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Reversing fibrosis in metabolic dysfunction–associated steatohepatitis—beyond telling patients to lose weight

ABSTRACT

To reverse fibrosis in late-stage metabolic dysfunction–associated steatohepatitis (MASH), guidelines recommend that patients shed at least 10% of their body weight. However, losing this much weight remains a challenge for most patients, especially with lifestyle modifications alone. Moreover, not all patients with MASH are overweight or obese. This review summarizes pharmacologic, surgical, and bariatric endoscopic treatments for MASH to guide primary care physicians and internists.

KEY POINTS

Two drugs have been approved by the US Food and Drug Administration for MASH with grade 2 or 3 fibrosis: resmetirom (which is suitable for lean patients) and semaglutide. Tirzepatide also shows promise.

Metabolic-bariatric surgery is recommended for patients with MASH and body mass index 30 kg/m² or higher; its MASH resolution rates range from 55% to 80%.

Endoscopic procedures show favorable safety profiles, but long-term efficacy data are needed for MASH; in the United States, insurance coverage might be a barrier to access.

METABOLIC DYSFUNCTION–ASSOCIATED steatohepatitis (MASH) can be reversed—and not only by advising patients to eat less and exercise more to lose weight. In the past 2 years, the US Food and Drug Administration (FDA) has approved 2 drugs for treating MASH, and bariatric surgical and endoscopic treatments are available as well. Here, we review these treatments and their effectiveness in reversing MASH.

■ METABOLIC-ASSOCIATED SYNDROMES ARE A GLOBAL PANDEMIC

In 2022, the World Health Organization estimated that 16% of adults globally—890 million people—had obesity (body mass index > 30 kg/m²),¹ and 830 million had type 2 diabetes.² The numbers are higher and getting worse in the United States, where a third of adults are estimated to have metabolic syndrome.³ Consequently, conditions linked with obesity, type 2 diabetes, and metabolic syndrome are becoming increasingly prevalent. In particular, MASH is a growing worldwide concern.³

Note that the terminology has changed. MASH used to be called *nonalcoholic steatohepatitis*, and it is a subtype of metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as *nonalcoholic fatty liver disease*.⁴ While MASLD is an umbrella term for hepatic steatosis (fat in the liver) in association with at

Bariatric surgery and bariatric endoscopy increase GLP-1 and peptide YY secretion, leading to improved insulin sensitivity; increase the proportion of acylated to desacyl ghrelin, leading to improved mitochondrial function; and modify the gut microbiome, with dominance of *Bacteroidetes* and *Proteobacteria* species

