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LETTER TO THE EDITOR

# GLP-1, GIP/GLP-1, and GCGR/GLP-1 receptor agonists: Novel therapeutic agents for metabolic dysfunction-associated steatohepatitis

Anmol Singh, Aalam Sohal, Akash Batta

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## Abstract

The global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is estimated at 32.4%, reflecting its growing clinical significance. MASLD, which includes MASLD and metabolic dysfunction-associated steatohepatitis (MASH) has been linked to increased metabolic, cardiovascular, and malignant morbidity. Progression into fibrotic stages of MASLD is also strongly associated with liver-related mortality. The past few years have seen a heightened focus on creating innovative therapeutic strategies for MASH management. GLP-1 receptor agonists (RA) have also emerged as a potential treatment option. Studies on GLP-1 agonists, such as liraglutide and semaglutide, have demonstrated efficacy in MASH management, albeit with limited histological improvement of fibrosis. However, recent investigations into GLP-1/GIP RA (tirzepatide) and Glucagon/GLP-1 RA (survodutide) have shown even more encouraging results, with higher rates of MASH resolution and fibrosis improvement. The tolerability of these medications due to their gastrointestinal side effects remains a major concern. Future research should focus on optimizing drug regimens, identifying patients most likely to benefit, and balancing efficacy with tolerability. The evolving landscape of MASH therapeutics suggests a bright future, with the potential for combination therapies to further enhance patient outcomes.

**Key Words:** Glucagon-like peptide-1 receptor agonists; Metabolic dysfunction-associated steatotic liver disease; Metabolic dysfunction-associated steatohepatitis; Liver fibrosis; Semaglutide; Tirzepatide; Survodutide

**Core Tip:** Metabolic dysfunction-associated steatotic liver disease (MASLD) affects 1/3rd of the global population, leading to significant morbidity and mortality. GLP-1 agonists may decrease the risk of progression of MASLD by reducing fatty acid oxidation and cytokine production. GLP-1/GIP receptor agonists (RA) (tirzepatide) and Glucagon/GLP-1 RA (survodutide, efinopegdutide and pemvidutide), have also shown promising results in resolving metabolic dysfunction-associated steatohepatitis (MASH) and demonstrating histological improvement in liver fibrosis. The advancing field of MASH management points to a promising future, with combination therapies likely to significantly improve patient outcomes.

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## TO THE EDITOR

We read with great interest the article by Soresi and Giannitrapani[1] on the role of GLP-1 receptor agonists (RA) in the management of metabolic dysfunction-associated steatotic liver disease (MASLD). The spectrum of MASLD includes metabolic dysfunction-associated steatotic liver and metabolic dysfunction-associated steatohepatitis (MASH), with recent studies estimating the worldwide prevalence to be 32.4%[2,3]. It is estimated that approximately 30%-40% of MASH (defined as Non-alcoholic steatohepatitis when the study was conducted) cases will develop liver fibrosis, among them, 15%-20% will progress to liver cirrhosis. Later, about 2%-3% of patients with MASH cirrhosis will develop hepatocellular carcinoma each year[4]. Recent modeling studies have estimated that the incidence of MASLD and MASH will increase by 21% and 63%, respectively by 2030[5]. In addition to liver injury, MASLD is also associated with an increased risk of cardiovascular disease, leading to increased mortality, likely secondary to shared cardiometabolic risk factors[6,7].

As such, MASLD and metabolic syndrome (type 2 diabetes mellitus, hypertension, obesity, hyperlipidemia) dose share a common pathogenesis with insulin resistance playing a major role[8]. Insulin resistance leads to an increase in increased hepatic production and decreased muscle uptake of glucose, along with lowering lipolysis and increasing hepatic lipogenesis, leading to a rise in levels of glucose and circulating free fatty acids levels[9]. To protect the body from increased levels of free fatty acids, adipose tissue hypertrophy, and hyperplasia occur, which ultimately leads to activation of macrophage and common inflammatory pathways[10,11]. Impaired fatty acid oxidation and adipose tissue deposition lead to the development of hepatic steatosis. As MASLD progresses, inflammation and hepatocyte ballooning lead to the development of fibrosis, cirrhosis, end-stage liver disease, and even hepatocellular carcinoma, leading to poor patient outcomes and increased mortality[12,13].

