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Dapagliflozin and metabolic dysfunction-associated steatohepatitis

Improves fibrosis and steatohepatitis

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Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a broad clinical spectrum, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. MASLD is currently the leading cause of chronic liver disease,[1 2] and one of the leading causes of cirrhosis and liver cancer,[3 -5] with an estimated prevalence of 30% worldwide.[6] Prevalence has increased substantially in recent decades, primarily driven by the worldwide rise of obesity and type 2 diabetes mellitus.[6 -8]

Current therapeutic pipelines primarily focus on the treatment of MASH. In this context, clinical trials typically assess two primary histological endpoints (using a liver biopsy) considered key for regulatory approval: resolution of steatohepatitis without worsening of fibrosis and improvement in fibrosis without worsening of steatohepatitis.[9]

In a linked trial in China, Lin and colleagues evaluated the efficacy and safety of dapagliflozin in individuals with MASH, both with and without type 2 diabetes mellitus.[10] A total of 154 patients with no cirrhosis were randomly assigned in this 48 week trial to receive either 10 mg of dapagliflozin or placebo once daily, with 125 patients (81%) completing an end of study biopsy. The primary endpoint—improvement in MASH without worsening of fibrosis—was met in 53% of patients in the treatment group compared with 30% in the placebo group. Among the secondary outcomes, resolution of steatohepatitis without worsening of fibrosis occurred in 23% of patients given dapagliflozin versus 8% in the placebo group. Additionally, improvement in fibrosis without worsening steatohepatitis was observed in 45% versus 20% of patients, respectively. Notably, the safety profile of dapagliflozin was favourable and consistent with previous studies. Adverse events were less frequent with dapagliflozin use (56% *v* 64%), and no serious events were reported in the dapagliflozin group. Insomnia, gout, and bone fractures were slightly more common in the dapagliflozin group. Emerging evidence from other studies indicates that this drug is well tolerated even in patients with cirrhosis.[11]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have grown in importance for the treatment of type 2 diabetes mellitus, showing proven efficacy in heart failure and chronic kidney disease.[12 -14] In addition to glycaemic control, SGLT2 inhibitors have improved lipid profile and blood pressure, induced modest weight loss, and offered cardiorenal protection—even in patients without diabetes.[15]

Before this trial, evidence supporting the use of SGLT2 inhibitors in people with MASLD and MASH was limited and mostly exploratory, constrained by small sample sizes, limitations in study design, or non-histological endpoints.[16]

After years without effective therapeutic options, two drugs from different classes have recently shown benefits and favourable safety profiles in people with MASH. Resmetirom, a thyroid hormone receptor β (THRβ) agonist, is the first drug approved in the US for this population.[17] Meanwhile, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown improvements in liver histology in a phase 3 trial.[18]

As is often the case at this stage of clinical research, head-to-head comparisons are not feasible; however, all three drugs have shown encouraging treatment effects.

For the outcome of MASH resolution without worsening fibrosis, the absolute differences in response rates versus placebo were 15% for dapagliflozin, 29% for semaglutide, and 20% for resmetirom.[10 18 19] For fibrosis improvement without worsening of steatohepatitis, the corresponding differences were 25% for dapagliflozin, 14% for semaglutide, and 12% for resmetirom.[10 18 19] Of note, the dapagliflozin trial included younger patients who were predominantly male and of Asian descent, with a lower body mass index, a lower prevalence of type 2 diabetes, and less fibrosis than participants in the resmetirom and semaglutide trials.

