JV, Ratziu V, et al (2023) A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Journal of Hepatology 79:1542–1556. https://doi.org/10.1016/j.jhep.2023.06.003

3. Newsome PN, Loomba R (2025) Therapeutic horizons in metabolic dysfunction–associated steatohepatitis. Journal of Clinical Investigation 135:e186425. https://doi.org/10.1172/jci186425

4. Zhang X, Lau HC-H, Yu J (2025) Pharmacological treatment for metabolic dysfunction–associated steatotic liver disease and related disorders: Current and emerging therapeutic options. Pharmacological Reviews 77:100018. https://doi.org/10.1016/j.pharmr.2024.100018

5. Abushamat LA, Shah PA, Eckel RH, et al (2024) The Emerging Role of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis. Clinical Gastroenterology and Hepatology 22:1565–1574. https://doi.org/10.1016/j.cgh.2024.01.032

6. Harrison SA, Bedossa P, Guy CD, et al (2024) A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. New England Journal of Medicine 390:497–509. https://doi.org/10.1056/nejmoa2309000

7. Newsome PN, Buchholtz K, Cusi K, et al (2021) A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. New England Journal of Medicine 384:1113–1124. https://doi.org/10.1056/nejmoa2028395

8. Sanyal AJ, Newsome PN, Kliers I, et al (2025) Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis. New England Journal of Medicine 392:2089–2099. https://doi.org/10.1056/nejmoa2413258

9. Page MJ, McKenzie JE, Bossuyt PM, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71. https://doi.org/10.1136/bmj.n71

10. Sterne JAC, Savović J, Page MJ, et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898. https://doi.org/10.1136/bmj.l4898

11. Higgins J, Thomas J, Chandler J, et al (2024) Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024), 6.5. Cochrane

12. Girish V, John S (2025) Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). In: StatPearls

13. Mustafa A, Kite C, Lagojda L, et al (2025) Cardiovascular Disease in the Context of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Comprehensive Narrative Review. International Journal of Molecular Sciences 26:11275. https://doi.org/10.3390/ijms262311275

14. Kim J-H, Lee Y, Nam C-M, et al (2025) Impact of cardiometabolic risk factors for metabolic dysfunction-associated steatotic liver disease on mortality. Nutrition, Metabolism and Cardiovascular Diseases 35:103965. https://doi.org/10.1016/j.numecd.2025.103965

15. Maldonado-Rojas A del C, Zuarth-Vázquez JM, Uribe M, Barbero-Becerra VJ (2024) Insulin resistance and Metabolic dysfunction-associated steatotic liver disease (MASLD): Pathways of action of hypoglycemic agents. Annals of Hepatology 29:101182. https://doi.org/10.1016/j.aohep.2023.101182

16. Lee W-H, Kipp ZA, Bates EA, et al (2025) The physiology of MASLD: molecular pathways between liver and adipose tissues. Clinical Science 139:1015–1046. https://doi.org/10.1042/cs20257571

17. Romanos M, Garcia Cordova JM, Villamarin J, et al (2026) Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Literature Review on Pathophysiology and Treatment. Diabetes, Obesity and Metabolism 28:19–30. https://doi.org/10.1111/dom.70659

18. HIRAYAMA AB, TALIBERTI IB, OLIVEIRA CPMS de, ALVES VAF (2025) LIPOTOXICITY PLAYS A KEY ROLE IN THE DEVELOPMENT OF ANGIOGENESIS AND MICROCIRCULATORY MODULATION IN MASLD SPECTRUM. Arquivos de Gastroenterologia 62:e25053. https://doi.org/10.1590/s0004-2803.24612025-053

19. Iturbe-Rey S, Maccali C, Arrese M, et al (2025) Lipotoxicity-driven metabolic dysfunction-associated steatotic liver disease (MASLD). Atherosclerosis 400:119053. https://doi.org/10.1016/j.atherosclerosis.2024.119053

20. Luthra R, Sheth A (2025) Understanding MASH: An Examination of Progression and Clinical Outcomes by Disease Severity in the TARGET-NASH Database. Advances in Therapy 42:1165–1195. https://doi.org/10.1007/s12325-024-03085-4

21. Chan W-K, Chuah K-H, Rajaram RB, et al (2023) Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. Journal of Obesity & Metabolic Syndrome 32:197–213. https://doi.org/10.7570/jomes23052

