INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Paper

Non-Alcoholic Fatty Liver Managment

Denisha Meghnathi*[1], Kiran Rathod[2], Chintankumar Tank[3], Shivani Herma[1], Himanshu Parmar[1], Pritesh Odedara[1]

[1]*B. pharm, Final Year Student, Faculty of Pharmacy, Dr. Subhash University, Junagadh, Gujarat, India*
[2]*Assistant Professor, School of Pharmacy, Dr. Subhash University, Junagadh, Gujarat, India*
[3]*Dean of School of Pharmacy, Dr. Subhash University, Junagadh, Gujarat, India*

ARTICLE INFO

Published: 28 Apr. 2025
Keywords:
Non-alcoholic steatohepatitis, orlistat, pioglitazone, vitamin E, GLP-1 receptor agonist, obeticholic acid, resmetirom
DOI:
10.5281/zenodo.15298763

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a common liver condition marked by fat accumulation in the liver without significant alcohol consumption. It ranges from benign non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), a more severe form involving inflammation and cell damage, which can progress to fibrosis, cirrhosis, and liver cancer. NAFLD is closely linked to metabolic syndrome, with key risk factors including obesity, type 2 diabetes, insulin resistance, dyslipidaemia, and sedentary lifestyle. Its pathophysiology involves increased free fatty acid delivery to the liver, insulin resistance, oxidative stress, and inflammation leading to liver damage and fibrosis. Diagnosis typically requires imaging or liver biopsy, while treatment focuses on lifestyle modifications such as weight loss and exercise. Pharmacological options include orlistat, pioglitazone, vitamin E, GLP-1 receptor agonists (e.g., semaglutide), and emerging agents like obeticholic acid and resmetirom. While these treatments can reduce liver fat and inflammation, only resmetirom has shown strong Phase III results for fibrosis improvement. Despite promising therapies, lifestyle change remains the cornerstone of NAFLD management.

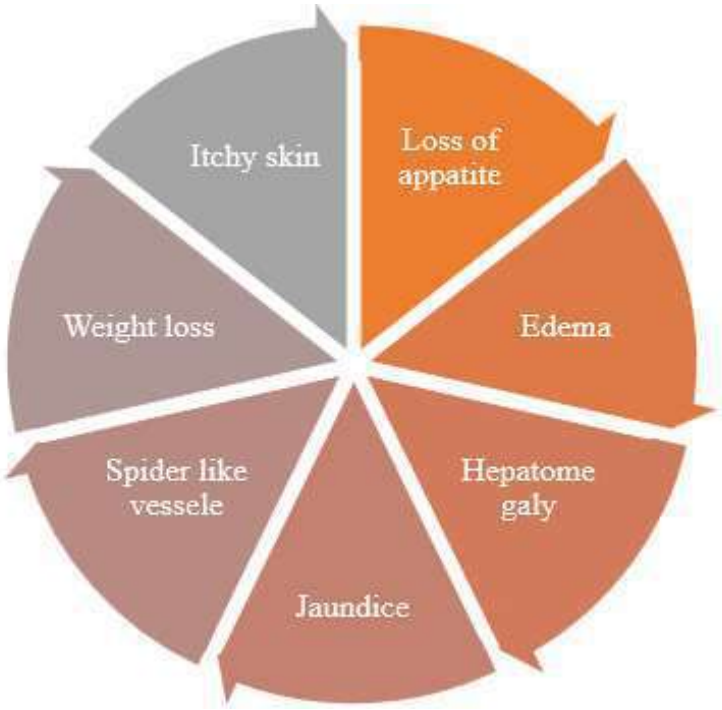
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is currently one of the most prevalent causes of chronic liver disease globally. It encompasses a range of liver conditions marked by fat accumulation in the liver (hepatic steatosis) without identifiable secondary causes, such as significant alcohol intake. The disease spectrum spans from non-alcoholic fatty liver (NAFL), which is typically benign, to non-alcoholic steatohepatitis (NASH), the more severe form characterized by inflammation and hepatocyte injury. Over time, NAFLD can advance to liver

***Corresponding Author:** Denisha Meghnathi
Address: *B. pharm, Final Year Student, Faculty of Pharmacy, Dr. Subhash University, Junagadh, Gujarat, India*
Email ✉: denishagoswami440@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

