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Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Evolving Insights into Pathogenesis, Progression, and Personalized Treatment Approaches

Paweł Kukiełka [PK]

pawel.kukielka2@gmail.com

ORCID: http://orcid.org/0009-0007-0303-6999

State Medical Institute of the Ministry of the Interior and Administration in Warsaw

Wołoska 137, 02-507 Warsaw, Poland

Katarzyna Moliszewska [KM]

k.moliszewska2899@wp.pl

ORCID http://orcid.org/0009-0009-5459-4338

Independent Public Central Clinical Hospital in Warsaw

ul. Banacha 1A, 02-097 Warsaw, Poland

Joanna Kośka [JK]

asia.koska@gmail.com

ORCID http://orcid.org/0009-0003-5971-6222

Military Institute of Medicine

Szaserów 128, 04-141 Warsaw, Poland

Kacper Dywan [KD]
kacper.dywan2@gmail.com
ORCID: http://orcid.org/0009-0006-4551-7902
Railway Hospital named after dr med. Włodzimierza Roeflera
Warsztatowa 1, 05-800 Pruszków, Poland

Michał Błaszkiewicz [MB]
michalblaszkiewicz1@gmail.com
ORCID http://orcid.org/0009-0005-5417-9688
State Medical Institute of the Ministry of the Interior and Administration in Warsaw
Wołoska 137, 02-507 Warsaw, Poland

Julia Mazurek **[JM]**
julia.mazurek04@gmail.com
ORCID http://orcid.org/0009-0003-7753-7797
Independent Public Clinical Hospital named after prof. Witold Orłowski CMKP
ul. Czerniakowska 231, 00-416 Warsaw, Poland

Julia Załęcka [JZ]
jzalecka@proton.me
ORCID http://orcid.org/0000-0003-3851-3066
Military Institute of Medicine
Szaserów 128, 04-141 Warsaw, Poland

Alicja Nowik [AN]
alicja.nowik6@gmail.com
ORCID http://orcid.org/0009-0004-0446-0116
Military Institute of Medicine
Szaserów 128, 04-141 Warsaw, Poland

Martyna Musiorska [MM]

martynamusiorka@gmail.com

ORCID http://orcid.org/0009-0000-9773-5449

Central Teaching Hospital Of The Medical University Of Lodz

Pomorska 251, 92-213 Łódź, Poland

Gabriela Łocik [GŁ]

gabriela.locik@gmail.com

ORCID http://orcid.org/0009-0000-8111-279X

Wolski Hospital named after dr Anna Gostyńska

Marcina Kasprzaka 17, 01-211 Warsaw, Poland

Corresponding Author
Paweł Kukiełka, pawel.kukielka2@gmail.com

Abstract

Background:

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), previously classified under non-alcoholic fatty liver disease (NAFLD), is an increasingly prevalent chronic liver disorder tightly linked to obesity, insulin resistance, and systemic metabolic dysfunction. It ranges from simple steatosis to nonalcoholic steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma.

Objective:

This review explores the current understanding of MASLD, emphasizing its multifactorial etiology, evolving pathophysiological mechanisms, clinical progression, and therapeutic strategies, including emerging pharmacological and lifestyle interventions.

Methods:

A structured review of peer-reviewed articles published between 2019 and 2025 was conducted using critical analysis of uploaded and curated literature focusing on MASLD's pathogenesis, comorbidities, and treatment modalities.

Findings:

MASLD is driven by a combination of genetic, environmental, metabolic, and immunological factors. Recent insights into lipid dysregulation, gut-liver axis, immune modulation, and endocrine pathways have clarified mechanisms of disease progression. Weight loss remains a

cornerstone of management, supported by emerging anti-obesity medications such as GLP-1 receptor agonists and dual agonists. Novel therapies targeting hepatic stellate cells, fibroinflammatory signaling, and microbiota-derived metabolites represent future avenues for precision-based treatment.

Conclusion:

Effective MASLD management necessitates an integrated approach combining lifestyle interventions, pharmacotherapy, and targeted therapeutics based on individual phenotypes. Continued research into molecular pathways and personalized strategies holds promise for disease reversal and improved patient outcomes.

