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Pioglitazone and NASH: A narrative review

Abstract

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by inflammation and fibrosis, primarily linked to metabolic syndrome. The rising prevalence of NASH reflects the global obesity epidemic, making it a significant public health concern. Current management strategies emphasize lifestyle modifications, including weight loss and dietary changes, alongside pharmacological interventions. Notably, pioglitazone, a thiazolidinedione, has demonstrated efficacy in improving liver histology by enhancing insulin sensitivity, although concerns regarding side effects persist. Semaglutide, a glucagon-like peptide-1 receptor agonist, also shows promise in promoting weight loss and improving liver outcomes. As research advances, novel therapeutic agents targeting various aspects of NASH are being explored. This review highlights the complexities of managing NASH within the broader context of metabolic disorders, underscoring the necessity for a comprehensive, individualized treatment approach to effectively combat this challenging condition.

Keywords: nonalcoholic steatohepatitis, lifestyle modifications, pioglitazone, semaglutide, insulin sensitivity, pharmacological interventions

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Abbreviations: NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; ROS, reactive oxygen species; ER, endoplasmic reticulum; EASL, European association for the study of the liver; AACE, American association of clinical endocrinology; AASLD, American association for the study of liver diseases; TZDs, thiazolidinediones; EOT, end of treatment; ALT, alanine aminotransferase; LFC, liver fat content

Introduction

Nonalcoholic steatohepatitis (NASH) affects approximately 3% to 6% of adults, and its prevalence is on the rise.[1] Recognized as a leading cause of chronic liver disease, NASH is closely linked with metabolic conditions like obesity, dyslipidemia, diabetes, and metabolic syndrome. A subset of patients with NASH may experience progression to severe fibrosis, cirrhosis, and hepatocellular carcinoma.[2] Often asymptomatic or presenting with vague symptoms, most NASH cases are incidentally identified during evaluations for unrelated health issues.[1] As an inflammatory subtype of nonalcoholic fatty liver disease (NAFLD), NASH is considered the most severe form and is marked by inflammatory cell infiltration, hepatocyte injury, and fat accumulation, with or without fibrosis.[3] Despite extensive research, the pathogenesis of NASH remains incompletely understood, although several factors have been identified.

The pathogenesis of NASH involves multiple interconnected mechanisms, including dietary and metabolic factors. A high-fat diet and insulin resistance contribute to excess fat accumulation in the liver, where triglycerides are stored but are not inherently toxic.[4–6] However, specific lipid species can induce "lipotoxicity," leading to mitochondrial dysfunction, oxidative stress, and reactive oxygen species (ROS) production, which collectively cause hepatocyte injury.[6,7] Endoplasmic reticulum (ER) stress from accumulated misfolded proteins further disrupts cellular function, triggering inflammation through pathways like NF-κBsignaling.[6,7] Additionally, gut barrier dysfunction permits bacterial translocation, elevating endotoxin levels and driving hepatic inflammation.[8–10] Together, these factors contribute to the onset and progression of NASH through complex and overlapping pathways.

Due to the complexity of the various pathways involved in NASH pathogenesis, effective treatment may need to target multiple aspects of the cellular and molecular processes.[11] Currently, there is no officially approved pharmacotherapy for NASH, and progress in developing drug treatments has been slow.[12] For now, dietary and lifestyle modifications are the primary recommendations for managing NASH.[13] Experimental studies indicate that diets rich in omega-3 polyunsaturated fatty acids can enhance insulin sensitivity,[14] reduce liver triglyceride levels, and improve steatosis. Exercise also offers established benefits, especially for cardiovascular health, which remains the leading cause of mortality in patients with NAFLD. These benefits, which include improved insulin resistance in both the liver and peripheral tissues, may occur independently of weight loss.[15] While these general approaches are effective, no specific drug has yet received FDA approval for NASH treatment.

However, several guidelines, including those from the American Association of Clinical Endocrinology (AACE), the European Association for the Study of the Liver (EASL) 2024 guidelines, the American Diabetes Association (ADA) 2024 guidelines, and the American Association for the Study of Liver Diseases (AASLD) 2023 guidelines, provide structured approaches to managing NASH, particularly when linked to metabolic comorbidities.