fibrosis and cirrhosis [1,2]. While NAFL is marked solely by hepatic steatosis, NASH features additional lobular inflammation and cell death, which increase the risk of fibrotic progression [3,4]. NASH can be classified from mild (F0–F1) to advanced fibrosis (≥F3, bridging) and finally cirrhosis (F4). Higher degrees of fibrosis influence survival and are related to more progressive disease states that may lead to liver cirrhosis, HCC, and eventually, a requirement for liver transplantation. [4] Prior to the mid-2010s, NASH was largely seen as a condition affecting primarily obese women, often with Type 2 Diabetes Mellitus (T2DM), and was believed to have a relatively mild course. However, these risk factors—T2DM, cardiovascular disease, and stroke—are now recognized as predictors of disease severity. NAFLD has shown a significant rise in prevalence in developed countries, currently affecting about 25% of the global population. It is increasingly common in individuals with central obesity, metabolic syndrome, T2DM, and dyslipidaemia [5]. For diagnostic purposes, liver biopsy remains the gold standard for assessing liver inflammation and damage. In NAFLD and related disorders, histological findings can vary from simple fat droplets (triglyceride deposits) in hepatocytes to more complex features indicative of NASH, such as inflammation and varying degrees of fibrosis. While most individuals with hepatic steatosis do not experience disease progression, a subset may develop NASH, which can lead to end-stage liver disease and hepatocellular carcinoma [5,6]. According to U.S. clinical guidelines, NAFLD is defined by at least 5% hepatic fat accumulation as seen on imaging or histology, without evidence of alcohol abuse, drug-induced liver damage, or viral hepatitis. Some patients may also show elevated liver enzyme levels [6]. Individuals with NAFLD frequently exhibit one or more traits of metabolic syndrome, including insulin resistance, hypertension, dyslipidaemia, or T2DM [7]. Visceral obesity has been increasingly linked to the development of NAFLD. Notably, metabolic syndrome is also a known contributor to cardiovascular disease, which is the leading cause of mortality among NAFLD patients. While the exact mechanisms connecting cardiovascular disease and NAFLD remain unclear, insulin resistance is believed to play a central role in the shared pathophysiology [7]. Evaluating abnormal liver function tests in otherwise asymptomatic patients can be challenging. NAFLD is often responsible for elevated liver enzyme levels, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in blood donors—accounting for up to 90% of such cases when other liver diseases are excluded [8,9]. WHO Global Health Observatory data from 2014 reported global obesity rates of 15% among women and 11% among men aged 18 and older. Studies estimate the prevalence of NASH in the U.S. to be between 5.7% and 17%. The diverse manifestations of NAFLD and its intricate link with metabolic syndrome present diagnostic and therapeutic challenges. This review seeks to provide a comprehensive overview of NAFLD, focusing on its pathophysiological basis, risk factors, diagnostic strategies, and both conservative and surgical management approaches.

SIGN & SYMPTOMS:



PATHOPHYSIOLOGY:

The pathophysiology of NAFLD involves adipose tissue dysfunction and increased supply of free fatty acids to the liver, dysregulation of adipokines, excessive free fatty uptake by the liver, problems in hepatic lipid production and processing, and decreased lipid clearance by the liver. [10] Increased free fatty acids in the blood have a role in the development of insulin resistance. [11] insulin resistance leads to changes in lipid metabolism which includes increased peripheral lipolysis causing increased blood-free fatty acids, Increased triglyceride synthesis, and increased hepatic uptake of the fatty acids which contribute to increased hepatocellular triglyceride accumulation. Apart from the supply of free fatty acids from the adipose Tissues, the liver also performs de novo lipogenesis and produces triacylglycerols that are stored within the hepatocytes as lipid droplets. In normal healthy individuals, this de-novo lipogenesis contributes to around 5% of triglyceride accumulation; however, in NAFLD, this share reaches upward Up to 26%.[12] The triacylglycerol production in NAFLD is regulated by multiple factors like diet, hepatic insulin resistance, and genetics. The etiopathogenesis is demonstrated in the progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis and cirrhosis the metabolism of free fatty acid by oxidation in the liver results in the production of reactive oxygen species which Are normally cleared by antioxidant pathways but get overwhelmed in nonalcoholic steatohepatitis (NASH) due to Excessive uptake and production. [13][14] The result is subsequent hepatocellular injury. there is recruitment of the hepatic stellate cells which are the resident fibroblastic cells of the Liver and key players involved in the progression to fibrosis. [15] Due to chronic hepatic injury and inflammation, a wound Healing process starts, and there is progressive deposition of extracellular matrix proteins which than later contribute to liver fibrosis.[16]

Risk Factor:

NAFLD is a multifactorial condition influenced by metabolic, genetic, lifestyle, and environmental factors. The primary risk factors include:

Metabolic Risk Factors:

Obesity, particularly central (visceral) obesity, is strongly associated with hepatic steatosis. Type 2 Diabetes Mellitus is a significant independent predictor of NAFLD and its progression to non-alcoholic steatohepatitis (NASH). Dyslipidaemia, characterized by elevated serum triglycerides and low high-density lipoprotein (HDL) cholesterol levels, is commonly observed in NAFLD patients. Insulin Resistance is central to the pathogenesis of NAFLD, contributing to increased hepatic lipid accumulation. Metabolic Syndrome, a constellation of conditions including obesity, hypertension, insulin resistance, and dyslipidaemia, is closely linked to NAFLD development.

