

## Treating nonalcoholic steatohepatitis with antidiabetic drugs: Will GLP-1 agonists end the struggle?

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is highly associated with insulin resistance (IR), type 2 diabetes mellitus and metabolic syndrome, being characterized as the hepatic component of metabolic syndrome. Despite its high prevalence, no pharmacological treatment has been established, as of yet. A growing body of evidence, however, shows that reducing IR can result in improvement of the biochemical and histological features of nonalcoholic steatohepatitis (NASH)-the aggressive form of NAFLD that can lead to cirrhosis and hepatocellular carcinoma. Unfortunately, the several trials that have assessed the effect of various antidiabetic agents to date have failed to establish an effective and safe treatment regimen for patients with NAFLD. Glucagon-like peptide-1 (commonly known as GLP-1) agonists are a novel class of antidiabetic drugs that improve insulin sensitivity and promote weight loss. They also appear to have a direct effect on the lipid metabolism of hepatocytes, reducing hepatic steatosis. Several trials have demonstrated that GLP-1 agonists can reduce aminotransferase levels and improve liver histology in patients with NAFLD, suggesting that these agents could serve as an alternative treatment option for these patients. This manuscript discusses the role and potential mechanisms of GLP-1 agonists in the treatment of NASH.

**Key words:** Nonalcoholic steatohepatitis; Cirrhosis; Glucagon-like peptide-1 receptor agonists; Nonalcoholic fatty liver disease

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**Core tip:** There is an urgent need for an effective treatment of nonalcoholic fatty liver disease (NAFLD). Growing evidence indicates that reducing insulin resistance can result in improvement of the biochemical

and histological features of patients with nonalcoholic steatohepatitis (NASH). However, no antidiabetic agent to date has been proven as both safe and effective for the treatment of patients with NASH. Recent studies have demonstrated that glucagon-like peptide-1 agonists, a novel class of antidiabetic drugs, may be effective in slowing the progression of NAFLD, highlighting their potential role in the treatment of this complex disease.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of clinical and histopathological conditions, ranging from simple steatosis [*i.e.*, nonalcoholic fatty liver (NAFL)] to liver injury [*i.e.*, nonalcoholic steatohepatitis (NASH), the aggressive form of NAFLD that can lead to cirrhosis and hepatocellular carcinoma]<sup>[1,2]</sup>. NAFLD is highly associated with metabolic syndrome and type 2 diabetes mellitus (T2DM)<sup>[3]</sup>. In fact, the prevalence of NAFLD in T2DM has been estimated to be around 60%<sup>[4]</sup>.

The pathophysiology of NAFLD is not yet fully elucidated; however, it is widely believed that insulin resistance (IR) may play a critical role in the pathogenesis of the disease. Several studies have shown that patients with NAFL and NASH are characterized by IR and hyperinsulinemia, irrespective of glucose tolerance or body mass index<sup>[5,6]</sup>. The multi-hit hypothesis, initially described by Day and James<sup>[7]</sup>, claims that IR is the key factor in the pathogenesis of steatosis. IR causes dysregulation of peripheral lipolysis and increases *de novo* lipogenesis, leading to elevated levels of circulating fatty acids and lipid accumulation within hepatocytes—the “first hit” that predisposes to liver injury, inflammation and fibrosis<sup>[8]</sup>. Disrupted insulin signaling is also involved in inflammatory cascade activation, lipid peroxidation and liver injury—“the second hit” leading to NASH<sup>[9]</sup>.

Currently, NAFLD is reported to be the most common chronic liver disease worldwide<sup>[10]</sup>. However, despite huge efforts, there is still no established pharmacotherapy. Lifestyle modifications remain the sole therapeutic approach<sup>[11]</sup>. Given that IR is considered as the main pathogenetic factor for the development of NAFLD, drugs targeting IR have been investigated the most as potential treatment options for NAFLD, but the studies have yielded conflicting results.

Metformin, the most widely used insulin-sensitizing agent, improves insulin sensitivity by mechanisms that are not yet fully understood<sup>[12]</sup>. A meta-analysis

assessing the effect of metformin in NAFLD revealed that, while it can improve the biochemical and metabolic features of NAFLD, it does not improve the patients’ histological response<sup>[13]</sup>. Metformin is not currently recommended for the treatment of NAFLD by either the American Association for the Study of Liver Diseases or the European Association for the Study of Liver (commonly referred to by their acronyms, AASLD and EASL, respectively)<sup>[14,15]</sup>.