Keywords:

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Pathogenesis, Anti-obesity pharmacotherapy, GLP-1 receptor agonists, Tirzepatide, Semaglutide, Liver fibrosis

Introduction

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is now recognized as the most common chronic liver disease worldwide. It affects about one in four adults and is closely linked to conditions such as obesity, type 2 diabetes, and other metabolic disorders (Portincasa, 2024). The term MASLD was recently introduced to replace "nonalcoholic fatty liver disease" (NAFLD) to better reflect its strong association with metabolic dysfunction, rather than focusing on what the disease is not (Stefan, 2024).

The development of MASLD is influenced by several causes, including poor diet, physical inactivity, genetic factors, and imbalances in gut bacteria. These factors lead to the buildup of fat in the liver, especially when the body's ability to process fats is overwhelmed (Stefan, 2024; Zhang et al., 2023). This fat buildup, or steatosis, marks the beginning of the disease. Over time, the condition can progress due to harmful processes inside the liver. These include damage caused by stress within liver cells, poor energy handling by mitochondria, and a strong immune response triggered by inflammation (Li, 2024; Yu et al., 2024). If not addressed, MASLD can worsen into a more serious form known as metabolic dysfunction-associated steatohepatitis (MASH), which involves liver cell damage and scarring. This can eventually lead to cirrhosis or liver cancer (Portincasa, 2024). Despite its growing impact, there are currently no approved medications specifically for MASLD. Treatment mostly relies on lifestyle changes such as healthy eating, regular exercise, and weight loss. Researchers are actively exploring new therapies that target the liver's metabolism, immune response, and gut microbiota (Zhang et al., 2023; Yu et al., 2024). In this article, we will explore the causes, underlying mechanisms, progression, and treatment approaches for MASLD. Understanding these aspects is essential to tackling one of the most pressing liver health issues of our time.

Etiology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

The etiology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is multifactorial, rooted in complex interactions between metabolic, genetic, environmental, and nutritional components. Central to its origin is the presence of metabolic syndrome,

particularly insulin resistance, obesity, and type 2 diabetes mellitus (Phoolchund & Khakoo, 2024). These factors not only increase hepatic fat deposition through enhanced de novo lipogenesis and impaired inhibition of adipose tissue lipolysis but also promote systemic and hepatic inflammation. MASLD frequently arises in individuals with visceral obesity and hyperglycemia, with its prevalence reaching 75% among obese populations and nearly 70% in type 2 diabetes cohorts (Stefan et al., 2024). This metabolic overload fuels hepatic steatosis by raising free fatty acid flux into the liver and altering lipid and glucose metabolism. Additionally, excess saturated fat and sugars such as fructose can exacerbate mitochondrial dysfunction and oxidative stress in hepatocytes, ultimately activating inflammatory and fibrogenic pathways (Stefan et al., 2024).

Emerging research highlights the importance of nutritional factors and amino acid metabolism in MASLD development. Shen et al. (2024) identified the amino acid transporter SLC7A11 as a key modulator in MASLD, with its overexpression linked to hepatic ferroptosis through serine and cysteine metabolic imbalance. These disruptions contribute to hepatocellular injury and inflammation, positioning altered nonessential amino acid handling as a novel etiological component of MASLD. Furthermore, the gut-liver axis is increasingly implicated, where dysbiosis and increased gut permeability permit endotoxins such as lipopolysaccharides (LPS) to enter the portal circulation, triggering hepatic inflammation (Phoolchund & Khakoo, 2024).

This multifactorial origin of MASLD is not only metabolic but also deeply embedded in systemic dysfunctions involving adipose tissue signaling, hepatokines, and gut microbiota-derived products. This complexity, as discussed by Portincasa (2024), reinforces the heterogeneity of MASLD and underscores the need for tailored diagnostic and therapeutic approaches that consider individual metabolic profiles and environmental exposures.