22. Sanyal AJ, Anstee QM, Trauner M, et al (2022) Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. Hepatology 75:1235–1246. https://doi.org/10.1002/hep.32204

23. Singh S, Allen AM, Wang Z, et al (2015) Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies. Clinical Gastroenterology and Hepatology 13:643-654.e9. https://doi.org/10.1016/j.cgh.2014.04.014

24. Zafer M, Tavaglione F, Romero-Gómez M, Loomba R (2025) Review Article: GLP -1 Receptor Agonists and Glucagon/ GIP / GLP -1 Receptor Dual or Triple Agonists—Mechanism of Action and Emerging Therapeutic Landscape in MASLD. Alimentary Pharmacology & Therapeutics 61:1872–1888. https://doi.org/10.1111/apt.70196

25. Ciardullo S, Morieri ML, Daniele G, et al (2024) GLP1-GIP receptor co-agonists: a promising evolution in the treatment of type 2 diabetes. Acta Diabetologica 61:941–950. https://doi.org/10.1007/s00592-024-02300-6

26. Kim S-J, Nian C, Widenmaier S, McIntosh CHS (2008) Glucose-Dependent Insulinotropic Polypeptide-Mediated Up-Regulation of β-Cell Antiapoptotic Bcl-2 Gene Expression Is Coordinated by Cyclic AMP (cAMP) Response Element Binding Protein (CREB) and cAMP-Responsive CREB Coactivator 2. Molecular and Cellular Biology 28:1644–1656. https://doi.org/10.1128/mcb.00325-07

27. Meier JJ, Gallwitz B, Siepmann N, et al (2003) Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. Diabetologia 46:798–801. https://doi.org/10.1007/s00125-003-1103-y

28. Chia CW, Carlson OD, Kim W, et al (2009) Exogenous Glucose–Dependent Insulinotropic Polypeptide Worsens Post prandial Hyperglycemia in T ype 2 Diabetes. Diabetes 58:1342–1349. https://doi.org/10.2337/db08-0958

29. Miyawaki K, Yamada Y, Ban N, et al (2002) Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nature Medicine 8:738–742. https://doi.org/10.1038/nm727

30. Katsi V, Koutsopoulos G, Fragoulis C, et al (2025) Retatrutide—A Game Changer in Obesity Pharmacotherapy. Biomolecules 15:796. https://doi.org/10.3390/biom15060796

31. Winther JB, Holst JJ (2024) Glucagon agonism in the treatment of metabolic diseases including type 2 diabetes mellitus and obesity. Diabetes, Obesity and Metabolism 26:3501–3512. https://doi.org/10.1111/dom.15693

32. Loomba R, Hartman ML, Lawitz EJ, et al (2024) Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. New England Journal of Medicine 391:299–310. https://doi.org/10.1056/nejmoa2401943

33. Prikhodko VA, Okovityi SV (2026) Current Drug Development Pipeline for MASLD and MASH: Focusing on Cardiovascular Comorbidities. Biomedicines 14:909. https://doi.org/10.3390/biomedicines14040909

34. Viebahn GK, Khurana A, Freund L, et al (2025) Retatrutide improves steatohepatitis in an accelerated mouse model of diet-induced steatohepatitis with a fructose binge. American Journal of Physiology-Gastrointestinal and Liver Physiology 329:G680–G695. https://doi.org/10.1152/ajpgi.00164.2025

35. Sanyal AJ, Kaplan LM, Frias JP, et al (2024) Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nature Medicine 30:2037–2048. https://doi.org/10.1038/s41591-024-03018-2

Statements and Declarations

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests:

The authors have no relevant financial or non-financial interests to disclose

Ethics approval and consent to participate:

Not applicable. This study synthesized published aggregate data and involved no direct recruitment of participants.

Data availability:

This study used data from the published reports cited in the manuscript. The extracted analysis dataset and analysis code are available upon request.

Author contributions:

Saad Masood and Asna Moghis screened titles and abstracts and assessed full-text eligibility. Musa Masood adjudicated screening disagreements. Muhammad Hamza Khalid and Hamna Ibrar extracted data, with verification by Abdul Wasay. Muhammad Hamza Khalid and Musa Masood assessed risk of bias. Saad Masood performed the statistical analysis. Muhammad Asfandyar Nadir, Muhammad Ans Asif, Muhammad Ahsan Asif and Arooba Suhaib contributed to drafting the manuscript. Muhammad Sohaib, Muhammad Ali Butt, and Ming Valerie Lin critically reviewed and edited the final versions.