Lifestyle and Dietary Factors:

Sedentary Behaviour: Lack of physical activity has been independently linked to increased hepatic fat content. High-Calorie and Western-Type Diets: Diets rich in saturated fats, fructose, and refined carbohydrates contribute to lipid accumulation in hepatocytes. Rapid Weight Loss: Sudden and severe caloric restriction may paradoxically exacerbate hepatic steatosis.

Hormonal and Endocrine Disorders:

Polycystic Ovary Syndrome (PCOS): Frequently associated with insulin resistance, PCOS is recognized as a significant risk factor for NAFLD in women. Hypothyroidism: May contribute to lipid dysregulation and hepatic fat accumulation. Hypopituitarism and Hypogonadism: These conditions are linked to increased risk of metabolic disturbances, including NAFLD. [17]

Other Medical Conditions:

Obstructive Sleep Apnea (OSA): Intermittent hypoxia and systemic inflammation in OSA are believed to contribute to NAFLD pathogenesis.

Chronic Kidney Disease: NAFLD is both a risk factor for and a consequence of renal dysfunction, indicating a bidirectional relationship.

Pharmacological and Iatrogenic Factors:

Certain Medications: Long-term use of drugs such as corticosteroids, amiodarone, methotrexate, tamoxifen, and some antiretrovirals has been associated with hepatic steatosis. [18]

TREATMENT:

Diet and Lifestyle Modification:

Non-pharmacological interventions for NAFLD primarily focus on reducing calorie intake and increasing physical activity. Both weight loss and regular exercise have proven benefits not only for managing NAFLD but also for lowering cardiovascular disease (CVD) risk. Achieving a moderate weight loss of 7% to 10% and engaging in physical activity can lead to improvements in liver histology, insulin resistance, and overall quality of life, making these strategies fundamental to treatment [19][20]. While overall calorie reduction is key, growing evidence highlights the harmful impact of high fructose intake, which has been linked to greater liver fibrosis in NAFLD patients. In terms of physical activity, recent findings suggest that high-intensity exercise may lead to better liver-related outcomes compared to lower-intensity activity [20]. However, many individuals struggle to adopt and maintain these lifestyle changes long-term Therefore, incorporating behavioural strategies, such as cognitive behavioural therapy or support from a dietitian, is recommended. Additionally, patients at risk of cardiovascular issues should be assessed before beginning an intensive exercise regimen. [21][22]

Pharmacological Therapy:

The current status of NAFLD therapy and an approach to its management is reviewed. While the evaluation of measures of response to treatment is beyond the scope of the present review, the primary objective of any NAFLD therapy is improvement in steatohepatitis and fibrosis, with the ultimate goal of preventing CVD- and liver-related death. Pharmacological options include orlistat, pioglitazone, vitamin E, GLP-1 receptor agonists (e.g., semaglutide), and emerging agents like obeticholic acid and resmetirom. While these treatments can reduce liver fat and inflammation, only resmetirom has shown strong Phase III results for fibrosis improvement.

Orlistat:

Orlistat is an anti-obesity medication that works by inhibiting gastric and pancreatic lipases, enzymes responsible for breaking down dietary fats in the gastrointestinal tract. By blocking fat digestion, it prevents approximately 30% of ingested fat from being absorbed, leading to caloric deficit and gradual weight loss. It is indicated for the management of obesity in individuals with a body mass index (BMI) of 30 kg/m² or greater, or 27 kg/m² with associated risk factors such as hypertension, type 2 diabetes, or dyslipidaemia. Orlistat is available in both prescription (Xenical, 120 mg) and over-the-counter (Alli, 60 mg) formulations, typically taken three times daily with meals containing fat. The most common side effects are gastrointestinal in nature, including oily stools, flatulence with discharge, and faecal urgency, which are often reduced by adhering to a low-fat diet. Orlistat may also impair the absorption of fat-soluble vitamins and interact with medications such as cyclosporine and warfarin. Due to its mechanism, it is contraindicated in pregnancy, chronic malabsorption syndromes, and cholestasis. Despite its side effects, orlistat remains a useful adjunct in weight management when combined with dietary changes and exercise. [23][24] Orlistat has been investigated as a potential adjunct therapy for Non-Alcoholic Steatohepatitis (NASH), primarily due to its ability to promote weight loss, which is a key therapeutic goal in NASH management. Although not specifically approved for NASH, orlistat is used off-label in obese patients with NASH to support lifestyle interventions, such as a reduced-calorie, low-fat diet and increased physical activity. By inhibiting intestinal fat absorption, orlistat can help achieve significant weight loss, which is known to improve liver steatosis, reduce inflammation, and potentially slow fibrosis progression. Clinical studies have shown that orlistat use may lead to improvements in liver enzymes such as ALT and AST, as well as reductions in hepatic fat content. However, its effects on liver histology are mainly attributed to the extent of weight loss rather than a direct pharmacological action on the liver. Common gastrointestinal side effects, such as oily stools and flatulence, can limit adherence in some patients. Overall, orlistat serves as a supportive agent in the broader management of NASH, particularly in patients with obesity, but is not considered a primary treatment for reversing liver fibrosis or inflammation. [25] [26]

