REVIEW ARTICLE

MASLD Pharmacotherapy: Current Standards, Emerging Treatments, and Practical Guidance for Indian Physicians

Ashish Kumar

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has become a significant public health issue worldwide, with a pronounced impact in India due to the escalating rates of obesity and type 2 diabetes mellitus (T2DM) driving its prevalence. This condition spans a range of hepatic disorders, from uncomplicated steatosis to metabolic dysfunction-associated steatohepatitis (MASH), accompanied by differing levels of hepatic fibrosis, heightening the likelihood of progression to cirrhosis, liver cancer, and cardiovascular complications. While lifestyle modification remains the cornerstone of MASLD management, pharmacologic therapies are increasingly recognized as essential for patients with progressive disease or those at higher risk of complications.

Recent insights into the pathogenesis of MASLD have led to the development of innovative therapies targeting key mechanisms such as hepatic steatosis, insulin resistance, inflammation, and hepatic fibrosis. Several pharmacological agents have shown encouraging results in clinical trials, including thyroid hormone receptor-β agonist resmetirom, glucagon-like peptide-1 receptor agonists (GLP-1RAs) like semaglutide, peroxisome proliferator-activated receptor (PPAR) agonists such as pioglitazone and saroglitazar, sodium-glucose cotransporter-2 inhibitors (SGLT2i), and vitamin E. Furthermore, emerging therapies, including the dual incretin agonist tirzepatide and fibroblast growth factor (FGF) analogs, hold the potential to transform future treatment strategies.

This review provides a comprehensive overview of current and evolving pharmacologic options for MASLD, with a focus on practical recommendations tailored for Indian physicians. A structured treatment algorithm for noncirrhotic MASLD (F0–F3 fibrosis) is presented, incorporating only drugs currently available in India and stratified based on diabetes status and hepatic fibrosis severity. Given India's vast and diverse patient population, ensuring access to cost-effective therapies remains a challenge, necessitating a pragmatic approach that balances efficacy, affordability, and real-world feasibility. This review serves as a practical clinical guide, equipping physicians with evidence-based recommendations to optimize MASLD management in routine practice.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has emerged as one of the most prevalent causes of chronic liver disease globally. Its rising incidence is closely associated with increasing obesity rates and the escalating burden of type 2 diabetes mellitus (T2DM), making MASLD a significant public health challenge, particularly in India.[1–3] Beyond being a liver-specific disorder, MASLD represents a systemic metabolic condition characterized by insulin resistance, lipotoxicity, and chronic low-grade inflammation. Individuals with MASLD have a two- to threefold higher likelihood of developing T2DM, while up to a quarter of those with T2DM already exhibit significant liver fibrosis (F2 or higher), predisposing them to adverse hepatic outcomes.[4] Additionally, while cardiovascular disease (CVD) remains the major cause of mortality in MASLD and T2DM patients, liver-related mortality becomes a primary concern in those with advanced hepatic fibrosis (F2–F4).

Although extensive research has been conducted, current management strategies for MASLD and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), are predominantly centered on lifestyle modifications, with few pharmacological treatments demonstrating consistent, robust efficacy.[5,6] Given the high risk of progression to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), especially in diabetics, early intervention is crucial. The treatment of MASLD/MASH should go beyond liver-targeted therapy to also address the associated metabolic and cardiovascular risks.

The aim of this review is twofold. Firstly, it aims to update readers about the current and evolving therapeutic landscape of MASLD, with special emphasis on drugs that have recently received regulatory approval or are undergoing advanced (phase 3) clinical trials. Secondly, the review provides practical guidance tailored specifically for physicians in India regarding drug therapy for MASLD, clearly distinguishing recommendations for diabetic and nondiabetic patient populations based on currently available pharmacological options. This practical approach is crucial given the unique epidemiology, resource constraints, and therapeutic availability within the Indian healthcare setting.

Drug Therapy for MASLD/MASH Targeting Key Pathogenetic Pathways

Metabolic dysfunction-associated steatotic liver disease/MASH is a complex metabolic disorder driven by hepatic fat accumulation, insulin resistance, chronic inflammation, and progressive hepatic fibrosis, with advanced hepatic fibrosis (F3–F4) being the strongest predictor of liver-related mortality (Fig. 1). Excess caloric intake and metabolic dysfunction lead to steatosis, where triglycerides accumulate in hepatocytes due to increased lipolysis, hepatic *de novo* lipogenesis (DNL), and impaired lipid export. Insulin resistance further exacerbates hepatic fat accumulation by promoting free fatty acid influx into the liver, while also impairing insulin-mediated suppression of gluconeogenesis. This persistent metabolic dysfunction induces lipotoxicity, oxidative stress, and hepatic inflammation, triggering activation of Kupffer cells and hepatic stellate cells, which contribute to hepatic fibrosis and extracellular matrix deposition. Over time, unresolved inflammation and hepatic fibrosis progression elevate the risk of liver cirrhosis, hepatic decompensation, and HCC. Furthermore, given the strong association between MASLD and CVD, treatment must address both hepatic and systemic metabolic

Professor, Department of Gastroenterology, Institute of Liver, Gastroenterology, and Pancreatico-Biliary Sciences, Sir Ganga Ram Hospital, Delhi, India; *Corresponding Author

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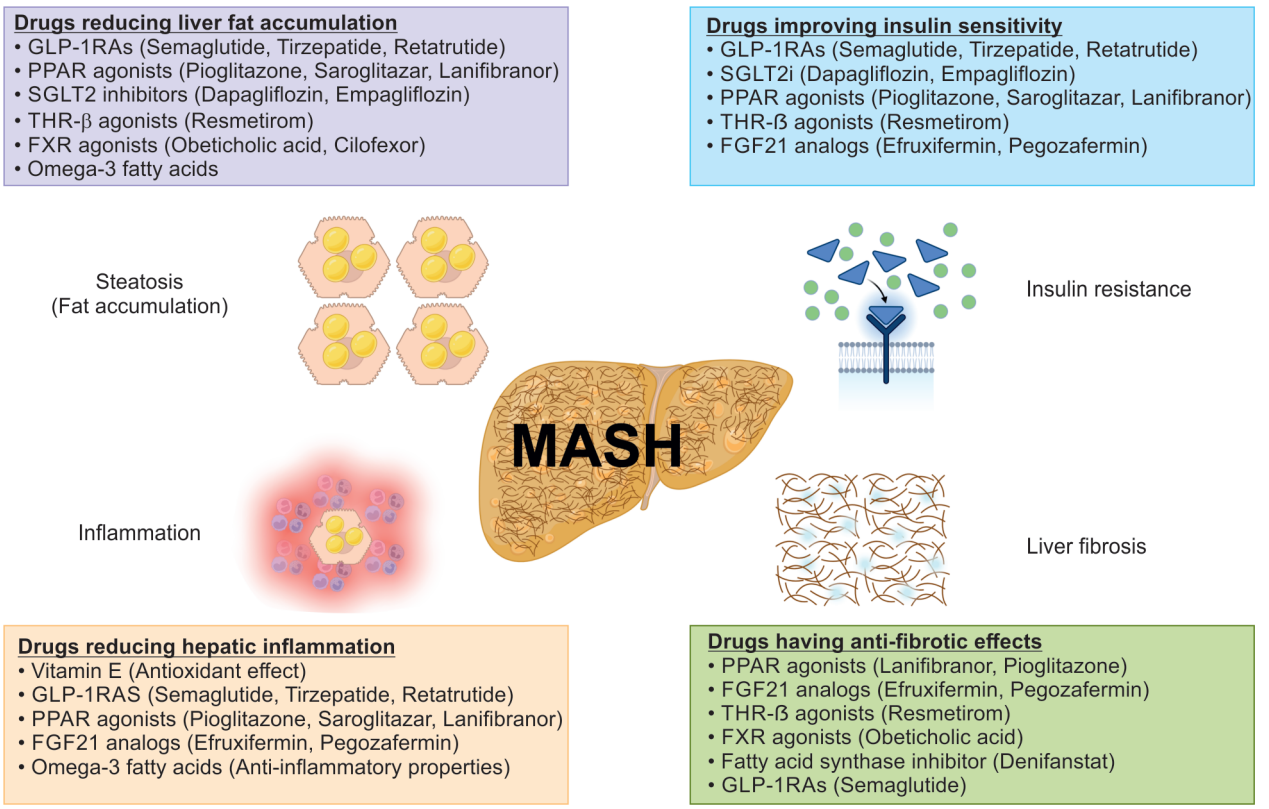

Fig. 1: Pharmacological approaches targeting key pathogenetic mechanisms in MASH. This figure illustrates the key pathogenetic mechanisms of MASH—fat accumulation, insulin resistance, inflammation, and fibrosis—and highlights the drugs targeting each of these mechanisms

dysfunction to reduce overall morbidity and mortality.

While lifestyle modification and weight loss remain the cornerstone of therapy, pharmacologic interventions serve as adjuncts by targeting key hepatic and metabolic pathways to mitigate disease progression. Hepatic steatosis is addressed by glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, tirzepatide, and retatrutide; peroxisome proliferator-activated receptor (PPAR) agonists, including pioglitazone, saroglitazar, and lanifibranor; sodium-glucose cotransporter-2 inhibitors (SGLT2i), such as dapagliflozin and empagliflozin; thyroid hormone receptor-beta (THR-β) agonists, including resmetirom; farnesoid X receptor (FXR) agonists, such as obeticholic acid (OCA) and cilofexor; and omega-3 fatty acids, all of which improve lipid metabolism and reduce hepatic steatosis. Insulin resistance, a central driver of MASLD, is improved by GLP-1RAs, SGLT2i, PPAR agonists, THR-β agonists, and fibroblast growth factor 21 (FGF21) analogs, such as efruxifermin and pegozafermin. To counteract hepatic inflammation, vitamin E, GLP-1RAs, PPAR agonists, FGF21 analogs, and omega-3 fatty acids have demonstrated anti-inflammatory effects. Liver fibrosis progression, a major therapeutic target, is addressed by lanifibranor, efruxifermin, resmetirom, OCA, fatty acid synthase (FASN) inhibitors, such as denifanstat and semaglutide, which reduce hepatic stellate cell activation and extracellular matrix deposition (Fig. 1).

Figure 2 shows a timeline highlighting key advancements in MASLD pharmacotherapy, showcasing pivotal clinical trials and meta-analyses that have influenced treatment strategies over the years. It reflects the shift from early interventions like vitamin E and pioglitazone to newer agents such as GLP-1 receptor agonists, THR-β agonists, and dual/triple incretin receptor agonists, which are now shaping the future of MASLD management. Several of these agents have either received regulatory approval or are in late-stage clinical trials, offering a transformative approach to MASLD treatment.

Table 1 shows an overview of pharmacological therapies for MASLD/MASH, their mechanisms of action, clinical status, and recommendations for Indian patients.

Vitamin E: Antioxidant Therapy for MASLD/MASH

Oxidative stress is a key driver of MASLD/MASH progression, contributing to lipid peroxidation, mitochondrial dysfunction, and hepatocyte injury. Vitamin E (α-tocopherol), a potent lipophilic antioxidant, has been investigated for its ability to neutralize reactive oxygen species (ROS), reduce hepatic inflammation, and improve hepatocyte survival. Given its antioxidant and anti-inflammatory properties, vitamin E has been evaluated as a therapeutic option for MASH, particularly in nondiabetic patients.