Pathogenesis of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

The pathogenesis of MASLD encompasses a complex and multifactorial network of interrelated mechanisms involving lipid accumulation, immune dysregulation, organelle stress, and genetic-environmental interactions. This multifaceted progression is best understood by dividing it into several mechanistic domains:

1. Dysregulated Lipid Metabolism and Hepatocellular Stress

At the core of MASLD lies an imbalance between hepatic lipid input and disposal. Excess caloric intake—especially from fructose and saturated fats—leads to upregulation of *de novo* lipogenesis (DNL), augmented by insulin resistance and hyperinsulinemia (Stefan et al., 2024; Portincasa, 2024). This results in intracellular accumulation of triglycerides and toxic lipid species like ceramides and diacylglycerols, promoting oxidative stress and mitochondrial dysfunction. These effects are exacerbated by hepatic insulin resistance, which impairs suppression of gluconeogenesis and intensifies steatosis (Syed-Abdul, 2023).

2. Immune Activation and Inflammation

The liver’s innate immune system plays a central role in MASLD progression. Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), detect damage-associated and pathogen-associated molecular patterns (DAMPs/PAMPs) and initiate inflammatory cascades (Yu et al., 2024). Kupffer cells, neutrophils, and monocytes respond by releasing TNF-α, IL-6, and other proinflammatory mediators (Meyer, 2024). In this context, *IL-17* and *IL-22*—type 3 cytokines—have dual roles: while IL-17 exacerbates inflammation, IL-22 can play a protective role by enhancing barrier function and hepatocyte survival (Abdelnabi, 2024). These findings underscore the immune system's nuanced role in modulating both damage and repair.

3. Neutrophil-Mediated Injury and Fibrosis

Neutrophils contribute directly to hepatocyte damage by producing reactive oxygen species (ROS), proteolytic enzymes, and neutrophil extracellular traps (NETs), which promote tissue injury and fibrosis (Shrestha, 2025). Their presence correlates with histological severity and progression to MASH, the inflammatory and fibrotic form of MASLD.

4. Gut–Liver Axis and Microbial Dysbiosis

Emerging evidence implicates the gut microbiota in MASLD pathogenesis. Increased intestinal permeability allows bacterial endotoxins like LPS to reach the liver via the portal vein, activating immune cells and triggering hepatic inflammation (Zhang, 2023; Benede-Ubieto, 2024). Additionally, beneficial microbial metabolites such as indole derivatives (e.g., indole-3-propionic acid) can modulate inflammation and improve lipid metabolism, suggesting a protective axis mediated by microbial-host signaling (Hyun Min, 2024).

5. Genetic and Epigenetic Contributions

Multiple genetic variants significantly influence susceptibility to MASLD. Variants in *PNPLA3*, *TM6SF2*, *MBOAT7*, and *GCKR* affect lipid remodeling, VLDL secretion, and triglyceride metabolism, enhancing the risk for steatosis, inflammation, and fibrosis (Stefan et al., 2024). Intriguingly, individuals with strong genetic predisposition—such as carriers of the PNPLA3 rs738409 G allele—often present with hepatic mitochondrial dysfunction and elevated liver fat, but may not have parallel risks for cardiovascular disease (Stefan et al., 2024). This suggests genotype-specific pathogenic pathways that diverge from metabolically driven disease.

6. Systemic and Endocrine Crosstalk

Portincasa (2024) and Hutchison (2023) emphasize the role of endocrine dysregulation in MASLD. Hormonal imbalances involving adiponectin, leptin, and sex hormones contribute to hepatic insulin resistance and steatosis. The liver, in turn, affects systemic metabolism by releasing hepatokines and procoagulant factors, establishing a bidirectional network between liver pathology and extrahepatic diseases, particularly cardiovascular disease.

7. Heterogeneity and Personalized Pathophysiology

MASLD does not progress uniformly in all individuals. As Stefan et al. (2024) argue, MASLD exists along a heterogeneous spectrum—some forms driven primarily by genetic predisposition, others by obesity, insulin resistance, or gut-derived inflammation. These divergent pathogenic tracks help explain variability in disease severity, risk of cirrhosis, and response to treatment.