The current recommendations for management focus on lifestyle modifications, which include physical activity with aerobic exercise, resistance exercise, weight loss, and strict adherence to a Mediterranean diet[14,15]. Weight loss of ≥ 7%-10% has shown significant improvement in histological-grade fibrosis and steatosis[16,17]. Anti-diabetic agents such as Pioglitazone and antioxidant agents like vitamin E were used based on the Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis trial that reported improvement in steatosis, without any improvement in fibrosis[18]. In recent years, there has been a growing interest in the potential of incretin analogs such as GLP-1 RA and GIP RAs[19]. These medications improve hemoglobin A1c and promote weight loss, thus targeting the metabolic mechanisms of the development of MASH. Although these medications are currently approved for the management of type 2 diabetes and obesity, there is now increasing evidence demonstrating their potential role in the management of MASLD. In this study, we aim highlight the role of novel incretin analogs can play in MASLD management.

### *GLP-1 RAs*

GLP-1 RAs stimulated insulin secretion after oral intake through incretin effect[20]. They also promote delayed gastric emptying, decrease glucagon production and decrease pancreatic β-cell apoptosis, along with promoting their proliferation[21]. In Murine models of MASH, GLP-1 RA has demonstrated a reduction of liver enzymes and oxidative stress, leading to improvement in liver histology[22,23]. Emerging studies have noted that GLP-1 RAs may also prevent the development of MASH by reducing fatty acid oxidation and cytokines, which are involved in the development of hepatic steatosis[24-26]. Liraglutide safety and efficacy in patients with nonalcoholic steatohepatitis trial was a phase 2 study, which compared liraglutide (1.8 mg once daily) *vs* placebo in 52 patients with biopsy-proven MASH at 48 weeks. The study noted higher rates of MASH resolution (39% *vs* 9%), with a relative risk (RR) of 4.3 (95%CI: 1-17.7, $P$ = 0.019 Liraglutide group as compared to the placebo[27]. Worsening of fibrosis was noted in 2 (9%) patients in the liraglutide as compared to 8 (36%) in the placebo group [RR 0.2 (95%CI: 0.1-1; $P$ = 0.04)]. They also noted a statistically significant improvement in metabolic factors such as glucose levels, glycated hemoglobin, body mass index, and high density lipoprotein (HDL) levels[27].

Semaglutide in another GLP-1 RA which has been approved for the management of type 2 diabetes has shown more profound metabolic effects[28]. In a phase 2 double-blind trial, Newsome *et al*[29] demonstrated that in patients with

biopsy-proven MASH and F1, F2, or F3 fibrosis, another GLP-1 agonist semaglutide led to MASH resolution without worsening of fibrosis after 72 weeks of treatment compared to placebo ($P < 0.001$ for semaglutide 0.4 mg once daily *vs* placebo) (Table 1). Improvement in at least one fibrosis stage without worsening of MASH was noted in 43% of patients on Semaglutide 0.4 mg compared to 33% of patients on placebo [odds ratio, 1.42 (95%CI: 0.62-3.28; $P = 0.48$)]. Similar to Liraglutide, improvement in metabolic factors such as HDL levels, very-low density lipoprotein, triglyceride, free fatty acid, triglyceride levels, body weight, glycated hemoglobin, and systolic blood pressure was noted, with increased effect size at the highest dose (Semaglutide 0.4 mg). All doses (0.1 mg, 0.2 mg and 0.4 mg; all once daily) of semaglutide also demonstrated improvement in the enhanced liver fibrosis (ELF) score compared to placebo where a 0.01 increase in the ELF score was noted. Even though the GLP-1 demonstrated resolution of MASH, they have not yet exhibited any histologically proven fibrosis regression.

### GLP-1/GIP RAs

GIP RAs have similar beneficial effects as the GLP-1 RAs, such as increase glucose dependent insulin decretion, reduction of β-cell apoptosis and increased β-cell mass[30,31]. Tirzepatide is a dual agonist of the GLP-1 receptor and GIP receptor, which has shown significant reduction in body weight in multiple trials. In a phase 2 study by Loomba *et al*[32], tirzepatide (once weekly) was compared with a placebo in patients with biopsy-proven MASH and stage F2 or F3 fibrosis. After 52 weeks, 44% of patients receiving 5 mg of tirzepatide showed resolution of MASH, compared to just 10% in the placebo group. The effect was dose-dependent, with 44%, 56%, and 62% of patients showing improvement at doses of 5 mg, 10 mg, and 15 mg, respectively (all doses showed statistically significant difference when compared to placebo; $P < 0.001$). Notably, 55% of patients receiving 5 mg of tirzepatide showed improvement in at least one fibrosis stage without worsening MASH compared to 30% of patients on placebo [risk difference 25 (95%CI: 5-46)]. Similar benefits were also noted with the higher doses of Tirzepatide.