The PIVENS trial,[7] a pivotal phase 3 study, evaluated the effects of vitamin E (800 IU/day) in nondiabetic patients with biopsy-confirmed MASH. Over 96 weeks, vitamin E therapy led to significant improvements in hepatic steatosis and inflammation, resulting in MASH resolution in 43% of patients compared to 19% in the placebo group ($p < 0.001$). However, no significant impact on hepatic fibrosis was observed.[7] A systematic review analyzing data from 11 studies confirmed that vitamin E reduces alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, hepatic fat accumulation, and inflammation in MASLD/MASH. Despite these benefits, its role in hepatic fibrosis regression remains uncertain, underscoring the need for long-term trials.[8] More recently, a randomized, double-blind, placebo-controlled multicenter study reported that a lower dose of vitamin E (300 mg/day for 96 weeks) improved liver

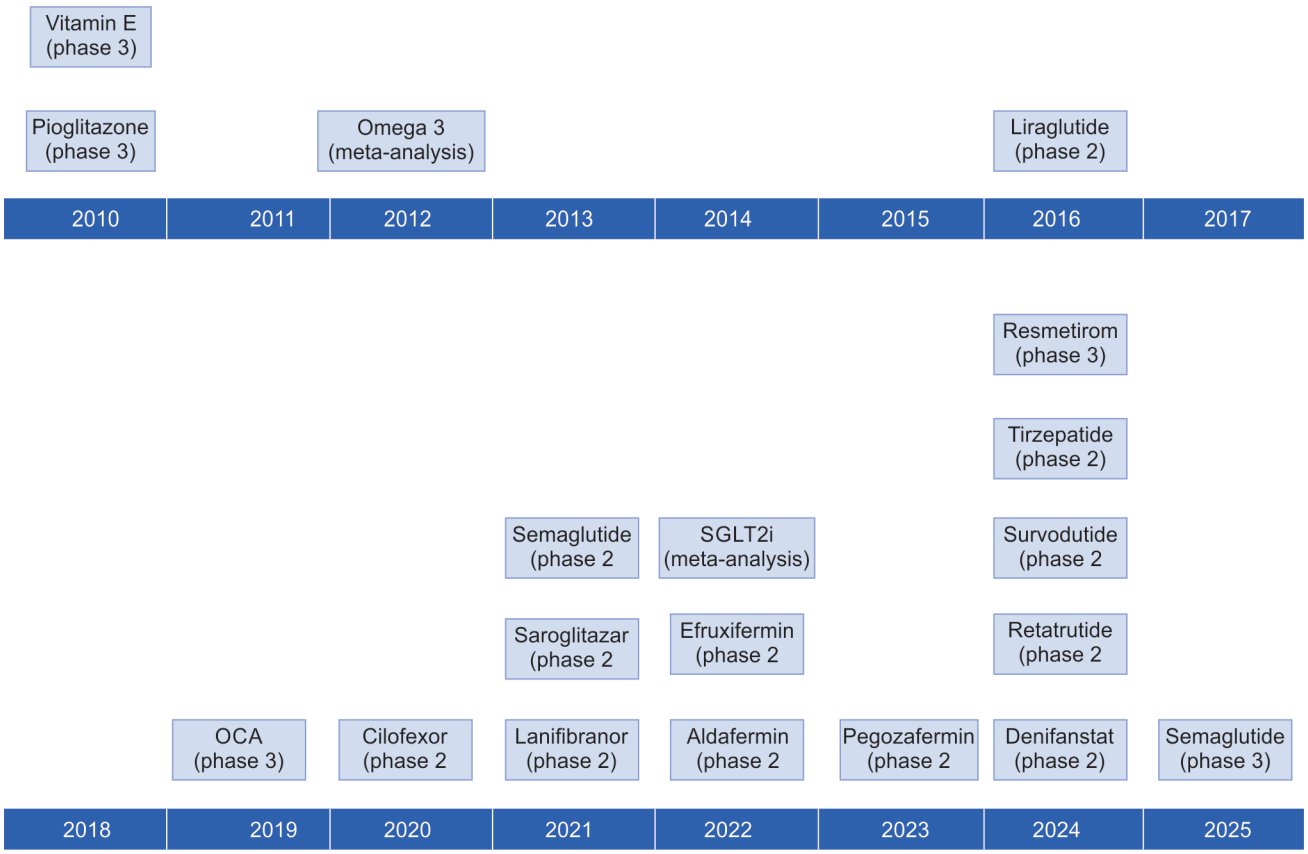

Fig. 2: Timeline of significant advancements in MASLD pharmacotherapy, highlighting key clinical trials and meta-analyses that have shaped the evolving treatment landscape

histology, including reductions in steatosis, lobular inflammation, and hepatic fibrosis, while also lowering liver stiffness and inflammatory markers, with no major safety concerns.[9]

Despite these benefits, concerns regarding long-term safety have been raised. Some studies suggest a potential increased risk of prostate cancer in men[10] and higher cardiovascular risk in certain populations with prolonged use.[11] As a result, vitamin E is currently recommended only for nondiabetic MASH patients and requires careful consideration in high-risk individuals such as diabetics, who already have heightened cardiovascular risks.

Vitamin E remains one of the few available treatments for nondiabetic MASH, demonstrating histological benefits in steatosis and inflammation but limited effects on hepatic fibrosis. Its use in diabetics is not currently recommended due to limited trial data and potential safety concerns. While it is recommended in select patients, concerns about long-term safety highlight the need for safer and more effective therapeutic alternatives in MASLD/MASH management. However, future trials may clarify its role in diabetic MASH patients, especially in combination with other metabolic drugs (e.g., pioglitazone, GLP-1RA, or SGLT2i).

Thyroid Hormone Receptor-B Agonists: A Novel Approach for MASLD/MASH

Thyroid hormone receptor-β agonists have emerged as a promising pharmacologic approach for treating MASLD/MASH, particularly by targeting hepatic lipid metabolism and fibrosis. The THR-β receptor is predominantly expressed in the liver, and its activation enhances mitochondrial β-oxidation, reduces DNL, and promotes hepatic cholesterol clearance. Unlike THR-α, which influences cardiac and skeletal muscle function, THR-β activation is hepatoselective, minimizing systemic side effects such as tachycardia or bone loss. This selective modulation of lipid metabolism and inflammation makes THR-β agonists an attractive therapy for MASH, particularly in patients with dyslipidemia.

Resmetirom, a selective THR-β agonist, is the most advanced candidate in clinical development for MASH with fibrosis. The MAESTRO clinical program[12] is a comprehensive phase 3 trial series designed to evaluate resmetirom for NASH treatment, incorporating multiple studies (MAESTRO-NAFLD-1,[13] MAESTRO-NAFLD-OLE, MAESTRO-NASH,[14] and MAESTRO-NASH-OUTCOMES) to assess its efficacy, safety, and impact on hepatic fibrosis and liver-related outcomes using biopsy, biomarkers, and imaging to support regulatory approval.[12] The first in the series, MAESTRO-NAFLD-1, demonstrated that resmetirom (80 and 100 mg) was safe, well tolerated, and significantly reduced hepatic fat, liver stiffness, low-density lipoprotein cholesterol (LDL-C), apoB, and triglycerides in adults with presumed NASH.[13] The MAESTRO-NAFLD-OLE trial is an open-label active treatment extension of the MAESTRO-NAFLD-1 trial, designed to collect additional safety data in subjects with noncirrhotic MASH and compensated MASH cirrhosis. The pivotal phase 3 MAESTRO-NASH trial[14] assessed the efficacy of resmetirom (80 and 100 mg daily) in 966 patients with biopsy-confirmed MASH and hepatic fibrosis (F1B–F3). After 52 weeks of treatment, MASH resolution without hepatic fibrosis progression was observed in 25.9% of patients receiving 80 mg and 29.9% receiving 100 mg, compared to 9.7% in the placebo group ($p < 0.001$).

Table 1: Overview of pharmacological therapies for MASLD/MASH, their mechanisms of action, clinical status, and recommendations for Indian patients

Drug	*Mechanism of action*	*Key clinical trials*	*Current status globally*	*Indian availability*	*Recommendation for Indian patients*
Vitamin E	Antioxidant, reduces oxidative stress and inflammation	Phase 3 (PIVENS[7])	Recommended for nondiabetic MASH	Available	Strongly recommended in nondiabetic MASH with F2/F3 fibrosis
Resmetirom	Enhances mitochondrial β-oxidation, reduces liver fat and fibrosis	Phase 3 (MAESTRO[14])	FDA approved in 2024	Available	Strongly recommended in F2/F3 fibrosis in both diabetic and nondiabetic MASH
Semaglutide	GLP-1 receptor agonist; reduces appetite, weight loss	Phase 2[17] Phase 3 (ESSENCE interim results[18])	Phase 3 ongoing (ESSENCE)	Available	Strongly recommended in diabetic MASLD Strongly recommended in F2/F3 nondiabetic MASH
Liraglutide	GLP-1 receptor agonist; reduces appetite, weight loss	Phase 2 (LEAN[25])	Approved for T2DM and obesity but not for MASLD	Available	Weakly recommended for diabetic MASLD
Tirzepatide	Dual GLP-1/GIP agonist; enhances metabolic effects	Phase 2 (SYNERGY-NASH[28])	Phase 3 ongoing	Available	Strongly recommended in diabetic MASLD Strongly recommended in F2/F3 nondiabetic MASH
Survodutide	Dual GLP-1/glucagon receptor agonist; metabolic benefits	Phase 2 (1404-0043 trial[29])	Phase 3 ongoing (LIVERAGE)	Not available	–
Retatrutide	Triple GLP-1/GIP/glucagon receptor agonist; enhances energy expenditure	Phase 2a[30]	Phase 3 ongoing	Not available	–
Pioglitazone	PPAR-γ agonist; improves insulin sensitivity, reduces steatosis	Phase 3 (PIVENS[7]) Several meta-analyses[31–36]	Approved for select MASH patients	Available	Strongly recommended in diabetic MASLD Strongly recommended in F2/F3 nondiabetic MASH
Saroglitazar	Dual PPAR-α/γ agonist; improves lipid metabolism and insulin sensitivity	Phase 2[37] Several meta-analyses[39,40,43]	Phase 3 ongoing. Approved in India by DCGI for MASH	Available	Strongly recommended in diabetic MASLD Strongly recommended in F2/F3 nondiabetic MASH
Lanifibranor	Pan-PPAR agonist; regulates lipid metabolism, inflammation and fibrosis	Phase 2b (NATIVE[44])	Phase 3 ongoing (NATiV3)	Not available	–
SGLT2 inhibitors	SGLT2 inhibitor; promotes glucose excretion, improves hepatic steatosis	Phase 3 (DEAN[55]). Meta-analysis, real world cohort studies[50–54]	Approved for diabetes. Has significant MASLD benefits	Available	Strongly recommended in diabetic MASLD Can be used in non-diabetic F2/F3 MASH
Efruxifermin	FGF21 analog; improves lipid metabolism, reduces fibrosis	Phase 2b (HARMONY[62])	Phase 3 ongoing	Not available	–
Pegozafermin	FGF21 analog; reduces inflammation and steatosis	Phase 2b (ENLIVEN[63])	Phase 3 ongoing	Not available	–
OCA	FXR agonist; regulates bile acid metabolism, reduces hepatic inflammation	Phase 3 (REGENERATE[64])	FDA rejected for MASH	Available	Not recommended. Can be used cautiously (off-label) in F2/F3 fibrosis in both diabetic and nondiabetic MASH
Cilofexor	FXR agonist; potential hepatic benefits with metabolic effects	Phase 2[66]	Phase 3 ongoing	Not available	–

