Are Weight-Loss Drugs the Answer for Fatty Liver Disease?

Semaglutide reduced liver fat and improved fibrosis in people with MASH—adding to the drug's growing list of benefits—and several other GLP-1 meds look promising.

May 2, 2025 By Liz Highleyman

Treatment of metabolic dysfunction-associated steatohepatitis (MASH) may soon be added to the growing list of indications for GLP-1 agonists such as semaglutide (sold as Ozempic and Wegovy). Some experts, however, stress that liver-directed medications are still needed for people with fibrosis or cirrhosis.

[Update: The Food and Drug Administration granted accelerated approval of Wegovy for MASH on August 18, 2025.]

The Phase III ESSENCE trial showed that nearly two thirds of participants treated with semaglutide experienced MASH resolution without worsening liver fibrosis, while more than a third showed fibrosis improvement without worsening MASH, Arun Sanyal, MD, of Virginia Commonwealth University School of Medicine, and colleagues reported this week in The New England Journal of Medicine.

"ESSENCE part 1 demonstrates the effects of semaglutide 2.4 mg on the key histological elements, which may reduce disease progression to cirrhosis and end-stage liver disease," Sanyal said in a Novo Nordisk news release. "This is crucial, given the strong link between MASH and other cardiometabolic conditions."

Breaking! Phase 3 ESSENCE trial results just out: Semaglutide 2.4 mg showed significant improvements for adults with #MASH-63% achieved resolution of steatohepatitis with no worsening of fibrosis vs. 34% on placebo at 72 weeks.

#LiverHealthhttps://t.co/5jpx9X7dme@NEJM

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— Scott Isaacs (@scottisaacsmd) April 30, 2025

A Long Road to Treatment

MASH, the new name for non-alcoholic steatohepatitis (NASH), is leading cause of advanced liver disease. The buildup of fat in the liver triggers inflammation, which over time can lead to cirrhosis and liver cancer. Estimates suggest that around 5% of people in the United States have MASH, and around a third have an earlier stage know as metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD).

As the new terminology suggests, MASLD and MASH are associated with obesity, type 2 diabetes and other metabolic abnormalities that raise the risk for cardiovascular disease. The first medication for MASH—Madrigal Pharmaceuticals' resmetirom (Rezdiffra)—was approved last year, but management still largely relies on lifestyle changes such as diet and exercise.

Developing treatments for fatty liver disease has proved challenging. Numerous drug candidates have shown promise in early studies but did not pan out in larger clinical trials, as the Food and Drug Administration's dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH is hard to meet.

GLP-1 (glucagon-like peptide-1) receptor agonists and related medications mimic natural hormones that suppress appetite, regulate insulin and blood sugar and slow emptying of the stomach. Originally developed to treat type 2 diabetes, semaglutide and Lilly's dual GLP-1 and GIP (glucose-dependent insulinotropic polypeptide)

agonist tirzepatide (sold as Mounjaro and Zepbound) are now widely used to manage obesity.

These drugs have been shown to reduce the risk of cardiovascular disease, kidney disease and several types of cancer, and ongoing research continues to show additional benefits, including improved cognitive function, reduced arthritis pain and lower alcohol consumption. One recent study of people with HIV suggests that semaglutide may even help slow biological aging.

Given their beneficial effects on weight and metabolism, there is growing interest in using these medications to treat fatty liver disease. As early as 2016, researchers showed that an older once-daily GLP-1 agonist, liraglutide (Saxenda), led to MASH resolution in 39% of treated patients, and it also appeared to slow fibrosis progression.

The ESSENCE Study

The ESSENCE trial (NCT04822181) enrolled 1,197 adults in 37 countries with biopsy-proven MASH and moderate to advanced fibrosis (stage F2 to F3). Just over half were women, the mean age was approximately 56 years and the study population was racially diverse. Most had obesity, and more than half had type 2 diabetes, but about 3% had MASH despite being lean.

The participants were randomly assigned to receive semaglutide administered as a 2.4 mg subcutaneous injection once weekly or a placebo for nearly five years, along with counseling about a healthy lifestyle. (This is the usual dosage for Wegovy, approved for weight loss; Ozempic, approved for diabetes, has a lower dose.) A planned interim analysis of the first 800 patients with follow-up liver biopsies was done at 72 weeks. Results were previously presented at the 2024 AASLD Liver Meeting.

The researchers reported that 63% of semaglutide recipients experienced resolution of steatohepatitis (liver inflammation due to fat accumulation) without worsening fibrosis, compared with 34% in the placebo group. In addition, 37% in the semaglutide group saw a reduction in liver fibrosis without worsening steatohepatitis, compared with 22% in the placebo group. Both differences were statistically significant.

What's more, people taking semaglutide were twice as likely to show both resolution of steatohepatitis and reduced liver fibrosis (33% versus 16%, respectively). Not surprisingly, semaglutide recipients lost about 11% of their baseline body weight, compared with just 2% in the placebo group. People taking semaglutide also showed more improvement in biomarkers of liver health.