Figure Legends:

Figure 1: PRISMA flow diagram illustrating the screening process

Figure 2: Forest plot of reduction in liver fat content (MRI-PDFF)

Figure 3: Forest plot of MASH Resolution

Figure 4: Forest plot of Fibrosis Improvement

Figures:

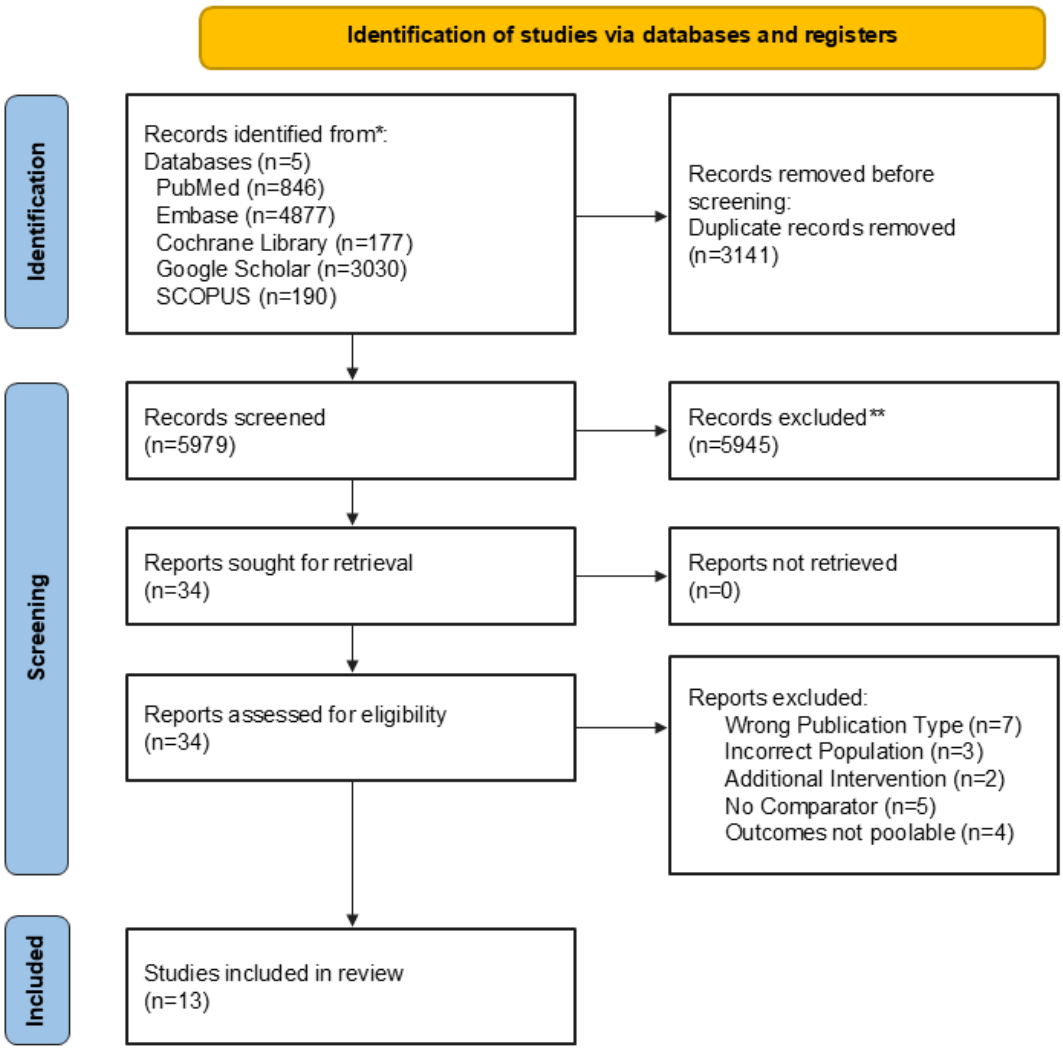


Figure 1: PRISMA flow diagram illustrating the screening process

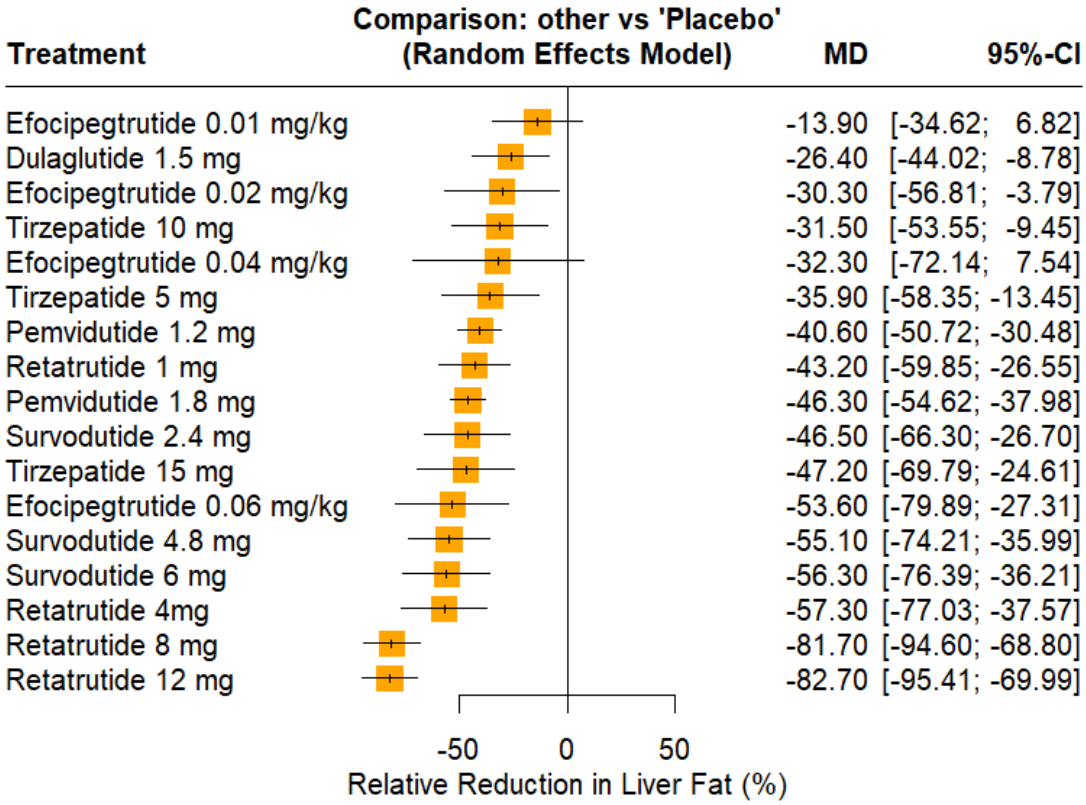


Figure 2: Forest plot of MRI-PDFF reduction