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Drug	*Mechanism of action*	*Key clinical trials*	*Current status globally*	*Indian availability*	*Recommendation for Indian patients*
Denifanstat	FASN inhibitor; inhibits DNL, reduces liver fat and fibrosis	Phase 2b[67]	Phase 3 ongoing (FASCINATE-3 and FASCINIT)	Not available	–
Aldafermin	FGF19 analog; reduces bile acid synthesis, improves lipid metabolism	Phase 2b (ALPINE[68])	Phase 3 ongoing	Not available	–
Omega 3	Omega-3 supplementation can reduce liver fat content and improve blood lipid profiles	Several meta-analyses[69–71]	Weak evidence of efficacy	Available	Weakly recommended in both diabetic and nondiabetic MASLD
UDCA	Modifies bile acid composition, reduces hepatic oxidative stress, and improves bile flow	Several meta-analyses[74–77]	Not effective	Available	Not recommended

Additionally, hepatic fibrosis improvement by at least one stage was achieved in approximately 24% in the 80 mg group and 26% in the 100 mg group, vs 14% in the placebo group ($p < 0.001$). Resmetirom also demonstrated favorable metabolic effects, significantly reducing LDL cholesterol levels (−13.6 and −16.3%), while maintaining a safety profile comparable to placebo, with mild gastrointestinal symptoms (diarrhea, nausea) being the most commonly reported adverse events.[14] These findings highlight resmetirom's dual impact on MASH resolution and hepatic fibrosis regression, positioning it as a leading candidate in MASLD/MASH treatment. Another trial, MAESTRO-NASH-OUTCOMES (NCT05500222, $n = 700$), focuses on well-compensated NASH cirrhosis, evaluating whether resmetirom can prevent hepatic decompensation events.

Recognizing its potential, the United States Food and Drug Administration (FDA) granted resmetirom accelerated conditional approval in March 2024 for patients with MASH and moderate to advanced hepatic fibrosis (F2–F3). Following this approval, both the AASLD[15] and EASL–EASD–EASO[16] guidelines have recommended resmetirom for noncirrhotic MASH with significant hepatic fibrosis (F2–F3), acknowledging its efficacy in improving steatohepatitis and hepatic fibrosis. The EASL–EASD–EASO guidelines support its use in European countries where locally approved, while the AASLD guidance aligns with the FDA approval, emphasizing that liver biopsy is not required for initiation. Instead, it advocates for noninvasive liver disease assessment (NILDA) techniques such as VCTE (FibroScan) or magnetic resonance imaging-proton density fat fraction (MRI-PDFF). However, both guidelines do not recommend resmetirom for MASH-related cirrhosis (F4).[15,16]

Glucagon-like Peptide-1 Receptor Agonists: a Metabolic Therapy for MASLD/MASH

Glucagon-like peptide-1 receptor agonists function by mimicking endogenous GLP-1, an incretin hormone released by intestinal L-cells in response to food intake. These agents regulate glucose metabolism by enhancing insulin secretion, inhibiting glucagon release, and delaying gastric emptying, leading to improved glycemic control and weight reduction. While GLP-1RAs are well established in the management of T2DM and obesity, they have also shown promise in MASLD/MASH by improving hepatic insulin sensitivity, attenuating inflammation, and reducing hepatic lipid accumulation. Their hepatic benefits primarily stem from weight loss, enhanced insulin action, and reduced hepatic glucose and lipid production rather than direct receptor activation in the liver. Additionally, GLP-1RAs offer cardiometabolic protection by significantly lowering the risk of major adverse cardiovascular events (MACE), heart failure, and chronic kidney disease (CKD) progression, underscoring their potential as a key therapeutic option for MASLD patients with high cardiometabolic risk. GLP-1RAs are generally well tolerated, though gallbladder-related events (cholelithiasis, cholecystitis) and mild heart rate elevation may occur, necessitating monitoring in high-risk individuals.

Semaglutide (Injectible): The Game Changer in Obesity and MASH Treatment

Semaglutide is the most commonly used GLP-1RA, approved by the FDA for both T2DM and obesity, with demonstrated benefits in glycemic control and weight loss. Beyond its established metabolic effects, semaglutide is emerging as a leading pharmacologic candidate for MASLD and MASH, with ongoing trials demonstrating its potential to improve liver fat, inflammation, and hepatic fibrosis. A phase 2 trial demonstrated that semaglutide (0.4 mg/day for 72 weeks) significantly increased MASH resolution (59 vs 17% with placebo, $p < 0.001$), although hepatic fibrosis improvement was not significant. Adverse events, particularly gastrointestinal side effects (nausea, vomiting, constipation), were notable at higher doses.[17] Further trials, including the currently ongoing phase 3 trial (NCT04822181, ESSENCE trial), aim to assess long-term efficacy in MASH resolution and hepatic fibrosis regression in broader patient populations, including nondiabetic and nonobese individuals. The interim findings from the ESSENCE trial revealed that once a week semaglutide (2.4 mg) led to significant liver histological improvements over a 72-week period. MASH resolution without worsening hepatic fibrosis was observed in 62.9% of patients receiving semaglutide, compared to 34.1% in the placebo group. Additionally, hepatic fibrosis improvement without aggravation of steatohepatitis occurred in 37% of semaglutide-treated individuals vs 22.5% with placebo. Semaglutide therapy also resulted in notable reductions in liver enzymes (AST, ALT), noninvasive hepatic fibrosis parameters, and liver stiffness, alongside an average weight loss of 10.5%. The treatment was well tolerated, with gastrointestinal symptoms being the most frequently reported adverse events. These findings highlight semaglutide's therapeutic potential in MASH, irrespective of diabetes status.[18] The final results of these trials will clarify semaglutide's role as a potential

therapeutic option for MASLD/MASH beyond its metabolic benefits.

Oral Semaglutide: The Power of Glucagon-like Peptide-1 in a Pill

Oral semaglutide, the first and only GLP-1RA available in an oral formulation, is FDA-approved for T2DM and has shown promising metabolic benefits, though its efficacy in MASLD/MASH is still being explored in clinical studies. In India, semaglutide is available only in oral formulation and has established its role in T2DM management. An Indian real-world study found that adding oral semaglutide to existing therapy in obese patients with moderately uncontrolled T2DM significantly improved hemoglobin A1c (HbA1c), weight, body mass index (BMI), lipids, liver enzymes, and body composition, with gastrointestinal side effects being the most common adverse events.[19]

The efficacy of oral semaglutide in improving MASLD/MASH is still being explored. A prospective multicenter observational study from Japan found that 48-week oral semaglutide in patients with MASLD and T2DM significantly improved liver steatosis, hepatic fibrosis markers, glycemic control, lipid profile, and body weight, with mild gastrointestinal side effects being the most common adverse events.[20] A *post hoc* analysis[21] of the Sapporo-Oral SEMA study[22] found that oral semaglutide significantly improved hepatic steatosis, fibrosis-4 index (FIB-4 index), and metabolic parameters in patients with T2DM, particularly benefiting those at high risk for hepatic fibrosis, even when switched from other diabetes medications. A Romanian study demonstrated that in patients with diabetic MASLD, oral semaglutide led to greater improvements in liver stiffness (measured by VCTE), HbA1c, and anthropometric parameters compared to dapagliflozin over 24 weeks, suggesting superior metabolic and hepatic benefits.[23] Another study from Egypt found that both oral and subcutaneous semaglutide significantly improved lipid profiles, liver steatosis, hepatic fibrosis parameters [FIB-4, liver stiffness measurement (LSM), controlled attenuation parameter (CAP)], and BMI in patients with T2DM and NAFLD, with subcutaneous semaglutide showing the most pronounced benefits (as compared to oral) over 12 months.[24]

Liraglutide and Dulaglutide: Early Contenders in the Glucagon-like Peptide-1 Arena

Liraglutide (once daily) and dulaglutide (once a week) are injectable GLP-1RAs that have demonstrated some benefits in MASLD/MASH, primarily through weight reduction, improved insulin sensitivity, and decreased hepatic lipogenesis. The LEAN trial, a phase 2 randomized controlled study, showed that liraglutide 1.8 mg daily for 48 weeks resulted in MASH resolution in 39% of patients compared to 9% in placebo ($p = 0.019$), with a significantly lower rate of hepatic fibrosis progression (9 vs 36% in placebo).[25] The D-LIFT study from India[26] has confirmed weekly dulaglutide's ability to reduce liver fat (MRI-PDFF), improve liver enzymes (ALT, AST), and enhance metabolic parameters in MASLD patients with T2DM. However, while these agents have shown histological improvements, their effects on hepatic fibrosis regression remain unclear, and they have been largely superseded by semaglutide, which demonstrates superior efficacy in MASH resolution and metabolic benefits.[18] A head-to-head comparison between liraglutide and semaglutide is limited, but phase 2 data suggest that semaglutide achieves greater weight loss, improved liver histology, and higher rates of MASH resolution at equivalent or lower doses. Nevertheless, given its availability and established safety profile, liraglutide remains an option for MASLD patients, especially in those requiring concurrent T2DM or obesity management, but semaglutide is now the preferred GLP-1RA for MASLD/MASH treatment.

Dual and Triple Incretin Agonists: A New Era in Metabolic Therapy

The next-generation therapies combining GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon may surpass current treatments in obesity, diabetes, and MASLD/MASH, offering a comprehensive metabolic approach with improved efficacy and safety.[27] The development of dual and triple agonists represents a significant advancement in metabolic disease treatment, leveraging the combined effects of multiple gut hormones to enhance weight loss, glycemic control, and hepatic health. Several dual and triple agonists are currently in phase 2 or 3 trials.

Dual agonists generally target the GLP-1 receptor in combination with either the GIP or glucagon receptors, enhancing metabolic effects while maintaining glucose balance and energy regulation. Among them, tirzepatide, a GLP-1/GIP receptor agonist, has demonstrated superior efficacy in weight reduction and glycemic control compared to traditional GLP-1RAs.[27] The SYNERGY-NASH trial,[28] a phase 2 multicenter, double-blind, placebo-controlled study, assessed tirzepatide in biopsy-confirmed MASH patients with F2–F3 hepatic fibrosis. A total of 190 patients were randomized to receive tirzepatide (5, 10, or 15 mg once weekly) or placebo for 52 weeks. The trial results showed that MASH resolution without hepatic fibrosis worsening occurred in 44% (5 mg), 56% (10 mg), and 62% (15 mg) of tirzepatide-treated patients, compared to only 10% in the placebo group ($p < 0.001$ for all doses). Additionally, hepatic fibrosis improvement by at least one stage without MASH progression was observed in 55% (5 mg), 51% (10 mg), and 51% (15 mg) of patients, vs 30% in the placebo arm. Gastrointestinal symptoms were the most common adverse events, though they were generally mild to moderate.[28] These findings suggest that tirzepatide offers significant histological and metabolic benefits in MASH, but further phase 3 trials are necessary to validate its long-term efficacy and safety. Although both semaglutide and tirzepatide demonstrate benefits in MASLD/MASH, direct comparative trials are lacking, making it unclear whether tirzepatide's additional GIP agonism provides superior liver outcomes.