Treatment with semaglutide was generally safe and well tolerated. Most people in the semaglutide group stayed on the target dose for the full 72 weeks. Rates of total and serious adverse events were similar in both groups, but those taking semaglutide were more likely to experience gastrointestinal side effects such as nausea, vomiting, diarrhea and constipation.

The second part of the study will follow participants long term to see whether semaglutide lowers the risk of clinical events such as cirrhosis and liver cancer.

"While these results must be treated with caution, the analysis shows semaglutide can be an effective tool to treat this advanced liver disease," said study coauthor Philip Newsome, PhD, of King's College London.

ESSENCE is the first major trial to show a clear double benefit of semaglutide for people with MASH, after previous studies yielded mixed results.

A Phase II study by Newsome and colleagues, published in 2021, showed that people with mild to advanced fibrosis (stage F1 to F3) who were randomly assigned to weekly low doses of semaglutide were more likely than placebo recipients to experience MASH resolution with no worsening of fibrosis (up to 59%, depending on the dose, versus 17%), but the likelihood of fibrosis improvement was statistically similar (43% versus 33%).

A more recent Phase II study of MASH patients who already had cirrhosis found that even the higher 2.4 mg semaglutide dose did not raise the odds of NASH resolution or fibrosis improvement—in fact, the placebo group fared better.

People living with HIV are at greater risk for fatty liver disease compared with the general population. A study reported last year, dubbed SLIM LIVER, found that a 1.0 mg dose of semaglutide reduced liver fat by 31% in HIV-positive people with less advanced MASLD, and more than a quarter experienced complete resolution.

Dual and Triple Targets in the Pipeline

Drugs with multiple targets are more effective for weight loss, and the same may be true for fatty liver disease. A growing number of candidates mimic two or more metabolic hormones. In particular, targeting glucagon is thought to be beneficial for MASLD and MASH because it directly affects fat metabolism in the liver. A pair of studies presented at the 2024 EASL Liver Congress and published in The New England Journal of Medicine looked at two drugs with dual targets.

Sanyal and colleagues presented findings from the Phase II SYNERGY-NASH trial. In this study, 190 people with MASH and stage F2 to F3 fibrosis were randomized to receive various doses of the GLP-1/GIP agonist tirzepatide via weekly injections or a placebo for 52 weeks. Up to 62% of tirzepatide recipients achieved MASH resolution without worsening of fibrosis versus 10% in the placebo group. Furthermore, up to 55% saw improvement of at least one fibrosis stage without worsening of MASH versus 30% in the placebo group.)

In the second Phase II study, 293 people with MASH and mild to advanced fibrosis were randomized to receive weekly injections of Boehringer Ingelheim and Zealand Pharma's experimental dual GLP-1/glucagon agonist survodutide or a placebo. In an analysis at 48 weeks, 62% of people on the optimal dose of survodutide showed improvement in MASH with no worsening of fibrosis compared with 14% in the placebo group. This rose to 83% among those with paired biopsies who stayed on their assigned dose. Up to 36% of survodutide recipients saw at least a one-stage improvement in fibrosis versus 22% in the placebo group. Gastrointestinal side effects were more common with survodutide, and 20% stopped treatment for this reason. Another analysis showed that survodutide was well tolerated in people with cirrhosis and reduced biomarkers of liver fat and fibrosis. Phase III trials underway.

Merck's dual GLP-1/glucagon agonist, efinopegdutide (licensed from South Korea's Hanmi Pharmaceutical), is also under investigation for fatty liver disease. In a Phase IIa study of 145 people with MASLD, researchers compared efinopegdutide versus low-dose semaglutide, both given as weekly injections. As reported at the 2023 EASL Liver Congress and in the Journal of Hepatology, patients randomized to efinopegdutide saw a significantly larger reduction in liver fat compared with semaglutide recipients at 24 weeks (73% versus 42%)—even though weight loss was similar—and two thirds fell below the 5% liver fat content threshold for MASLD. Those who used efinopegdutide also had a slightly higher rate of drug-related adverse events, mainly gastrointestinal side effects. These results appear to favor efinopegdutide, but this study used less

than half the semaglutide dose tested in ESSENCE.

Another study by the late Stephen Harrison, MD, of the University of Oxford, and colleagues, published in the Journal of Hepatology, found that pemvidutide, a dual GLP-1/glucagon agonist from Altimmune, also significantly reduced liver fat. This study enrolled 94 people with MASLD according to MRI imaging and little or no fibrosis. A majority were women, and the mean age was about 50; three quarters were Latino, a group with a high prevalence of fatty liver disease. After three months of weekly injections, liver fat content decreased by 69% in the optimal pemvidutide dose group versus 4% in the placebo group. What's more, 56% in this group fell below the 5% liver fat content threshold. A related preclinical study suggested that the drug also improved inflammation and fibrosis biomarkers. Pemvidutide was generally well tolerated, with mostly gastrointestinal side effects.