Clinical trial:

Several clinical studies have explored the role of orlistat in the management of Non-Alcoholic Steatohepatitis (NASH), focusing primarily on its weight-loss-mediated effects on liver health. In a randomized controlled trial by Zelber-Sagi et al. (2006), overweight and obese patients with non-alcoholic fatty liver disease (NAFLD) were treated with orlistat alongside a calorie-restricted diet for six months. The study reported significant improvements in liver enzymes and reductions in hepatic fat content, assessed via ultrasound, in the orlistat group compared to diet alone, indicating the added benefit of pharmacological support for

weight loss. [27] Similarly, Harrison et al. (2009) conducted a prospective, randomized trial evaluating orlistat in patients with biopsy-proven NASH. The results demonstrated that patients who achieved significant weight loss with orlistat experienced modest histological improvements, including reductions in steatosis and lobular inflammation. However, the study also highlighted that these benefits were largely dependent on the degree of weight reduction, rather than a direct pharmacological action of orlistat on liver tissue. [28] Another pivotal study by Bugianesi et al. (2005) assessed the impact of orlistat-facilitated weight loss on liver histology in NASH patients and found that those who lost more than 10% of their body weight showed marked improvements in steatosis and necroinflammation on liver biopsy. Collectively, these trials suggest that while orlistat does not exert a direct anti-inflammatory or anti-fibrotic effect on the liver, it can serve as an effective adjunct in NASH management by enhancing weight loss outcomes and improving metabolic and hepatic parameters when used in conjunction with lifestyle interventions. [29]

Pioglitazone:

Pioglitazone is an oral antidiabetic medication belonging to the thiazolidinedione class, primarily used to manage type 2 diabetes mellitus. It works by enhancing insulin sensitivity in peripheral tissues, especially in adipose tissue, skeletal muscle, and the liver, through activation of the peroxisome proliferator-activated receptor-gamma (PPAR-γ). By improving insulin action, pioglitazone helps lower blood glucose levels and reduces insulin resistance, which is a hallmark of type 2 diabetes. Beyond glycemic control, pioglitazone has shown beneficial effects on lipid profiles and may reduce liver fat content, making it of interest in conditions like non-alcoholic fatty liver disease (NAFLD). However, its use may be associated with side effects such as weight gain, fluid retention, risk of heart failure, and potential concerns about bladder cancer with long-term use. Therefore, while effective, its administration should be carefully considered, especially in patients with underlying cardiovascular or bladder conditions. [30] Pioglitazone has been studied extensively as a treatment option for non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) characterized by liver inflammation, hepatocellular injury, and fibrosis. As a PPAR-γ agonist, pioglitazone improves insulin sensitivity, reduces hepatic glucose production, and promotes lipid metabolism, which collectively help decrease liver fat accumulation and inflammation. Clinical trials have demonstrated that pioglitazone can significantly improve histological features of NASH, including steatosis, ballooning, and inflammation, and in some cases, may even lead to fibrosis regression. It is particularly effective in patients with type 2 diabetes or prediabetes who have NASH. However, its use must be balanced against potential adverse effects, such as weight gain, fluid retention, and risk of bone fractures. Despite these concerns, pioglitazone remains one of the few pharmacologic agents with proven histological benefits in NASH and is recommended in certain clinical guidelines for patients with biopsy-proven NASH and metabolic risk factors. [31]

Clinical trial:

We randomly assigned 55 patients with impaired glucose tolerance or type 2 diabetes and liver biopsy-confirmed non-alcoholic steatohepatitis to 6 months of treatment with a hypocaloric diet (a reduction of 500 kcal per day in relation to the calculated daily intake required to maintain body weight) plus pioglitazone (45 mg daily) or a hypocaloric diet plus placebo. Before and after treatment, we assessed hepatic histologic features, hepatic fat content by means of magnetic

resonance spectroscopy, and glucose turnover during an oral glucose tolerance test ([14C] glucose given with the oral glucose load and [3H] glucose given by intravenous infusion). Diet plus pioglitazone, as compared with diet plus placebo, improved glycemic control and glucose tolerance (P<0.001), normalized liver aminotransferase levels as it decreased plasma aspartate aminotransferase levels (by 40% vs. 21%, P=0.04), decreased alanine aminotransferase levels (by 58% vs. 34%, P<0.001), decreased hepatic fat content (by 54% vs. 0%, P<0.001), and increased hepatic insulin sensitivity (by 48% vs. 14%, P=0.008). Administration of pioglitazone, as compared with placebo, was associated with improvement in histologic findings with regard to steatosis (P=0.003), ballooning necrosis (P=0.02), and inflammation (P=0.008). Subjects in the pioglitazone group had a greater reduction in necroinflammation (85% vs. 38%, P=0.001), but the reduction in fibrosis did not differ significantly from that in the placebo group (P=0.08). Fatigue and mild lower-extremity edema developed in one subject who received pioglitazone; no other adverse events were observed. [32]