Survodutide, a dual glucagon plus GLP-1 receptor agonist, leverages combined receptor activation to enhance metabolic effects beyond those of GLP-1RAs alone. Through simultaneous glucagon and GLP-1 receptor stimulation, survodutide facilitates significant weight loss, increased lipolysis, and improved hepatic lipid and glucose metabolism, positioning it as a promising therapy for patients with MASH and hepatic fibrosis. The phase 2 randomized, placebo-controlled trial (1404-0043 trial[29]) evaluated survodutide (2.4, 4.8, or 6.0 mg weekly) in biopsy-proven MASH patients with hepatic fibrosis stages F1–F3 over 48 weeks. Survodutide achieved MASH resolution without hepatic fibrosis worsening in 47% (2.4 mg), 62% (4.8 mg), and 43% (6.0 mg) of patients compared to 14% in placebo ($p < 0.001$). Significant liver fat reduction (≥30%) occurred in 57–67% of survodutide-treated patients vs 14% in placebo, with hepatic fibrosis improvement (≥1 stage) observed in 34–36 vs 22% with placebo. Mild to moderate GI symptoms (nausea, diarrhea, vomiting) were the most common adverse events, while serious adverse events occurred at similar rates between survodutide and placebo groups. Survodutide demonstrated significant histological and metabolic improvements in MASH patients, supporting its progression to phase 3 trials. Further studies will assess long-term efficacy, safety, and impact on hepatic fibrosis regression.[29]

Triple agonists extend this approach by incorporating glucagon receptor activation along with GLP-1 and GIP, which enhances lipid oxidation, boosts energy expenditure,

and facilitates fat mobilization. This combined mechanism contributes to significant weight reduction and metabolic improvements, making these agents promising for the treatment of obesity, MASLD/MASH, and T2DM.[27] Retatrutide, a next-generation triple agonist, has been developed to optimize metabolic regulation by improving insulin secretion, accelerating fat metabolism, and reducing hepatic fat deposition. Given its robust metabolic effects, retatrutide is currently under investigation as a potential therapy for MASLD/MASH. In a phase 2a randomized, double-blind, placebo-controlled trial,[30] retatrutide administered weekly at doses of 1, 4, 8, or 12 mg resulted in significant reductions in liver fat content (42.9–82.4%) over 24 weeks, compared to a negligible change with placebo (+0.3%, $p < 0.001$ for all doses). Furthermore, between 27 and 86% of patients receiving retatrutide achieved liver fat normalization (<5%), while no such improvement was observed in the placebo group. These reductions in hepatic fat were strongly associated with marked weight loss, decreased abdominal adiposity, and improved insulin sensitivity.[30] Given these promising results, retatrutide is now progressing to larger phase 3 trials to further evaluate its efficacy and safety in MASLD/MASH management.

Peroxisome Proliferator-activated Receptor Agonists: a Multi-pathway Therapeutic Approach for MASLD/MASH

Peroxisome proliferator-activated receptors are ligand-activated nuclear receptors that regulate lipid metabolism, glucose homeostasis, inflammation, and hepatic fibrosis, making them attractive therapeutic targets for MASLD/MASH. The three PPAR isoforms exert distinct but complementary effects: PPAR-α (activated by fibrates) enhances fatty acid oxidation, PPAR-γ [targeted by thiazolidinediones (TZDs) like pioglitazone] regulates adipogenesis and insulin sensitivity, and PPAR-δ modulates glucose metabolism, inflammation, and mitochondrial function. Given the multifactorial nature of MASLD/MASH, PPAR agonists offer a promising therapeutic approach by targeting hepatic steatosis, insulin resistance, inflammation, and hepatic fibrosis.

Pioglitazone: The First Peroxisome Proliferator-activated Receptor Agonist Studied in MASLD/MASH

Pioglitazone, a PPAR-γ agonist, has been extensively studied for MASLD/MASH due to its role in enhancing insulin sensitivity, reducing hepatic fat accumulation, and modulating inflammation. The PIVENS trial,[7] a pivotal phase 3 study, evaluated pioglitazone (30 mg/day) in biopsy-confirmed MASH patients without diabetes, showing a significant improvement in liver histology, with MASH resolution achieved in 47% of treated patients compared to 21% in the placebo group ($p < 0.001$). However, its impact on hepatic fibrosis was not statistically significant.

Multiple meta-analyses reinforce the effectiveness of pioglitazone in MASLD/MASH, particularly in improving steatosis, inflammation, and hepatocellular ballooning. Studies by Lian and Fu[31] and Zhao et al.[32] highlighted reductions in liver enzymes, fasting glucose, triglycerides, and HbA1c, although hepatic fibrosis outcomes remained inconsistent. Panunzi et al.[33] and Gu et al.[34] reported comparable efficacy between pioglitazone, GLP-1RAs, and vitamin E in histological improvement, whereas Wang et al.[35] found similar benefits in both diabetic and nondiabetic patients, with edema being a notable side effect in diabetics. Additionally, Boettcher et al.[36] demonstrated that pioglitazone outperformed rosiglitazone, showing greater improvements in necroinflammation and hepatic fibrosis. Collectively, these findings support pioglitazone as a valuable option for MASLD/MASH, especially in individuals with significant liver fibrosis (F2–F3).

Beyond its hepatic effects, pioglitazone has demonstrated cardiovascular benefits, reducing the risk of MACE in insulin-resistant individuals. However, its clinical use is often limited by weight gain, edema, and a potential risk of heart failure, particularly at higher doses. Lower-dose regimens (15 mg/day) are being explored to optimize benefits while mitigating these risks.

Saroglitazar: A Dual Peroxisome Proliferator-activated Receptor-α/γ Agonist with a Favorable Profile

Saroglitazar, a dual PPAR-α/γ agonist, has been approved by the Drug Controller General of India (DCGI) for the treatment of MASLD and metabolic disorders due to its ability to modulate lipid metabolism, enhance insulin sensitivity, and reduce liver fat accumulation. Unlike pioglitazone, which primarily activates PPAR-γ and is associated with weight gain, saroglitazar exerts a balanced effect on both lipid and glucose metabolism. This results in significant triglyceride reduction, better glycemic control, and decreased ALT levels.

A phase 2 randomized controlled trial (RCT)[37] evaluated saroglitazar in 106 patients with NAFLD/MASH who had elevated ALT and a BMI of ≥25 kg/m^2. After 16 weeks of treatment with saroglitazar 4 mg, patients exhibited substantial improvements, including a 45.8% reduction in ALT compared to a 3.4% increase in the placebo group ($p < 0.001$). Additionally, liver fat content decreased by 19.7% in the saroglitazar group, whereas it increased by 4.1% with placebo. The drug also significantly reduced insulin resistance (HOMA-IR) and triglyceride levels ($p < 0.05$ for all). Saroglitazar was well tolerated, although a modest weight gain of 1.5 kg was noted.[37] These findings underscore saroglitazar's potential as a therapeutic option for MASLD/MASH, particularly in individuals with coexisting metabolic dysfunction and dyslipidemia.

Several subsequent studies have evaluated the efficacy of saroglitazar (4 mg daily) in MASLD/MASH, demonstrating significant metabolic and hepatic benefits.[38–42] A pooled analysis of phase 2 and 3 trials by Siddiqui et al. showed that saroglitazar significantly improved atherogenic dyslipidemia, reducing total cholesterol, triglycerides, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and small dense LDL-C, irrespective of comorbidities or statin use.[39] A meta-analysis by Bandyopadhyay et al. confirmed that saroglitazar significantly reduced ALT, AST, and liver stiffness (–2.22 kPa), while also improving glycemic control (HbA1c reduction by 0.59%) and lipid profile, with a favorable safety profile.[40] A comprehensive review with subgroup meta-analysis by Roy et al. further supported these findings, highlighting improvements in transaminases, liver fat content, metabolic health, and liver stiffness.[43] These studies suggest that saroglitazar has both hepatic and cardiometabolic benefits, making it a promising therapeutic option in MASLD/MASH, particularly in patients with dyslipidemia and insulin resistance.

Lanifibranor: A Pan-peroxisome Proliferator-activated Receptor Agonist with Antifibrotic Potential

Lanifibranor is a pan-PPAR agonist that activates all three PPAR isoforms, contributing to multiple beneficial effects in MASLD/MASH. Through PPAR-α activation, it promotes the reduction of hepatic steatosis, while PPAR-δ activation suppresses inflammation, and PPAR-γ activation plays a role in inhibiting hepatic stellate cell activation and hepatic fibrosis progression.

The NATIVE trial,[44] a phase 2b randomized, double-blind, placebo-controlled study, evaluated lanifibranor in patients with biopsy-confirmed MASH who did not have cirrhosis. Over 24 weeks, participants were assigned to receive lanifibranor at doses of 800 or 1200 mg, or a placebo. The primary endpoint of

the study was achieving at least a two-point reduction in the activity component of the SAF (steatosis, activity, fibrosis) score without exacerbation of hepatic fibrosis. Secondary endpoints examined changes in steatosis, hepatocellular ballooning, inflammation, hepatic fibrosis progression, and metabolic markers. The study demonstrated significant histological improvement, including reduced inflammation and hepatic fibrosis markers, compared to placebo. Lanifibranor was well tolerated, with no major safety concerns identified.[44] Additionally, a recent phase 2 trial in MASLD with T2DM showed that lanifibranor led to a significant reduction in intrahepatic triglyceride content (~50%) and improved insulin sensitivity.[45] These findings support pan-PPAR agonism as a promising strategy for treating MASLD/MASH by addressing metabolic dysfunction, hepatic fibrosis, intrahepatic steatosis, as well as insulin resistance, simultaneously. These findings led to the phase 3 NATiV3 trial (NCT04849728, *n* = 1000), where patients receive 800 or 1200 mg for 72 weeks, with MASH resolution and hepatic fibrosis improvement as primary outcomes. An extended treatment phase will assess long-term outcomes, including cirrhosis-free survival.[46]

Peroxisome proliferator-activated receptor agonists represent a versatile therapeutic class for MASLD/MASH, addressing hepatic steatosis, insulin resistance, inflammation, and hepatic fibrosis. While pioglitazone remains an established option, its side effects limit widespread use. Saroglitazar offers metabolic advantages with a better safety profile, while lanifibranor is emerging as a leading candidate in phase 3 trials for hepatic fibrosis regression and MASH resolution. As ongoing studies progress, PPAR-based therapies could become mainstay treatments for metabolic and fibrotic liver diseases.