MASLD represents a complex liver disorder where metabolic dysregulation, immune activation, genetic susceptibility, and gut-liver crosstalk converge. A deep understanding of these intertwined mechanisms is critical for the development of targeted and individualized therapeutic strategies.

Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease

The progression of metabolic dysfunction-associated steatotic liver disease (MASLD) represents a complex continuum that evolves from simple hepatic steatosis to steatohepatitis (MASH), fibrosis, cirrhosis, and potentially hepatocellular carcinoma (HCC). At the early stage, MASLD is characterized by lipid accumulation in hepatocytes due to metabolic imbalances like insulin resistance and dyslipidemia. Persistent metabolic stress and inflammatory stimuli can lead to hepatocyte injury, ballooning, and necrosis, which herald the onset of MASH. A crucial driver of disease advancement is chronic inflammation, often sustained by increased gut-liver axis permeability, immune activation, and oxidative stress, leading to progressive hepatocellular damage and fibrogenesis (Provera et al., 2024).

Importantly, MASLD does not remain confined to hepatic manifestations. It plays a systemic role, contributing to cardiovascular, renal, and muscular complications. The concept of lipotoxic inflammatory "spillover" has been proposed to explain how hepatic inflammation propagates to extrahepatic tissues, further complicating the disease course (Sandireddy et al., 2024). Moreover, cardiovascular disease remains the leading cause of death among MASLD patients. Mechanistically, this is driven by insulin resistance, systemic inflammation, oxidative stress, and endothelial dysfunction, all of which promote atherosclerosis and myocardial impairment (Mollace et al., 2024).

Fibrosis is the most critical histological feature for predicting MASLD outcomes. Advanced fibrosis increases the risk of cirrhosis and liver failure, yet hepatocellular carcinoma may develop even in non-cirrhotic livers—a phenomenon particularly noted in MASLD-related HCC. This atypical path of carcinogenesis poses a challenge for early diagnosis and surveillance, as many patients do not meet the conventional cirrhosis-based criteria for screening (Shi et al., 2024). MASLD-related HCC is often diagnosed late, partly due to a lack of consensus on surveillance strategies for this patient population.

Another layer of complexity in MASLD progression stems from molecular mechanisms such as mitochondrial dysfunction, DNA damage, endoplasmic reticulum stress, and immune exhaustion. These factors compromise hepatocellular regenerative capacity while promoting carcinogenic signaling pathways (Provera et al., 2024; Shi et al., 2024). Also, genetic and epigenetic alterations, including variations in PNPLA3, TM6SF2, and ACSL5, have been shown to modulate disease trajectory by altering lipid metabolism and inflammatory responses (Hu et al., 2025) .

Collectively, MASLD's progression is shaped by an interplay of hepatic, systemic, genetic, and environmental factors, making it a multisystem disorder with implications beyond the liver. Recognizing and intervening at early stages, especially at the MASH transition point, is crucial to prevent irreversible outcomes such as cirrhosis, organ failure, and malignancy.

Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease

General Therapeutic Targets in MASLD Treatment

The management of MASLD requires a multifaceted therapeutic approach due to its complex interplay between hepatic, metabolic, inflammatory, and systemic factors. The primary targets of MASLD therapy include reduction of hepatic steatosis, improvement of insulin sensitivity, suppression of chronic inflammation, reversal or prevention of fibrosis, and mitigation of cardiometabolic comorbidities such as type 2 diabetes, dyslipidemia, and cardiovascular disease (Chan, 2023; Portincasa, 2024). A crucial component in treatment strategy involves breaking the cycle of lipotoxicity and immune activation, which contributes to hepatic injury and fibrosis progression. For instance, agents like USP29 that stabilize fatty acid-metabolizing enzymes such as ACSL5 demonstrate the potential for modulating intracellular lipid processing and thus represent a direct intervention at the lipotoxicity level (Hu, 2025).

Moreover, therapeutic interventions increasingly aim to address systemic manifestations of MASLD, such as sarcopenia, chronic kidney disease, and atherosclerotic cardiovascular disease, which are often driven by hepatic inflammation and cytokine spillover into peripheral organs (Sandireddy et al., 2024). As emphasized by Provera et al. (2024), targeting inflammatory mediators and pathways that promote immune exhaustion may not only slow MASLD progression but also prevent its transformation into hepatocellular

carcinoma (HCC). Indeed, novel immunomodulatory strategies and anti-fibrotic interventions are being explored to restore immune surveillance and limit oncogenic signaling pathways.