VITAMINE:

Vitamin E is a fat-soluble antioxidant that plays a crucial role in protecting cells from oxidative damage. It exists in several forms, with alpha-tocopherol being the most biologically active in humans. Vitamin E helps neutralize free radicals, which are harmful byproducts of cellular metabolism that can damage lipids, proteins, and DNA. This antioxidant activity is particularly important in tissues with high fat content, such as the brain and liver. In clinical settings, vitamin E has been studied for its potential benefits in a variety of conditions, including cardiovascular disease, eye disorders, and neurodegenerative diseases. In liver health, particularly non-alcoholic fatty liver disease (NAFLD), vitamin E has been shown to reduce inflammation and liver cell injury. Its anti-inflammatory and antifibrotic properties make it a promising therapeutic agent in certain cases, especially in non-diabetic individuals with biopsy-proven non-alcoholic steatohepatitis (NASH). However, high doses of vitamin E supplementation should be used cautiously, as excessive intake may pose risks such as increased bleeding tendency or, in some studies, all-cause mortality. Overall, vitamin E remains an important nutrient with therapeutic potential when used appropriately. [33]

Clinical trial:

The PIVENS trial (Pioglitazone, Vitamin E, or Placebo for NASH), conducted by the NASH Clinical Research Network, was a randomized, double-blind, placebo-controlled trial involving non-diabetic adults with biopsy-proven NASH. Patients received either vitamin E (800 IU/day), pioglitazone, or placebo for 96 weeks. The results showed that vitamin E significantly improved key histological features of NASH, including steatosis, lobular inflammation, and hepatocellular ballooning, when compared to placebo. Importantly, 43% of patients in the vitamin E group achieved a histological improvement in NASH without worsening fibrosis, compared to 19% in the placebo group. However, the trial noted no significant improvement in fibrosis. Another important study was the TONIC trial (Treatment of Non-alcoholic Fatty Liver Disease in Children), which evaluated vitamin E in paediatric patients with NAFLD. Children were randomized to receive vitamin E, metformin, or placebo for 96 weeks. The trial found that vitamin E significantly improved liver histology and reduced hepatocellular ballooning compared to placebo, although it did not lead to a significant reduction in ALT levels (a marker of liver injury). While these trials support the use of vitamin E in non-diabetic patients with NASH, especially those with

biopsy-confirmed disease, its use remains controversial in diabetic patients or those with advanced fibrosis due to potential risks associated with long-term high-dose supplementation, such as increased all-cause mortality and haemorrhagic stroke in some meta-analyses. Therefore, vitamin E is currently recommended selectively, particularly in non-diabetic adults with biopsy-proven NASH, as per guidelines from the American Association for the Study of Liver Diseases (AASLD). [34]

GLP-1 RA:

Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) are a class of medications primarily used in the treatment of type 2 diabetes mellitus and, more recently, obesity. These agents mimic the action of the endogenous hormone GLP-1, which is secreted by the intestines in response to food intake. GLP-1 RAs enhance glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety, leading to improved glycaemic control and significant weight loss. Commonly used GLP-1 RAs include liraglutide, semaglutide, dulaglutide, and exenatide. Recent studies have also shown that GLP-1 RAs may have beneficial effects on cardiovascular health and liver fat content, making them potentially useful in managing conditions like non-alcoholic fatty liver disease (NAFLD). These drugs are generally well-tolerated, though gastrointestinal side effects such as nausea, vomiting, and diarrhoea are common, especially during the initiation phase. [35]

Clinical Trial:

GLP-1 receptor agonists (GLP-1 RAs) are showing promise in clinical trials for treating non-alcoholic steatohepatitis (NASH), a progressive liver disease. These drugs, initially developed for diabetes and obesity, have demonstrated benefits in reducing liver fat, improving liver inflammation, and, in some cases, addressing fibrosis. In a 72-week Phase II trial, semaglutide achieved NASH resolution in up to 59% of patients without worsening fibrosis, compared to 17% in the placebo group. However, improvements in fibrosis were not statistically significant.Similarly, liraglutide showed a 39% resolution rate of NASH over 48 weeks, though fibrosis improvements were modest. Emerging GLP-1 RA therapies are also under investigation. Tirzepatide, a dual GLP-1/GIP agonist, demonstrated a 62% NASH resolution rate in a 52-week trial, with up to 55% of patients showing fibrosis improvement, though not always statistically significant. Survodutide, a GLP-1/glucagon receptor agonist, achieved MASH improvement in 83% of patients over 48 weeks, with significant fibrosis improvements. Efinopegdutide, another dual agonist, reduced liver fat by 72.7% over 24 weeks, outperforming semaglutide's 42.3% reduction. [36] While these findings are encouraging, most GLP-1 RAs are not yet approved for NASH treatment. Ongoing Phase III trials, such as the ESSENCE trial for semaglutide, aim to confirm their efficacy and safety. Common side effects include gastrointestinal symptoms like nausea and diarrhoea. In summary, GLP-1 RAs are a promising avenue for NASH therapy, offering potential benefits in liver health and weight management. However, further research is necessary to establish their role in standard treatment protocols. [37]