Thiazolidinediones, another class of insulin-sensitizers, act by redistributing fat from ectopic tissues to the adipose tissue, and by increasing levels of adiponectin—an adipokine that has insulin-sensitizing properties<sup>[16,17]</sup>. Several studies have evaluated the efficacy of thiazolidinediones in patients with NAFLD. The “Pioglitazone vs vitamin E vs placebo for the treatment of nondiabetic patients with nonalcoholic steatohepatitis” trial (published as the PIVENS trial) was the largest one performed, involving 247 nondiabetic patients with biopsy-proven NASH<sup>[18]</sup>. The patients were randomized to receive either pioglitazone (30 mg/d) or vitamin E (800 IU/d) or placebo. The pioglitazone treatment was associated with a significant reduction in steatosis and lobular inflammation compared to placebo; however, it did not improve fibrosis. A randomized, placebo-controlled trial performed in patients with NASH and prediabetes or T2DM showed that pioglitazone achieved the primary endpoint of an  $\geq 2$ -point decrease in NAFLD activity score without worsening fibrosis, and was associated with improvement in steatosis, inflammation and ballooning necrosis<sup>[19]</sup>. The AASLD and EASL have suggested the use of pioglitazone in patients with biopsy-proven NASH<sup>[14,15]</sup>, although concerns about the side effects and long-term safety of this drug have limited its widespread use. Pioglitazone has been associated with weight gain that is persistent (even after discontinuation of the treatment), fluid retention, deterioration of heart failure, bone fractures, and increased risk of bladder cancer<sup>[20-23]</sup>.

## ROLE OF GLUCAGON-LIKE PEPTIDE-1 AGONISTS IN NAFLD

Glucagon-like peptide-1 (GLP-1) agonists represent a novel class of antidiabetic drugs. They mimic the action of endogenous GLP-1, a gastrointestinal hormone of the incretin class of proteins that is secreted from Langerhans cells in response to nutrient ingestion<sup>[24]</sup>. This hormone has several metabolic effects, including the stimulation of glucose-dependent insulin secretion, inhibition of glucagon release, induction of pancreatic  $\beta$ -cell proliferation, and delay of gastric emptying<sup>[25]</sup>. While native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (otherwise known as DPP-4), GLP-1 agonists have increased resistance to DPP-4, thus prolonging the half-life time<sup>[26]</sup>. These agents have been shown to have beneficial effects on IR and weight control<sup>[25]</sup>. Several studies have demonstrated the

presence of GLP-1 receptor in hepatocytes, implying that GLP-1 agonists may also exert a direct effect on the liver. Gupta *et al.*<sup>[27]</sup> found that the GLP-1 receptor plays a key role in the decrease of hepatic steatosis *in vitro*, by modulating elements of the insulin signaling pathway. GLP-1 agonists have demonstrated protection of hepatocytes from fatty acid-related death by prohibition of a dysfunctional endoplasmic reticulum stress response. They also appear to reduce fatty acid accumulation by activation of both macroautophagy and chaperone-mediated autophagy<sup>[28]</sup>. Evidence suggests that GLP-1 secretion is impaired in patients with NAFLD and NASH, highlighting the role of GLP-1 agonists as potential candidates for NAFLD treatment<sup>[29]</sup>.

### Liraglutide

Multiple trials have evaluated the efficacy of GLP-1-based therapies in NAFLD. Among the GLP-1 agonists, liraglutide is the most widely studied drug. In the "Liraglutide Efficacy and Action in NASH" study (published as the LEAN study), a double-blind randomized control trial, Armstrong *et al.*<sup>[30]</sup> assessed the effect of 48 wk of treatment with liraglutide in patients with biopsy-proven NASH. Fifty-two patients with ( $n = 17$ ) or without ( $n = 35$ ) T2DM were randomly allocated to receive either liraglutide (1.8 mg/d) or placebo. The primary endpoint of the study was the resolution of definite steatohepatitis without worsening fibrosis. Secondary histological endpoints included change in the overall NAFLD activity score (steatosis, ballooning, lobular inflammation) and its individual components. Overall, 9/23 patients in the liraglutide group showed resolution of NASH with no worsening fibrosis compared to 2/22 patients in the placebo group ( $P = 0.019$ ), successfully meeting the primary endpoint. Regarding the secondary outcomes, fewer patients in the liraglutide group showed progression in fibrosis compared to the placebo group (2/23 vs 8/22,  $P = 0.04$ ). However, results concerning lobular inflammation and overall NAFLD activity score were not statistically significant when compared between the two groups. The authors used histological primary endpoints, being able to evaluate the direct effect of liraglutide on the liver. The study was performed on patients with biopsy-proven NASH, avoiding the inclusion of those without definite NASH. Their findings suggested that liraglutide led to the histological resolution of NASH, with the small sample size being, however, a major limitation.

