Glucagon-like-peptide 1 receptor agonist for metabolic dysfunction-associated steatotic liver disease: hype or hope?

Metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly becoming a significant clinical burden globally, including in Singapore.[1] Mirroring the rising prevalence of obesity and diabetes mellitus (DM), the prevalence of MASLD is anticipated to increase from 1.5 million to 1.8 million between 2019 and 2030, with a potential corresponding clinical burden of liver cirrhosis, hepatocellular carcinoma (HCC) and death.[2] While lifestyle interventions, such as improved physical activity, dietary measures, and weight loss, remain the cornerstone of treatment for MASLD, sustaining these changes in the long term is challenging. There is, therefore, a pressing need to develop more effective therapeutic agents for MASLD, with glucagon-like peptide-1 (GLP-1) has emerged as a promising therapeutic option.

The mechanisms of GLP-1 receptor agonist (RA) include improving insulin resistance by enhancing insulin secretion from beta cells, while inhibiting glucagon secretion from alpha cells in response to hyperglycaemia. Additionally, GLP-1 RAs induce postprandial satiety through direct central nerve system stimulation and reduce gastric emptying. Collectively, these mechanisms improve glycaemic control and promote weight loss. Owing to their beneficial effects on glycaemic control and weight loss,[3] GLP-1 agonists, such as liraglutide, semaglutide, and exenatide, are primarily used for managing type 2 DM and obesity. In a meta-analysis of 15 GLP-RAs, tirzapetide was found to be the most effective for glycaemic control and haemoglobin A1c reduction, while the combination of semaglutide and cagrilintide was the most effective in inducing weight loss (mean difference −14 kg, 95% confidence interval −17 to −11 kg).[3]

With MASLD being closely associated with various metabolic risk factors, such as obesity and DM, the benefits of GLP-1 RA have been explored in several MASLD trials. In early clinical trials, GLP-1 RAs have been shown to reduce liver fat content, promote metabolic dysfunction-associated steatohepatitis (MASH) resolution, induce weight loss, and improve metabolic parameters, including glycaemic control and lipid profiles.[4-6] Liraglutide, a daily subcutaneous GLP-1 RA injection, resulted in MASH resolution without worsening of fibrosis in 39% of patients compared to 9% in the placebo group.[4] Similarly, semaglutide, a weekly injection, led to MASH resolution in 59% of patients compared to 17% in the placebo group[5] Dual receptor agonists, such as tirzapetide (a dual GLP-1/GIP agonist) and survodutide (a dual GLP-1/glucagon receptor agonist) have also demonstrated positive results for MASH.[6,7] Further data from several large prospective phase III GLP-1 RA studies will provide greater insight into clinically relevant outcomes, particularly the major adverse liver outcomes (MALO), such as the development of cirrhosis, HCC and liver-related mortality. Notably, emerging data from large real-world cohort studies indicate that GLP-1 RAs, as compared with other antidiabetic medications, are associated with a lower incidence of cirrhosis-related complications and HCC.[8,9]

A meta-analysis of randomised trials suggests that GLP-1 RAs provide a mortality benefit by improving cardiovascular and renal outcomes in patients with type 2 DM.[10] Both hepatic and extrahepatic benefits make a strong case for the use of GLP-1 RAs in MASLD, as cardiovascular-related mortality remains the leading cause of death in noncirrhotic MASLD, which represents the majority of MASLD cases.[11] Therefore, optimising cardiovascular risk factors must be incorporated into the management of MASLD patients. As the risk of liver-related complications begins to rise when patients progress beyond advanced fibrosis, stepwise risk stratification through noninvasive methods is needed to identify at-risk MASLD patients early and provide intensive treatment to prevent progression to cirrhosis.[11]

While GLP-1 RAs offer promising benefits, several concerns need to be addressed. As mentioned, the long-term benefits of GLP-1 RAs for MASLD remain unclear, particularly considering the high cost of these medications and the potential need for long-term use. Additionally, the impact of GLP-1 RAs on MASLD-related cirrhosis requires further investigation. Early pilot data suggest that semaglutide, administered once weekly via subcutaneous injection, was not superior to placebo in resolving MASH or improving fibrosis in a small cohort of 71 patients with MASH-associated compensated cirrhosis.[6] Furthermore, while GLP-1 RAs are effective in promoting weight loss, caution is warranted, as excessive weight loss may lead to sarcopenia and, in rare cases, exacerbate liver deterioration, as observed in the context of bariatric surgery. Although some studies on GLP-1 RAs have reported reductions in lean muscle mass, it has also been suggested that the corresponding improvements in muscle fat contribute to better overall muscle composition.[12] Another concern is the potential risk of thyroid hyperplasia and medullary thyroid carcinoma with long-term GLP-1 RA use.[13] As most studies included only short- to medium-term follow-ups, the long-term safety profile remains to be determined. Currently, GLP-1 RAs are contraindicated in patients with a history of thyroid cancer or multiple endocrine neoplasia syndromes. Separately, the most common side effects of GLP-1 RAs are gastrointestinal in nature. However, as these effects are dose-dependent and transient, they are generally manageable.