Guideline based approaches in NASH treatment

The AACE guidelines recommend lifestyle modifications as the primary approach for managing NAFLD, highlighting the importance of exercise (150 minutes weekly) and diets like the Mediterranean, which improves liver health more effectively than high-fat, low-carbohydrate diets. A weight loss of 3%-5% of baseline body weight can help reduce liver fat, while 7%-10% is needed to improve fibrosis and histological features of NASH. For individuals with a BMI over 35 kg/m^2, bariatric surgery is advised. Pharmacotherapy for NAFLD/NASH is limited to confirmed cases, with pioglitazone, liraglutide, and vitamin E as options, while empagliflozin shows promise for reducing hepatic fat in diabetes. Although underutilized, statins are safe for NAFLD/NASH patients and lower cardiovascular risk, offering additional protective effects on liver health.[16]

The European Association for the Study of the Liver (EASL) guidelines for NASH prioritize lifestyle changes (weight loss, diet, exercise) as the cornerstone of treatment. Liver biopsy remains the gold standard for diagnosis, though non-invasive tests like FibroScan can assess fibrosis. Pharmacotherapy, including vitamin E (800 IU/day for non-diabetic adults with biopsy-proven NASH) and pioglitazone, may be considered in specific cases, but lifestyle changes are crucial for managing NASH and preventing disease progression.[17]

The American Diabetes Association's 2024 guidelines emphasize the importance of managing Non-Alcoholic Fatty Liver Disease (NAFLD) in individuals with type 2 diabetes mellitus (T2DM) and prediabetes, given their heightened cardiovascular risk. Recognizing that NAFLD-related liver fibrosis and cardiovascular disease significantly affect prognosis and mortality, these guidelines recommend regular screening, evaluation, and management strategies for NAFLD and liver fibrosis in these populations. Key preventive measures include lifestyle modifications, weight loss, and optimized blood glucose control, all of which are essential for reducing liver inflammation, slowing fibrosis progression, and minimizing cardiovascular risk.[18]

The ASLD guidelines for NAFLD management prioritize screening only for high-risk groups, such as patients with T2DM, obesity, or family cirrhosis history, using FIB-4 and imaging as needed for advanced fibrosis. Lifestyle interventions, including calorie-restricted, Mediterranean-style diets and increased physical activity, are essential, with bariatric surgery recommended for qualifying patients. While no FDA-approved drugs exist for NAFLD, semaglutide and pioglitazone may benefit NASH patients without cirrhosis, and statins are endorsed for cardiovascular protection across the NAFLD spectrum. Alcohol intake should be minimized, especially in advanced fibrosis, and family members of NASH cirrhosis patients are encouraged to get screened.[19]

Mechanism of action of pioglitazone

Pioglitazone, an oral antidiabetic from the thiazolidinedione class, is FDA-approved for managing type 2 diabetes in adults as a supplement to diet and exercise. Treatment guidelines suggest using pioglitazone as a third-line option, or in some cases, as a second-line therapy if primary and secondary antidiabetics fail to maintain glycemic control. It is particularly recommended when patients exhibit significant insulin resistance, are prone to hypoglycemia, have non-alcoholic fatty liver disease or steatohepatitis, or face cost or insurance limitations with first- or second-line therapies.20

The anti-diabetic effect of thiazolidinediones (TZDs) like pioglitazone is primarily through enhancing insulin sensitivity in muscle, adipose tissue, and liver by activating the peroxisome proliferator-activated receptor-gamma (PPAR-γ). This activation modifies gene transcription involved in glucose and lipid metabolism, influencing genes like fatty acid transporter protein, lipoprotein lipase, glucokinase, and GLUT4, thus reducing insulin resistance.[21] Pioglitazone, a PPAR-γ and PPAR-α agonist, affects adipocytes and releases adipokines that impact muscle and liver via endocrine signaling. It is metabolized by CYP2C8 and CYP3A4, and interactions with agents affecting these enzymes or with other anti-diabetics can influence its efficacy and side effects, such as fluid retention and increased hypoglycemia risk with insulin.[22]

The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, has garnered interest for their potential in NASH management. In a recent 72-week, double-blind, phase 2 trial (NCT02970942), the efficacy and safety of subcutaneous semaglutide were evaluated in patients with biopsy-confirmed NASH and fibrosis stages F1 to F3. This study included 320 participants, with 230 patients presenting advanced fibrosis (F2 or F3). Participants were randomized to receive semaglutide in doses of 0.1 mg, 0.2 mg, or 0.4 mg daily, or placebo. The trial's primary endpoint was the resolution of NASH without fibrosis progression, and the secondary endpoint focused on fibrosis improvement without worsening NASH.[23]