The overarching therapeutic goals in MASLD include halting disease progression at the steatosis and steatohepatitis stages, restoring metabolic homeostasis, reducing extrahepatic complications, and preventing end-stage outcomes such as cirrhosis and HCC (Shi et al., 2024). As the disease spectrum becomes increasingly recognized for its systemic involvement, the future of MASLD therapy lies in multi-targeted and personalized interventions integrating metabolic, inflammatory, and fibrotic control mechanisms.

Non-Pharmacological Treatment of MASLD

Non-pharmacological interventions remain the cornerstone of MASLD management, especially in early-stage disease. These approaches focus on correcting the metabolic dysfunctions at the heart of the condition—primarily through weight loss, dietary modification, physical activity, and behavioral therapy. Such strategies not only reduce hepatic steatosis and inflammation but also prevent progression to advanced fibrosis, cirrhosis, and associated cardiovascular complications.

1. Weight Reduction: A Central Pillar

Sustained weight loss is the most robust intervention to reverse liver fat and inflammation. Evidence indicates that a weight loss of ≥7% of total body weight improves hepatic steatosis, while losses over 10% can significantly reduce inflammation and even reverse fibrosis (Chan, 2023; Portincasa, 2024). The magnitude of histological improvement is proportional to the degree of weight reduction, reinforcing its role as a therapeutic target.

2. Dietary Interventions

Diet composition and eating patterns critically influence MASLD outcomes. The Mediterranean diet, characterized by high intake of fruits, vegetables, whole grains, fish, and monounsaturated fats (especially olive oil), has consistently been associated with reduced liver fat and improved insulin sensitivity (Portincasa, 2024; Melemkiaer, 2024). Similarly, the EAT–Lancet diet, emphasizing plant-based and low-sugar foods, showed protective effects against MASLD through beneficial metabolomic signatures (Wu, 2024).

Recent studies have also examined the impact of specific food types:

- Sugar-sweetened beverages and diet sodas are independently associated with higher MASLD prevalence due to fructose-induced DNL and gut-liver axis disruption (Wu, 2023).
- A gluten-free diet may benefit MASLD patients with concurrent celiac disease, reducing systemic inflammation and gut permeability (Cezac, 2024).
- The timing of food intake matters as well. Circadian-aligned eating patterns help regulate metabolic flux and may reduce the risk of MASLD progression to hepatocellular carcinoma (Malakmahmoudi, 2024).

Conversely, inappropriate dietary habits—particularly high saturated fat and refined carbohydrate intake—exacerbate visceral adiposity and drive insulin resistance, which in turn worsens hepatic steatosis (Xiang, 2024).

3. Physical Activity

Exercise exerts anti-inflammatory and metabolic benefits independent of weight loss. Regular aerobic exercise (e.g., brisk walking, cycling) and resistance training improve hepatic insulin

sensitivity, reduce fat accumulation, and mitigate cardiovascular risks. Guidelines recommend a minimum of 150–300 minutes per week of moderate-intensity physical activity, which improves not only liver enzymes but also overall cardiometabolic health (Chan, 2023; Mollace, 2024).

4. Behavioral and Multidisciplinary Interventions

Addressing psychological, social, and behavioral factors is critical to achieving long-term adherence. Multidisciplinary programs that incorporate nutritional education, physical coaching, and cognitive behavioral therapy demonstrate higher success rates in sustaining lifestyle changes. This is especially important given the chronic and often silent progression of MASLD, which can reduce patient motivation for preventive measures (Portincasa, 2024).

Non-pharmacological management is effective, safe, and foundational in the treatment of MASLD. Its success depends on personalized, sustained interventions targeting dietary habits, weight control, and physical activity. Future strategies may include nutritional timing, microbiota-targeted nutrition, and precision dietary planning based on genetic and metabolomic profiling.