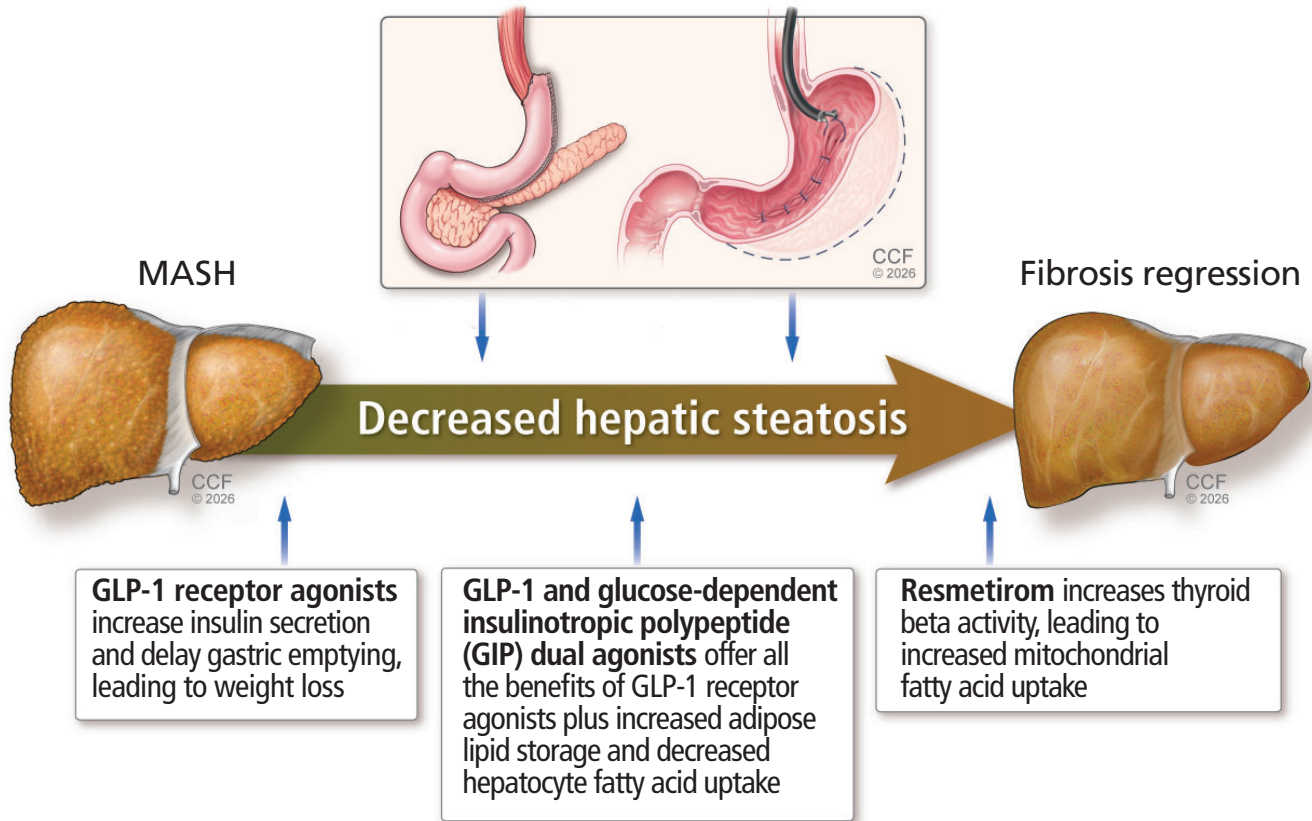


Figure 1. Mechanism of fibrosis regression in metabolic dysfunction–associated steatohepatitis (MASH).

GLP-1 = glucagon-like peptide 1

least 1 metabolic risk factor (overweight or obesity, type 2 diabetes, dyslipidemia, hypertension), in MASH there is also hepatic inflammation and hepatocyte ballooning, with a high risk of progression and fibrosis.⁵

MASLD affects up to 30% of adults in the United States and more than half of people with type 2 diabetes, in whom the prevalence of MASH has been found to be 37%.⁶ With the increasing trends in type 2 diabetes and obesity, the overall prevalence of MASLD is expected to rise to 55% by 2040, and with it, MASH rates will escalate as well.⁷

Untreated, MASH can lead to fibrosis, cirrhosis, and, potentially, hepatocellular carcinoma; thus, it is 1 of the top 2 reasons for liver transplants in the United States, along with alcoholic liver disease.⁸

Currently, clinical trials are reporting the effectiveness of MASH treatments in terms of the percentage of participants whose liver fibrosis decreases by at least 1 stage on a scale ranging from 0 (normal) to 4 (cirrhosis). To reverse fibrosis, we need to get rid of the fat in the liver, as fat is a key driver of stellate cell activation and fibrogenesis.

The various treatments for MASH—lifestyle modifications, glucagon-like peptide (GLP) 1 receptor agonists, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual agonists, resmetirom, metabolic-bariatric surgery, and metabolic-bariatric endoscopic procedures—reduce steatosis by distinct but converging pathways (**Figure 1**).