Sodium-glucose Cotransporter-2 Inhibitors: a Metabolic Therapy with Hepatoprotective Potential

Sodium-glucose cotransporter-2 inhibitors are a class of antidiabetic drugs that lower blood glucose levels by promoting urinary glucose excretion, thereby preventing renal glucose reabsorption. In addition to urinary glucose excretion, SGLT2i promote natriuresis and diuresis, leading to reductions in blood pressure and plasma volume, which may contribute to their cardioprotective effects in MASLD patients at high risk of CVD. Initially developed for T2DM, SGLT2i have demonstrated broad cardiovascular and renal protective benefits, leading to their expanded use beyond glycemic control. Emerging evidence suggests that SGLT2i may also have hepatoprotective effects in MASLD/MASH by improving hepatic steatosis, inflammation, and hepatic fibrosis through weight loss, insulin sensitization, and reduction of oxidative stress. Additionally, SGLT2i enhance lipid metabolism by promoting lipolysis, ketogenesis, and reducing hepatic DNL, which collectively mitigate liver injury and hepatic fibrosis progression. Although generally well tolerated, SGLT2i are associated with an increased risk of genitourinary infections, volume depletion, and, rarely, Fournier's gangrene.[47] While early concerns about increased amputation and fracture risk were noted in the CANVAS trial, subsequent meta-analyses have not confirmed this association.[48,49]

Clinical Evidence Supporting Sodium-glucose Cotransporter-2 Inhibitors in MASLD/MASH with Type 2 Diabetes Mellitus

A large nationwide cohort study by Bea et al.[50] using data from the Korean National Health Insurance Service (2014–2022) evaluated the hepatic benefits of SGLT2i compared to GLP-1RAs and TZDs in MASLD patients. The study included over 22,000 patients for the SGLT2i vs GLP-1RA analysis and nearly 1,92,000 for the SGLT2i vs TZD comparison. Findings indicated that SGLT2i significantly lowered the risk of hepatic decompensation events, including ascites, variceal bleeding, hepatic failure, or liver transplantation, compared to TZDs (HR 0.77, 95% CI: 0.72–0.82). However, their effectiveness was comparable to GLP-1RAs (HR 0.93, 95% CI: 0.76–1.14). The protective effects of SGLT2i were more pronounced in females and patients younger than 65 years, suggesting specific subgroups that may derive enhanced hepatic benefits from this therapy.[50]

Similarly, a nationwide claims database analysis by Kawaguchi et al.[51] in Japan assessed the impact of SGLT2i on liver-related outcomes and extrahepatic cancer risk in T2DM patients with suspected MASLD. In a propensity-matched cohort of 8,408 patients [SGLT2i vs dipeptidyl peptidase-4 (DPP4) inhibitors], SGLT2i significantly reduced ALT levels and improved hepatic fibrosis indices (FIB-4 index) over 12 months. While overall liver-related event rates did not differ significantly, SGLT2i led to a marked reduction in the risk of esophageal varices (HR 0.12, 95% CI: 0.01–0.95, $p = 0.044$). Additionally, a notable 50% reduction in extrahepatic cancer incidence (HR 0.50, 95% CI: 0.30–0.84, $p = 0.009$) was observed, suggesting a potential oncoprotective effect of SGLT2i in MASLD patients with T2DM.[51]

A meta-analysis of seven RCTs (390 patients) found that dapagliflozin significantly reduced ALT, AST, HOMA-IR, body weight, BMI, LDL-C, and triglycerides in NAFLD patients, improving liver function and metabolic outcomes. However, it caused a slight increase in total cholesterol, and its effect on GGT was not significant.[52] A systematic review and meta-analysis of four RCTs (244 NAFLD patients) found that empagliflozin significantly reduced BMI, liver stiffness measurement (LSM), AST, and HOMA-IR, indicating improvements in body composition, insulin resistance, and liver fibrosis. While these findings suggest empagliflozin as a potential therapy for NAFLD, further studies are needed to prove its long-term efficacy and safety.[53] The most recent systematic review and meta-analysis evaluating 18 RCTs ($n = 1,330$ patients) demonstrated that SGLT2 inhibitors significantly improved hepatic steatosis (assessed by MRI-PDFF, CAP, and L/S ratio) and hepatic fibrosis (assessed by LSM and FIB-4 index) in patients with NAFLD, primarily those with T2DM. Additionally, histological improvement in liver fibrosis and hepatocellular ballooning was observed, highlighting the potential therapeutic benefits of SGLT2 inhibitors in MASLD/MASH management.[54]

The DEAN trial (Dapagliflozin Efficacy and Action in NASH, NCT03723252) was a multicenter, randomized, double-blind, placebo-controlled phase 3 study conducted in China to evaluate the efficacy of dapagliflozin in biopsy-proven MASH (both diabetic and non-diabetic). At 48 weeks, dapagliflozin significantly improved MASH without worsening fibrosis in 53% of patients (vs 30% with placebo), with higher rates of MASH resolution and fibrosis improvement compared to placebo, and a favorable safety profile.[55]

While earlier studies with SGLT2 inhibitors demonstrated improvements in hepatic steatosis and non-invasive fibrosis markers, the lack of biopsy-proven histological data limited definitive conclusions about their efficacy in MASH. However, the recent DEAN trial[55] has now provided the first robust evidence of histological benefit, showing that dapagliflozin significantly improves MASH and fibrosis without worsening either. Current guidelines now recommend SGLT2 inhibitors for patients with diabetic MASLD/MASH[56], and based on emerging evidence, they may soon be considered for non-diabetic MASH as well.

Emerging Evidence on Sodium-glucose Cotransporter-2 Inhibitors in Nondiabetic MASLD/MASH

The role of SGLT2i in nondiabetic MASLD was previously less certain. Early evidence suggests SGLT2i may reduce hepatic fat and improve metabolic parameters in

nondiabetic individuals. A randomized placebo-controlled trial demonstrated that empagliflozin (10 mg daily, 52 weeks) significantly lowered hepatic fat (MRI-PDFF: −2.49 vs −1.43%, $p = 0.025$), along with improved weight, waist circumference, glucose levels, and ferritin, although complete steatosis resolution was not significant.[57] Another small study showed dapagliflozin (12 weeks) significantly reduced ALT levels and body fat mass, despite no significant change in hepatic steatosis.[58]

These effects likely stem from indirect metabolic improvements rather than direct hepatic mechanisms.[59] Notably, responsiveness to empagliflozin appears linked to specific gut microbiota profiles, highlighting the potential for personalized therapy based on microbiome composition.[60] While promising, these preliminary results warrant further research before routine clinical use in nondiabetic MASLD patients. The DEAN trial[55] provided important insights into the efficacy of SGLT2 inhibitors in non-diabetic MASH. Notably, 55% of enrolled participants did not have type 2 diabetes, yet dapagliflozin demonstrated significant histological benefits across the full cohort. This suggests that the hepatic benefits of SGLT2 inhibitors—namely MASH resolution and fibrosis improvement—may extend beyond glycemic control. These findings support the potential role of SGLT2 inhibitors in non-diabetic MASH and may pave the way for future guideline inclusion and regulatory approval in this broader population.

Fibroblast Growth Factor 21: A Master Regulator of Energy and Lipid Metabolism

Fibroblast growth factor 21 is a hepatokine with a key role in regulating glucose and lipid metabolism, energy balance, and inflammation.[61] Secreted mainly by the liver, FGF21 exerts its metabolic effects by binding to FGF receptor 1c (FGFR1c) and its coreceptor β-Klotho (KLB), influencing adipose tissue, skeletal muscle, and the central nervous system. This signaling pathway enhances insulin sensitivity, promotes fatty acid oxidation, and reduces hepatic lipogenesis, making FGF21 a promising therapeutic target for MASLD and related metabolic disorders. Unlike FGF19, which regulates bile acid metabolism, FGF21 is primarily induced by nutrient stress such as fasting, ketogenic diets, and overnutrition, helping to enhance insulin sensitivity, promote fatty acid oxidation, and reduce hepatic steatosis. In MASLD/MASH, FGF21 has been shown to protect hepatocytes, reduce inflammation, and prevent hepatic fibrosis progression by modulating mitochondrial function and macrophage activity. However, native FGF21 has a very short half-life (~30 minutes), necessitating the development of long-acting FGF21 analog with improved stability and efficacy.[61] Several FGF21 analog are being evaluated in late-stage clinical trials for MASLD/MASH, demonstrating promising histological and metabolic improvements.

The HARMONY trial was a phase 2b, multicenter, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of efruxifermin, a bivalent FGF21 analog, in individuals with biopsy-confirmed MASH and moderate to severe hepatic fibrosis (F2–F3).[62] Conducted across 41 US sites, the trial enrolled 128 patients, who were assigned to receive either placebo, 28, or 50 mg of efruxifermin *via* weekly subcutaneous injections. After 24 weeks, hepatic fibrosis improvement of ≥1 stage without worsening of MASH was observed in 39% (28 mg) and 41% (50 mg) of participants, compared to 20% in the placebo group ($p = 0.025$, $p = 0.036$, respectively). The most frequent adverse events were mild to moderate gastrointestinal symptoms, including nausea and diarrhea, leading to five treatment discontinuations. A single serious adverse event, ulcerative esophagitis, was reported as drug-related. These results indicate that efruxifermin significantly improved hepatic fibrosis and MASH resolution, warranting further evaluation in phase 3 trials.[62]

The ENLIVEN trial, another phase 2b, randomized, double-blind, placebo-controlled study, assessed the efficacy of pegozafermin, a long-acting glycopegylated FGF21 analog, in patients with MASH and F2–F3 hepatic fibrosis.[63] The trial enrolled 222 participants, who were randomized to receive pegozafermin (15 or 30 mg weekly, 44 mg every 2 weeks) or placebo for 24 weeks. Hepatic fibrosis improvement (≥1 stage) without worsening of MASH was achieved in 22% (15 mg), 26% (30 mg, $p = 0.009$), and 27% (44 mg, $p = 0.008$), compared to 7% in the placebo group. Additionally, MASH resolution occurred in 37% (15 mg), 23% (30 mg), and 26% (44 mg) of patients, vs only 2% with placebo. Gastrointestinal side effects such as nausea and diarrhea were the most commonly reported adverse events, though treatment was generally well tolerated.[63] These findings support further phase 3 trials to evaluate pegozafermin as a promising therapy for MASLD/MASH.

Additional FGF21 analog in development, including BIO89-100 and LLF580, are in early clinical stages, aiming to provide longer half-life, enhanced metabolic benefits, and hepatic fibrosis improvement. These FGF21-based therapies offer a unique metabolic and antifibrotic approach to MASLD/MASH treatment, with favorable safety profiles and minimal mitogenic risks compared to FGF19 analog. Ongoing phase 3 trials will further define their long-term efficacy and potential for regulatory approval.

Farnesoid X Receptor Agonists: Targeting Bile Acid Metabolism for MASLD/MASH

Farnesoid X receptor agonists are a class of drugs that modulate bile acid metabolism, glucose homeostasis, and hepatic inflammation, making them promising therapeutic agents for MASLD/MASH. FXR is a nuclear receptor highly expressed in the liver and intestines that, upon activation, regulates bile acid synthesis by inhibiting CYP7A1, the enzyme responsible for converting cholesterol into bile acids. By reducing hepatocyte exposure to excess bile acids, FXR activation helps mitigate hepatic inflammation, hepatic fibrosis, and metabolic dysfunction.

