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Review

Care of Fatty Liver in Primary Care: Challenges and Glimpse of Clinical Approach

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ABSTRACT

Background: Metabolic dysfunction-associated steatosis liver disease (MASLD) presents a significant challenge in primary care due to inconsistencies in diagnostic tools, difficulty in symptom recognition, absence of approved pharmacological treatments, and limited disease awareness. However, early diagnosis and management are crucial to preventing progression to more severe liver disease.[1]

Identifying at-risk populations for appropriate testing enhances the predictive accuracy of non-invasive tests (NITs) and aligns with sequential testing frameworks recommended by the American Gastroenterology Association (AGA) and the European Association for the Study of the Liver (EASL).[2] Risk factors such as type 2 diabetes (T2DM) and metabolic syndrome are well-established indicators of an increased risk for metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis. Combining a FIB-4 score ≥1.3 with diabetes as a criterion may reduce indeterminate results requiring additional testing, such as vibration-controlled transient elastography (VCTE). Some screening algorithms rely solely on NITs to stratify risk, minimizing the need for liver biopsy. Given that most at-risk patients are seen in primary care, the American Association of Clinical Endocrinology (AACE) emphasizes the role of primary care providers in identifying individuals at risk for advanced fibrosis.[2]

The Indian National Association for the Study of the Liver (INASL) provides India-specific, consensus-based guidelines for the nomenclature, diagnosis, and management of Nonalcoholic Fatty Liver Disease (NAFLD), recommending the continued use of the term "NAFLD" over alternatives like MAFLD. For diagnosis, non-invasive tools such as abdominal ultrasound and controlled attenuation parameter (CAP) via transient elastography are advised for detecting steatosis, while APRI and FIB-4 are recommended as initial fibrosis screening tools at primary and secondary care levels, with referral to tertiary centers for advanced assessment using vibration-controlled transient elastography (VCTE) when needed. Management focuses on lifestyle changes—targeting a 7–10% weight loss through calorie restriction and daily physical activity—as first-line therapy, with pharmacological options like vitamin E for non-diabetics and pioglitazone for selected patients. INASL, along with national endocrine, cardiology, and gastroenterology societies, underscores NAFLD's strong link with metabolic syndrome and associated risks like cardiovascular disease and diabetes, promoting a multidisciplinary care model.[3]

Representing a growing "silent epidemic," MASLD affects approximately 25–30% of the general population. Beyond its hepatic implications, MASLD significantly increases cardiovascular risk due to strong associations with obesity, T2DM, and metabolic syndrome, contributing to both economic and health-related burdens. Many patients face challenges in achieving and maintaining weight loss, often due to barriers in adhering to dietary and lifestyle modifications. Given these complexities, a shift towards person-centered and compassion-based approaches—similar to those used in managing other chronic conditions—may enhance patient adherence and improve long-term outcomes.[4]

Materials and Method: Review and extracting data from Articles which have published data related to management of MASLD in primary care settings.

Results and Conclusion: Several studies have found that MASLD, the leading cause of chronic liver disease globally, is strongly associated with metabolic conditions such as obesity, insulin resistance, and type 2 diabetes. Diagnosis remains challenging due to the disease's asymptomatic nature and the lack of standardized diagnostic tools. Early intervention through lifestyle modifications, particularly weight loss and exercise, is crucial for preventing progression.

The FDA approval of resmetirom for MASH with moderate to advanced fibrosis marks a major advancement, with additional therapies targeting key disease pathways on the horizon. MASLD is a growing health concern, and early diagnosis and management are critical to prevent severe liver complications. Although new pharmacological treatments are still under research, recently approved medicines and lifestyle interventions still remain the cornerstone of treatment. Non-invasive screening and a multidisciplinary care approach offer hope for improved patient outcomes and more effective management of MASLD in the future.

Keywords: MASLD, primary setting, primary healthcare provider, challenges, management

Introduction

Aim: The aim of this review was to gain more understanding about the management or care of MASLD in the Primary Setting.

Methods: Several articles related to the topic of discussion "Care of Fatty Liver in Primary Care" were reviewed and data was extracted from them.

Results and Conclusion: MASLD, the leading cause of chronic liver disease, is closely linked to metabolic conditions like obesity, insulin resistance, and type 2 diabetes. Diagnosis is challenging due to its asymptomatic nature and lack of standardized tools. Early intervention through lifestyle modifications, such as weight loss and exercise, is crucial for preventing progression. Resmetirom has been approved by the FDA for the treatment of adults with MASH and moderate to advanced fibrosis marking a significant shift in the therapeutic landscape.