■ DIET AND EXERCISE TO LOSE WEIGHT: EASIER SAID THAN DONE

The cornerstone of MASH treatment is lifestyle modification and weight loss.⁹ Dietary recommendations include consuming more fruits, vegetables, whole grains, and healthy fats and less alcohol, simple sugars, and processed foods. The goal for physical activity is at least 150 minutes of exercise per week.¹⁰

These modifications aim to reduce metabolic risk factors and promote weight loss, decreasing fat accumulation in the liver by creating a negative energy balance and promoting lipolysis, ultimately reducing fibrosis. In a study from Cuba, Vilar-Gomez et al¹¹ reported that of 29 patients who managed to lose at least 10% of their body weight, 26 (90%) had MASH resolution and 13 (45%) had fibrosis regression.

However, most patients find it hard to lose this much weight and keep it off through lifestyle modifications alone. Thus, pharmacologic, surgical, and endoscopic treatments are needed.

■ GLP-1 RECEPTOR AGONISTS

GLP-1 receptor agonists enhance insulin secretion, delay gastric emptying, promote lipolysis, and stimulate weight loss, indirectly improving hepatic inflammation and fibrosis.

The FDA's approval of GLP-1 receptor agonists for type 2 diabetes mellitus and obesity, principally supported by their cardiovascular benefits,^{12,13} raised interest in their potential role in treating MASH.

LEAN (Liraglutide Efficacy and Action in Nonalcoholic Steatohepatitis),¹⁴ a phase 2 study in 52 patients with biopsy-confirmed MASH, was the first to show the efficacy of a GLP-1 receptor agonist in treating MASH. After 48 weeks, 9 (39%) of the 23 patients who received liraglutide 1.8 mg daily and underwent a follow-up biopsy achieved MASH resolution, compared with only 2 (9%) of 22 patients in the placebo group ($P = .019$).

The **ESSENCE** (Effect of Semaglutide in Subjects With Noncirrhotic Nonalcoholic Steatohepatitis) trial,¹⁵ a phase 3 study, enrolled 800 patients with biopsy-proven MASH and stage 2 or 3 fibrosis. At 72 weeks, MASH had resolved without fibrosis worsening in 62.9% of the group receiving semaglutide 2.4 mg once weekly, compared with 34.3% in the placebo group ($P < .001$). Fibrosis improved by at least 1 stage without MASH worsening in 36.8% vs 22.4% in the placebo group ($P < .001$), and the combined end point of both MASH resolution and fibrosis improvement was achieved in 32.7% vs 16.1% ($P < .001$). The

semaglutide group lost a mean 10.5% of their total body weight, vs 2.0% in the placebo group.

But once patients start a GLP-1 receptor agonist, they may need to keep taking it indefinitely. In the STEP-4 (Effect and Safety of Semaglutide 2.4 mg Once-Weekly in Subjects With Overweight or Obesity Who Have Reached Target Dose During Run-in Period) trial,¹⁶ participants who discontinued semaglutide after 20 weeks regained a mean 6.9% of their baseline body weight over 48 weeks. Given that the benefits of semaglutide stem from weight loss–mediated metabolic improvements, stopping it may lead to recurrence of hepatic steatosis and fibrosis.

In August 2025, the FDA approved semaglutide to treat MASH with moderate to advanced liver fibrosis. As this indication is recent, universal prior authorization criteria for drug approval are still uncertain and can vary by state and insurance policy. While patients require a medical history of MASH, liver biopsy might not be absolutely required for medication approval and may be supplemented by liver fibrosis imaging (transient elastography [FibroScan] or magnetic resonance elastography) and noninvasive fibrosis scoring (fibrosis-4 index). Importantly, patients must agree to adhere to lifestyle changes regarding diet, exercise, and behavior (no excessive alcohol consumption).