Pharmacological Treatment of MASLD

Pharmacological intervention in MASLD aims to address its metabolic, inflammatory, and fibrotic dimensions, particularly in patients who fail to respond adequately to lifestyle modifications. With MASLD representing the hepatic manifestation of systemic metabolic dysfunction, the pharmacological approach must target both liver-specific and systemic abnormalities.

Metabolic Modulators and Antidiabetic Agents

Several metabolic agents, particularly those developed for type 2 diabetes, have shown promise in MASLD. Pioglitazone, a PPARγ agonist, remains one of the most studied and recommended drugs, especially in patients with biopsy-proven MASH (Zeng et al., 2024). GLP-1 receptor agonists (GLP-1 RAs), such as semaglutide, have emerged as powerful tools for MASLD management, with their benefits extending beyond glucose regulation to include weight loss and histological improvement of hepatic steatosis and inflammation (Ciardullo et al., 2024; Newsome, 2024). The ongoing ESSENCE trial specifically investigates semaglutide 2.4 mg in patients with MASH, providing pivotal data for its liver-specific benefits.

Anti-inflammatory and Immunomodulatory Agents

Recent discoveries in the immunological landscape of MASLD have led to the exploration of agents that target immune signaling. Ursolic acid, a naturally derived compound, has shown effectiveness in inhibiting SPP1-mediated Th17 cell differentiation and reducing liver inflammation through ERK signaling modulation (Zheng et al., 2024). Additionally, agents targeting cytokines like IL-17 and IL-22 are under investigation for modulating hepatic inflammation and fibrosis, as highlighted by Abdelnabi et al. (2024).

Antifibrotic Therapies and HSC-Targeted Interventions

Fibrosis is a key driver of disease progression and adverse outcomes in MASLD. Thus, antifibrotic therapies are central to long-term pharmacological strategies. A groundbreaking study by Young Kim et al. (2025) identified hepatic stellate cell (HSC) targets such as SERPINE1 (PAI-1), SPON1, and GAS7, whose inhibition prevents fibrosis in MASH models. This opens new therapeutic avenues aimed at cellular sources of fibrogenesis.

Combination and Multi-target Approaches

Given the heterogeneous pathophysiology of MASLD, combination therapies are being actively pursued. Brouwers et al. (2024) explored incretin-based investigational therapies combining GLP-1 RAs with GIP or glucagon receptor agonists, offering enhanced metabolic and hepatic benefits. These agents may serve dual roles in glycemic control and liver protection.

Clinical Guidelines and Emerging Therapies

The 2024 EASL-EASD-EASO guidelines emphasize individualized pharmacotherapy based on disease severity, comorbidities, and response to lifestyle interventions (EASL, 2024). Several novel agents, including FGF21 analogs, FXR agonists (e.g., obeticholic acid), and ACC inhibitors are in late-stage clinical development, and are expected to reshape the MASLD treatment landscape in the near future (Machado, 2023).

Anti-Obesity Pharmacotherapy in MASLD

Obesity is a key driver in the pathogenesis and progression of MASLD, and successful weight loss is directly correlated with improvements in hepatic steatosis, inflammation, and fibrosis. As many patients are unable to achieve or sustain sufficient weight loss through lifestyle interventions alone, anti-obesity medications (AOMs) have emerged as an essential adjunctive strategy in the treatment of MASLD.

GLP-1 Receptor Agonists: Semaglutide and Liraglutide

- Among currently available anti-obesity agents, GLP-1 receptor agonists (GLP-1 RAs) stand out for their efficacy in weight reduction and multi-system benefits. Semaglutide, administered once weekly, leads to an average weight loss exceeding 15% of baseline body weight and significantly reduces liver fat content and biomarkers of inflammation. In the ESSENCE trial, semaglutide 2.4 mg is being tested in MASLD patients with MASH, demonstrating early promise in improving liver histology without fibrosis worsening (Newsome, 2024). Furthermore, Weghuber et al. (2022) confirmed its robust impact in adolescents, suggesting early intervention potential.
- Liraglutide also shows histological benefit in reducing steatosis and lobular inflammation. These effects are likely due to enhanced satiety, delayed gastric emptying, improved insulin sensitivity, and reduced glucagon secretion (Brouwers, 2024).