MASLD requires early diagnosis and management to prevent severe liver complications. Lifestyle changes remain the cornerstone of treatment, with non-invasive screening and multidisciplinary care offering hope for better patient outcomes.

Discussion

Overview about MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most common chronic liver disease worldwide, affecting over one-third of the global adult population. Its prevalence is estimated at 25–30% in adults and is typically asymptomatic, often delaying early diagnosis. Given its strong associations with type 2 diabetes mellitus (T2DM) and obesity, the prevalence of MASLD is expected to rise further. These metabolic links prompted the recent shift in terminology from non-alcoholic fatty liver disease to MASLD.[5] Metabolic dysfunction-associated steatohepatitis (MASH) is a subset of MASLD characterized by the presence of steatohepatitis and/or fibrosis progression (previously known as NASH).[2]

From NAFLD to MASLD: Evolving Nomenclature

In 2023, three multinational liver associations proposed the term metabolic dysfunction-associated steatotic liver disease (MASLD) to replace non-alcoholic fatty liver disease (NAFLD). This change aimed to better reflect the metabolic underpinnings of the disease and reduce stigma by removing the terms "fatty" and "alcoholic." MASLD is closely linked to obesity, insulin resistance, and type 2 diabetes, sharing common pathogenetic mechanisms with these conditions.[5] Additionally, MASLD has been recognized as a major risk factor for cardiovascular disease, hepatocellular carcinoma (HCC), extra-hepatic malignancies, and chronic kidney disease.[6]

Diagnosing and managing MASLD remains a significant challenge in primary care due to the lack of standardized diagnostic tools, difficulty in symptom identification, absence of approved pharmacological treatments, and limited disease awareness. However, early detection and management are crucial to prevent disease progression.[1]

Accurately identifying at-risk populations enhances the predictive accuracy of non-invasive tests (NITs) and supports the sequential testing framework recommended by the American Gastroenterology Association (AGA) and the European Association for the Study of the Liver (EASL). MASLD risk factors, including type 2 diabetes mellitus (T2DM) and metabolic syndrome, are well-established contributors to the development of metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis. Combining a FIB-4 score ≥1.3 with diabetes as a screening criterion may minimize indeterminate results requiring additional VCTE assessment. Some screening algorithms rely exclusively on NIT-based risk stratification, reducing the need for liver biopsy. Given that most at-risk patients are seen in primary care clinics, the American Association of Clinical Endocrinology (AACE) highlights the crucial role of primary care providers in detecting individuals at risk for advanced fibrosis.[2]

Role of Primary Care Providers in Early Detection and Management

Primary care plays a pivotal role in managing patients with MASLD, particularly in prevention and early diagnosis. However, primary care providers (PCPs) often face challenges in effectively addressing the condition. A study by Islam et al. revealed that many PCPs lacked confidence in diagnosing MASLD and were inconsistent in its management. Similarly, a survey by Said et al. found that while 83% of PCPs recognized MASLD as an important health issue, 85% underestimated its prevalence, and only 46% offered screening to patients with obesity and diabetes. Additionally, 58% reported that a lack of confidence in understanding MASLD was a major barrier to management.[4]

To improve PCPs' ability to diagnose and manage MASLD, Wong et al. emphasized the importance of enhanced education, starting in medical school and continuing through conferences and workshops. A recent European collaboration developed a continuing medical education program focused on MASLD/NASH care in primary care, with PCPs expressing high satisfaction and increased confidence following the program. This suggests that such educational interventions can improve knowledge and care for MASLD/NASH and should be extended to other languages.[4]

While MASLD is typically managed in primary care, some patients, particularly those with NASH and multiple cardiovascular risk factors, may require referral to secondary care. Early screening is critical due to the often-asymptomatic nature of the disease.[4]

A study reviewing MASLD management in northeast England found significant variability in care at hospital clinics, especially regarding lifestyle advice and metabolic risk factor management. However, patients seen at specialized MASLD clinics were more likely to achieve significant weight loss and have metabolic risk factors addressed. The introduction of a care bundle improved the implementation of MASLD management, suggesting it could help standardize care and improve patient outcomes.[4]

