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Semaglutide might be a key for breaking the vicious cycle of metabolically associated fatty liver disease spectrum?

Cigrovski Berkovic M *et al.* Semaglutide in MAFLD

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Abstract

Metabolically associated fatty liver disease (MAFLD) is a liver manifestation of metabolic syndrome potentially related to unfavorable hepatic and extrahepatic outcomes and progression to cirrhosis. Up to date, there are no approved pharmacotherapies for the treatment of MAFLD, so management focused on lifestyle interventions to encourage weight loss, and treatment of coexisting conditions is the only available option. Unfortunately, the aforementioned is often not potent enough to offer reversal or slow down hepatic inflammation and fibrosis. Glucagon-like peptide-1 receptor agonists have a favorable effect on glycemic management and weight loss of patients with type 2 diabetes mellitus and recently published data suggest their potential in MAFLD treatment. In addition, some of the agents have proven cardiovascular and renal benefits in dedicated cardiovascular outcome trials, making them an interesting therapeutic option. In this opinion review, we discuss the role of semaglutide in MAFLD.

Key Words: Semaglutide; Non-alcoholic fatty liver disease; Glucagon-like peptide-1 receptor agonists; Metabolically associated fatty liver disease

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Core Tip: The pathogenesis of metabolically associated fatty liver disease (MAFLD) is closely interrelated to type 2 diabetes mellitus (T2DM), with insulin resistance and hyperinsulinemia as key characteristics. Glucagon-like peptide-1 receptor agonists have a favorable effect on glycemic management and weight loss in T2DM patients. Semaglutide is an especially interesting agent with favorable metabolic actions in patients sharing T2DM and MAFLD (but also sole MAFLD) phenotype, available in injectable and oral formulation, thus more attractive for a broader spectrum of patients.

INTRODUCTION

MAFLD: THE TRIGGER OF THE VICIOUS CYCLE ENDING IN CARDIOVASCULAR DISEASE, CIRRHOSIS, AND LIVER CANCER. WHAT TO OFFER TO OUR PATIENTS?

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease that includes a broad spectrum of clinical and histopathological conditions, from simple steatosis (non-alcoholic fatty liver) to liver inflammation and injury with or without fibrosis (non-alcoholic steatohepatitis - NASH) that can further progress to cirrhosis and hepatocellular carcinoma (HCC)^[1]. Exclusion of patients with alcohol intake, or other chronic liver diseases is mandatory for the diagnosis. Nowadays, NAFLD is the leading cause of liver disease worldwide. Its prevalence is rising, becoming a major cause of liver disease-related deaths and liver transplantation^[2,3]. Additionally, it carries an increased risk for cardiovascular disease (CVD) morbidity and mortality^[4]. The condition is strongly associated with obesity and type 2 diabetes mellitus (T2DM) and is considered a liver manifestation of metabolic syndrome. The definition of NAFLD is relatively narrow and based on exclusion. Thus, in recent years, a new concept has emerged, better represented by the term metabolically associated fatty liver disease

³ (MAFLD). The diagnosis of MAFLD is based on the presence of hepatic fat (diagnosed by histology, imaging, or blood biomarkers) along with at least one of these three metabolic conditions: overweight/obesity, T2DM, or evidence of metabolic dysregulation^[5]. The latter is defined by at least two criteria in patients with normal body mass index (BMI): enlarged waist circumference; hypertension or anti-hypertensive treatment; increased triglycerides or treatment with hypolipemic drugs; low high-density lipoprotein cholesterol; prediabetes; high Homeostatic Model Assessment of Insulin Resistance score; and high-sensitivity C-reactive protein^[6]. In addition, MAFLD diagnosis does not exclude excessive alcohol consumption and other causes of liver disease.

The pathogenesis of MAFLD is multifactorial and closely interrelated to the pathogenesis of T2DM, with insulin resistance (IR) and hyperinsulinemia as key shared characteristics of both conditions. Moreover, individuals with MAFLD are more insulin resistant than those without MAFLD, irrespective of glucose tolerance and BMI^[7]. IR acts on adipose tissue, worsens adipocyte dysfunction, induces lipolysis, and releases adipokines and proinflammatory cytokines. IR increases de novo lipogenesis in the liver, resulting in elevated free fatty acids and lipid accumulation within hepatocytes, predisposing to liver injury and inflammation^[8]. Proinflammatory environment further contributes to CVD^[9].

The relationship between T2DM and NAFLD/MAFLD is bidirectional; T2DM is a risk factor for the progression of NAFLD/MAFLD to fibrosis^[10,11], as well as HCC^[12], and conversely, NAFLD/MAFLD increases the risk of developing T2DM^[13]. In addition, patients with NAFLD are known to have high cardiovascular (CV) risk and CVD is the leading cause of death in NAFLD patients^[4]. Furthermore, given its broader definition, it should be expected that MAFLD is associated with higher CVD morbidity and mortality compared to NAFLD. However, the data comparing the two are inconclusive and scarce. In consideration that MAFLD is inclusive of patients with alcohol consumption and other liver disease, and it is relatively new concept additional

studies are needed to define group of patients that are especially at risk of CVD morbidity and mortality^[14].