Tirzepatide and Dual Agonists

- Tirzepatide, a dual GLP-1 and GIP receptor agonist, has recently demonstrated superior weight loss effects (over 20% in some trials), along with improvements in insulin resistance, lipotoxicity, and inflammatory markers. Given these properties, it holds promise for MASLD, especially in patients with concurrent diabetes or cardiovascular risk factors (Hamza, 2025).

Dual and triple incretin receptor agonists are under rapid development and show synergistic effects on hepatic metabolism, adiposity, and inflammatory pathways. Brouwers et al. (2024) detail several such investigational therapies currently in late-phase trials.

Other FDA-Approved Anti-Obesity Drugs

- Other pharmacologic agents approved for chronic weight management include:

a. Naltrexone-bupropion, which modulates appetite and reward signaling
b. Orlistat, a pancreatic lipase inhibitor reducing fat absorption
c. Phentermine-topiramate, which enhances satiety and decreases food cravings

While these drugs are not specifically approved for MASLD, long-term weight loss (>10%) achieved with them can lead to significant hepatic improvement. According to Weintraub et al. (2023), sustained pharmacotherapy has proven effective in maintaining clinically meaningful weight loss over five years, making it a cornerstone for MASLD adjunct therapy.
Anti-obesity drugs represent a vital therapeutic pillar in MASLD management by addressing its most modifiable root cause: excess adiposity. Their use not only promotes significant hepatic benefits but also reduces associated cardiometabolic risks. As newer, more targeted agents are introduced, integrating these therapies into individualized treatment regimens will be essential for optimized MASLD outcomes.

Future and Emerging Therapies in MASLD
Despite promising developments in lifestyle and pharmacological approaches, MASLD remains a condition with no currently approved curative therapy. This has galvanized intensive research into future and emerging treatments that target the disease's complex pathophysiology at the molecular, metabolic, immune, and fibrotic levels.
1) Cholecystokinin A receptor agonists and MC4R agonists

Emerging agents such as CAGRAs (cholecystokinin A receptor agonists) and MC4R agonists offer alternative mechanisms for weight loss. New drugs under investigation also target specific inflammatory or fibrotic pathways linked to obesity and MASLD, expanding the pharmacological arsenal (Melson, 2024; Muller, 2022).
2) Fibrosis-Targeting Molecules and Stellate Cell Inhibitors

Liver fibrosis is the strongest predictor of poor outcomes in MASLD. As such, antifibrotic agents that inhibit hepatic stellate cell (HSC) activation are a major research focus. In a recent study, Young Kim et al. (2025) used multi-modal analysis to identify SERPINE1, SPON1, and GAS7 as fibrosis-driving targets in human HSCs. Blocking these targets in vivo led to dramatic reductions in fibrosis and liver injury, presenting a novel therapeutic avenue for late-stage MASLD.
3) FXR Agonists and Lipid Modulators

Farnesoid X receptor (FXR) agonists, such as obeticholic acid, are in late-stage trials. These agents regulate bile acid metabolism, reduce hepatic lipogenesis, and exhibit anti-inflammatory effects. However, their use is limited by pruritus and lipid elevation. Modified FXR ligands with improved tolerability are now in development (Ciardullo, 2024).
Similarly, agents targeting acetyl-CoA carboxylase (ACC) and diacylglycerol acyltransferase (DGAT2) aim to reduce hepatic lipogenesis and improve lipid export. Some of these have demonstrated potent effects on liver fat reduction, though gastrointestinal and lipid-related side effects remain challenges.
4) Immunomodulators and Anti-Inflammatory Therapies

Emerging research continues to explore immune-based therapies for MASLD. For example, ursolic acid, which modulates Th17 cells and reduces hepatic inflammation, has shown promise in preclinical studies (Zheng, 2024). Additional compounds are targeting type 3

cytokine pathways (IL-17, IL-22) or pattern recognition receptors to modulate liver immunity and prevent transition to steatohepatitis (Abdelnabi, 2024; Yu, 2024).