### GCGR/GLP-1 RAs

Even though GLP-1 RAs have shown efficacy in improvement of MASH, these effects are proposed to be secondary to improvement in the metabolic factors as the hepatocytes lack GLP-1 receptors[33]. Unlike the GLP-1 receptor, the liver is dense with GCGRs, where the direct effect of glucagon include stimulation of hepatic-oxidation of fatty acids and a reduction in de novo lipogenesis[34,35]. As a result, dual agonists such as GCGR/GLP-1 RA might offer even more hepatoprotective effects due to a combination of both of these mechanisms[36]. In a recent phase 2 study, Sanyal *et al*[37] investigated the efficacy of Survodutide, a GCGR/GLP-1 RA, compared to placebo in patients with biopsy-confirmed MASH and fibrosis ranging from F1 to F3 stages. The study involved four groups, with patients receiving one of three doses of Survodutide (2.4 mg, 4.8 mg, or 6 mg once weekly) or a placebo in a 1:1: 1:1 ratio. Notable improvements in MASH were observed in 47% of patients in the 2.4 mg group, 62% in the 4.8 mg group, and 43% in the 6 mg group, compared to only 14% in the placebo group ($P < 0.001$ for the quadratic dose-response curve). Additionally, improvement in fibrosis by at least one stage was seen in 34% of patients in both the 2.4 mg and 6 mg groups, 36% in the 4.8 mg group, and 22% in the placebo group. They also assessed the liver fat content with magnetic resonance imaging-proton density fat fraction a noted a least 30% reduction in liver fat content in 63% of the participants in the survodutide 2.4-mg group, 67% of those in the 4.8-mg group, and 57% of those in the 6.0-mg group, as compared with 14% of those in the placebo group.

Efinopegdutide and pemvidutide are other GCGR/GLP-1 RAs that have been studied recently. In a phase II randomized control trial, Romero-Gómez *et al*[38] assessed the effects of efinopegdutide 10 mg once weekly on the liver fat content (LFC) in patients with MASH as compared to semaglutide 1 mg once weekly at 24 weeks. They demonstrated a statistically significant decrease in mean LFC in the efinopegdutide (72.7%) group as compared to the semaglutide (42.3%) with the LS RR reduction being 30.4% (90%CI: 22.1-38.7; $P < 0.001$). Even at 24 weeks, a RR reduction of 10% was noted in the efinopegdutide group. In addition, greater reduction in metabolic risk factors such as HDL levels, LDL levels, body weight, and TGL were noted in the efinopegdutide group compared to semaglutide. In a study comparing pemvidutide (1.2 mg, 1.8 mg, and 2.4 mg once weekly) *vs* placebo, the 1.2 mg and 1.8 mg demonstrated a statistically significant reduction in the liver fat content when compared to the placebo[39]. The absolute reduction noted in the treatment groups was 8.9% (95%CI: -12.4 to -5.4; $P < 0.001$), 14.7% (95%CI: -18.0 to -11.4; $P < 0.001$), and 11.3% (95%CI: -15.3 to -7.4; $P < 0.001$) respectively. With initial promising results with these medications, phase 3 trials are warranted for further investigation.

## Discussion

Based on the findings of the current studies using the incretin analogs alone or in combination, we can see a reduction in the fibrosis progression among these patients, with a reduction in fibrosis without worsening of MASH noted in as high as 50% of the participants (Table 1). One of the factors which can potentially limit their application is the adverse events. The most common ones are gastrointestinal adverse events such as nausea, diarrhea, and vomiting. As such the slow titration of doses of these medications over weeks has shown to improve patients' ability to tolerate these medications. In a head-to-head comparison between efinopegdutide and semaglutide, gastrointestinal adverse events such as abdominal pain, abdominal pain upper, and constipation were noted to occur at a higher rate in the efinopegdutide. Otherwise, no difference in the adverse events profile was noted.

Earlier this year, Resmetirom, a liver-directed thyroid hormone receptor beta-selective agonist that has shown efficacy in the resolution of MASH was approved by the FDA[40]. However there are limitations associated with the study such as the short follow-up period of the studies, lack of cost-effective assessment, and generalizability[41]. As noted above, the current evidence supports GLP-1, GIP/GLP-1, and GCGR/GLP-1 RAs, as an appealing and effective therapeutic