MASLD and MASH: Insights from Physicians

MASLD is increasingly prevalent but underrecognized in primary care and endocrinology clinics, presenting significant challenges in diagnosis and management.[6] The lack of consensus on diagnostic tools, difficulties in identifying symptoms, absence of approved pharmacological treatments, and limited awareness contribute to this issue. Early diagnosis and management are crucial to prevent progression to more severe liver disease. Raising awareness and improving understanding of MASLD among both patients and physicians is essential, as patient-reported outcomes are important in advancing our knowledge and guiding treatment strategies.[7]

MASLD and MASH are common in patients with cardiovascular and metabolic conditions, including asymptomatic patients. These individuals are at an increased risk of developing more severe forms of the disease, underscoring the importance of screening in high-risk populations. Key risk factors for MASLD include obesity, insulin resistance, hypertension, and hypertriglyceridemia, with the global prevalence increasing in line with rising obesity rates. A meta-analysis documented a MASLD prevalence of 75.27% in obese individuals, with lipid metabolism disorders driving fatty liver development.[7]

Until recently, no pharmacological therapies had received approval from the US Food and Drug Administration (FDA) specifically for MASLD or MASH, with existing treatment strategies primarily aimed at managing associated cardiometabolic comorbidities such as type 2 diabetes (T2D), dyslipidemia, and obesity. However, the therapeutic landscape for non-cirrhotic MASH shifted significantly in March 2024 with the FDA's accelerated approval of resmetirom—formerly known as MGL-3196 and now marketed under the brand name Rezdiffra™. This approval was granted based on surrogate endpoints that

are reasonably likely to predict clinical benefit (Harrison et al., 2024). Resmetirom is indicated for adults with MASH and moderate to advanced liver fibrosis (stages F2 to F3), and is to be used alongside diet and exercise. It is administered orally once daily at a fixed dose of 80 mg for individuals weighing less than 100 kg and 100 mg for those weighing 100 kg or more, with or without food.[8]

Resmetirom is a selective thyroid hormone receptor-β (THR-β) partial agonist that is orally administered and primarily targets hepatic tissue, demonstrating approximately 84% of the activity of the natural thyroid hormone triiodothyronine (T3) (Kelly et al., 2014). By selectively activating the THR-β isoform—predominantly expressed in the liver—resmetirom plays a crucial role in modulating lipid metabolism, cholesterol synthesis, and fatty acid oxidation. At the same time, it minimizes systemic thyromimetic effects by limiting activation of THR-α, which is primarily located in non-hepatic tissues such as the heart. Resmetirom improves hepatic lipid metabolism by enhancing the catabolism of cholesterol through upregulation of the hepatic enzyme cholesterol 7-alpha-hydroxylase (CYP7A1), while simultaneously inhibiting de novo lipogenesis via downregulation of sterol regulatory element-binding protein-1 (SREBP-1).[8]

Separately, the dual peroxisome proliferator-activated receptor alpha/gamma (PPARα/γ) agonist saroglitazar has been approved by the Drug Controller General of India (DCGI) for the treatment of MASH. Preclinical studies have shown that saroglitazar significantly improves hepatic steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis in diet-induced mouse models of MASLD.[9]

With pharmacological therapies for MASLD and MASH—such as resmetirom and saroglitazar—now available, lifestyle modifications remain a vital complementary strategy in disease management. Interventions like weight loss and improved metabolic control continue to play a critical role in enhancing treatment outcomes and slowing disease progression. However, clinicians often face challenges in promoting these changes, including time limitations during consultations, patient reluctance, and inadequate access to structured support services.[7]

At the same time, non-invasive diagnostic tools are increasingly recommended for fibrosis screening and ongoing assessment in both primary and secondary care settings. These tools offer a valuable alternative to liver biopsy, which is limited by its invasive nature, potential complications, and patient hesitancy. Despite their utility, there is still a need for more accurate non-invasive options to improve diagnostic precision and support risk stratification.[7]

Unmet needs and proposed improvements to the patient journey

In a study conducted on MASLD patients, they expressed several unmet needs in the diagnosis and treatment process. Patients wanted improvements in how clinicians listen to and address their concerns, often feeling that their symptoms were not taken seriously, which led to delayed diagnosis. They were also dissatisfied with the way diagnoses were communicated, either receiving too little information or being overwhelmed with information too quickly. Patients suggested that the amount and quality of information about MASH should improve, as they generally received minimal details from clinicians and had difficulty finding information on their own or through support groups.[10] (Fig. 1)