5) Precision and Phenotype-Based Medicine

As MASLD is a heterogeneous disease, future treatments are likely to be personalized based on phenotypes, including obesity subtype, metabolic status, liver fibrosis stage, and even microbiota composition. Acosta et al. (2021) demonstrated that phenotype-guided selection of weight loss agents leads to improved outcomes—a concept that may extend to liver-specific drugs in MASLD.

6) Natural Compounds and Microbiome-Modulating Agents

Several natural compounds, including indole derivatives from gut microbiota, show potential in reducing steatosis and inflammation (Hyun Min, 2024). Future therapies may include postbiotics or engineered microbes that restore gut-liver axis integrity and modulate hepatic metabolism.

The future of MASLD therapy is moving toward multi-targeted, individualized, and less invasive pharmacological approaches. From advanced incretin-based agents to HSC-specific antifibrotics, the pipeline is expanding rapidly. Integrating these therapies with lifestyle and systemic metabolic control will be essential for managing the full clinical spectrum of MASLD—from simple steatosis to cirrhosis and hepatocellular carcinoma.

Conclusion

The treatment of MASLD represents one of the most complex challenges in hepatology and metabolic medicine, owing to the disease's multifactorial origins, systemic involvement, and progressive nature. Current therapeutic strategies emphasize a holistic, multimodal approach, integrating lifestyle modification, pharmacological therapies, and targeted anti-obesity interventions.

Non-pharmacological measures, particularly sustained weight loss through diet, physical activity, and behavior change, remain the cornerstone of MASLD management. Even modest reductions in body weight (5–10%) have been consistently associated with improvements in steatosis, inflammation, and early fibrosis. However, long-term adherence to these strategies remains challenging, underscoring the need for adjunct pharmacologic support. Pharmacotherapy for MASLD has evolved significantly with the emergence of agents originally developed for type 2 diabetes and obesity. GLP-1 receptor agonists, notably semaglutide and liraglutide, have demonstrated efficacy in improving both hepatic and metabolic endpoints. Novel agents such as tirzepatide and investigational multi-receptor incretin agonists offer even more robust benefits in liver fat reduction and systemic insulin sensitivity. Additional therapies targeting hepatic inflammation (e.g., ursolic acid, IL-17/22 modulation) and fibrosis (stellate cell inhibitors) show potential to halt or reverse advanced disease.The integration of anti-obesity drugs into MASLD management reflects a paradigm shift, acknowledging obesity as a treatable, disease-modifying factor. Pharmacological weight loss agents, when tailored to patient phenotype and metabolic profile, can provide significant hepatic and extrahepatic benefits, as shown in both clinical trials and real-world studies.

Looking ahead, emerging therapies promise to further individualize and optimize MASLD treatment. Fibrosis-specific agents, immunomodulators, FXR agonists, and gut microbiota-targeted compounds are advancing through preclinical and clinical pipelines. Importantly, future care will likely incorporate precision medicine, leveraging genetic, phenotypic, and metabolomic data to guide therapy selection. Ultimately, the path forward in

MASLD management lies in early detection, patient-centered care, and synergistic combinations of lifestyle and pharmacological strategies, enabling clinicians to not only treat liver damage but address the broader metabolic syndrome spectrum that drives this growing epidemic.

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Authors' contribution

Conceptualization: Paweł Kukiełka

Methodology: Katarzyna Moliszewska, Joanna Kośka

Software: Kacper Dywan, Michał Błaszkiewicz

Check: Julia Mazurek, Julia Załęcka

Formal analysis: Gabriela Łocik, Martyna Musiorska

Investigation: Resources: Paweł Kukiełka, Michał Błaszkiewicz

Data curation: Alicja Nowik, Kacper Dywan

Writing- rough preparation Paweł Kukiełka, Julia załęcka

Writing - review and editing: Gabriela Łocik, Julia Mazurek

Visualization: Martyna Musierowska, Michał Błaszkiewicz

Supervision: Alicja Nowik, Paweł Kukiełka

Project administration:

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