To reach the full therapeutic potential of drugs, treatment must be accompanied by structured dietary interventions and sustained lifestyle modifications, ideally supported by motivational strategies. This principle is reinforced by consistent histological improvements observed in placebo groups across multiple MASH trials, with nearly one in five patients assigned to placebo having meaningful histological benefit.[10 18 19] These outcomes likely reflect, in part, the structured lifestyle counselling and close clinical monitoring typically provided to participants in clinical trials. Such public health and social measures remain a cornerstone of MASLD management and are strongly recommended by major clinical practice guidelines.[4 5]

The coming years are expected to be particularly exciting in the field of pharmacological treatment for MASH. As more drugs become available, therapeutic decisions will likely become increasingly tailored to individual patient profiles. Given the shared pathophysiological mechanisms linking MASLD, type 2 diabetes, and obesity, particularly insulin resistance and lipotoxicity, identifying therapeutic drugs capable of improving overall metabolic control while also targeting liver disease remains a key goal.[16]

Ideally, such treatments should provide cardiovascular benefit, have an established safety profile, and be accessible to broad and diverse patient populations.

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1 Riazi K, Azhari H, Charette JH, etal. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2022;7:-61. doi: 10.1016/S2468-1253(22)00165-0 pmid: 35798021

2 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:-84. doi: 10.1002/hep.28431 pmid: 26707365

3 Younossi ZM, Henry L. Fatty liver through the ages: nonalcoholic steatohepatitis. *Endocr Pract* 2022;28:-13. doi: 10.1016/j.eprac.2021.12.010 pmid: 34952219

4 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, etal. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:-835. doi: 10.1097/HEP.0000000000000323 pmid: 36727674

5 European Association for the Study of the Liver (EASL)European Association for the Study of Diabetes (EASD)European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;81:-542. doi: 10.1016/j.jhep.2024.04.031 pmid: 38851997

6 Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023;77:-47. doi: 10.1097/HEP.0000000000000004 pmid: 36626630

7 Tinajero MG, Malik VS. An update on the epidemiology of type 2 diabetes: a global perspective. *Endocrinol Metab Clin North Am* 2021;50:-55. doi: 10.1016/j.ecl.2021.05.013 pmid: 34399949

8 Lin X, Xu Y, Pan X, etal. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020;10:. doi: 10.1038/s41598-020-71908-9 pmid: 32901098

9 US Food and Drug Administration. *Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment – guidance for industry.* FDA, 2018.

10 Lin J, Huang Y, Xu B, etal. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. *BMJ* 2025;389:e083735.

11 Saffo S, Taddei T. SGLT2 inhibitors and cirrhosis: A unique perspective on the comanagement of diabetes mellitus and ascites. *Clin Liver Dis (Hoboken)* 2018;11:-4. doi: 10.1002/cld.714 pmid: 30992805

12 Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. *Cardiovasc Diabetol* 2022;21:. doi: 10.1186/s12933-022-01512-w pmid: 35614469

13 Heerspink HJL, Langkilde AM, Wheeler DC. Dapagliflozin in patients with chronic kidney disease [reply]. *N Engl J Med* 2021;384:-90.pmid: 33503362

14 Solomon SD, McMurray JJV, Claggett B, etalDELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:-98. doi: 10.1056/NEJMoa2206286 pmid: 36027570

15 Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia* 2018;61:-107. doi: 10.1007/s00125-018-4669-0 pmid: 30132034

16 Genua I, Cusi K. Pharmacological approaches to nonalcoholic fatty liver disease: current and future therapies. *Diabetes Spectr* 2024;37:-58. doi: 10.2337/dsi23-0012 pmid: 38385098

17 Lazarus JV, Ivancovsky Wajcman D, Mark HE, etal. Opportunities and challenges following approval of resmetirom for MASH liver disease. *Nat Med* 2024;30:-5. doi: 10.1038/s41591-024-02958-z pmid: 38641752

18 Sanyal AJ, Newsome PN, Kliers I, etalESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med* 2025. doi: 10.1056/NEJMoa2413258. pmid: 40305708

19 Harrison SA, Bedossa P, Guy CD, etalMAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in MASH with liver fibrosis. *N Engl J Med* 2024;390:-509. doi: 10.1056/NEJMoa2309000 pmid: 38324483