Incretin based therapy in the management of metabolic dysfunction-associated steatotic liver disease (MASLD): one piece of the puzzle

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Metabolic dysfunction–associated steatotic liver disease (MASLD), previously named as non-alcoholic fatty liver disease, is the leading cause of chronic liver disease worldwide. MASLD has been widely recognized as the hepatic manifestation of a dysmetabolic state. Since obesity and type 2 diabetes mellitus are major drivers of MASLD and its severe form metabolic dysfunction-associated steatohepatitis (MASH), drugs originally designed for these pathological modulators have also thus been tested in patients with MASLD/MASH. Traditional antidiabetic agents such as thiazolidinedione (TZD) and dipeptidyl peptidase-4 inhibitors have been identified with antisteatotic efficacy. Of late, incretins including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have also become the targets of MASLD/MASH treatment, due to their influence on energy metabolism, body weight control, insulin sensitivity, and liver steatosis (as summarized in figure 1). A recent network meta-analysis from Korea by Park et al. compared the effects of GLP-1 receptor agonist (GLP-1RA, liraglutide, semaglutide, and dulaglutide) and TZD (pioglitazone and rosiglitazone) on liver fat content, body mass index, and waist circumference in overweight or obese patients with MASLD. This study supports the superiority of GLP-1RA over TZD for the treatment of MASLD, highlighting the application of incretin-based therapy in relevant patients. However, incretin-based therapy may not address all pain points of MASLD treatment. There are still some issues to solve. Although earlier studies reported opposite results when comparing GLP-1RA and TZD in MASLD, Park et al. strengthened their findings by including numerous randomized clinical trials regarding GLP-1RA after 2016. In this study, GLP-1RA significantly surpassed TZD, according to proton magnetic resonance spectroscopy and anthropometric outcomes. Such findings are not surprising, as GLP-1RA potently lowers body weight while TZD is usually associated with body weight gain. But considering controlled attenuation parameter and liver biopsy-based outcomes, GLP-1RA only showed a tendency of superiority over TZD, without any statistical difference. The mismatches between anthropometric outcomes and invasive and non-invasive liver outcomes here are worth exploring. GLP-1RA tends to achieve better efficacy in resolving MASH without worsening of fibrosis than improving liver fibrosis without worsening of MASH. One possible explanation is that the follow-up durations of currently available studies were relatively short. According to a former meta-analysis that included 500 biopsy-proven MASH patients, TZD could improve liver fibrosis even in patients without diabetes. In a recent clinical trial, PXL065 (the deuterium-stabilized enantiomer form of pioglitazone, 7.5mg) achieved ≥1 stage fibrosis improvement in 40% MASH patients (vs. 17% for placebo). Combining the findings of Park et al., it could be assumed that GLP-1RA therapy may also effectively relieve MASH related fibrosis.
Clinical trials included in this study targets overweight or obese MASLD population. However, approximately 40% of MASLD patients are non-obese and about 20% are even lean\textsuperscript{11}. The exact role of incretin-based therapy in the management of lean subjects with MASLD definitely requires further investigation. Including non-obese or lean subjects in future clinical trials of MASLD should be taken into account. This issue is in line with the need to refine MASLD clinical trial design in order to reflect disease heterogeneity in clinical realms.

Incretin-based therapy for diabetes, obesity and MASLD is under rapid development. A dual agonist for both GIP receptor and GLP-1 receptor, tirzepatide, has been designed and tested in patients with type 2 diabetes. According to subgroup analysis, tirzepatide significantly reduced liver fat content, visceral adipose tissue volume and abdominal subcutaneous adipose tissue volume when compared with long-term insulin, which leads to the launch of a clinical trial on MASH\textsuperscript{12}. Similarly, the recently developed GIP, GLP-1, and glucagon receptor triple agonist, retatrutide, has been studied in patients with diabetes or obesity\textsuperscript{13,14}, and maybe in MASH as well in the near future. Besides repurposing agents for obesity and diabetes to treat MASLD, molecules that specifically target liver itself have also been investigated for drug development, among which, thyroid hormone receptor β agonist, fibroblast growth factor 21 (FGF21) and pan- peroxisome proliferator-activated receptor agonist have received much attention, especially the first FDA-approved drug for MASH, resmetirom. However, in the phase 3 clinical trial involving biopsy-proven MASH patients, resmetirom only achieved MASH resolution without worsening of fibrosis in fewer than 30% participants and ≥1 stage fibrosis improvement without worsening of the MASH in around 25% participants\textsuperscript{15}. It’s worth mentioning that treatment groups of many available clinical trials achieved the MASH resolution rate and ≥1 stage fibrosis improvement rate of ≈30%. The approval of resmetirom may augur well for the field of MASLD drug development. Head-to-head studies could be carried out to compare efficacies of these novel therapies for MASLD, including incretin-based therapy.

MASLD is a complex disease involving heterogeneous alterations in multiple organs, while pathogenic mechanism of the disease is far from elucidation. Accurate molecular classification and phenotypic identification of patient subgroups are challenging so far. Generally, metabolic abnormalities, inflammation, and fibrosis are intertwined in MASLD development and disease progression. Therefore, it’s reasonable to aim at diverse drivers of the disease, with either agents that cover multiple signaling pathways or the combination of drugs that target different manifestations of the complicated MASLD pathophysiology\textsuperscript{16}. Specifically, incretin-based therapy could serve as a corrector of MASLD related metabolic abnormalities and remarkably prevent disease progression at the early stage. And on this basis, other drugs that specifically target hepatic inflammation and fibrosis could complement with incretins,
especially for MASH patients with advanced fibrosis and cirrhotic patients. Actually, clinical trial to test this hypothesis are underway. The combination of semaglutide with cilofexor (a farnesoid X receptor agonist) and/or the firsocostat (an acetyl-coenzyme A carboxylase inhibitor) achieved significant improvements in liver steatosis, liver biochemistry, and non-invasive tests of fibrosis than semaglutide therapy alone, in MASH patients. As recently reported, addition of efruxifermin (an Fc-FGF21 analog) significantly improved the therapeutic effects of GLP-1RAs in MASH patients, as reflected by noninvasive markers of hepatic steatosis, liver injury, fibrosis, and serum biochemistry test of glucose and lipids.

In summary, incretin-based therapy is promising in relieving obesity and metabolic abnormalities and could be recognized as an important component of the comprehensive prevention and treatment against MASLD/MASH. Future studies with better design and longer follow-up duration should be carried out to evaluate the efficacy of incretin-based therapy on hepatic histological endpoints or liver related events and to test the interaction between incretins and other MASLD agents.

Authors’ contribution
Tian-Yi Ren drafted the manuscript. Mohammed Eslam and Jian-Gao Fan reviewed and finalized the manuscript.

Conflicts of Interest
The authors have no conflicts to disclose.

Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>FGF21</td>
<td>fibroblast growth factor 21</td>
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<tr>
<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<td>GLP-1RA</td>
<td>glucagon-like peptide-1 receptor agonist</td>
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<td>GIP</td>
<td>glucose-dependent insulinotropic polypeptide</td>
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<td>MASH</td>
<td>metabolic dysfunction-associated steatohepatitis</td>
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<td>MASLD</td>
<td>metabolic dysfunction–associated steatotic liver disease</td>
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<td>TZD</td>
<td>thiazolidinedione</td>
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References


4. Newsome PN, Ambery P. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. J Hepatol 2023;79:1557-1565.


Fig 1. A simplified diagram demonstrating how incretins affect multiple organs implicated in MASLD pathophysiology. GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; MASLD, metabolic dysfunction-associated steatotic liver disease.