Referral Pathway for MASLD Patients

MASLD is the leading cause of chronic liver disease and liver-related morbidity and mortality. Addressing the public health threat of obesity and obesity-related diseases, including MASLD, requires involvement from all stakeholders. A simple, clear assessment and referral pathway using non-invasive tests is essential for identifying patients with severe MASLD for specialist care, while those with less severe disease can remain in primary care.[11]

When and Whom to Refer MASLD Patients:

1. **Referral for Advanced Fibrosis:** Patients at high risk of advanced fibrosis, as indicated by a FIB-4 score of ≥2.67 and/or liver stiffness measurements above 7.9 kPa, should be referred to a hepatologist or gastroenterologist for further evaluation and management, including potential treatment options.[12,13]
2. **Referral for Indeterminate Risk:** For patients whose risk level is classified as intermediate or indeterminate based on initial non-invasive assessments, further evaluation, such as liver stiffness measurements, is recommended to determine whether a specialist referral is necessary.[12]

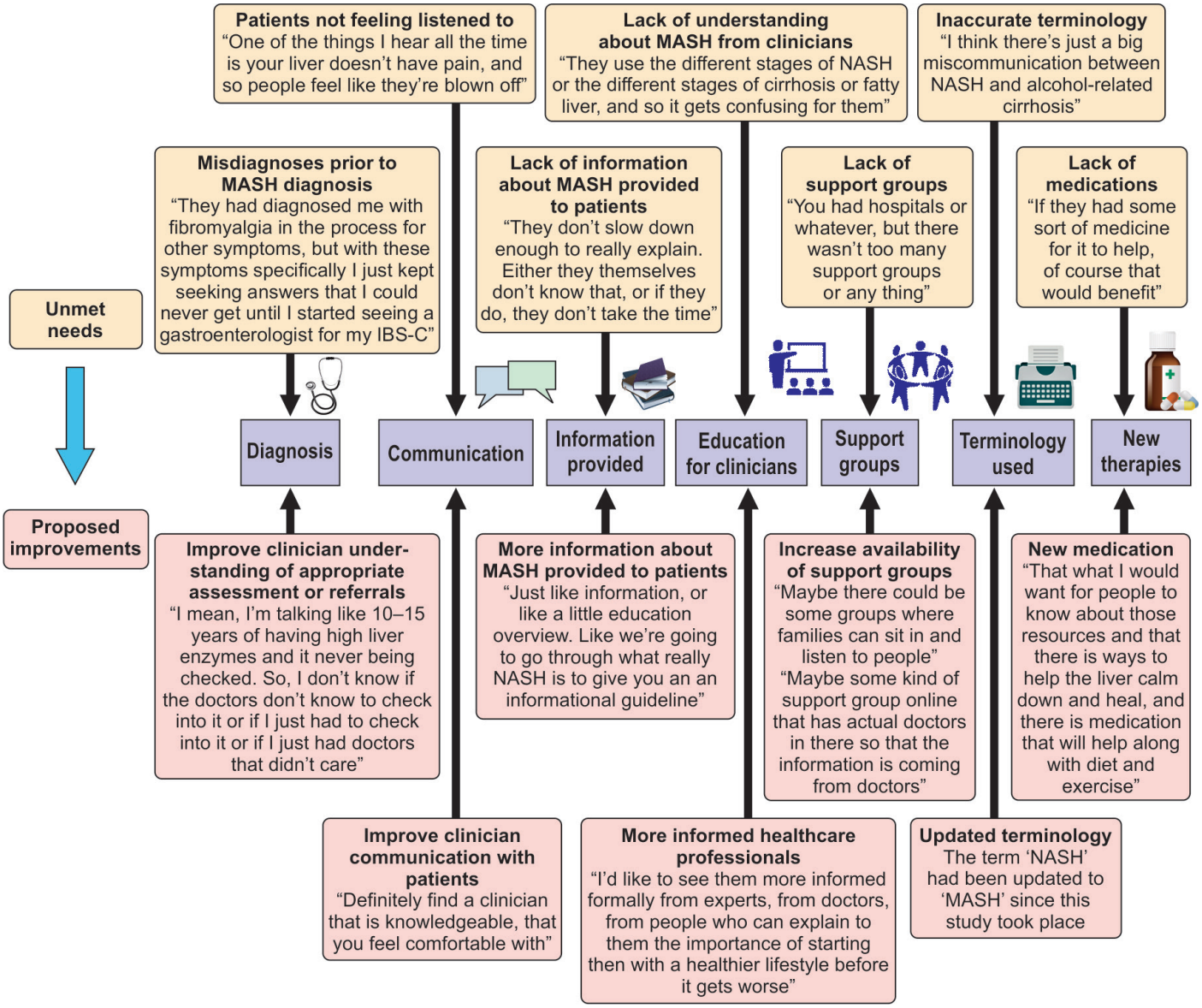

Fig 1. Unmet needs and proposed improvements to the patient journey.[10]

