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**Potential therapeutic targets for nonalcoholic fatty liver disease: Glucagon-like peptide 1**

Yin YH *et al*. Efficacy and safety of semaglutide in NAFLD

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**Abstract**

Nonalcoholic fatty liver disease (NAFLD) is the most rapidly growing contributor to liver mortality and morbidity. Hepatocellular injury in nonalcoholic steatohepatitis (NASH) is caused by an increase in metabolic substrates (glucose, fructose, and fatty acids), leading fatty acids to participate in pathways that cause cellular injury and a poor response to injury. The pathogenesis of this disease is largely associated with obesity, type 2 diabetes, and increasing age. To date, there are no Food and Drug Administration-approved treatments for NAFLD/NASH or its associated fibrosis. Since one of the pathogenic drivers of NASH is insulin resistance, therapies approved for the treatment of type 2 diabetes are being evaluated in patients with NASH. Currently, the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is a safe, well-studied therapeutic for NAFLD/NASH patients. Existing research demonstrates that semaglutide can increase the resolution of NASH but not improve fibrosis. However, improving the fibrosis of NAFLD is the only way to improve the long-term prognosis of NAFLD. Given the complex pathophysiology of NASH, combining therapies with complementary mechanisms may be beneficial. Researchers have conducted trials of semaglutide in combination with antifibrotic drugs. However, the results have not fully met expectations, and it cannot be ruled out that the reason is the short trial time. We should continue to pay increasing attention to GLP-1RAs.

**Key Words:** Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Antidiabetic drugs; Glucagon-like peptide 1; Semaglutide

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**Core Tip:** Semaglutide is effective and safe for nonalcoholic fatty liver disease (NAFLD) but does not improve fibrosis. The treatment of NAFLD requires further combinations of drugs with different and complementary mechanisms of action.

**TO THE EDITOR**

We read with great interest the work by Zhu *et al*[1], who further validated that semaglutide can improve the resolution of nonalcoholic steatohepatitis (NASH) but not fibrosis by summarizing the histological results of semaglutide in the treatment of nonalcoholic fatty liver disease[1,2].

To date, there are no Food and Drug Administration-approved treatments for nonalcoholic fatty liver disease (NAFLD)/NASH or its associated fibrosis. Fibrosis or cirrhosis has been recognized in recent guidelines as the main diagnostic and therapeutic target to halt the progression of NASH to end-stage liver disease, change the natural history of the disease, and improve the long-term prognosis of patients with NASH[3,4].

Because insulin resistance is a shared characteristic of type 2 diabetes and obesity and is a key pathogenic driver of NASH[5], pharmacologically, antidiabetic drugs with weight loss effects should be effective against NASH. Therefore, most of the antidiabetic drugs used to treat NASH focus on peroxisome proliferator-activated receptor (PPAR) agonists, glucagon-like peptide-1 receptor agonists (GLP-1RAs), or sodium-glucose transporter 2 (SGLT2) inhibitors[6,7]. Pioglitazone can improve fibrosis in NASH[7]. However, its harmful adverse effects limit its use, and its long-term benefits are not obvious, thus reducing enthusiasm for its use[8,9]. Currently, SGLT-2 is and GLP-1 RAs are gaining more attention in the treatment of NAFLD/NASH metabolic dysfunction-associated fatty liver disease.

GLP-1 RAs may represent the most promising treatment option for improving hepatic steatosis and liver enzyme levels (serum aspartate transaminase, alanine transaminase and gamma-glutamyl transferase) in patients with NAFLD[10]. As a GLP-1 RA, semaglutide appears to be more prominent in the treatment of NASH[11]. Semaglutide activates the hepatic PPAR-α, thereby reducing apolipoprotein C production and breaking down fats and triglycerides in plasma, delaying gastric emptying, prolonging satiety, and reducing waist circumference[3]. Moreover, semaglutide increases insulin production and secretion and decreases glucagon secretion[3]. Current studies have demonstrated that semaglutide is effective in reducing hepatic steatosis and inflammation but not fibrosis[2,5]. The complex pathophysiology of the disease and the multiple often redundant "escape" treatment pathways strongly suggest that combinations of therapies with different but complementary mechanisms of action are considered the best way to improve efficiency, slow disease progression, and even reverse NASH[7].

Alkhouri *et al*[12] conducted a phase 2 clinical trial to validate the potential value of combination therapy[7]. The results of this experiment showed that GLP-1 RA in combination with antifibrotic drug therapy [cilofexor (nonsteroidal FXR agonist)/firsocostat (carboxylase inhibitor)] demonstrates greater improvement in hepatic steatosis, liver biochemistry, and noninvasive fibrosis measured by the magnetic resonance imaging-estimated proton density fat fraction, despite similar weight loss (7%-10%) compared to semaglutide monotherapy[12-15]. The role of GLP-1 RAs is undeniable, and combinations of GLP-1 RAs and other incretin receptor agonists have been developed with good results[16]. Cotadutide, a GLP-1R/GcgR agonist, significantly improves glucose tolerance and decreases C3M plasma levels and P4NP7S circulating levels compared to liraglutide and obeticholic acid in biological experiments[17]. Tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors, has associated therapeutic effects and can induce significant weight loss, improve glycaemic control, and improve plasma lipids in trials related to the treatment of obesity and diabetes[16,18]. In addition, the new drugs lanifibranor (a pan-PPAR agonist) and Aramchol (a partial inhibitor of hepatic stearoyl-CoA desaturase) have performed well as an antifibrotic therapy for NASH, but it is unclear whether there is an unintended effect when combined with GLP-1 RAs[7,19].

Although GLP-RA monotherapy does not perform well as an antifibrotic therapy, it is undeniable that its associated combinations have a role in NASH. In addition, GLP-1RAs have outstanding performance in fat loss, weight loss, and improvement of insulin resistance and have a potential protective effect against the complications of NASH. Thus, we should pay closer attention to GLP-1RAs.

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