■ GLP-1 AND GIP DUAL AGONISTS SHOW PROMISE

GLP-1 and GIP dual agonists offer additional hepatic benefits by activating GIP receptors on adipocytes, promoting healthy adipose tissue expansion, increasing dietary lipid storage, and preventing lipid “spillover” to the liver.¹⁷ They also downregulate CD36 (fatty acid translocase), reducing hepatocyte fatty acid uptake, and they upregulate bile acid metabolism.¹⁸

The **SYNERGY-NASH** (A Study of Tirzepatide [LY3298176] in Participants With Nonalcoholic Steatohepatitis) trial,¹⁹ a phase 2b dose-finding study, randomized 190 patients with biopsy-confirmed MASH and stage 2 or 3 fibrosis to receive weekly injections of the GLP-1 and GIP dual agonist tirzepatide 5 mg, 10 mg, or 15 mg or placebo for 52 weeks. MASH resolved without fibrosis worsening in 44% of patients in the 5-mg group, 56% in the 10-mg group, and 62% in the 15-mg group, compared with only 10% in the placebo group (all $P < .001$). Losing more weight correlated with higher MASH resolution rates, and tirzepatide's effects appeared to exceed those of GLP-1 receptor agonists alone.

■ THE THYROID HORMONE RECEPTOR BETA AGONIST RESMETIROM

In 2024, resmetirom became the first drug approved by the FDA for treating MASH with moderate to advanced fibrosis (stage 2 or 3).²⁰ Its target, thyroid hormone receptor beta, is predominantly expressed in the liver: apparently, even people with normal thyroid hormone levels systemically can have *intrahepatic* hypothyroidism, leading to hepatic steatosis and inflammation, which this drug can counteract.²¹

The MAESTRO-NASH trial^{22–24} reported that steatohepatitis resolved without worsening of fibrosis in 25.9% of patients receiving resmetirom 80 mg and in 29.9% of those receiving 100 mg, compared with 9.7% in the placebo group, and fibrosis improved without worsening of steatohepatitis in 24.2% and 25.9%, respectively, compared with 14.2% with placebo. Resmetirom also provided secondary benefits such as lowering levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B.

Resmetirom is generally well tolerated. The most common adverse effects include gastrointestinal symptoms (diarrhea in up to 30% of patients and nausea in 22%) and mild aminotransferase elevations (typically transient and asymptomatic); rarely, it can cause gallbladder-related adverse events such as cholelithiasis and acute cholecystitis.²²

Continued research is required to evaluate the cardiovascular effects of resmetirom in patients with MASH, who face a higher risk of death from cardiovascular disease.²¹

Resmetirom is FDA approved and supported by American Association for the Study of Liver Diseases (AASLD) guidelines²⁰ for patients with MASH and stage 2 or 3 fibrosis, which does not need to be confirmed by liver biopsy. The recommended dose is 80 mg/day for patients weighing less than 100 kg (220.5 lb), and 100 mg/day for those weighing 100 kg or more. Although the FDA has not approved any techniques for monitoring the response to this drug, AASLD guidelines recommend noninvasive liver assessments such as vibration-controlled transient elastography or magnetic resonance elastography or blood-based assessments.

Resmetirom is not recommended for patients with cirrhosis, in whom it has not been tested. It should also be avoided in patients with coexisting uncontrolled liver diseases (eg, autoimmune hepatitis), uncontrolled hypothyroidism or hyperthyroidism, symptomatic gallstone-related diseases, and ongoing alcohol consumption of 20 g or more per day for women or 30 g or

more per day for men.²⁰ If any of these contraindications are suspected or confirmed, a hepatologist should be consulted before starting or continuing resmetirom.

Is resmetirom a better option for lean patients with MASH?

Up to 20% of patients with MASLD worldwide have a normal body mass index (defined as < 25 kg/m² in Western populations or < 23 kg/m² in Asian populations) and are classified as having “lean MASLD.”^{25,26} Despite their normal body mass index, many of them have central obesity (elevated waist circumference) and visceral adiposity, and they have a higher prevalence of MASLD-related genetic polymorphisms such as the I148M variant in *PNPLA3*.²⁷ Importantly, meta-analyses suggest that patients with lean MASLD may have a higher all-cause mortality rate than those with nonlean MASLD (hazard ratio 1.61, 95% confidence interval 1.37–1.89), independent of traditional risk factors.²⁸