Results showed that NASH resolution occurred in 59% of patients receiving the highest semaglutide dose (0.4 mg), compared to only 17% in the placebo group ($P<0.001$). However, improvements in fibrosis stage did not differ significantly between the semaglutide 0.4 mg group (43%) and placebo (33%, $P=0.48$). Additionally, patients in the 0.4 mg semaglutide group experienced considerable weight loss (13%) versus a 1% reduction in the placebo group. Common adverse effects included nausea (42%), constipation (22%), and vomiting (15%) in the 0.4 mg group. Although rare cases of malignant neoplasms were observed in the semaglutide group (affecting 1% of patients), no specific organ pattern was noted. Overall, the study highlights semaglutide's potential in resolving NASH, though its role in fibrosis regression remains unclear, underscoring the need for further research.[23]

Clinical efficacy of pioglitazone in NASH

Pioglitazone (Pio), a PPARγ agonist, has demonstrated efficacy in improving liver histology and metabolic parameters in patients with non-alcoholic steatohepatitis (NASH). However, its utility has been limited by side effects associated with PPARγ activation. New formulations and comparative studies continue to evaluate pioglitazone's clinical benefits in diverse patient populations, including those with type 2 diabetes mellitus (T2DM), prediabetes, and Asian NASH patients**.**

Efficacy in non-diabetic and diabetic patients with NASH

A study involving patients with NASH and either T2DM or prediabetes evaluated pioglitazone's efficacy over 18 months. In this study, 48% of patients with T2DM and 46% of those with prediabetes achieved the primary endpoint, defined as a reduction in the NAFLD activity score (NAS) by ≥2 points without worsening fibrosis. NASH resolution was achieved in 44% of diabetic patients compared to 26% of non-diabetic patients, suggesting greater histological improvement in T2DM patients. Furthermore, a significant reduction in fibrosis and enhanced insulin sensitivity in adipose tissue were observed in T2DM patients, while hepatic and skeletal muscle insulin sensitivity differences were not significant. These findings suggest that pioglitazone may have greater histological and metabolic benefits in NASH patients with T2DM, highlighting the importance of glycemic status in treatment responseoglitazone's Impact on Liver Histology in Asian NASH Patients.[24]

A double-blind, randomized, placebo-controlled trial involving 90 Asian NASH patients demonstrated significant improvements in liver function and histology following 24 weeks of pioglitazone treatment (30 mg/day). At the end of treatment (EOT), alanine aminotransferase (ALT) levels significantly decreased, and the NAS improved notably in the pioglitazone group compared to placebo. The study reported NASH improvement without worsening of fibrosis in 46.7% of patients receiving pioglitazone versus 11.1% in the placebo group, with substantial reductions in liver fat content as measured by MRI-PDFF. These results underscore pioglitazone's efficacy in reducing inflammation and liver steatosis in NASH patients, especially in an Asian cohort.[25]

To address the PPARγ-driven side effects of traditional pioglitazone, a phase II trial evaluated PXL065, a deuterium-stabilized R-enantiomer of pioglitazone lacking PPARγ activity but retaining non-genomic activity. Over 36 weeks, patients with NASH (≥8% liver fat, NAS ≥4, F1–F3 fibrosis) treated with PXL065 showed significant reductions in liver fat content (LFC) compared to placebo, with up to 40% of patients in the high-dose group achieving a ≥30% reduction in LFC. Favorable changes in fibrosis markers, metabolic parameters (HbA1c, HOMA-IR), and adiponectin levels were observed, alongside the absence of dose-dependent weight gain or peripheral edema. These findings indicate that PXL065 retains pioglitazone's therapeutic benefits in NASH with an improved safety profile, suggesting potential for further clinical testing.[26]

Role of sirtuins in NASH and implications for pioglitazone therapy

Hepatic SIRT1 expression is consistently reduced in NAFLD rodent models induced by methionine-choline-deficient, high-fat, high-fat high-sucrose, and high-fat high-carbohydrate diets.[27–29] SIRT1 is of particular therapeutic relevance, as it activates AMPK and exerts lipid-lowering effects in vitro and in vivo.[30]

Importantly, pioglitazone acts as a SIRT1 activator, aligning pharmacotherapy with lifestyle strategies such as calorie restriction and dietary modifications that preserve or enhance SIRT1 activity.[31–33] Diets low in xenobiotics, mycotoxins, and advanced glycation products, and adequate in zinc and nitric oxide balance, may further optimize SIRT1 function.[25] Thus, the success of NASH management with pioglitazone may depend on concurrent lifestyle measures that sustain SIRT1 activity, as consumption of SIRT1 activators versus inhibitors may ultimately influence treatment outcomes.