Obeticholic Acid: The Leading Farnesoid X Receptor Agonist and Its Setback

Obeticholic acid, a semi-synthetic FXR agonist, was among the first agents in this class to undergo extensive evaluation for MASH therapy. Early-phase studies demonstrated its ability to enhance insulin sensitivity, reduce hepatic steatosis, and lower hepatic fibrosis biomarkers, supporting its potential role in MASLD/MASH management. By activating FXR, OCA modulates bile acid metabolism, suppresses hepatic lipogenesis, and exerts antifibrotic effects, which were observed in both preclinical and clinical studies. However, concerns related to pruritus, lipid abnormalities, and long-term cardiovascular safety have impacted its regulatory approval process, necessitating further investigation into its overall risk-benefit profile.

The phase 3 REGENERATE trial[64] evaluated 10 and 25 mg OCA daily in NASH patients with F2–F3 hepatic fibrosis. The primary endpoint was ≥1-stage hepatic fibrosis improvement without worsening MASH. While OCA showed significant hepatic fibrosis reduction, the FDA rejected its New Drug Application (NDA), citing concerns about drug-induced liver and

kidney injury and questioning the validity of hepatic fibrosis improvement assessments, as some were based on noninvasive biomarkers instead of biopsy. This setback has halted OCA's approval for MASH, shifting research focus toward safer FXR agonists with improved tolerability.

A recent analysis of the REGENERATE trial[65] reaffirmed that OCA 25 mg provides significant hepatic fibrosis improvement in patients with precirrhotic MASH. At 18 months, 22.4% of patients achieved at least a one-stage hepatic fibrosis reduction, compared to 9.6% in the placebo group ($p < 0.0001$). However, the rate of MASH resolution without worsening hepatic fibrosis did not attain statistical significance (6.5 vs 3.5%, $p = 0.093$). Additional histological assessments from 1,607 participants further supported the antifibrotic effects of OCA. Long-term safety data covering over 8,000 patient-years indicated that OCA was generally well tolerated, with pruritus being the most frequently reported side effect. Importantly, serious adverse events were comparable across treatment groups, reinforcing a favorable benefit-risk profile for OCA in patients with hepatic fibrosis due to MASH.[65]

Given the antifibrotic efficacy demonstrated in the REGENERATE trial, off-label use of OCA may be considered in selected MASH patients with significant hepatic fibrosis (F2–F3) but without cirrhosis, particularly in those at high risk of progression. However, caution is warranted due to safety concerns, and patients should be closely monitored.

Emerging Farnesoid X Receptor Agonists: The Next Generation

Given OCA's safety concerns, several next-generation FXR agonists are being developed to retain efficacy while minimizing side effects. Cilofexor is a nonsteroidal FXR agonist that modulates bile acid metabolism, influencing synthesis, conjugation, and excretion. By activating FXR, cilofexor reduces hepatic bile acid accumulation, decreases lipogenesis, and exerts anti-inflammatory and antifibrotic effects, making it a potential therapeutic candidate for MASLD/MASH. The phase 2 trial (NCT02854605) evaluated cilofexor, a nonsteroidal FXR agonist, in 140 noncirrhotic NASH patients over 24 weeks. Cilofexor 100 mg significantly reduced hepatic steatosis (–22.7% MRI-PDFF, $p = 0.003$) and bile acid markers, but had no significant effect on liver stiffness or hepatic fibrosis markers. The drug was well tolerated, though moderate to severe pruritus occurred in 14% at the 100 mg dose.[66] FXR agonists offer a mechanistically sound approach to treating MASLD/MASH, but safety concerns with OCA have slowed clinical progress. Future research is focused on refining FXR-based therapies to achieve hepatic fibrosis regression with fewer adverse effects, ensuring that these drugs can be safely integrated into MASLD/MASH management.

Denifanstat: a Fatty Acid Synthase Inhibitor for MASLD/MASH

Denifanstat is a first-in-class oral inhibitor of fatty acid synthase, a key enzyme involved in DNL. Excessive DNL contributes to lipotoxicity, hepatocyte injury, inflammation, and hepatic fibrosis, making FASN a promising therapeutic target for MASLD/MASH. By blocking hepatic fat synthesis, denifanstat aims to reduce liver fat accumulation, improve metabolic parameters, and prevent hepatic fibrosis progression.

Denifanstat was evaluated in a phase 2b, multicenter, double-blind, randomized, placebo-controlled trial conducted across 100 sites in the USA, Canada, and Poland.[67] The study included 168 biopsy-confirmed MASH patients with F2–F3 hepatic fibrosis, randomized to receive 50 mg of denifanstat or placebo once daily for 52 weeks. At week 52, 38% of denifanstat-treated patients achieved a ≥2-point reduction in NAFLD Activity Score (NAS) without worsening hepatic fibrosis, in comparison to 16% in the placebo arm ($p = 0.0035$). MASH resolution with improvement in NAS score was seen in 26% of denifanstat patients vs 11% with placebo ($p = 0.0173$). The drug was well tolerated, with COVID-19 infections, mild dry eye symptoms, and alopecia being the most commonly reported adverse events, though no serious drug-related adverse events occurred.[67] These findings support denifanstat's potential as a metabolic and antifibrotic therapy for MASLD/MASH and justify its progression to phase 3 trials.

Fibroblast Growth Factor 19: a Key Regulator of Bile Acid Metabolism and Liver Health

Fibroblast growth factor 19 is an endocrine hormone predominantly synthesized by ileal enterocytes in response to bile acid-mediated activation of the FXR. Once secreted into circulation, FGF19 binds to fibroblast growth factor receptor 4 (FGFR4) in hepatocytes, with KLB acting as a coreceptor, to regulate bile acid homeostasis. A key function of FGF19 signaling is the suppression of bile acid synthesis by inhibiting cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the bile acid synthesis pathway. This process is essential for regulating hepatic lipid metabolism, maintaining energy balance, and modulating inflammation, positioning FGF19 analog as promising therapeutic candidates for MASLD/MASH. This regulatory role prevents excessive bile acid accumulation, thereby protecting hepatocytes from bile acid toxicity. Beyond its role in bile acid homeostasis, FGF19 has metabolic and hepatoprotective effects, including reducing hepatic lipogenesis, promoting glycogen synthesis, and improving insulin sensitivity. However, concerns exist regarding its mitogenic potential, as elevated FGF19 levels have been linked to HCC in preclinical models. To mitigate this risk, nonmitogenic FGF19 analog, such as aldafermin (NGM282), have been developed and have demonstrated promising efficacy results in reducing liver steatosis and fibrosis in patients with MASH.[61] The phase 2b ALPINE 2/3 trial evaluated aldafermin, an FGF19 analog, in 171 NASH patients with stage 2–3 hepatic fibrosis over 24 weeks. Although aldafermin demonstrated some improvements in secondary endpoints, it failed to produce a significant dose-dependent effect on hepatic fibrosis, reducing its viability as a standalone therapy for NASH.[68]

Omega-3 Fatty Acids in MASLD/MASH: a Potential Therapeutic Option

Omega-3 polyunsaturated fatty acids (PUFAs) have gained attention for their anti-inflammatory and lipid-lowering properties, making them a promising option for MASLD/MASH management. These fatty acids primarily work by reducing hepatic triglyceride accumulation, improving insulin sensitivity, and modulating inflammation, which are central to the pathophysiology of MASLD/MASH. While early clinical studies have demonstrated a potential benefit of omega-3 supplementation in reducing liver fat and improving metabolic parameters, the optimal dosage, duration, and type (marine vs plant-based sources) remain unclear.

A meta-analysis[69] involving nine studies (355 patients) reported a significant reduction in liver fat ($p < 0.001$) and AST levels ($p = 0.02$) following omega-3 PUFA supplementation, though the effect on ALT levels was not significant ($p = 0.06$). A sub-analysis of

RCTs confirmed the benefit for hepatic fat reduction, but improvements in liver enzymes remained inconclusive, emphasizing the need for well-structured RCTs to establish the true therapeutic impact.[69] Another meta-analysis that included 22 RCTs (1,366 patients) demonstrated omega-3 PUFA supplementation led to a notable reduction in steatosis (RR 1.52, 95% CI: 1.09–2.13) and improved triglycerides, total cholesterol, HDL, and BMI, indicating potential metabolic benefits.[70] Additionally, a meta-analysis by Moore et al. assessed six RCTs (362 patients) investigating plant-based omega-3 supplementation in MASLD. The study observed significant reductions in ALT levels and triglycerides, alongside improvements in BMI, waist circumference, and body weight, particularly when combined with lifestyle interventions.[71] However, further research is warranted to determine optimal plant-based omega-3 sources and their long-term impact on liver hepatic fibrosis and histological outcomes.

Current evidence suggests that omega-3 supplementation, particularly marine-derived forms, may reduce hepatic fat accumulation and improve metabolic parameters in MASLD/MASH patients. However, its role in hepatic fibrosis improvement remains unclear, and further high-quality, long-term trials are required to determine optimal dosing and patient selection criteria.

Ursodeoxycholic Acid in MASLD/MASH: An Unfulfilled Promise

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, has been widely used for cholestatic liver diseases like primary biliary cholangitis (PBC). Due to its cytoprotective, antiapoptotic, and anti-inflammatory properties, UDCA has been explored as a potential treatment for MASLD/MASH. UDCA enhances bile flow, reduces oxidative stress, and modulates lipid metabolism.

Despite its theoretical benefits, UDCA has shown mixed results in MASLD/MASH. A 2004 randomized trial by Lindor et al. found that UDCA at 13–15 mg/kg/day did not significantly improve liver histology compared to placebo, though it was well tolerated.[72] Similarly, the 2010 high-dose UDCA trial by Leuschner et al. (23–28 mg/kg/day) found no significant improvements in overall histology, though lobular inflammation improved in some subgroups.[73] Several meta-analyses and systematic reviews have evaluated UDCA's efficacy in MASLD/MASH. A 2013 systematic review by Xiang et al.[74] analyzed 12 RCTs, including six from China, and reported that UDCA monotherapy led to improvements in liver function in five studies and hepatic fibrosis regression in two. However, the overall quality of evidence was deemed low, particularly in studies conducted in China. A subsequent 2018 meta-analysis by Pavlov et al.,[75] which included four RCTs with 510 participants, found no significant impact of UDCA on hepatic fibrosis, steatosis, or hepatic inflammation, although the drug was well tolerated. These findings suggest that while UDCA may provide some biochemical benefits, its efficacy in MASLD/MASH remains unproven, warranting further investigation through high-quality, well-powered clinical trials. A 2022 meta-analysis by Lin et al., reviewing eight RCTs with 655 patients, confirmed that UDCA significantly reduced ALT and γGT but did not improve liver histology.[76] The most recent 2024 meta-analysis by Patel et al. further reinforced these findings, demonstrating that UDCA significantly lowered ALT, AST, and γGT levels but had no impact on bilirubin, alkaline phosphatase, or liver histology.[77]

Thus, while UDCA may have biochemical benefits in MASLD/MASH, particularly in reducing liver enzymes, it has not demonstrated robust histological efficacy as monotherapy. High-dose UDCA may provide some biochemical improvements but lacks significant histological benefits. Routine use of UDCA for MASLD/MASH is not recommended, except in selected cases where concurrent cholestatic liver disease is present. Further well-designed clinical trials are needed to assess its role, particularly in combination therapies.