Lean patients with MASH and stage 2 or 3 fibrosis can receive either resmetirom or semaglutide, as FDA approval of these drugs was based on fibrosis stage rather than body mass index. However, lean patients have been underrepresented in studies. For instance, in the ESSENCE trial, only 14 (3%) of the 534 patients in the semaglutide group had a body mass index less than 25 kg/m², as did 8 (3%) of the 266 patients in the placebo group.¹⁵

Resmetirom, which does not require weight loss for efficacy, may be a better option for lean patients with MASH fibrosis. GLP-1 receptor agonists can also be considered, though weight loss targets differ: guidelines recommend a 3% to 5% weight loss for lean patients instead of 10% or more for patients with obesity.²⁶

■ METABOLIC-BARIATRIC SURGERY

Metabolic-bariatric surgery and endoscopic procedures modulate gut hormones (eg, GLP-1, peptide YY, ghrelin), improve insulin sensitivity and mitochondrial function, and reshape the gut microbiome, all of which contribute to decreasing hepatic steatosis.

Metabolic-bariatric surgery is an option for patients with MASLD or MASH and obesity, as it can promote weight loss, liver health, remission of type 2 diabetes, and reduction of cardiovascular risk. The 2022 American Society for Metabolic and Bariatric Surgery and International Federation for Surgery and Other Therapies for Obesity guidelines²⁹ recommend metabolic-bariatric surgery for patients with MASLD or MASH whose body mass index is 30 kg/m² or higher who do not achieve substantial weight loss with non-

surgical methods. For Asian people, surgery should be offered if the body mass index is 27.5 kg/m² or higher.

A meta-analysis found that metabolic-bariatric surgery improved steatohepatitis in 59% of patients and improved or resolved liver fibrosis in 30%.³⁰

Procedures include gastric diversions such as the Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy. Notably, the Roux-en-Y procedure has a greater impact on MASLD than the other procedures, improving or resolving steatosis in 91% of patients and liver fibrosis in 31%.³⁰ Furthermore, in the BRAVES (Bariatric Surgery vs Nonalcoholic Steatohepatitis) trial,³¹ MASH resolved without worsening of fibrosis in 56% of patients who underwent Roux-en-Y gastric bypass, compared with 16% of patients in the lifestyle modification control group.

Laparoscopic sleeve gastrectomy is recommended for patients with MASH and type 2 diabetes or obesity.³² It involves surgically removing 80% of the stomach to create a small gastric lumen to restrict food intake and induce weight loss. A study showed that laparoscopic sleeve gastrectomy produced significant weight loss, with a body mass index reduction of 10.31 kg/m² in 12 months, and improved steatosis grade, lobular inflammation, and fibrosis stage.³²

Metabolic-bariatric surgery has become remarkably safe, with 30-day mortality rates of 0.1% for laparoscopic sleeve gastrectomy and 0.2% for Roux-en-Y gastric bypass.³³ Overall, metabolic-bariatric surgery is supported by durable evidence showing significant improvement in liver fibrosis and steatosis in patients with MASH.

■ ENDOSCOPIC BARIATRIC AND METABOLIC THERAPIES

Endoscopic bariatric and metabolic therapies are a promising alternative to traditional metabolic-bariatric surgery. They aim to enhance weight loss, often ranging from 10% to 30% total body weight loss, and reduce liver fibrosis in MASH. They also demonstrate favorable safety profiles, with rates of serious adverse events of 2.2% in a meta-analysis of endoscopic sleeve gastroplasty and short recovery times of 1 to 3 days.³⁴ Referral to a specialist in these procedures can be considered if medical therapy alone does not produce the desired results and the patient is not a candidate for or has declined metabolic-bariatric surgery.

Although endoscopic therapies have lower nominal hospital costs than metabolic-bariatric surgery, they result in more out-of-pocket expenses for patients in the United States.³⁵ For instance, metabolic-bariatric

surgery is covered by more than 90% of US private insurers for patients meeting criteria,³⁵ whereas endoscopic therapies are generally not covered by insurance and may require full out-of-pocket payment.