Given its multisystemic nature, a holistic approach to MASLD treatment is crucial. Weight loss, whether achieved through GLP-1 RAs or other means, should not be oversimplified as the sole therapeutic strategy for MASLD. Instead, a combination of exercise and dietary modifications, in addition to weight loss, should remain the cornerstone of MASLD management.[14] Meanwhile, resmetirom, a liver-directed thyroid hormone receptor beta-selective agonist, is the first medication to receive conditional approval from the Food and Drug Administration for the treatment of noncirrhotic MASH, heralding a new era in MASH therapeutics.[15] While resmetirom demonstrated improvements in MASH resolution and fibrosis, it had a neutral effect on body weight, insulin resistance and blood pressure — all of which are key factors in MASLD pathogenesis that require attention.[16] The GLP-1 RAs may help optimise and address these additional metabolic aspects. Hence, depending on the dominant driver of pathogenesis, different pharmacological approaches, including combination therapy, may be considered. Newer therapies targeting MASH resolution or fibrosis regression have been developed. A recent meta-analysis of randomised trials ranked pegozafermin and GLP-1 RAs as the most effective options for achieving MASH resolution.[17]

In summary, GLP-1 RAs have emerged as a promising adjunct for optimising metabolic risk factors in diabetic patients with MASLD. They contribute to glycaemic control, weight management, improvements in liver biochemistries and liver fat, MASH resolution, and reduction in cardiorenal complications. Pending further data from anticipated phase III studies, it would not be unexpected for GLP-1 RAs to become a core component of the therapeutic armamentarium against MASLD.

Financial support and sponsorship

Nil.

Conflicts of interest

Wong YJ and Goh GBB are members of the *SMJ* Editorial Board and were thus not involved in the peer review and publication decisions of this article.

Yu Jun Wong[1,2], **FRCP, FAMS, George Boon-Bee Goh**[2,3], **MBBS, MRCP**

[1]Department of Gastroenterology and Hepatology, Changi General Hospital, [2]Duke-NUS Medical School, [3]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore

Correspondence: Dr Yu Jun Wong,
Consultant, Department of Gastroenterology and Hepatology,
Changi General Hospital, 2 Simei Street 3, 529889, Singapore.
E-mail: eugene.wong.y.j@singhealth.com.sg

Received: 14 Mar 2025 **Accepted:** 25 Mar 2025 **Published:** 22 Apr 2025

REFERENCES

1. Feng G, Targher G, Byrne CD, Yilmaz Y, Wai-Sun Wong V, Adithya Lesmana CR, *et al*. Global burden of metabolic dysfunction-associated steatotic liver disease, 2010 to 2021. JHEP Rep 2024;7:101271.
2. Estes C, Chan HLY, Chien RN, Chuang WL, Fung J, Goh GB, *et al*. Modelling NAFLD disease burden in four Asian regions-2019-2030. Aliment Pharmacol Ther 2020;51:801-11.
3. Yao H, Zhang A, Li D, Wu Y, Wang CZ, Wan JY, *et al*. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: Systematic review and network meta-analysis. BMJ 2024;384:e076410.
4. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, *et al*. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): A multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679-90.
5. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, *et al*. A Placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-24.
6. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, *et al*. Tirzapetide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299-310.
7. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, *et al*. A Phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391:311-9.
8. Kanwal F, Kramer JR, Li L, Yang YX, Cao Y, Yu X, *et al*. GLP-1 receptor agonists and risk for cirrhosis and related complications in patients with metabolic dysfunction-associated steatotic liver disease. JAMA Intern Med 2024;184:1314-23.
9. Wang L, Berger NA, Kaelber DC, Xu R. Association of GLP-1 Receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. Gastroenterology 2024;167:689-703.
10. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, *et al*. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653-62.
11. Wong YJ, Urias E, Song MW, Goyal T, Tay WX, Han NX, *et al*. Combination of Fibrosis-4, liver-stiffness measurement, and Fibroscan-AST score to predict liver-related outcomes in non-alcoholic fatty liver disease. Hepatol Commun 2023;7:e0244.
12. Pandey A, Patel KV, Segar MW, Ayers C, Linge J, Leinhard OD, *et al*. Effect of liraglutide on thigh muscle fat and muscle composition in adults with overweight or obesity: Results from a randomized clinical trial. J Cachexia Sarcopenia Muscle 2024;15:1072-83.
13. Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, *et al*. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384-90.
14. Eslam M, Fan JG, Yu ML, Wong VWS, Cua IH, Liu CJ, *et al*. The Asian Pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic dysfunction-associated fatty liver disease. Hepatol Int 2025. doi: 10.1007/s12072-024-10774-3.
15. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, *et al*. A Phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390:497-509.
16. Cusi K. Selective agonists of thyroid hormone receptor beta for the treatment of NASH. N Engl J Med 2024;390:559-61.
17. Souza M, Al-Sharif L, Antunes VLJ, Huang DQ, Loomba R. Comparison of pharmacological therapies in metabolic dysfunction-associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis. Hepatology 2025. doi: 10.1097/HEP.0000000000001254.

DOI: 10.4103/singaporemedj.SMJ-2025-051 **Website:** https://journals.lww.com/SMJ

How to cite this article: Wong YJ, Goh GBB. Glucagon-like-peptide 1 receptor agonist for metabolic dysfunction-associated steatotic liver disease: hype or hope? Singapore Med J 2025;66:173-4.