Obeticholic Acid:

Obeticholic acid (OCA) is a semi-synthetic bile acid analogue that functions as a potent agonist of the farnesoid X receptor (FXR), a nuclear receptor involved in regulating bile acid, lipid, and glucose metabolism. Originally approved for the treatment of primary biliary cholangitis (PBC), OCA has

also been investigated as a potential therapy for non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD). By activating FXR, OCA reduces hepatic lipogenesis, enhances insulin sensitivity, and exerts anti-inflammatory and anti-fibrotic effects, all of which are crucial in addressing NASH pathophysiology. Clinical trials, such as the REGENERATE trial, have demonstrated that OCA can improve liver histology in NASH patients, particularly by reducing fibrosis. However, its use has been associated with side effects like pruritus and changes in lipid profiles, including increased LDL cholesterol, which necessitates careful patient monitoring. Despite these concerns, OCA remains a promising pharmacological agent in the therapeutic landscape of chronic liver diseases. [38]

Clinical trial:

In the REVERSE study of 919 randomized subjects with compensated cirrhosis due to NASH, 11.1% (p=NS) of subjects who were randomized to receive once-daily oral OCA 10 mg and 11.9% (p=NS) of subjects who were randomized to receive OCA 10 mg titrated to 25 mg (OCA 10-to-25 mg) after three months achieved a ≥1-stage improvement in fibrosis with no worsening of NASH after up to 18 months of treatment, compared with 9.9% of subjects who received placebo. Though the REVERSE study did not succeed on the histological evaluation of the primary endpoint, a positive impact on liver stiffness as defined by transient elastography was noted in both OCA 10 mg and OCA 10-to-25 mg arms. Safety was evaluated in 916 subjects who took at least one dose of study drug (placebo, OCA 10 mg or OCA 10-to-25 mg). Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs) and deaths were balanced across all treatment groups in Reverse. The most common TEAE was pruritus (31% in placebo, 41% in OCA 10 mg and 57% in OCA 10-to-25 mg) and pruritus was the most common reason for treatment discontinuation. Serious gallbladder-related events were balanced across arms (0.6% in placebo, 1.0% in OCA 10 mg, 1.0% in OCA 10-to-25 mg). Consistent with the known mechanism of action of FXR-agonists, the OCA 10-to-25 mg arm had a higher incidence of gallstones. [39]

Resmetirom:

Resmetirom (brand name: Rezdiffra) is a first-in-class, oral, liver-directed selective thyroid hormone receptor-β (THR-β) agonist developed for the treatment of non-alcoholic steatohepatitis (NASH), particularly in patients with significant fibrosis (stages F2–F3). Unlike systemic thyroid hormone therapies, resmetirom specifically targets THR-β, which is predominantly expressed in the liver, thereby minimizing off-target effects such as cardiovascular or skeletal side effects associated with THR-α activation. THR-β activation in the liver enhances mitochondrial biogenesis, fatty acid β-oxidation, and reduces lipogenesis, leading to decreased hepatic fat accumulation, improved insulin sensitivity, and anti-inflammatory effects. [40] In March 2024, resmetirom received FDA approval, marking a significant milestone as the first drug approved specifically for the treatment of NASH with fibrosis. Its approval is seen as a breakthrough in the management of a condition that has long lacked effective pharmacological therapies. Ongoing trials continue to evaluate its long-term safety, efficacy, and potential in combination regimens, further supporting its role as a cornerstone in the evolving landscape of NASH therapy. [42]

MECHANISM OF ACTION:

Resmetirom selectively activates the THR-β subtype of thyroid hormone receptors, which are primarily found in the liver. This selectivity helps to avoid some of the side effects associated with non-selective thyroid hormone therapies.

↓

By activating THR-β, resmetirom promotes the regulation of genes involved in lipid metabolism. This leads to reduced liver fat accumulation, decreased cholesterol levels, and improved overall lipid profiles.

↓

Resmetirom also enhances insulin sensitivity, which can benefit metabolic health, particularly in conditions like non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome.

