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Review article

Advances in the treatment of nonalcoholic steatohepatitis: current status and future directions

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ABSTRACT

Non alcoholic steatohepatitis (NASH), a progressive subtype of nonalcoholic fatty liver disease (NAFLD), has become a major global health concern Because it can lead to cirrhosis, hepatocellular cancer, and liver failure. Obesity, type 2 diabetes, and metabolic syndrome are intimately associated with NASH, resulting in a substantial disease burden. As of 2024, there is no FDA-approved treatment for NASH despite continued research. While new treatments including GLP-1 receptor agonists, FXR agonists, and PPAR modulators are being thoroughly studied, current management concentrates on lifestyle changes and off-label pharmaceuticals like pioglitazone and vitamin E. This review examines the changing therapeutic landscape based on recent clinical trials, explains the pathophysiology of NASH, and reviews current and upcoming treatments. Understanding treatment modalities is crucial to improving results and lowering the burden of disease, which is why this review is being done.

Keywords: Interleukin-1, Interleukin-1 receptor type 1, Neuroinflammation, CNS diseases, Tracability, Brain injury.

INTRODUCTION

Hepatic steatosis, lobular inflammation, hepatocyte ballooning, and different degrees of fibrosis are the hallmarks of nonalcoholic steatohepatitis (NASH), a chronic, progressive liver disease in people who drink little or no alcohol. An estimated 25% of people worldwide suffer from nonalcoholic fatty liver disease (NAFLD), which is represented by this aggressive variant. Up to 30% of people with NAFLD may develop NASH, which can lead to end-stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The global growth in obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus (T2DM) is substantially responsible for the rising prevalence of NASH.

In fact, NASH is already the second most common reason for liver transplantation in the US and is expected to overtake all other causes within the next ten years. Early detection and intervention are particularly difficult due to its asymptomatic early phases and absence of noninvasive diagnostic techniques. Based on the results of a liver biopsy, which include inflammation, hepatocyte ballooning, and steatosis affecting more than 5% of hepatocytes, NASH is confirmed histologically. One important prognostic marker is fibrosis, which is frequently rated on a range of F0 to F4. Fibrosis stage is a crucial target in the development of treatments because it has a substantial correlation with both liver-related and all-cause mortality [1].

NASH is a multisystem illness rather than just a liver condition due to its systemic metabolic foundations. Cardiovascular disease (CVD), which continues to be the primary cause of death for these people, is often linked to it. As a result, therapeutic approaches have changed from being liver-centric to being holistic and metabolic. There are currently no licensed medications especially for the treatment of NASH, despite the substantial burden. The cornerstone is still lifestyle treatments, although they are hard to maintain and rarely lead to histological improvement until substantial weight loss is attained. There are presently few pharmacological treatments available in clinical practice, despite ongoing research.

The goal of this analysis is to present a thorough and current summary of NASH therapy options that are both approved and under investigation. It discusses potential candidates in late-stage clinical studies, current off-label treatments, dietary and lifestyle changes, and future approaches to the treatment of this complicated illness [2].

Current standard of care

Management of nonalcoholic steatohepatitis (NASH) currently focuses on lifestyle modification and off-label pharmacologic agents, as no drugs have yet been approved by regulatory agencies for its direct treatment. Early intervention to reverse hepatic steatosis and delay fibrosis progression is critical for long-term outcomes.

Lifestyle modification

The mainstay of NASH treatment continues to be lifestyle modifications. Numerous studies demonstrate that a weight loss of at least 7–10% results in notable histological improvements, such as the resolution of NASH and the regression of fibrosis.

It has been demonstrated that dietary strategies like the Mediterranean diet can lower liver fat and increase insulin sensitivity.

Even in the absence of weight loss, physical activity (aerobic and strength training) independently improves metabolic health and hepatic steatosis. Long-term adherence is still a significant barrier despite compelling data [3].

Pharmacologic treatments

Although not yet licensed particularly for NASH, a number of pharmacologic treatments are used off-label and are backed by results from clinical trials.

In patients with type 2 diabetes, pioglitazone, a PPAR-γ agonist, reduces inflammation, ballooning, and steatosis. However, heart failure risk and weight increase are issues.