Nevertheless, a treatment that addresses all of the above conditions would be strongly recommended.

Currently, no specific therapies alter the natural history of MAFLD and its progression to more severe forms of steatohepatitis ending in liver cirrhosis and/or liver cancer. Lifestyle modification remains the cornerstone of treatment^[15,16].

Considering that IR is the pathogenetic factor involved in MAFLD, antihyperglycemic agents, especially insulin sensitizers, emerged as the potential therapeutic option. Pioglitazone is currently the only pharmacological agent recommended in patients with biopsy-proven NASH as it improves liver histology, both in patients with and without T2DM^[15-17].

In recent years, newer antihyperglycemic agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs), have exhibited beneficial direct and indirect effects on metabolism and weight loss, raising the interest as a new drug class with potential in MAFLD prevention and treatment. Moreover, some of these agents showed CV protection in dedicated CV outcome trials, placing them in the spotlight for broader use in additional indications, particularly suitable for patients sharing diabetes and MAFLD phenotype (Figure 1).

GLP-1RAs: LIGHT AT THE BEGINNING, MIDDLE OR AT THE END OF THE TUNNEL?

GLP-1RAs are agents available to treat T2DM patients, especially those with atherosclerotic CVD and obesity. Either daily (liraglutide, lixisenatide, exenatide) or weekly injectable GLP1-RA preparations (dulaglutide, semaglutide, exenatide once weekly) have been available, and recently, a daily oral formulation (semaglutide) was approved^[18]. GLP-1RAs have many beneficial effects, including stimulating glucose-dependent insulin secretion, inhibition of glucagon secretion and stimulation of β -cell proliferation, delay of gastric emptying, and increasing satiety *via* central nervous

system pathways^[18]. In dedicated randomized control trials (RCTs), including T2DM patients all over the diabetes spectrum, GLP-1RAs have proven glucose-lowering and significant weight-lowering effects alongside their cardio- and renoprotective properties^[19,20]. Also, GLP-1RAs can improve serum transaminase levels in patients with MAFLD^[21]. Additionally, patients with MAFLD have exhibited a decrease in endogenous GLP-1 secretion, highlighting GLP-1RAs as a potential treatment^[22]. Given their multifactorial effects and targeting many pathways involved in MAFLD, including IR, inflammation, obesity, and offering cardiovascular protection, GLP-1 RAs are emerging as a promising treatment for MAFLD patients.

PREVENTION/SLOWING DOWN THE PROGRESSION TO NASH

The hepatic effects of GLP-1 RAs are mostly evident indirectly by reducing body weight, IR and improving fatty acid metabolism. Obese ⁸ patients with NAFLD are insulin resistant at the level of adipose tissue, liver, and skeletal muscle. They exhibit a progressive deterioration in metabolic parameters, hepatic IR, and liver fibrosis as adipose tissue IR worsens^[23]. The liver acts as a metabolic sensor of dysfunctional adipose tissue, and insulin resistant adipose tissue is closely connected to intrahepatic triglyceride accumulation^[24]. By acting favorably on body weight, GLP1-RAs decrease adipose tissue (primarily visceral) and indirectly reduce intrahepatic fat content and lead to MAFLD prevention/amelioration. Additionally, GLP-1RAs show a beneficial effect on lipoprotein metabolism, modulating reverse cholesterol transport, reducing triglyceride production rate from the liver and intrahepatic triglyceride content, and consequently reducing fasting and postprandial concentration of triglycerides^[25].

But what about their direct effects on the liver? We know that GLP-1RAs exert their effects by binding to receptors found in islet cells and other extrapancreatic tissues (lung, kidney, brain, nervous system, gastrointestinal system, *etc.*). Gupta *et al*^[26] found GLP-1 receptors on human hepatocytes in vitro, showing a direct role in improving hepatic steatosis by modulating insulin signaling pathways and decreasing hepatic IR and fatty acid synthesis. Furthermore, GLP-1 RAs improved hepatocyte survival and

reduced hepatic steatosis by inhibiting endoplasmic reticulum stress response and reducing fatty acid accumulation by inducing autophagy^[27,28]. Still, the direct effects of GLP-1 RAs on the liver remain not fully understood, and large-scale RCTs are needed to investigate the efficacy and safety of GLP-1-based therapies in treating patients with MAFLD.