Endoscopic sleeve gastroplasty

Endoscopic sleeve gastroplasty is a technique in which full-thickness sutures are endoscopically placed along the stomach's greater curvature to reduce gastric volume.³⁶ It has shown promise in improving fibrosis in MASH while achieving significant weight loss.^{37,38} A multicenter randomized controlled trial showed that patients undergoing endoscopic sleeve gastroplasty with lifestyle modifications experienced significant reductions in liver stiffness measurements compared with sham endoscopy.³⁶

Intragastric balloons

A saline-filled balloon, temporarily placed in the stomach, promotes weight loss by occupying gastric space and increasing satiety. In 2 series of patients with obesity and MASLD with advanced fibrosis, balloon placement resulted in significant weight loss (mean total body weight loss 11.7% at 6 months in 1 study)³⁹ and reductions in liver stiffness and fibrosis-4 index scores.⁴⁰

Duodenal-jejunal bypass liners

This device is an endoscopically implanted impermeable sleeve that blocks nutrient absorption from the duodenum to the proximal jejunum for up to 12 months, mimicking surgical duodenal-jejunal bypass. A randomized trial by Karlas et al⁴¹ showed that having the liner in place for 48 weeks significantly reduced the FibroScan-AST score by 0.21 points ($P < .001$; possible scores range from 0 to 1.0), indicating potential protection against liver fibrosis progression.

Endoscopic revisional procedures

Revisional endoscopic techniques can be used for patients who do not lose enough weight or gain it back after surgery or endoscopic procedures. Surgical revisions such as a repeat surgical sleeve or conversion to a Roux-en-Y gastric bypass (from laparoscopic sleeve gastrectomy) carry a higher morbidity risk than the initial surgery, but endoscopic revisional procedures have lower adverse event rates than surgical revision.^{38,42}

Endoscopic revisional gastroplasty involves suturing the stomach that has dilated and increased in volume following sleeve gastrectomy, to reduce the gastric volume and re-create the gastric sleeve.⁴² Future studies are needed to evaluate the impact of endoscopic revisional gastroplasty on hepatic fibrosis outcomes.

TABLE 1
Landmark studies of therapeutic options for MASH fibrosis regression

| Intervention (year) | Study type | Population, criteria | Fibrosis regression | Mean total body weight loss |
|--|-------------------------------------|--|---|---|
| Semaglutide (2025) ¹⁵ | Phase 3 randomized controlled trial | 800 adults MASH, fibrosis stage 2 or 3 | 36.8% improved ≥ 1 stage (vs 22.4% placebo) | 10.5% at 72 weeks |
| Tirzepatide (2024) ¹⁹ | Phase 2 randomized controlled trial | 190 adults MASH, fibrosis stage 2 or 3 | 44% in 5-mg group improved ≥ 1 stage (vs 30% placebo) | 11%–16% at 52 weeks |
| Resmetirom (2021, ²² 2024 ²³) | Phase 3 randomized controlled trial | 966 adults MASH, fibrosis stage 2 or 3 | 24%–26% improved ≥ 1 stage (vs 14% placebo) | No clinically meaningful weight loss observed |
| Roux-en-Y gastric bypass (2023) ³¹ | Randomized controlled trial | 288 adults MASH, obesity, noncirrhotic | 37% improved ≥ 1 fibrosis stage; 56% had MASH resolution (vs 16% lifestyle modification) | 32% at 1 year |
| Laparoscopic sleeve gastrectomy (2020) ³² | Prospective cohort | 94 adults MASH, obesity | 42% had MASH resolution with significant fibrosis improvement | 25%–30% at 1 year |
| Endoscopic sleeve gastroplasty (2021) ³⁸ | Prospective cohort | 118 adults Obesity, MASH | 20% improved from fibrosis stage 3 or 4 or indeterminate to stage 0–2 | 16% at 2 years |
| Intragastric balloon (2021) ³⁹ | Prospective cohort | 21 adults Radiologically proven steatosis and fibrosis, obesity | 50% improved ≥ 1 fibrosis stage | 11.7% at 6 months |
| Duodenal-jejunal bypass liner (2022) ⁴¹ | Randomized controlled trial | 32 adults Obesity, MASH | Mean FibroScan-AST score reduced by 0.21 ($P < .001$, surrogate for fibrosis or MASH) | 11% at 48 weeks |
| Transoral outlet reduction (2023) ⁴³ | Retrospective cohort | 40 adults MASLD or fibrosis after Roux-en-Y gastric bypass and weight regain | Fibrosis-4 index score decreased from 1.56 ± 0.46 to 1.24 ± 0.58 ($P = .05$) | 8.5% at 1 year, 8.8% at 5 years |