**Table 1 GLP-1 agonist and their demonstrated effects on Metabolic-associated steatohepatitis and liver fibrosis**

| Drug | Mechanism of action | Method of testing | Effect on MASH | Effect on fibrosis |
|---|---|---|---|---|
| Liraglutide[24] | GLP-1 RA | Biopsy | Improvement in MASH with no worsening of fibrosis; Liraglutide 18 mg–resolution in 39%; Placebo-resolution in 9% | Improvement in fibrosis stage: liraglutide 6 (26%) *vs* Placebo 3 (14%) (RR = 1.9, 95%CI: 0.5-6.7; *P* = 0.46)<br><br>Worsening of Fibrosis stage: liraglutide 2 (9%) *vs* Placebo 8 (36%) [RR = 0.2 (95%CI: 0.1-1; *P* = 0.04)] |
| Semaglutide [26] | GLP-1 RA | Biopsy | Improvement in MASH with no worsening of fibrosis<br><br>Semaglutide 0.1 mg-resolution in 40% patients<br><br>Semaglutide 0.2 mg-resolution in 36%<br><br>Semaglutide 0.4 mg-resolution in 59%<br><br>Placebo-resolution in 17% | Improvement of at least one stage of fibrosis with no worsening of MASH: (1) Semaglutide 0.1 mg-49%; (2) Semaglutide 0.2 mg-32%; (3) Semaglutide 0.4 mg-43%; and (4) Placebo-33% (none were statistically significant); Worsening of Fibrosis stage: (1) Semaglutide 0.1 mg-10%; (2) Semaglutide 0.2 mg-8%; (3) Semaglutide 0.4 mg-5%; and (4) Placebo-19% |
| Tirzepatide[27] | GLP-1/GIP RA | Biopsy | Improvement in MASH with no worsening of fibrosis: Tirzepatide 5 mg-resolution in 44%; Tirzepatide 10 mg-resolution in 56%; Tirzepatide 15 mg-resolution in 62%; Placebo-resolution in 10% | Improvement of at least one stage of fibrosis: (1) Tirzepatide 5 mg-55%; (2) Tirzepatide 10 mg-51%; (3) Tirzepatide 15 mg-51%; (4) Placebo-30% |
| Survodutide [30] | GCGR/GLP-1 RA | Biopsy | Improvement in MASH with no worsening of fibrosis: Survodutide 2.4 mg-47%; Survodutide 4.8 mg-62%; Survodutide 6 mg–in 43%; Placebo-14% | Improvement of alteast one stage of fibrosis: (1) Survodutide 2.4 mg-34%; (2) Survodutide 4.8 mg-36%; and (3) Survodutide 6 mg-34%; and (4) Placebo-22% |
| Efinopegdutide [31] | GCGR-1/GLP-1 RA | MRI-PDFF | The least squares mean relative reduction in LFC: Efinopegdutide 10 mg-72.7%; Semaglutide 1 mg-42.3% | No data available |
| Pemvidutide [32] | GCGR/GLP-1 RA | MRI-PDFF | Absoluted reduction in LFC: Pemvidutide at 1.2 mg-8.9%; Pemvidutide 1.8 mg-14.7%; Pemvidutide 2.4 mg-11.3%; Placebo-4.4% | No data available |

MASH: Metabolic-associated steatohepatitis; LFC: Liver fat content; Glucagon RA: Glucagon receptor agonist; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction.

option due to their effect on multiple pathways[42-45]. As MASLD is a multisystem disease with associated significant complications such as cardiovascular disease, chronic kidney disease, and malignancies, the use of these drugs seems logical with potential benefit likely arising from multiple pathways. As a result, further stage 3 studies are for further demonstration of their efficacy and safety. An interesting future avenue might be utilizing incretin analogs and Resmetirom together for the management of MASH, with Resmetirom acting downstream by increasing fatty acids oxidation and the incretin analogs acting upstream leading to a decrease in fatty acid production *via* their effect on insulin resistance and lipid metabolism.

## CONCLUSION

MASLD is a systemic disease with signficant hepatic and extra-hepatic complications leading to increased morbidity and mortality. Recent evidence supports the use of incretin analogs alone or in combination for MASH with a success rate reported to the tune of 50% in terms of fibrosis reduction. Among these GLP-1 analogues such as liraglutide and semaglutide have emerged as a potential management options. Investigation into GLP-1/ GIP RA (tirzepatide) and Glucagon/GLP-1 RA (survodutide) have shown even more encouraging results, with higher rates of MASH resolution and fibrosis improvement. The tolerability of these medications due to their gastrointestinal side effects still remains a major concern. Future research should focus on optimizing drug regimens, identifying patients most likely to benefit, and balancing efficacy with tolerability.

## FOOTNOTES

**Author contributions:** Sohal A and Batta A designed the Editorial; Singh A and Sohal A performed the literature review and data

collection; Batta A supervised the study and provided key feedback and suggestions; Singh A and Batta A analyzed the data and wrote the manuscript and subsequently revised it; all authors have read and approved the final manuscript.

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