↓

The drug may exert anti-inflammatory effects, contributing to improvements in liver function and reducing hepatic inflammation

Clinical trial:

966 participants in total (322 in the 80 mg resmetirom group,323 in the 100 mg resmetirom group and 321 in the placebo group)made up the primary analytic population.in comparison to 9.7% of patients in the placebo group, 25.9% of patients in the 80 mg resmetirom group 29.9% of patients in the 100 mg resmetirom group experienced NASH resolution with no progression of fibrosis (P<0.001 for both compression with placebo).24.2% of patients in the 80 mg resmetirom group and 25.9% of patients in the 100mg resmetirom group experienced fibrosis improvement of at least one stage without a worsening of the NAFLD activity score ,compared to 14.2% of patients in placebo group (P<0.001 for both compression with placebo). The 80 mg resmetirom group experienced 13.6% change in low density lipoprotein cholesterol level from baseline to week 24, while in the 100 mg resmetirom group experienced a-16.3% change. This was in contract to the 0.1% change in the placebo group (P<0.001 for both compression with placebo). compared to a placebo resmetirom was associated with high frequency of nausea and diarrhoea. The trial group saw comparable rates of significates adverse events:10.9% for the 80mg resmetirom group,12.7% for the 100mg resmetirom group and 11.5% for the placebo group.

Table:1 Summarized of drug used in NAFLD

Drug/Class	Mechanism of Action	Effect on Liver Histology	FDA Approval for NASH	Key Notes
Orlistat	Inhibits fat absorption (lipase inhibitor)	Indirect benefit via weight loss; modest steatosis ↓	No	GI side effects common; best used with lifestyle changes
Pioglitazone (TZD)	PPAR-γ agonist, improves insulin sensitivity	Steatosis ↓, Inflammation ↓, Fibrosis ↓	No	Effective in biopsy-proven NASH, especially with diabetes

GLP-1 RAs (e.g., liraglutide, semaglutide)	Enhances insulin secretion, promotes weight loss	Steatosis ↓, Inflammation ↓, some fibrosis improvement	No (under investigation)	Dual benefit for obesity and T2DM; semaglutide promising
Vitamin E	Antioxidant	Steatosis ↓, Inflammation ↓	No	Recommended in non-diabetic patients with biopsy-proven NASH
Obeticholic acid	FXR agonist – reduces bile acid synthesis and inflammation	Fibrosis ↓ (primary endpoint met in REGENERATE trial)	No (resubmitted to FDA)	Pruritus and LDL elevation are side effects
Resmetirom	THR-β agonist – increases fat metabolism in liver	Steatosis ↓, Fibrosis ↓	No (Phase 3 positive)	Seen as a promising emerging agent

CONCLUSION:

NAFLD is a common chronic liver disease linked to fat accumulation, potentially progressing to NASH, fibrosis, and cirrhosis. Risk factors include obesity, T2DM, and metabolic syndrome. Diagnosis often requires biopsy. Treatment focuses on lifestyle changes (diet and exercise) for weight loss. Pharmacological options like orlistat, pioglitazone, vitamin E, GLP-1 RAs, obeticholic acid, and the newly approved resmetirom aim to reduce liver fat, inflammation, and fibrosis. Resmetirom is the first drug with strong evidence of fibrosis improvement.

Conflict of Interest:

I am declare that there are no conflicts of interest related to the content of this manuscript. I have no financial, personal, or professional relationships with individuals or organizations that could inappropriately influence (or be perceived to influence) the work reported in this paper.

REFERENCES

1. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic fatty liver disease review: diagnosis, treatment, and outcomes. Clinical Gastroenterology and Hepatology. 2015 Nov 1;13(12):2062-70.
2. Machado MV, Diehl AM. Pathogenesis of nonalcoholic steatohepatitis. Gastroenterology. 2016 Jun 1;150(8):1769-77.
3. Nasr P, Ignatova S, Kechagias S, Ekstedt M. Natural history of nonalcoholic fatty liver disease: a prospective follow-up study with serial biopsies. Hepatology communications. 2018 Feb;2(2):199-210.
4. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nature reviews Gastroenterology & hepatology. 2018 Jan;15(1):11-20.
5. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004 Dec;40(6):1387-95.
6. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012 Jun 1;142(7):1592-609.