MASH = metabolic dysfunction–associated steatohepatitis, MASLD = metabolic dysfunction–associated steatotic liver disease

Transoral outlet reduction is performed in patients who regain weight after Roux-en-Y gastric bypass. A reason for weight regain is dilation of the gastrojejunal anastomosis; thus, transoral outlet reduction aims to reduce the size of the anastomosis via endoscopic suturing. Transoral outlet reduction in patients with MASH demonstrated significant improvements in alanine and aspartate aminotransferase levels and fibrosis-4 index scores.⁴³ Currently, no histologic or validated elastography data exist to confirm true fibrosis regression after

revisional endoscopic techniques, but current data are promising.

Landmark studies of pharmacologic and bariatric surgical and endoscopic options for MASH fibrosis regression are summarized in **Table 1**.^{15,19,22,23,31,32,38,39,41,43}

■ TAKE-HOME MESSAGE

Lifestyle modification remains the foundation of MASH management,⁹ with weight loss of at least 10%

associated with fibrosis regression in most patients.¹¹ However, achieving and maintaining this degree of weight loss is challenging, making pharmacologic and procedural interventions essential tools in clinical practice.

Two FDA-approved medications now exist for MASH with moderate-to-advanced fibrosis: resmetirom and semaglutide. Resmetirom works independently of weight loss and is particularly well-suited for lean patients, who represent 10% to 20% of the MASH population and often lack procedural options due to body mass index requirements.^{25,26} GLP-1 receptor agonists and GLP-1 and GIP dual agonists additionally offer the dual benefit of substantial weight loss and direct hepatic improvement.

Metabolic-bariatric surgery is strongly supported by AASLD and American Society for Metabolic and Bariatric Surgery guidelines^{20,29} for patients with MASH and obesity, with sleeve gastrectomy and Roux-en-Y gastric bypass demonstrating MASH resolution rates of 55% to 80% and meaningful fibrosis regression.³⁰⁻³² Updated guidelines now recommend metabolic-bariatric surgery for patients with body mass index 30 kg/m² or greater with metabolic disease, including MASH.

Endoscopic procedures, particularly endoscopic sleeve gastroplasty, offer a favorable safety profile and are an alternative for patients who do not want to undergo metabolic-bariatric surgery, though they

currently lack insurance coverage in the United States. While the AASLD acknowledges endoscopic approaches as promising for MASH improvement and fibrosis regression, long-term efficacy data are still needed.²⁰

As the prevalence of MASH continues to rise globally, primary care physicians and internists play a critical role in identifying patients who may benefit from these interventions. The treatment approach should be individualized:

- Pharmacotherapy for all eligible patients with stage 2 or 3 fibrosis (including lean patients)
- Metabolic-bariatric surgery for those meeting body mass index criteria, and
- Endoscopic options for patients seeking alternatives to metabolic-bariatric surgery who can manage the out-of-pocket costs.

Early referral to hepatology, metabolic-bariatric surgery, or bariatric endoscopy specialists can help ensure patients receive timely care before progression to cirrhosis. ■

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Dr. Simons-Linares has disclosed consulting for 3-D Matrix, Boston Scientific, Medtronic, and STERIS Corporation. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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