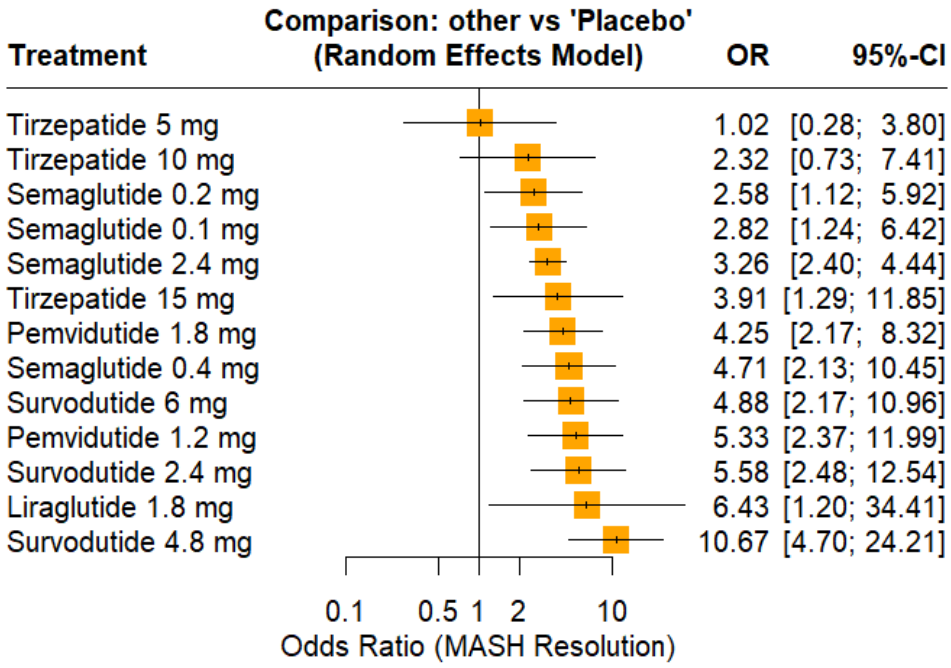


Figure 3: Forest plot of MASH Resolution

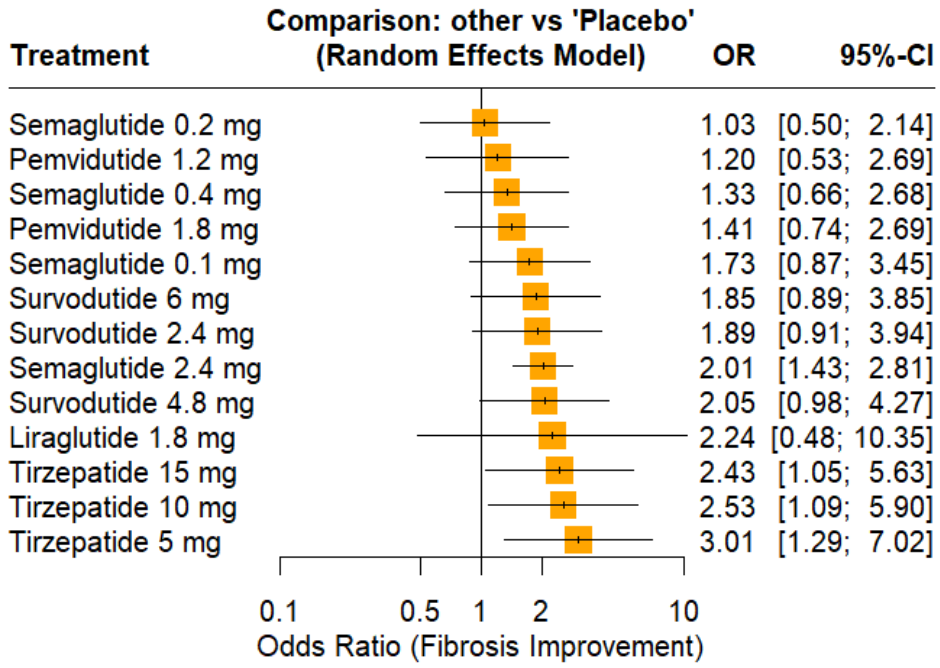


Figure 4: Forest plot of Fibrosis Improvement

Tables:

Table 1: Baseline Characteristics of Included Studies

Study	Population (n)		Age, Mean (SD)		Gender (M/F)		Baseline BMI, Mean (SD)		NAFLD Activity Score, Mean (SD)		Liver Fat (MRI-PDFF) %, Mean (SD)		ELF Score, Mean (SD)	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Armstrong 2016	26	26	50 (11)	52 (12)	18 M / 8 F	13 M / 13 F	34.2 (4.7)	37.7 (6.2)	4.9 (0.9)	4.8 (0.9)	-	-	-	-
Noureddin (2025)	41 (1.2 mg) 85 (1.8 mg)	86	55.2 (13) (1.2 mg) 53.4 (12.4) (1.8 mg)	52.5 (12.2)	16 M / 25 F (1.2 mg) 35 M / 50 F (1.8 mg)	38 M / 48 F	39.2 (8.4) (1.2 mg) 38.7 (6.9) (1.8 mg)	38.3 (8.4)	5.1 (1.0) (1.2 mg) 5.2 (1.0) (1.8 mg)	5.2 (0.9)	20.0 (7.1) (1.2 mg) 19.0 (6.8) (1.8 mg)	19.6 (6.4)	10.0 (0.8) (1.2 mg) 9.9 (1.0) (1.8 mg)	9.7 (0.8)