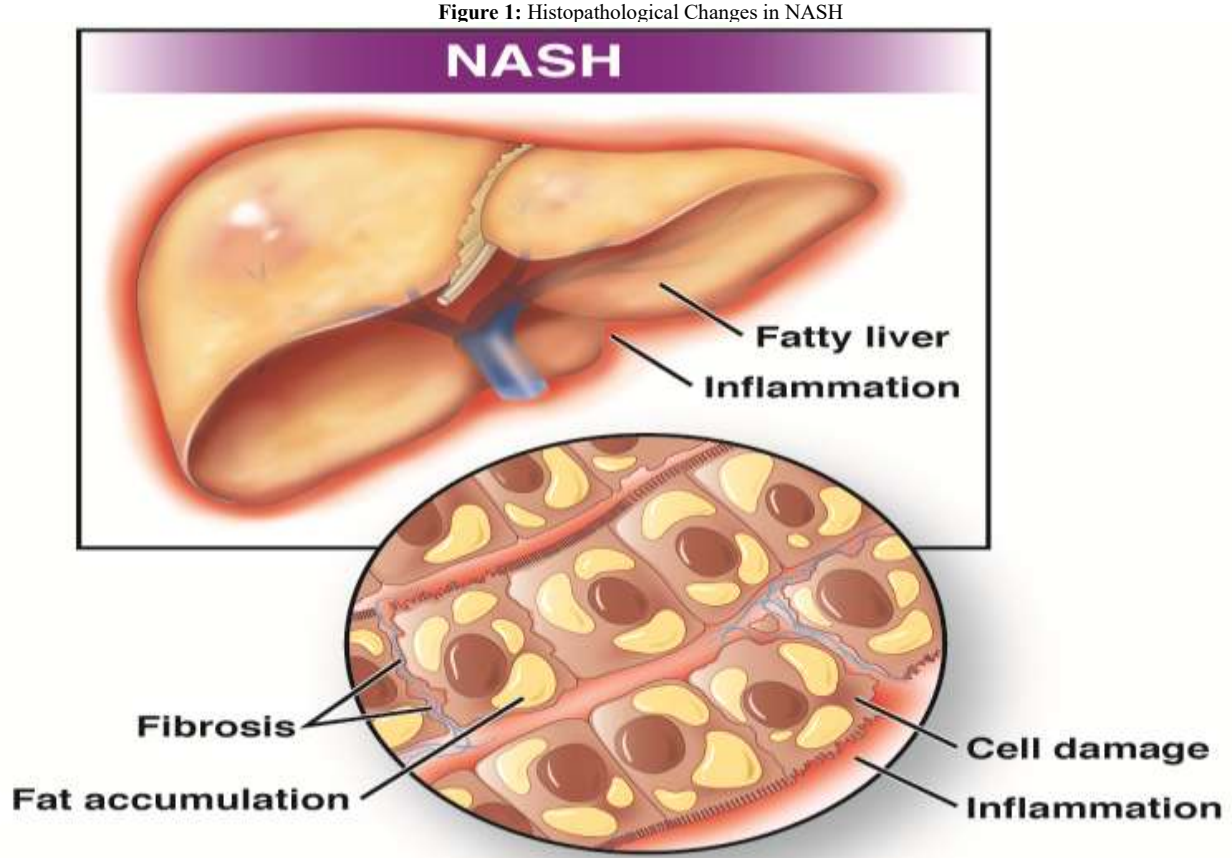
By lowering oxidative stress and inflammation, vitamin E (800 IU/day) has demonstrated effectiveness in nondiabetic NASH patients. Due to unclear long-term safety, it is not advised for people with diabetes.

GLP-1 receptor agonists, such as semaglutide and liraglutide, have demonstrated that weight loss and NASH resolution was attained without worsening fibrosis in recent trials. These medications offer significant advantages, but they are limited by hazards unique to each patient and uneven fibrosis regression [4].