Safety and limitations of pioglitazone

Pioglitazone has shown efficacy in treating nonalcoholic steatohepatitis (NASH), particularly in improving liver histology and metabolic parameters; however, there are important considerations regarding its long-term safety and potential side effects. Studies have demonstrated significant improvements in liver function among NASH patients, with a resolution rate of approximately 60% in those with prediabetes or type 2 diabetes mellitus.[24,34] In a randomized trial, patients treated with pioglitazone showed reduced alanine aminotransferase (ALT) levels and a decreased NAFLD activity score, indicating improvements in liver health.[24,25]

Regarding safety, the adverse event rate with pioglitazone is similar to that of a placebo, suggesting a generally favorable safety profile.[34] However, weight gain is a common side effect, with patients experiencing an average increase of 2.5 kg during treatment.[34] Additional limitations include a rebound in liver function markers following pioglitazone discontinuation, which may signal a recurrence of the disease.[25] Furthermore, response to treatment can vary, with some patients requiring higher drug concentrations to achieve optimal effects.[35] Although pioglitazone offers benefits for NASH management, its long-term use requires careful monitoring due to potential weight gain and the risk of recurrence upon stopping the medication.

Future perspectives

The potential for combination therapies with pioglitazone in treating nonalcoholic steatohepatitis (NASH) is gaining attention due to the multifactorial nature of the disease. Combining pioglitazone with other agents may enhance therapeutic efficacy by targeting various pathophysiological pathways involved in NASH.

The study by Sathyanarayana et al. found that the combination of exenatide and pioglitazone significantly reduced hepatic fat content and increased adiponectin levels in patients with type 2 diabetes mellitus (T2DM).[36] In a cohort of 24 randomized patients (21 completed), magnetic resonance spectroscopy (MRS) showed a reduction in hepatic fat from 12.1% ± 1.7% at baseline to 4.7% ± 1.3% after 12 months ($P < 0.001$), which was significantly greater than the reduction with pioglitazone alone (11.0% ± 3.1% to 6.5% ± 1.9%, $P < 0.05$). ALT levels improved more in the combination group, with adiponectin increasing from 7.9 ± 0.9 to 23.2 ± 2.7 μg/mL ($P < 0.001$).[36]

Similarly, Yoneda et al. reported improvements in ALT and MRI-PDFF with tofogliflozin and pioglitazone, with MRI-PDFF reductions of -3.38% ± 4.90% and -5.56% ± 3.92% for monotherapies ($P = 0.0061$ and $P < 0.001$, respectively) and even greater reductions in combination therapy.[37] The DURATION-8 study by Gastaldelli et al. demonstrated significant improvements in the fatty liver index (FLI) and NAFLD liver fat score (NLFS) with combination therapy over 52 weeks ($P < 0.01$), with significant reductions in FIB-4 scores at 28 and 52 weeks ($P = 0.0135$ and $P = 0.0308$).[38] Loomba et al. showed that cilofexor combined with firsocostat resulted in a ≥2-point improvement in NAFLD activity score (35% vs. 11%, $P = 0.002$). Finally, a phase II trial of semaglutide and firsocostat showed significant reductions in liver fat by MRI-PDFF (-11% vs. -8%, $P = 0.0353$) and improved liver fat normalization rates (38.1-41.2% vs. 29.4% with semaglutide alone), underscoring the potential of combination therapies in addressing liver-related outcomes in T2DM and NAFLD/NASH.[39]

Conclusion

In summary, nonalcoholic steatohepatitis (NASH) poses a significant challenge linked to metabolic disorders. Current management focuses on lifestyle changes and pharmacotherapy, with pioglitazone and semaglutide showing efficacy in improving liver histology. While pioglitazone enhances insulin sensitivity, its potential side effects must be considered. Ongoing research into new therapies aims to optimize treatment outcomes, emphasizing the need for a multifaceted approach to address the complex nature of NASH and its associated metabolic conditions.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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