3. **Specialist Referral for Comprehensive Evaluation:** Patients requiring a thorough evaluation of liver health, including advanced fibrosis assessment, liver biopsy, or magnetic resonance elastography (MRE), should be referred to a hepatologist or gastroenterologist for specialized care.[14]

The FDA's approval of resmetirom for MASH with fibrosis (F2–F3) marked a major therapeutic advancement.[8] In India, saroglitazar, a dual PPARα/γ agonist, is also approved for MASH, showing preclinical benefits in MASLD.[9] Lifestyle changes remain a complementary yet key component of MASLD management, with cardiovascular risk requiring close attention.[11]

Non-invasive tests allow for the identification of compensated advanced chronic liver disease and clinically significant portal hypertension, helping to stratify patients based on their risk of liver-related complications. Additionally, prevention and management of sarcopenia should be considered in the care of patients with MASLD.[11]

Integrating MASLD Care into Primary Practice: A Practical Example

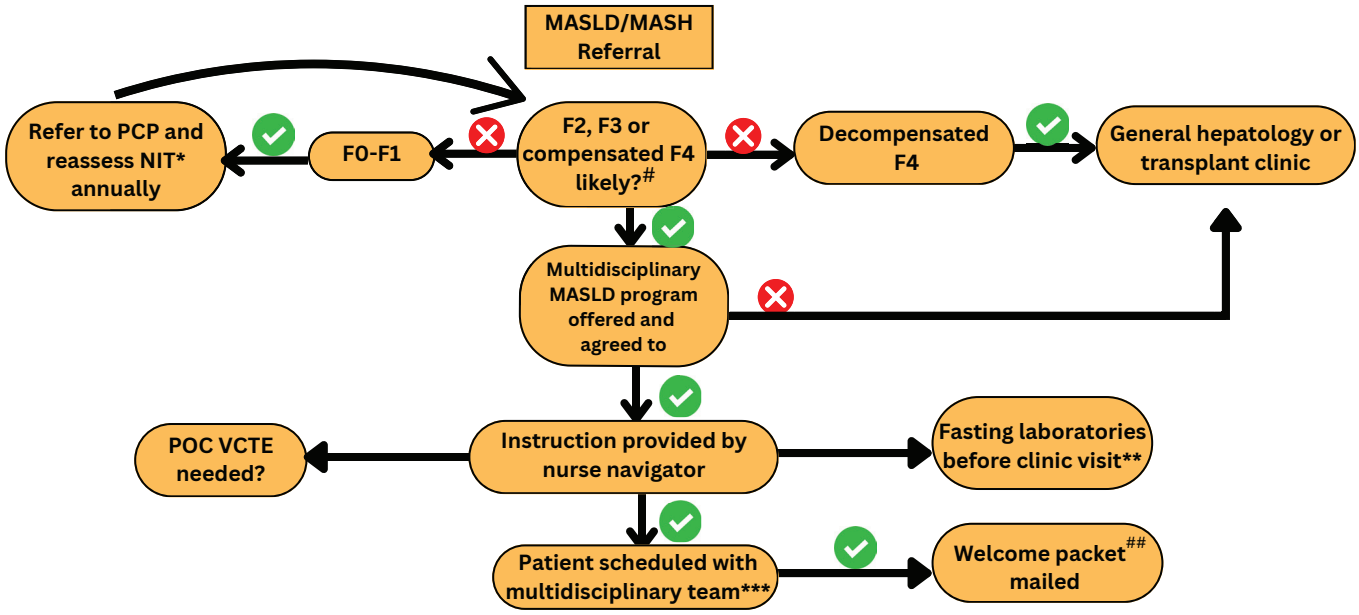

Fig 2. Multidisciplinary MASLD clinic referral pathway and preclinic visit testing.[15]
[#] FIB-4 >1.3 or VCTE >8 kPa or MRE >2.55 kPa or ELF >7.7 or liver biopsy
[*] FIB-4 or VCTE
[##] Clinic instructions, Questionnaires (AUDIT-C, CLDQ, DASI, Dietary recall 24h, FFQ, Exercise barriers survey, IPAQ, PAVS, STOP-BANG)
[**] CBC, CMP, ELF, ferritin, HbA1c, IgA, INR, lipid panel, PETH, TSH (FIB-4, ASCVD calculated from these labs)
[***] Clinical Research, Endocrinology, Exercise Physiology, Hepatology, Registered Dietitian, Obesity Medicine, Preventative Medicine

This study demonstrated that a multidisciplinary care model for adults with metabolic dysfunction-associated steatohepatitis (MASH) and significant liver fibrosis improved multiple outcomes, highlighting the benefits of a comprehensive care team approach. (Fig. 2) The program achieved this through individualized treatment plans that included patient education, lifestyle intervention, and drug therapy, all agreed upon after individual evaluation and team discussions, with pre-agreed therapeutic targets.[15]

While multidisciplinary care models are endorsed by clinical guidelines, limited data existed on their efficacy and sustainability. This program's unique strength lay in incorporating healthcare specialists often overlooked in other models, such as exercise physiologists, obesity medicine providers, and clinical psychologists, which played a key role in the program's success.[15]

The study's potential limitations included a short follow-up period, no comparator arm, small sample size, and possible selection bias. However, its strengths included a comprehensive multidisciplinary approach, observed efficacy across multiple therapeutic targets, and real-world implementation in a robust population. Further studies are needed to validate these findings and assess the cost-effectiveness of multidisciplinary care models, as well as to test the model in more diverse populations.[15]