Kuchay 2020	32	32	46.6 (9.1)	48.1 (8.9)	23 M / 9 F	22 M / 10 F	29.6 (3.6)	29.9 (3.9)	-	-	-	-	-	-
Loomba 2024	47 (5 mg) 47 (10 mg) 48 (15 mg)	48	55.0 (11.6) 5 mg 54.3 (12.1) 10 mg 54.9 (10.0) 15 mg	53.5 (11.6)	20 M / 27 F (5 mg) 21 M / 26 F (10 mg) 19 M / 29 F (15 mg)	21 M / 27 F	36.1 (6.0) 5 mg 36.6 (6.3) 10 mg 35.9 (5.9) 15 mg	36.0 (6.7)	5.4 (1.0) 5 mg 5.3 (0.9) 10 mg 5.0 (0.9) 15 mg	5.3 (1.0)	19.0 (6.9) 5 mg 17.6 (7.5) 10 mg 18.8 (8.3) 15 mg	18.2 (6.8)	9.9 (1.0) 5 mg 9.8 (0.8) 10 mg 9.7 (0.6) 15 mg	9.9 (0.8)
Newsome 2020	80 (0.1 mg) 78 (0.2 mg) 82 (0.4 mg)	80	55.2 (10.9) 0.1 mg 58.1 (9.9) 0.2 mg 54.3 (10.2) 0.4 mg	52.4 (10.8)	29 M / 51 F (0.1 mg) 26 M / 52 F (0.2 mg) 35 M / 47 F (0.4 mg)	36 M / 44 F	36.1 (6.4) 0.1 mg 35.6 (6.1) 0.2 mg 35.2 (6.6) 0.4 mg	36.1 (6.6)	4.9 (0.8) 0.1 mg 4.9 (0.9) 0.2 mg 4.8 (0.9) 0.4 mg	4.9 (0.9)	-	-	9.8 (1.0) 0.1 mg 9.8 (0.9) 0.2 mg 9.9 (1.0) 0.4 mg	9.6 (0.9)
Romero 2023	72	73	48.1 (11.0)	50.9 (10.9)	39 M / 33 F	41 M / 32 F	35.2 (5.7)	33.5 (5.0)	-	-	21.1 (8.1)	19.4 (8.1)	8.8 (0.9)	9.1 (0.9)
Sanyal 2024 (Reta)	20 (1 mg) 19 (4 mg) 22 (8 mg) 18 (12 mg)	19	50.4 (13.1) 1 mg 45.3 (10.0) 4 mg 47.7 (11.6) 8 mg 43.4 (14.3) 12 mg	45.5 (10.7)	11 M / 9 F (1 mg) 11 M / 8 F (4 mg) 13 M / 9 F (8 mg) 8 M / 10 F (12 mg)	9 M / 10 F	38.6 (5.6) 1 mg 38.3 (4.7) 4 mg 37.1 (4.9) 8 mg 39.7 (6.1) 12 mg	38.6 (4.6)	-	-	-	-	-	-
Sanyal 2024 (Survo)	73 (2.4 mg) 72 (4.8 mg) 74 (6.0 mg)	74	49.6 (13.7) 2.4 mg 50.2 (12.9) 4.8 mg 50.4 (13.1) 6.0 mg	53.0 (11.5)	37 M / 36 F (2.4 mg) 38 M / 34 F (4.8 mg) 33 M / 41 F (6.0 mg)	30 M / 44 F	35.30 (5.05) 2.4 mg 35.00 (6.97) 4.8 mg 37.42 (6.84) 6.0 mg	35.49 (6.44)	5.2 (1.0) 2.4 mg 5.3 (1.0) 4.8 mg 5.1 (1.0) 6.0 mg	5.2 (1.1)	19.75 (7.56) 2.4 mg 21.09 (8.26) 4.8 mg 17.85 (6.34) 6.0 mg	19.62 (7.59)	-	-