Other Antidiabetic Drugs in MASLD/MASH: Limited Role beyond Glycemic Control

Role of Metformin in Diabetic MASLD

Metformin remains the first-line therapy for T2DM and should be continued in all diabetic MASLD patients unless contraindicated.[78] As an insulin sensitizer, it provides cardiovascular benefits, improves metabolic parameters, and reduces insulin resistance, a central mechanism in MASLD pathogenesis. However, metformin does not directly improve liver histology or hepatic fibrosis. Studies such as the TONIC trial[79] and a meta-analysis[80] have demonstrated biochemical improvements (ALT/AST reduction) but no significant histological benefit. Several observational studies have reported an association between metformin use and a reduced risk of HCC in individuals with T2DM.[81,82] However, despite its metabolic benefits, current guidelines do not support metformin as a specific treatment for MASLD. Instead, diabetic patients with MASLD should receive additional pharmacologic interventions that address both metabolic dysfunction and hepatic outcomes. Depending on hepatic fibrosis severity, GLP-1RAs (e.g., semaglutide), SGLT2i, pioglitazone, and saroglitazar are recommended as more targeted therapeutic options. Thus, while metformin remains the backbone for diabetes management, it should be complemented with agents that specifically address MASLD progression.

Role of Dipeptidyl Peptidase-4 Inhibitors in Diabetic MASLD

Dipeptidyl peptidase-4 inhibitors have been investigated for their potential anti-inflammatory and metabolic effects in MASLD/MASH. Preclinical studies suggested improvements in hepatic steatosis and hepatic fibrosis; however, clinical trials have not demonstrated significant histological benefits. A meta-analysis of RCTs found that while DPP-4 inhibitors modestly reduced liver enzymes, they did not significantly impact hepatic fibrosis or histological improvement.[83] Given the availability of more effective agents like GLP-1RAs and SGLT2i, DPP-4 inhibitors are not currently recommended for MASLD treatment.

Role of Sulfonylureas and Insulin in Diabetic MASLD

The impact of sulfonylureas on MASLD remains poorly characterized. These insulin secretagogues primarily act by stimulating pancreatic β-cells to enhance insulin secretion, thereby improving glycemic control. However, sulfonylureas do not directly address the underlying pathophysiological mechanisms of MASLD, such as insulin resistance, hepatic steatosis, or hepatic fibrosis. Some studies suggest that chronic hyperinsulinemia induced by sulfonylureas may exacerbate hepatic lipogenesis and fat accumulation, potentially worsening MASLD progression.[84,85] Despite their widespread use in diabetes management, there is insufficient evidence to recommend sulfonylureas for MASLD treatment, and their use should be carefully considered, particularly in patients with significant hepatic involvement. Whenever possible, agents with demonstrated hepatic and metabolic benefits, such as GLP-1RAs or SGLT2i, should be prioritized in MASLD patients with T2DM.[4]

Insulin therapy reduces hepatic glucose production and improves insulin resistance, which may have indirect benefits on hepatic

steatosis. However, studies assessing insulin therapy in MASLD patients have not shown clear improvements in MASH or hepatic fibrosis. A trial comparing insulin glargine to liraglutide in diabetic MASLD patients found similar reductions in MRI-measured hepatic fat content, indicating that insulin alone does not significantly alter liver histology.[86] Therefore, while insulin remains a cornerstone in diabetes management, it should be used cautiously in MASLD patients, with preference given to agents that improve both glycemic control and liver health.

Algorithm for the Management of Noncirrhotic MASLD in India

India bears a significant burden of MASLD, driven by the rising prevalence of obesity, T2DM, and metabolic syndrome. Lifestyle modification remains the cornerstone of MASLD therapy, but pharmacologic interventions play an adjunctive role, particularly in patients with progressive disease or those at higher risk of complications. Unlike Western countries, where hepatologists primarily manage MASLD, in India, the majority of MASLD patients are diagnosed and treated by general physicians and diabetologists. Despite the growing disease burden, India currently lacks a widely adopted, practical, and simplified pharmacological algorithm for MASLD management in primary care settings (Fig. 3).

The algorithm (Fig. 3) presented here is specifically designed for the pharmacological management of noncirrhotic MASLD in India, tailored for use by general physicians and diabetologists. It incorporates only those drugs currently available in the country, ensuring feasibility and practical application. This India-specific algorithm provides structured guidance on pharmacologic options tailored to hepatic fibrosis stage and diabetes status, aiming to bridge the gap between evidence-based recommendations and real-world clinical practice.

This algorithm applies specifically to patients with F0–F3 fibrosis. Subjects with F4 fibrosis (cirrhosis) require specialized hepatology care due to an increased risk of complications such as portal hypertension, HCC, and liver failure. Referral to a hepatologist is recommended, and these patients should undergo comprehensive evaluation, including screening for esophageal varices, HCC surveillance, and risk assessment for hepatic decompensation, with consideration for liver transplantation in eligible cases.

Lifestyle Modifications: Foundation of MASLD Treatment

All patients with MASLD, irrespective of hepatic fibrosis stage or diabetes status, should receive comprehensive lifestyle interventions, focusing on:

- Dietary modifications: Emphasize a hypocaloric, nutritionally balanced diet rich in whole grains, legumes, vegetables, fruits, nuts, and healthy fats, while minimizing refined carbohydrates, added sugars, and processed foods. This dietary approach supports metabolic health, reduces hepatic steatosis, and aids in weight management, which is crucial for MASLD/MASH management. Protein intake should be optimized, with a preference for plant-based sources or lean animal proteins. Reducing saturated fats and replacing them with unsaturated fats (e.g., nuts, seeds, and mustard oil) can be beneficial, along with avoiding sugar-sweetened beverages and excessive alcohol intake. Regular coffee consumption has been associated with reduced hepatic fibrosis progression and a lower risk of HCC, supporting its inclusion in MASLD dietary strategies.[87,88] Additionally, fatty fish rich in omega-3 fatty acids (e.g., salmon, mackerel, sardines) may provide anti-inflammatory and lipid-lowering benefits. A macronutrient distribution of approximately 50% carbohydrates, 30% fats, and 20% proteins is generally recommended for balanced nutrition in MASLD management.[89–92]
- Physical activity: Patients should aim for 150–300 minutes of moderate-intensity exercise per week, such as brisk walking, cycling, or swimming, as it enhances insulin sensitivity, reduces hepatic fat, and improves cardiometabolic health. Incorporating nonexercise physical activity (NEPA) (e.g., walking breaks, household chores) and targeting a daily step count of 8,000–10,000 steps can further support MASLD/MASH management.[93,95] In addition to structured exercise, NEPA—such as taking the stairs, walking short distances, standing more frequently, and engaging in household chores—should be encouraged to increase daily energy expenditure.[95] A daily step count of 8,000–10,000 steps, if feasible, is a practical goal to enhance overall activity levels and metabolic health.[96]
- Weight loss goal: Achieving a weight loss of at least 10% has been strongly linked to improvements in MASLD, including regression of the disease, resolution of MASH, and reduction in hepatic fibrosis. Vilar-Gomez et al.[97] demonstrated that such weight loss leads to MASH resolution in nearly 90% of patients, with hepatic fibrosis improvement observed in up to 45%. Even a modest reduction of 5–7% in body weight can significantly decrease hepatic steatosis and liver enzyme levels, though the most pronounced benefits in hepatic fibrosis regression occur with greater weight loss. Given this compelling evidence, sustained weight reduction through a combination of dietary changes, regular exercise, and behavioral strategies remains a fundamental aspect of MASLD management.

Pharmacological Therapy

Pharmacological therapy, as described below, is considered an adjunct to lifestyle measures for select patients based on diabetes status and hepatic fibrosis severity (Fig. 3).

A summary of the pharmacologic agents recommended for MASLD/MASH in India, along with their dosage and key adverse effects, is provided in Table 2.

Nondiabetic MASLD Patients

Nondiabetic MASLD with F0–F1 Hepatic Fibrosis (LSM <8 kPa)

In nondiabetic patients with no or minimal hepatic fibrosis, pharmacotherapy is not strongly recommended, as evidence for additional benefit beyond lifestyle modifications is insufficient.

The following drugs may be weakly recommended on a case-by-case basis, particularly in those who do not respond to lifestyle measures alone:

- Vitamin E: The PIVENS trial[7] demonstrated that 800 IU/day of vitamin E improved histological steatohepatitis in nondiabetics. However, its effect on hepatic fibrosis remains uncertain, and long-term safety concerns (e.g., increased prostate cancer risk) limit its widespread use. More recently, a lower dose (300 mg/day for 96 weeks) has shown improvements in steatosis, inflammation, hepatic fibrosis, and liver stiffness with a better safety profile.[9] If vitamin E is considered, a lower dose (300 mg/day) may be preferable in patients at higher risk of adverse effects.
- Omega-3 fatty acids: Meta-analyses by Parker et al. and Lee et al., 2020, suggest omega-3 reduces hepatic steatosis but does not consistently improve hepatic fibrosis or inflammation, leading to its weak recommendation.[69,70]

Thus, lifestyle modifications remain the cornerstone of management in this group, and vitamin E (preferably at a lower dose) or omega-3 may be considered in select cases.

Nondiabetic MASLD with F2–F3 Hepatic Fibrosis (LSM 8–15 kPa)

Patients with moderate to advanced hepatic fibrosis are at higher risk of disease progression, and pharmacological therapy is strongly recommended. The following drugs have shown proven efficacy in clinical trials, and any of them can be chosen:

- Semaglutide: The ESSENCE trial (2024, interim analysis) confirmed that semaglutide significantly improves MASH resolution and moderately improves hepatic fibrosis, justifying its strong recommendation.[18]
- Tirzepatide: The SYNERGY-NASH trial[28], a phase 2 multicenter, double-blind, placebo-controlled study, showed that tirzepatide significantly improved both MASH resolution and fibrosis compared to placebo across all tested doses.
- Resmetirom: The phase 3 MAESTRO-NASH trial14 showed that resmetirom significantly improved both MASH resolution and fibrosis compared to placebo, with added metabolic benefits and a favorable safety profile. These results position resmetirom as a promising therapy for both non-diabetic as well as diabetic MASH.
- Saroglitazar: A dual PPAR-α/γ agonist, saroglitazar has demonstrated reductions in transaminases and liver fat in many trials and has been approved by DCGI for MASLD.[37,39,40,43,91]
- Vitamin E: Despite concerns, PIVENS confirmed its role in MASH resolution, making it a strong candidate for nondiabetics with F2–F3 hepatic fibrosis.[7]

The following drugs are weakly recommended, specifically if first-line drugs cannot be given:

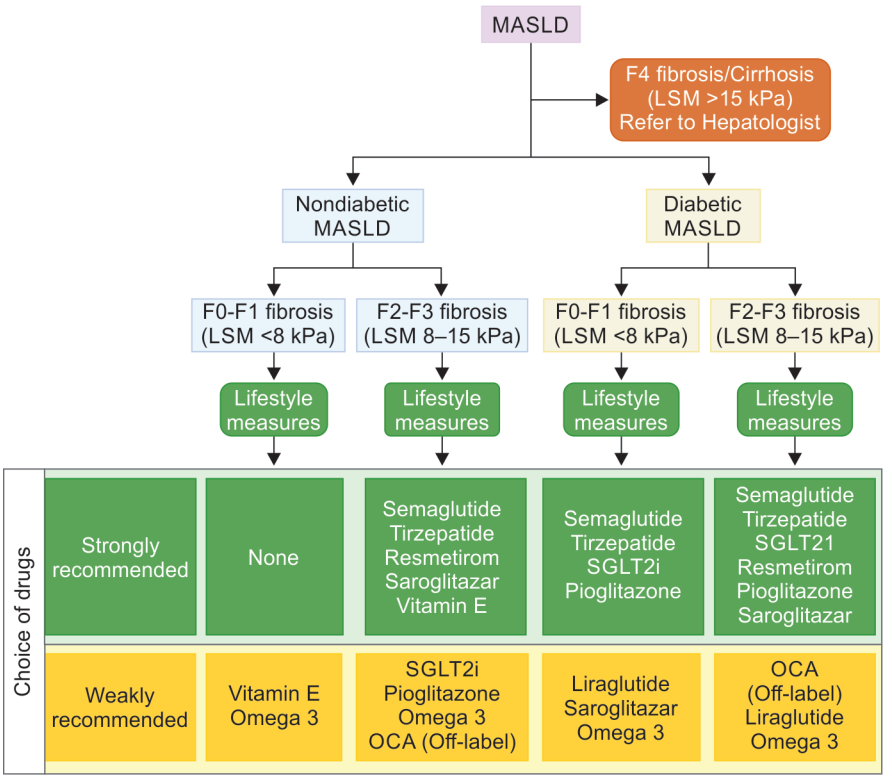

Fig. 3: Algorithm for pharmacological management of MASLD/MASH in Indian patients

Table 2: Pharmacologic agents recommended for MASLD/MASH in India

Drug	*Recommended Dosage*	*Common Adverse Effects*	*Rare Adverse Effects*
Oral Semaglutide	Start at 3 mg/day, titrate to 7 mg or 14 mg/day	Nausea, vomiting, delayed gastric emptying	Pancreatitis, gallbladder disease
Injectable Semaglutide	Start at 0.25 mg/week, titrate to 1.0–2.4 mg/week (subcutaneous)	Nausea, vomiting, delayed gastric emptying	Pancreatitis, gallbladder disease
Tirzepatide	Start at 2.5 mg/week, titrate to 5–15 mg/week (subcutaneous)	Nausea, decreased appetite, diarrhea	Pancreatitis, hypersensitivity reactions
Resmetirom	Start at 80 mg/day, titrate to 100 mg/day (oral)	Diarrhea, nausea, pain	Cholecystitis, Pancreatitis (both rare)
Saroglitazar	4 mg/day	Mild weight gain, peripheral edema	Fluid retention (rare)
Pioglitazone	15–30 mg/day	Weight gain, fluid retention	Increased risk of fractures, heart failure in predisposed individuals
SGLT2 Inhibitors (Dapagliflozin, Empagliflozin)	Dapagliflozin 10 mg/day, Empagliflozin 10–25 mg/day	Genital infections, increased urination, mild dehydration	Euglycemic ketoacidosis (rare), Fournier's gangrene
Vitamin E (Non-diabetic MASLD)	800 IU/day (high dose) or 300 mg/day (low dose)	GI upset, fatigue	Increased prostate cancer risk (high dose), hemorrhagic stroke
Liraglutide	Start at 0.6 mg daily, titrate to 1.2 mg or 1.8 mg daily	Nausea, vomiting, diarrhea	Pancreatitis, gallbladder disease
Omega-3 Fatty Acids	2–4 g/day	GI intolerance, burping, mild bleeding risk	Increased LDL cholesterol (with certain formulations)
Obeticholic Acid (OCA) (Off-label use)	Start at 5 mg/day, titrate to 10 mg/day. Higher doses (e.g., 25 mg/day) may offer greater fibrosis reduction but are associated with a significantly increased risk of adverse effects, particularly pruritus.	Pruritus, dyslipidemia	Increased cardiovascular risk, worsening liver function in advanced cirrhosis

- Sodium-glucose cotransporter-2 inhibitors: Emerging data suggest potential benefits, but evidence in nondiabetics is insufficient for strong endorsement.[50–55]
- Pioglitazone: The PIVENS trial and several meta-analyses support MASH resolution and hepatic fibrosis stabilization, making it a viable option in non-diabetic MASLD.[7,31–36]
- Omega-3 fatty acids: Limited hepatic fibrosis data restrict its use to a weak recommendation.[69,70]
- Obeticholic acid (off-label use): The REGENERATE trial demonstrated hepatic fibrosis improvement,[64] but FDA rejection and pruritus risk warrant its weak off recommendation.

Diabetic MASLD Patients

Diabetic MASLD with F0–F1 Hepatic Fibrosis (LSM <8 kPa)

In diabetic MASLD patients with no or minimal hepatic fibrosis, apart from lifestyle modifications, metformin remains the backbone of diabetes management. In addition to metformin, the following antidiabetic drugs with proven MASLD benefits are strongly recommended:

- Semaglutide: The ESSENCE trial and other studies confirmed robust weight loss, insulin sensitivity improvement, and MASH resolution in diabetics.[17,18]
- Tirzepatide: The SYNERGY-NASH trial[28] a phase 2 multicenter, double-blind, placebo-controlled study, showed that tirzepatide significantly improved both MASH resolution compared to placebo across all tested doses.
- Sodium-glucose cotransporter-2 inhibitors: Meta-analyses confirm that SGLT2i reduce hepatic fat, improve insulin resistance, and lower liver enzymes, justifying strong recommendation.[50–55]
- Pioglitazone: Has MASH resolution benefits in diabetics.[98]

The following drugs are weakly recommended in these patients:

- Liraglutide: As a GLP-1RA, liraglutide has demonstrated substantial weight loss, insulin sensitization, and hepatic fat reduction in diabetic MASLD. The LEAN trial[25] confirmed its ability to improve hepatic steatosis and MASH resolution. Although semaglutide has largely replaced liraglutide due to greater efficacy and weight loss, liraglutide remains a reasonable option in diabetic MASLD patients when semaglutide is unavailable or contraindicated.
- Saroglitazar: While DCGI-approved for MASLD, it lacks histological evidence in early-stage MASLD, making it weakly recommended in F0–F1 hepatic fibrosis.[37]
- Omega-3 fatty acids: As in nondiabetics, weakly recommended due to inconsistent hepatic fibrosis data.[69,70]

Diabetic MASLD with F2–F3 Hepatic Fibrosis (LSM 8–15 kPa)

For diabetic patients with significant hepatic fibrosis, aggressive treatment is warranted due to the higher risk of progression to cirrhosis. Metformin remains the backbone drug, while the following drugs are strongly recommended:

- Semaglutide: The most effective GLP-1RA for MASH resolution, based on ESSENCE and other trials.[17,18]
- Tirzepatide: The SYNERGY-NASH trial[28], a phase 2 multicenter, double-blind, placebo-controlled study, showed that tirzepatide significantly improved both MASH resolution and fibrosis compared to placebo across all tested doses.
- Sodium-glucose cotransporter-2 inhibitors: Well-studied in diabetic MASLD, with confirmed metabolic and hepatic benefits.[50–55,99]
- Resmetirom: The phase 3 MAESTRO-NASH trial14 showed that resmetirom significantly improved both MASH resolution and fibrosis compared to placebo, with added metabolic benefits and a favorable safety profile. These results position resmetirom as a promising therapy for both non-diabetic as well as diabetic MASH.
- Pioglitazone: Strong data support hepatic fibrosis stabilization and MASH resolution.[14–19]
- Saroglitazar: DCGI-approved for MASLD in diabetics, with strong effects on dyslipidemia and hepatic steatosis.[37,39,40,43,98]

The following drugs are weakly recommended in this group:

- Obeticholic acid (off-label use): The REGENERATE trial supports hepatic fibrosis improvement, but safety and regulatory concerns restrict its recommendation.[64]
- Liraglutide: While semaglutide is the preferred GLP-1RA, liraglutide has shown MASH resolution benefits in the LEAN trial[25] and remains an alternative in diabetic MASLD patients with F2–F3 hepatic fibrosis when semaglutide is unavailable or contraindicated.
- Omega-3 fatty acids: Weakly recommended due to limited hepatic fibrosis effects.[69,70]

Future Directions

The management of MASLD is on the brink of a major transformation, with several promising drugs advancing through phase 3 trials and many expected to receive FDA approval in the near future. Novel agents such as FGF21 analogs (efruxifermin, pegozafermin), THR-β agonists (resmetirom), and dual/triple incretin receptor agonists (tirzepatide, retatrutide, survodutide) have shown encouraging results in improving hepatic steatosis, inflammation, and hepatic fibrosis. Additionally, ongoing research into genetics, epigenetics, and gut microbiome alterations is expected to pave the way for precision medicine in MASLD, allowing for personalized therapeutic strategies that target specific disease mechanisms at an individual level.

In India, too, several new drugs are likely to become available in the coming years, expanding the therapeutic arsenal for MASLD management. However, given India's vast and diverse population, with a significant proportion in the lower and lower-middle socioeconomic strata, ensuring equitable access to effective and affordable treatments remains a critical challenge. While high-cost novel therapies may offer superior efficacy, it is essential to prioritize evidence-based, cost-effective treatment strategies that are accessible to the majority of patients. A tailored, pragmatic approach—integrating proven metabolic therapies, lifestyle interventions, and affordable pharmacological options—will be key to bridging the gap between cutting-edge advancements and real-world applicability in India.

Conclusion

The landscape of pharmacologic therapy for MASLD is evolving rapidly, with an expanding array of metabolic, anti-inflammatory, and antifibrotic agents demonstrating efficacy in clinical trials. While lifestyle modification remains the foundation of MASLD management, pharmacotherapy is crucial for patients with progressive disease or high-risk metabolic profiles. Established agents such as GLP-1RAs, SGLT2i, PPAR agonists, and vitamin E (in nondiabetic patients) have demonstrated histological benefits, whereas newer drugs like resmetirom and FGF21 analogs hold promise for future MASLD/MASH treatment.

In India, MASLD presents unique challenges due to its high disease burden, limited awareness, and socioeconomic disparities in healthcare access. Given that most MASLD patients are managed by general physicians and diabetologists rather than hepatologists, a structured yet practical treatment algorithm is essential. The proposed pharmacologic approach, stratified by diabetes status and hepatic fibrosis severity, provides Indian clinicians with clear,

evidence-based recommendations utilizing currently available drugs.

As therapeutic advancements continue, a balanced approach integrating effective pharmacologic options with lifestyle interventions will be key to optimizing MASLD management in India. By ensuring equitable access to affordable and evidence-based treatments, physicians can improve long-term outcomes for MASLD patients, mitigating the risk of cirrhosis, CVD, and metabolic complications.

Credit Authorship Statement

The author contributed to this manuscript as follows: conceptualization, original draft preparation, writing-review, and editing.

Notes and Disclaimers

- Obeticholic acid for MASH with fibrosis (off-label use): OCA has shown antifibrotic effects but is not FDA approved for MASLD/MASH. Its use should be restricted to select cases under specialist supervision.

Orcid

Ashish Kumar https://orcid.org/0000-0001-6680-7227

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