Although clinical guidelines support multidisciplinary care for MASLD, evidence on its effectiveness in real-world settings remained limited. This study provided novel evidence that a comprehensive, multidisciplinary model can significantly improve liver and metabolic health through sustained lifestyle intervention and targeted pharmacological therapies. These findings suggested that expanding such programs could improve clinical outcomes for all patients with MASLD.[15]

Lifestyle and Pharmacologic Management

Lifestyle Modifications

Calorie restriction and increased physical activity, leading to weight loss, can significantly improve MASLD.[11]

A study on patients with biopsy-proven MASH showed that weight loss resulted in:[11]

- 90% resolution of MASH
- 45% improvement in liver fibrosis

Another study demonstrated that lifestyle intervention led to resolution of simple liver disease (SLD) in up to 97% of patients.[11]

- **The APASL guidelines recommend:**[11]
  - Gradual weight loss (up to 1 kg/week) through a hypocaloric diet (500 kcal deficit) and physical activity
  - Exercise recommendations: 30 minutes of moderate intensity exercise for at least 5 days/week (150 minutes/week), or 20 minutes of vigorous intensity exercise for at least 3 days/week (75 minutes/week).

Lifestyle intervention should be emphasized at all levels of patient care to improve MASLD, cardiometabolic health, and overall well-being. Weight loss can enhance blood pressure, glycemic and lipid profiles, and reduce CVD risk, among other benefits.[11]

With the FDA approval of resmetirom, the therapeutic paradigm for MASLD—particularly non-cirrhotic MASH with moderate to advanced fibrosis (F2–F3)—has shifted from a predominantly lifestyle-centered approach to a more integrated strategy combining pharmacological and non-pharmacological interventions.[10,19] While lifestyle modification, including adherence to a Mediterranean diet and regular physical activity, remains the first-line intervention and a critical component of disease management, it is no longer the exclusive option for clinical care.[11]

Although lifestyle interventions remain indispensable, especially for their broad cardiometabolic benefits and role in early-stage disease, pharmacotherapy is increasingly recognized as necessary for patients with more advanced fibrosis or those who fail to achieve histological improvement with lifestyle measures alone. In this context, resmetirom provides a mechanistically targeted treatment option that complements rather than replaces lifestyle change.