Table 1: Summary of Current Pharmacologic Treatments for NASH

Drug	Class	Indication	NASH Impact	Key Limitations
Pioglitazone	PPAR-γ agonist	T2DM with biopsy-proven NASH	Improves histology, reduces fibrosis	Weight gain, fluid retention
Vitamin E	Antioxidant	Nondiabetic NASH	Reduces steatosis and inflammation	Long-term safety unclear
Liraglutide	GLP-1 RA	Obese/NASH + T2DM	NASH resolution, weight loss	GI side effects, cost

Figure 1: Histopathological Changes in NASH



Current limitations

The FDA has not approved any treatments specifically for NASH.

Comorbidity, disease stage, and patient adherence all affect effectiveness.

A major therapeutic target, fibrosis, is not consistently improved by most medicines.

New NASH treatments

As of 2024, several experimental medications have demonstrated encouraging outcomes in improving metabolic markers and correcting liver damage in NASH. The majority are in Phase II or III trials that focus on important biological processes like inflammation, lipid metabolism, and fibrosis.

Agonists of FXR

The farnesoid X receptor (FXR) agonist obeticholic acid (OCA) improves bile acid balance and insulin sensitivity. OCA (25 mg) considerably reduced fibrosis without making NASH worse in the REGENERATE experiment. Pruritus and high LDL cholesterol are still drawbacks, albeit.

Agonists of PPAR

In the NATIVE trial, lanifibranor, a pan-PPAR agonist (α/δ/γ), demonstrated histologic improvement, including elimination of NASH and fibrosis. Phase III evaluation is currently underway. Clinical research is also underway for other selective drugs such as saroglitazar (dual α/γ) and elafibranor (PPAR-α/δ) [5].

THR-β Agonists

The selective thyroid hormone receptor-β (THR-β) agonist resmetirom (MGL-3196) aims to reduce hepatic fat. One of the most promising options in the pipeline, phase III data (MAESTRO-NASH) demonstrated notable decreases in liver fat and noninvasive fibrosis markers.

FGF Analogs

A derivative of FGF21 called pegbelfermin improves insulin sensitivity and lipid metabolism. In Phase II trials, it showed anti-fibrotic qualities and reduced liver fat. But more information on histologic results is required.

GLP-1 & Dual Agonists

Semaglutide and other GLP-1 receptor agonists are still promising. Semaglutide (0.4 mg/day) reduced NASH by 59% in a Phase II trial without exacerbating fibrosis. Tirzepatide, a combined GLP-1/GIP agonist approved for type 2 diabetes and obesity, is undergoing phase II research in NASH; initial findings suggest synergistic metabolic and hepatic benefits [6].

Figure 2: Disease Progression Pathway of NASH Leading to Cirrhosis and Liver Cancer