7. Dixon JB, Bhathal PS, O'brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001 Jul 1;121(1):91-100.
8. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Official journal of the American College of Gastroenterology| ACG. 2003 May 1;98(5):960-7.
9. Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. Clinics in liver disease. 2007 Feb 1;11(1):75-104.
10. Manne V, Handa P, Kowdley KV. Pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Clinics in liver disease. 2018 Feb 1;22(1):23-37.
11. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. The American journal of clinical nutrition. 2005 Mar 1;81(3):555-63.
12. Kral JG, Lundholm K, Björntorp P, Sjöström L, Schersten T. Hepatic lipid metabolism in severe human obesity. Metabolism. 1977 Sep 1;26(9):1025-31.
13. Sanyal AJ, Campbell–Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology. 2001 Apr 1;120(5):1183-92.
14. Basaranoglu M, Basaranoglu G, Bugianesi E. Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. Hepatobiliary surgery and nutrition. 2015 Apr;4(2):109.
15. Marra F, Tacke F. Roles for chemokines in liver disease. Gastroenterology. 2014 Sep 1;147(3):577-94.
16. Angulo P. Treatment of nonalcoholic fatty liver disease. Annals of hepatology. 2002;1(1):12-9.
17. Arefhosseini S, Ebrahimi-Mameghani M, Najafipour F, Tutunchi H. Non-alcoholic fatty liver disease across endocrinopathies: Interaction with sex hormones. Frontiers in Endocrinology. 2022 Nov 7;13:1032361.
18. Rabinowich L, Shibolet O. Drug induced steatohepatitis: an uncommon culprit of a common disease. BioMed research international. 2015;2015(1):168905.
19. Marchesini G, Day CP, Dufour JF, Canbay A, Nobili V, Ratziu V, Tilg H, Roden M, Gastaldelli A, Yki-Jaevinen H, Schick F. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of hepatology. 2016 Jun 1;64(6):1388-402.
20. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor?. European heart journal. 2012 May 1;33(10):1190-200.
21. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. New England Journal of Medicine. 2010 Sep 30;363(14):1341-50.
22. Ou H, Fu Y, Liao W, Zheng C, Wu X. Association between smoking and liver fibrosis among patients with nonalcoholic fatty liver disease. Canadian Journal of Gastroenterology and Hepatology. 2019;2019(1):6028952.
23. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease

among type 2 diabetic patients. Diabetes care. 2007 May 1;30(5):1212-8.

24. Filippatos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS. Orlistat-associated adverse effects and drug interactions: a critical review. Drug safety. 2008 Jan;31:53-65.
25. Guerciolini R. Mode of action of orlistat. International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity. 1997 Jun 1;21:S12-23.
26. Bray GA, Purnell JQ. An historical review of steps and missteps in the discovery of anti-obesity drugs. Endotext [Internet]. 2022 Jul 10.
27. Zelber-Sagi S, Kessler A, Brazowsky E, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2006;4(5):639-644. doi:10.1016/j.cgh.2006.02.004
28. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology. 2009;49(1):80-86. doi:10.1002/hep.22575.
29. Bugianesi E, Manzini P, D'Antico S, et al. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology. 2009;49(1):80-86. doi:10.1002/hep.22575.
30. Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Alimentary pharmacology & therapeutics. 2012 Jan;35(1):66-75.
31. Shah P, Mudaliar S. Pioglitazone: side effect and safety profile. Expert opinion on drug safety. 2010 Mar 1;9(2):347-54.
32. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, Austin AS, Freeman JG, Morgan L, Webber J. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology. 2008 Oct 1;135(4):1176-84.
33. Sato K, Gosho M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, Nakade Y, Ito K, Fukuzawa Y, Yoneda M. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Nutrition. 2015 Jul 1;31(7-8):923-30.
34. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. New England Journal of Medicine. 2010 May 6;362(18):1675-85.
35. Hamed K, Alosaimi MN, Ali BA, Alghamdi A, Alkhashi T, Alkhaldi SS, Altowarqi NA, Alzahrani H, Alshehri AM, Alkhaldi RK, Alqahtani KW. Glucagon-like peptide-1 (GLP-1) receptor agonists: exploring their impact on diabetes, obesity, and cardiovascular health through a comprehensive literature review. Cureus. 2024 Sep 1;16(9).
36. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K, Abouda G, Aldersley MA, Stocken D. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. The Lancet. 2016 Feb 13;387(10019):679-90.
37. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS, Harrison SA. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic

steatohepatitis. New England Journal of Medicine. 2021 Mar 25;384(12):1113-24.
38. Shah RA, Kowdley KV. Obeticholic acid for the treatment of nonalcoholic steatohepatitis. Expert review of gastroenterology & hepatology. 2020 May 3;14(5):311-21.
39. Roy PP, Al Mahtab M, Rahim MA, Yesmin SS, Islam SB, Akbar SM. Treatment of nonalcoholic steatohepatitis by obeticholic acid: Current status. Euroasian journal of hepato-gastroenterology. 2022 Jul;12(Suppl 1):S46.
40. Brisnovali NF, Haney C, Goedeke L. Rezdiffra™(resmetirom): a THR-β agonist for non-alcoholic steatohepatitis. Trends in Pharmacological Sciences. 2024 Sep 19.
41. Levien TL, Baker DE. Resmetirom. Hospital Pharmacy. 2025 Feb;60(1):12-20.
42. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. New England Journal of Medicine. 2024 Feb 8;390(6):497-509.

HOW TO CITE: Denisha Meghnathi*, Kiran Rathod, Chintankumar Tank, Shivani Herma, Himanshu Parmar, Pritesh Odedara, Non-Alcoholic Fatty Liver Managment, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 4, 3191-3204. https://doi.org/10.5281/zenodo.15298763