Sanyal 2025	534	266	56.3 (11.4)	55.4 (12.0)	221 M / 313 F	122 M / 144 F	34.3 (7.2)	35.0 (7.1)	-	-	-	-	9.95 (0.94)	9.95 (0.98)
Shankar 2024	25 (300 µg) 25 (600 µg)	24	55.9 (10.5) 300 µg 59.4 (11.9) 600 µg	52.2 (13.5)	13 M / 12 F (300 µg) 10 M / 15 F (600 µg)	10 M / 14 F	37.3 (7.1) 300 µg 37.0 (5.3) 600 µg	37.6 (5.1)	-	-	-	-	-	-
Flint 2021	34	33	59.5 (10.1)	60.5 (8.5)	23 M /11 F	24 M / 9 F	-	-	-	-	-	-	-	-
GLORY-1*	25 (4 mg) 22 (6 mg)	22	-	-	-	-	-	-	-	-	-	-	-	-
AbdulMalek 2020*	45 (9 in each group)	15	-	-	-	-	-	-	-	-	-	-	-	-

I = Intervention; C = Control; BMI = Body Mass Index; NAS = NAFLD Activity Score; MRI-PDFF = Magnetic Resonance Imaging-Proton Density Fat Fraction; ELF = Enhanced Liver Fibrosis; SD = Standard Deviation

**Outcome data from GLORY-1 and AbdulMalek 2020 were retrieved from abstracts*

Table 2: Study Characteristics of Included Studies

Author (Year)	Study Design	Locality	Dosage of Intervention	Intervention Group	Control Group	Trial duration
Armstrong (2016)	Randomized Controlled Trial	United Kingdom	1.8 mg Once daily	Liraglutide (Subcutaneous)	Placebo	48 weeks (12 weeks of follow-up)
Noureddin (2025)	Randomized Controlled Trial	United States and Australia	1.2 mg 1.8 mg Once weekly	Pemvidutide (Subcutaneous)	Placebo	48 weeks
Kuchay (2020)	Randomized Controlled Trial	India	0.75 mg 1.5 mg Once weekly	Dulaglutide (Subcutaneous)	Standard Care	24 weeks
Loomba (2024)	Randomized Controlled Trial	Multicenter*	5 mg 10 mg	Tirzepatide (Subcutaneous)	Placebo	52 weeks (4 weeks of follow-up)

			15 mg Once weekly			
Newsome (2020)	Randomized Controlled Trial	Multicenter **	0.1 mg 0.2 mg 0.4 mg Once daily	Semaglutide (Subcutaneous)	Placebo	72 weeks (7 weeks of follow-up)
Romero (2023)	Randomized Controlled Trial	Multicenter	10 mg Once weekly	Efinopegdutide (Subcutaneous)	Semaglutide	24 weeks (5 weeks of follow-up)
Sanyal (2024) **Retratrutide**	Randomized Controlled Trial	United States and Canada	1 mg 4 mg 8 mg 12 mg Once weekly	Retatrutide (Subcutaneous)	Placebo	48 weeks (4 weeks of follow up)
Sanyal 2024 Survodutide	Randomized Controlled Trial	Multicenter	2.4mg 4.8mg 6.0mg Once weekly	Survodutide (Subcutaneous)	Placebo	48 weeks
Sanyal 2025	Randomized Controlled Trial	Multicenter	2.4mg Once weekly	Semaglutide (Subcutaneous)	Placebo	72 weeks (Ongoing Follow-up)
Shankar 2024	Randomized Controlled Trial	United States and Puerto Rico	300 µg 600 µg Once daily	Cotadutide (Subcutaneous)	Placebo	19 weeks (4 weeks of follow-up)
Flint 2021	Randomized Controlled Trial	Germany	0.4 mg Once daily	Semaglutide (Subcutaneous)	Placebo	72 weeks

GLORY-1	Randomized Controlled Trial (Post-Hoc)	China	4 mg 6 mg Once weekly	Mazdutide (Subcutaneous)	Placebo	-
AbdulMalek (2020)	Randomized Controlled Trial	-	0.01 mg/kg 0.02 mg/kg 0.04 mg/kg 0.06 mg/kg 0.08 mg/kg Once weekly	Efocipegtrutide (Subcutaneous)	Placebo	-

**The SYNERGY-NASH trial was conducted at 130 different sites across 10 countries (Belgium, France, Israel, Italy, Japan, Mexico, Poland, Spain, United Kingdom, United States)*

***Newsome (2020) trial was conducted at 143 different sites across 16 countries (Austria, Belgium, France, Germany, Italy, Russia, Spain, Sweden, United Kingdom, Canada, United States, Australia, Japan, South Korea, Taiwan, Mexico)*

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ESM1.docx