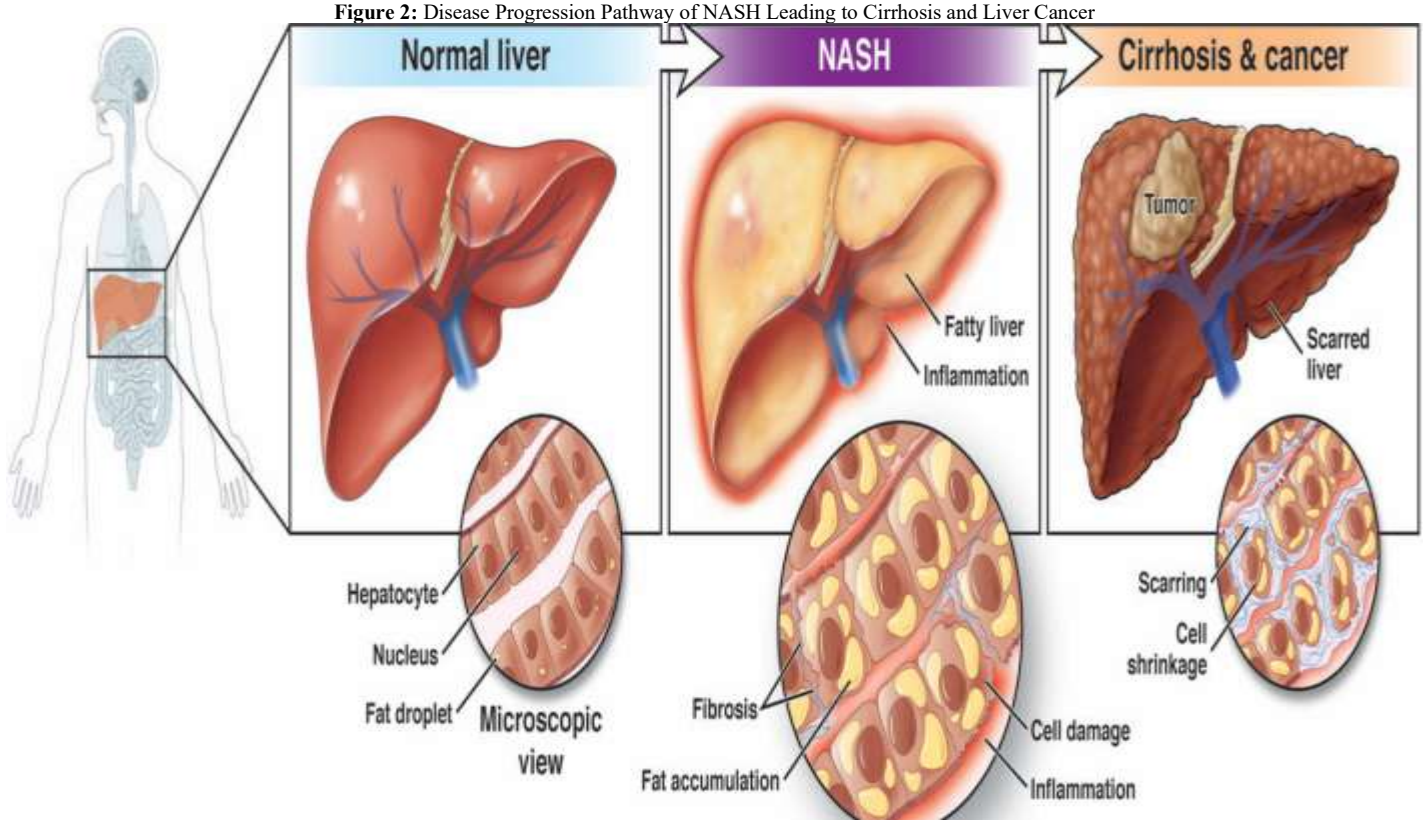


Table 2: Emerging Therapies for NASH (Key Highlights)

Drug	Class/Target	Trial Phase	Key Outcomes	Limitations
Obet cholic acid	FXR agonist	Phase III	Fibrosis improvement	Pruritus, ↑LDL
Lanifibranor	Pan-PPAR (α/δ/γ)	Phase III	NASH + fibrosis resolution	Edema, mild GI symptoms
Resmetirom	THR-β agonist	Phase III	Liver fat ↓, fibrosis biomarker ↓	Muscle-related side fx
Pegbelfermin	FGF21 analog	Phase II	↓ Hepatic steatosis, improved markers	Long-term data needed
Semaglutide	GLP-1 RA	Phase II	59% NASH resolution	GI side effects
Tirzepatide	GLP-1/GIP agonist	Phase II	Dual metabolic & hepatic benefit (early)	Still under trial

Combination therapies and multi-target approaches

Because nonalcoholic steatohepatitis (NASH) has a complex pathogenesis that includes steatosis, insulin resistance, inflammation, hepatocyte damage, and fibrosis, monotherapies frequently fail to produce a complete clinical improvement. Consequently, combination treatments have become a potential approach to simultaneously address several disease processes.

Why combine therapies?

Combination therapy for NASH is justified by its capacity to:

Address several pathological pathways (such as fibrosis, inflammation, and steatosis).

Increase efficacy through pharmacological synergy.

Reduce side effects by lowering the dosage of individual drugs [7].

Additive or synergistic histology advantages can result from the use of medicines with complementary mechanisms, according to studies. Furthermore, patients with co-occurring diseases like obesity or type 2 diabetes may benefit more from multi-target strategies in terms of metabolism and the liver.