Notably, patients in the pemvidutide group had lost only about 5% of their body weight at the 12-week mark—not much more than the placebo group—suggesting that the drug's beneficial effect on liver fat is not solely attributable to weight loss. Likewise, a real-world observational study of more than 300 people with MASLD and diabetes treated in a U.K. liver clinic found that GLP-1 agonists seemed to reduce liver fat even in people who didn't lose weight.

Drugs with three targets are also in the pipeline, including Lilly's GLP-1/GIP/glucagon agonist retatrutide. A Phase II study with 338 participants found weekly injections of retatrutide led to substantial weight loss. In a substudy of 98 people with MASLD and little or no fibrosis, those who received the highest dose saw an 82% reduction in liver fat at 48 weeks, and 86% dropped below the 5% fat content threshold, while placebo recipients had a slight gain.

Hanmi is also working on a triple GLP-1/GIP/glucagon agonist dubbed efocipegtrutide. Results from a Phase Ib/IIa study of 66 non-diabetic people with obesity, MASLD and minimal fibrosis were reported at the 2024 Liver Meeting. Participants randomized to the highest dose of efocipegtrutide saw a 59% reduction in liver fat content at week 12 by MRI imaging. Preclinical animal studies showed improvements in liver inflammation and fibrosis. A larger Phase II study is underway.

Is Early Treatment Better?

The studies to date are not strictly comparable. They enrolled participants with different levels of liver fat and fibrosis severity, tested different doses, used a variety of liver disease measures (including biopsies, biomarkers or MRI) and had variable follow-up durations. In some trials, recommended lifestyle changes led to substantial improvements in the placebo groups, making it harder to discern the effects of the drugs.

But overall, clinical trial results align with what clinicians are seeing in the real world.

An analysis of data from the Veterans Health Administration, for example, looked at more than 16,000 people with diabetes and presumed MASLD who started GLP-1 agonists between 2006 and 2022, comparing them against matched patients who started a different type of diabetes drug

(DPP-4 inhibitors). Most were men and the mean age was 60; about 9% had cirrhosis. Many used older GLP-1 drugs like liraglutide (Victoza) and dulaglutide (Trulicity), but about 75% ultimately used semaglutide.

People who used GLP-1 agonists had a 14% lower risk of developing cirrhosis, a 22% lower risk of cirrhosis complications (decompensation, liver cancer or liver transplant) and an 11% lower risk of death from any cause. But people with established cirrhosis saw limited benefit, suggesting that earlier treatment is more effective.

Likewise, an analysis of data from Swedish healthcare registries found that people with chronic liver disease and type 2 diabetes who consistently used GLP-1 agonists over time had a lower risk of major adverse liver outcomes over 10 years.

Taken together, the research shows that GLP-1 agonists and related drugs do a good job reducing weight and liver fat and may be able to slow or halt liver disease progression, but they are not as beneficial for managing advanced fibrosis or cirrhosis. This suggests that these medications may be more useful for people with MASLD or early-stage MASH who have not yet developed substantial liver scarring.

“The implications of this trial are, we could wipe out the fat very early in the course of this disease before it becomes a real threat to the liver, and, potentially, reduce the long-term cardiac, metabolic, renal and liver-related harm from obesity,” Sanyal said in a news release about the retatrutide substudy.

Sanyal and other experts think people who have progressed to advanced fibrosis or cirrhosis may also need specific liver-directed therapies, such as resmetirom, in addition to GLP-1 agonists to reverse existing liver damage.

“We need to be able to identify patient populations that can be solely managed with a GLP-1 and populations that need a liver-targeted therapy in addition to weight-loss therapy,” Sanyal wrote for Healio. “In my opinion, a combination therapy would make sense in patients who have significant fibrosis and active disease.”

Even before any GLP-1 agonists or related drugs have received an indication for fatty liver disease, research on combination regimens is already underway, and some companies are working on all-in-one meds that incorporate metabolic hormone analogs plus liver-directed agents.

What’s Next?

According to STAT’s Obesity Drug Tracker, around a fifth of the more than 100 obesity medications on the market or in development are also being studied for fatty liver disease. These include more effective oral options, which will mean greater ease of use, simpler production and potentially lower cost.

Novo Nordisk has submitted a supplemental New Drug Application for Wegovy to treat MASH in

adults with moderate to advanced liver fibrosis, and the FDA has slated it for priority review. Given the unmet need, several related drugs in the pipeline have breakthrough therapy status or other designations intended to speed up their review and approval.

For all their known and unknown benefits, GLP-1 agonists and related medications are not a panacea. Most require weekly shots, they can lead to loss of lean muscle as well as fat, they may cause difficult side effects that lead to treatment discontinuation and most people regain weight when they stop taking them.

Access is also an issue. Wegovy and Zepboud can cost upwards of $1,000 per month. Many private insurers and state Medicaid programs do not cover these meds for weight loss alone, and Medicare is currently prohibited from doing so. This is the subject of ongoing political battles: Some claim the medications will save health care costs in the long run, while others argue that their prices are too high to be sustainable if everyone who could benefit is covered.

The weight-loss medication field is sure to remain an active area for both research and policymaking as scientists earn more about what these drugs can do.

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