Ohki *et al.*<sup>[31]</sup> performed a retrospective cohort study evaluating the efficacy of liraglutide compared to sitagliptin and pioglitazone in patients with NAFLD. They reported a significant reduction in serum aminotransferase levels for all groups, while the aspartate aminotransferase (AST)-to-platelet counts ratio index was significantly reduced only for the liraglutide and pioglitazone groups. Body weight significantly decreased in the liraglutide group, while it increased in

the pioglitazone group and did not retain a statistically significant difference for the sitagliptin group. Administration of liraglutide was identified as an independent factor for body weight reduction in multivariate analysis.

In a recent open-label trial by Feng *et al.*<sup>[32]</sup>, 87 patients with NAFLD were randomized to receive liraglutide, metformin or gliclazide for 24 wk. All three groups showed reduced intrahepatic fat, but the liraglutide group had the greatest reduction. In addition, the researchers found a statistically significant decrease in serum AST and alanine aminotransferase levels only in the liraglutide and metformin group, reporting slightly better results for the liraglutide group. However, a study by Khoo *et al.*<sup>[33]</sup> demonstrated that liraglutide was as effective as structured lifestyle modification for reduction of liver fat fraction and serum aminotransferase levels.

### Exenatide

Two trials examined the use of exenatide in patients with NAFLD and T2DM<sup>[34,35]</sup>. In the first, Shao and colleagues<sup>[34]</sup> studied 60 patients with NAFLD and T2DM<sup>[34]</sup>. The patients were randomized to receive exenatide plus insulin glargine U-100 (exenatide group) or insulin glargine U-100 plus insulin aspart (intensive insulin group) for 12 wk. The levels of alanine aminotransferase, AST, and gamma-glutamyl transferase were significantly lower in the exenatide group than in the intensive insulin group. The exenatide plus insulin glargine treatment was also found to be superior to the intensive insulin therapy concerning the reversal rate of fatty liver (93.3% vs 66.7%, respectively). The second study, conducted by Fan *et al.*<sup>[35]</sup>, compared the efficacy of exenatide *versus* metformin in patients with NAFLD and T2DM. The results revealed that exenatide was more effective than metformin in reducing body weight and improving liver enzymes. Nevertheless, the efficacy of exenatide has not been evaluated in randomized trials with histological outcomes in patients with NASH, as of yet. Lastly, a recent meta-analysis of six studies assessing the efficacy of GLP-1 agonists (liraglutide and exenatide) in NAFLD, revealed that these agents improve liver histology and reduce serum aminotransferase levels, indicating that they might be effective in patients with biopsy-proven NASH<sup>[36]</sup>.

### Semaglutide

Semaglutide is a novel long-acting GLP-1 analogue, and has been recently approved for T2DM<sup>[37]</sup>. It has 94% sequence homology to human GLP-1 and a half-life of 165 h, supporting a once weekly scheme of administration<sup>[38]</sup>. Semaglutide has shown beneficial effects on glucose control and weight loss compared to placebo and other antidiabetic drugs in patients with T2DM in the "SUSTAIN" trial program<sup>[37,38]</sup>. It is currently under investigation for its potential as a treatment option for patients with NASH. A 72-wk, randomized, double-blind trial of 372 patients comparing the effi-

cacy and safety of three dose levels of subcutaneous semaglutide once daily vs placebo in NASH patients is ongoing (NCT02970942). This trial is expected to be completed during 2019 and will provide additional information on the effectiveness of GLP-1 agonists in patients with NAFLD.

## CONCLUSION

GLP-1 agonists are not currently recommended by the AASLD and EASL for the treatment of NAFLD. In their latest guidelines, it was pointed out that it is still premature to consider these agents as a specific treatment for patients with NASH without diabetes, due to inadequate evidence<sup>[14,15]</sup>. Future research is, therefore, needed to confirm their efficacy in these patients.

In conclusion, current evidence suggests that GLP-1 agonists may be an attractive therapeutic option for patients with NAFLD. However, larger studies of longer duration with histological endpoints are still required to establish their exact role in the management of NAFLD.

### Perspective for future study

GLP-1 agonists have been shown to be effective in improving liver histology and reducing aminotransferase levels in patients with NASH. So, the question arises as to whether these agents could serve as a treatment option for such patients. While data are promising, they are still limited. Large-scale randomized, placebo-controlled trials with complete histological outcomes are warranted to elucidate the efficacy of GLP-1 agonists in treating NASH. Another major limitation of the currently available studies is the lack of long-term outcomes. Studies of longer duration are required to properly evaluate the histological improvement in NASH. What is more, it would be interesting if future trials would include both diabetic and nondiabetic patients, in order to clarify the effect of GLP-1 agonists in NASH, regardless of changes in glycemic control. It will also be significant to assess whether GLP-1 agonists affect NAFLD in a dose-dependent manner, in order to search for preferred doses.

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