Examples of investigational combinations

Several combinations are under active clinical or preclinical evaluation:

Semaglutide + Cilofexor + Firsocostat

This triple treatment, which targets GLP-1 receptors, FXR pathways, and acetyl-CoA carboxylase (ACC) inhibition, was investigated in the ATLAS Phase II trial. Both the fibrosis stage and NASH resolution were improved with the combination.

Lanifibranor + SGLT2 inhibitors

While SGLT2 inhibitors support fat mobilisation and glycemic management, lanifibranor is a pan-PPAR agonist (α/δ/γ). Their combined use is still being evaluated, but initial findings point to improved metabolism and normalised lipid profiles.

Resmetirom + GLP-1 receptor agonists

This combination, which is currently in its early conceptual stages, offers a viable avenue for future trials by combining systemic metabolic effects with liver-specific thyroid hormone modulation [8].

Table 3: Leading Combination Therapies Under Investigation

Combination	Targets/Pathways	Trial Phase	Outcomes
Semaglutide + Cilofexor + Firsocostat	GLP-1 RA, FXR, ACC	Phase II (ATLAS)	Improved NASH resolution & fibrosis
Lanifibranor + SGLT2 inhibitors	PPAR (α/δ/γ) + glycemic control	Pilot trials	Reduced steatosis, improved insulin
Resmetirom + GLP-1 RA	THR-β agonist + metabolic axis	Preclinical/planned	Proposed synergy, under evaluation

Challenges in combination therapy

Combination medicines encounter clinical and regulatory obstacles despite their tremendous potential**.**

Complicated trial design

Longer durations and larger patient cohorts are necessary for multi-arm studies.

Overlap of adverse effects

For instance, combining FXR and GLP-1 medications may increase dyslipidemia and GI side effects.

Cost and compliance

Patients may experience increased pill burden and financial pressure as a result of multi-drug regimens.

Unclear procedures for approval

Guidelines for NASH combo approvals have not yet been finalised by regulatory agencies such as the FDA.

Challenges and future perspectives

Current challenges in NASH management

The subject of NASH research and therapy has numerous scientific, clinical, and regulatory obstacles despite continuous clinical advancements:

Absence of approved therapies

As of 2024, neither the FDA nor the EMA had approved a single treatment for NASH. The majority of medications are still in the research phase, which restricts therapeutic access and clinician trust.

Diagnostic restrictions

The gold standard for diagnosis, liver biopsy, is intrusive, expensive, and prone to sampling error. For staging and long-term surveillance, noninvasive biomarkers and imaging techniques like FibroScan and MRI-PDFF are still not perfect [9].

Trial design and objectives

Histologic confirmation is necessary for objectives such as "NASH resolution without fibrosis worsening," and trials are costly and time-consuming. Progress is slowed by the absence of established surrogate measures for long-term outcomes [10].

Regulatory ambiguity

Development routes are delayed by the FDA and EMA's lack of uniform acceptance of combination therapy and surrogate endpoints, such as imaging-based fibrosis regression [11].

Patient heterogeneity and adherence

Comorbid obesity, type 2 diabetes, and cardiovascular disease are common in NASH patients. Trial inclusion, generalizability, and long-term adherence to pharmaceutical or lifestyle therapies are all complicated by this heterogeneity [12].

Future directions

Research, technology, and personalised medicine developments will probably influence NASH treatment in the future:

Noninvasive diagnostics

To increase screening and monitoring accuracy, future research will concentrate on circulating biomarkers (such as CK-18 and PRO-C3) and machine learning-based imaging technologies.

Personalized medicine

Rather than relying solely on liver histology, genomic and transcriptome profiling (such as PNPLA3 and TM6SF2 polymorphisms) may be used to stratify patients and customise treatments based on molecular phenotype.

Digital monitoring and telehealth

AI-powered platforms, wearable technology, and mobile health apps can check liver indicators, enhance adherence, and provide real-time feedback in lifestyle treatments

Next-Generation drug development

Immune modulators, gene editing tools, and multi-target therapies targeted at reversing fibrosis are all part of this pipeline. These new classes could offer alternatives to combination therapy [13].

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