Other pharmacological agents with off-label use or under investigation include pioglitazone, GLP-1 receptor agonists (liraglutide, semaglutide), and SGLT2 inhibitors, each offering distinct metabolic and histological benefits.[11] Additionally, saroglitazar—a dual PPARα/γ agonist approved in India—has shown antifibrotic and anti-inflammatory effects in preclinical MASH models.[9] (Fig. 3)

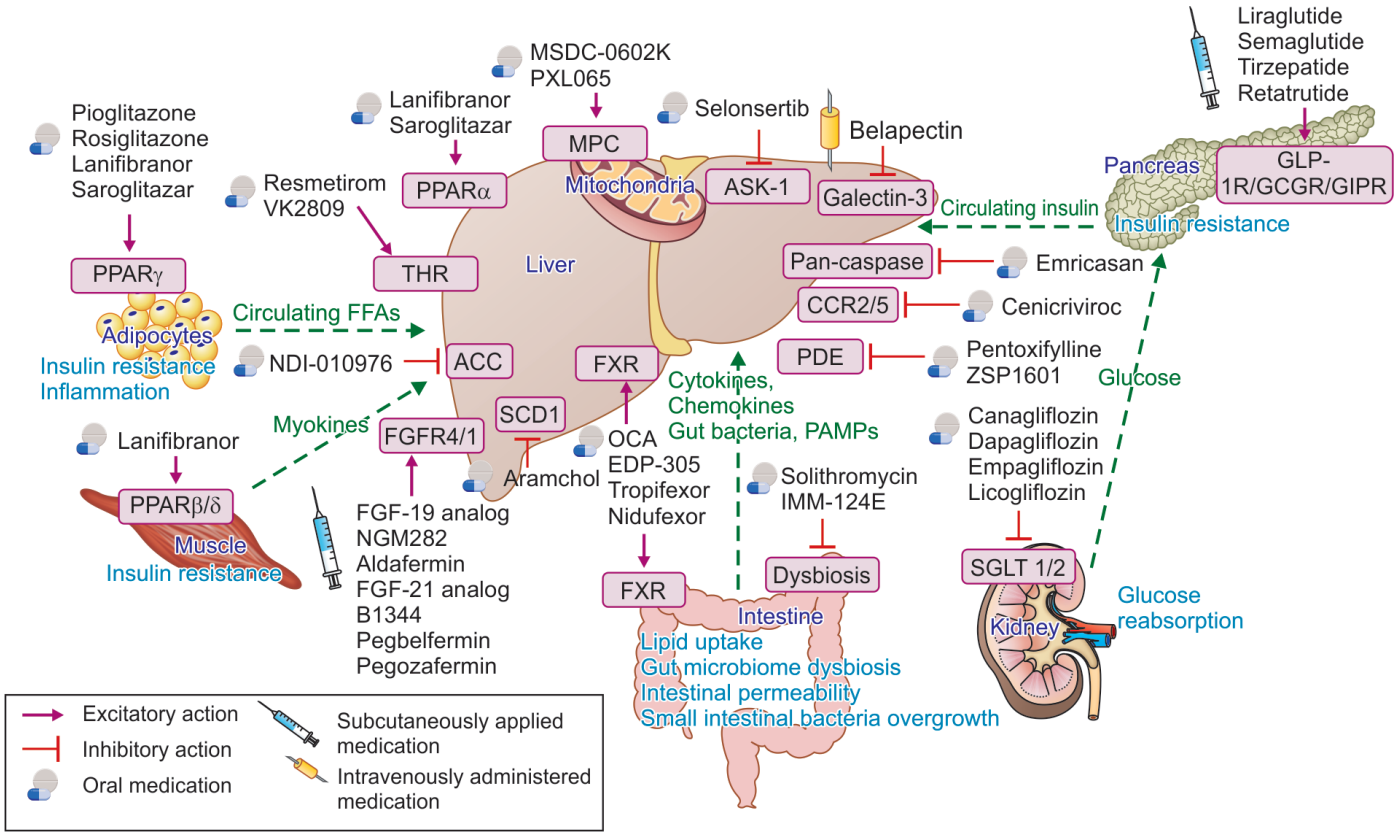

Fig 3. Potential candidates for MASLD and their mechanisms of action.[16]

Emerging investigational therapies, such as denifanstat (a fatty acid synthase inhibitor), efruxifermin (a recombinant Fc-FGF21 analog), and lanifibranor (a pan-PPAR agonist), hold further promise.[17–19] These therapies target key pathophysiologic pathways involved in hepatic disease initiation and progression in MASLD and MASH.[20]

Resmetirom: A Breakthrough in MASLD/MASH Management

Resmetirom, works by selectively targeting THR-β in liver tissue, sparing THR-α receptors that are linked to cardiovascular and bone side effects. Through activating THR-β, resmetirom promotes mitochondrial fatty acid oxidation, reduces fat production in the liver, and boosts cholesterol efflux. It enhances the expression of genes involved in lipid metabolism, such as carnitine palmitoyltransferase 1 (CPT-1), while downregulating the lipogenic gene sterol regulatory element-binding protein 1c (SREBP-1c), effectively reducing hepatic triglyceride accumulation. Additionally, it inhibits pro-inflammatory and pro-fibrotic factors like transforming growth factor-beta (TGF-β), while decreasing lipogenesis by reducing fatty acid synthase (FASN) and acetyl-CoA carboxylase 1 (ACC1) expression, both of which are elevated in MASLD.[21]

At doses of 80 mg and 100 mg per day, resmetirom has shown significant improvements in liver health, particularly in reducing liver fibrosis. Clinical trials have confirmed its effectiveness, showing notable reductions in low-density lipoprotein (LDL) cholesterol levels. Patients on an 80 mg daily dose experienced a 13.6% reduction in LDL cholesterol, while those on the higher 100 mg dose saw an even more substantial decrease of 16.3%. Unlike older thyroid hormone analogs, resmetirom is designed to minimize systemic effects. Its focused action on liver metabolism reduces de novo lipogenesis, improves insulin sensitivity, and lowers serum lipid levels without negatively impacting weight, glucose control, or cardiovascular health. Clinical evidence suggests that resmetirom may even lower the risk of major cardiovascular events in individuals with MASLD/MASH.[21]

However, resmetirom is not suitable in patients with decompensated cirrhosis, as it can increase the risk of adverse events due to enhanced drug exposure in cases of moderate to severe liver impairment.[21]

Evidence from Trials

Resmetirom's effectiveness has been extensively evaluated in clinical trials, starting with Phase 1 studies that confirmed its pharmacokinetics, safety, and lipid-lowering effects. These early trials demonstrated significant reductions in LDL cholesterol, triglycerides, and non-HDL cholesterol. The drug was generally well tolerated, with mild gastrointestinal symptoms being the most common side effects, and no significant changes were noted in thyroid function or cardiac biomarkers. The safety data suggested that resmetirom is a safer alternative to older thyroid hormone analogs, especially with regard to thyroid function.[21]

In Phase 2 trials, resmetirom was tested in patients with biopsy-confirmed metabolic-associated steatotic liver disease (MASH). The results showed that an 80 mg daily dose led to a 32.9% reduction in hepatic fat, a substantial improvement over the 10.4% reduction observed in the placebo group. Secondary outcomes also indicated significant improvements in lipid profiles, liver enzymes, and fibrosis biomarkers. Notably, 61% of patients experienced an improvement in fibrosis stage, and 56% showed fibrosis resolution. Side effects were mild, with diarrhea and nausea being the most common.[21]

The Phase 3 MAESTRO clinical program further solidified resmetirom's potential. In the MAESTRO-NAFLD-1 trial, resmetirom was tested in a larger population of 1,400 patients with non-cirrhotic MASH and MASH cirrhosis. Positive results showed that resmetirom improved liver health, with a focus on safety and efficacy across diverse patient populations. Additional data from the MAESTRO-NASH trial showed a 29.9% resolution rate for MASH, compared to 9.7% with placebo, along with a 25.9% improvement in fibrosis stage. Resmetirom also demonstrated promise in pediatric patients with obesity, showing significant improvements in both steatohepatitis and fibrosis.[21]

As of October 2024, the MAESTRO-NASH OUTCOMES trial has completed enrollment and is expected to provide critical insight into resmetirom's potential for full approval, particularly in high-risk patients with compensated NASH cirrhosis. If successful, the trial could support the expansion of resmetirom's indication to include a broader range of MASH cases, reinforcing its role in managing liver disease and improving patient outcomes.[21,22]

Conclusion

MASLD is a significant and growing health concern linked to metabolic diseases, with early diagnosis and management being critical to preventing progression to more severe liver conditions. While pharmacological treatments are still in the research phase, lifestyle changes, especially weight loss and exercise, remain the cornerstone of treatment. Primary care providers, along with non-invasive screening tools and emerging therapies, have the potential to improve patient outcomes. The ongoing development of treatment options, coupled with advancements in multidisciplinary care approaches, holds promise for better management of MASLD in the future.

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