REVERSAL/IMPROVEMENT OF NASH

In recent years, several studies have examined the efficacy of GLP-1 RAs in managing MAFLD in patients with and without T2DM. These studies mainly evaluated exenatide and liraglutide in the treatment of MAFLD/NASH, primarily in patients with concomitant T2DM. Liraglutide was the most widely studied among GLP-1 RAs and, until recently, the only one that showed improvement in liver histology for patients with biopsy-proven NASH. The LEAN study (liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis)^[29] included patients with and without T2DM and showed the histological resolution of NASH in patients treated with liraglutide. In addition to improvements in histological steatosis and hepatocyte ballooning, fewer patients had fibrosis progression. Other trials with liraglutide were not conducted in biopsy-proven NASH. Few studies compared liraglutide to other antihyperglycemic agents in NAFLD and T2DM. Ohki *et al*^[30] conducted a retrospective study evaluating the efficacy of liraglutide vs sitagliptin and pioglitazone. A significant decrease in serum aminotransferase levels for all groups was reported, while the aspartate aminotransferase (AST)-to-platelet counts ratio index was significantly reduced only for the liraglutide and pioglitazone groups^[30]. Another trial by Feng *et al*^[31] randomized T2DM patients with NAFLD to receive liraglutide, metformin, or gliclazide. The liraglutide group showed the greatest reduction in intrahepatic steatosis and liver enzymes^[31]. Few trials compared exenatide to other hypoglycaemic agents in NAFLD patients with T2DM. Shao *et al*^[32] compared exenatide plus insulin glargine U-100 (exenatide group) with insulin glargine U-100 plus insulin aspart (intensive insulin group). The liver enzymes were significantly lower, and the reversal rate of liver

steatosis was higher in the exenatide group than in the intensive insulin group^[32]. Another RCT¹ compared the efficacy of exenatide vs metformin in patients with NAFLD and T2DM, concluding that exenatide was more effective than metformin in reducing body weight and improving liver enzymes^[33]. Exenatide has not been studied in RCTs with liver histology outcomes in NASH patients. Nevertheless, a recent meta-analysis⁴ of eight studies with exenatide and liraglutide in patients with T2DM and MAFLD found significant improvements in hepatic fat content, liver biochemistry, body composition, metabolic parameters (glucose parameters, lipid parameters, insulin sensitivity), and inflammatory markers following GLP-1 RAs treatment. Moreover, GLP-1RAs also improved fibrosis markers without statistical significance^[34]. The mentioned meta-analysis did not include studies that examined liver histology. The data regarding dulaglutide and NAFLD are limited and primarily based on retrospective studies^[35]. Only one RCT evaluated the effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD (D-LIFT trial). This study compared patients receiving dulaglutide (add-on to usual care) vs the usual care. The dulaglutide group showed a significant reduction in liver fat content and gamma-glutamyl transferase levels in participants with NAFLD. The dulaglutide group showed non-significant reductions in pancreatic fat content, liver stiffness, serum AST, and serum alanine aminotransferase (ALT) levels^[36]. Lastly, an updated meta-analysis included eleven placebo-controlled or active-controlled phase-2 RCTs² that used liraglutide ($n = 6$ RCTs), exenatide ($n = 3$ RCTs), dulaglutide ($n = 1$ RCT) or semaglutide ($n = 1$ RCT) to specifically treat NAFLD or NASH, detected by liver biopsy ($n = 2$ RCTs) or imaging techniques ($n = 9$ RCTs). Compared to placebo or reference therapy, treatment with GLP-1 RAs was associated with significant reductions in liver fat content on magnetic resonance-based techniques and serum aminotransferase levels, as well as with the greater histological resolution of NASH without worsening of liver fibrosis (for liraglutide and semaglutide only)^[37].

¹ **WHY SEMAGLUTIDE?**

Semaglutide is a novel GLP-1 receptor agonist that has been recently approved for the treatment of T2DM and obesity. Two formulations are currently available, once-weekly subcutaneous semaglutide and once-daily oral semaglutide, the subcutaneous form in different dose ranges depending on the indication (for T2DM subcutaneous semaglutide up to 1 mg weekly and oral semaglutide up to 14 mg daily; for obesity subcutaneous semaglutide 2.4 mg weekly). Currently completed studies with subcutaneous in T2DM^[38-56] and oral semaglutide^[57-67] are presented in Tables 1-3.

Across the SUSTAIN program, once-weekly subcutaneous semaglutide showed more pronounced metabolic effects than active comparators (including liraglutide, a widely used GLP-1RA)^[68]. Semaglutide was associated with reduced CV risk among patients with T2DM at high CV risk^[43]. Recently published data from STEP RCTs, on patients receiving subcutaneous semaglutide in dose 2.4 mg once weekly for treatment of obesity suggest its favorable and prolonged effect on weight reduction (twice as many patients reduced more than 5% of initial weight compared to placebo, with a range of weight loss of 10% to 20% in the majority of patients on semaglutide), which is associated with clinically meaningful improvements in cardiovascular and metabolic risk factors and more pronounced when compared to reduction achieved on liraglutide 3.0 mg sc daily^[69]. In addition, a new oral formulation is available, with similar efficacy and safety profile to the subcutaneous formulation, confirmed across the PIONEER program.. Furthermore, oral semaglutide offers an alternative for patients with concerns regarding injectable treatment and creates an opportunity to expand the utilization of GLP-1 RAs^[68].

Semaglutide has been shown to significantly reduce ALT and markers of inflammation^[70]. Recently, a RCT comparing subcutaneous semaglutide vs placebo in subjects with NAFLD assessed by MRI was conducted. The trial investigated the effects of subcutaneous semaglutide on liver stiffness, a marker of fibrosis, and liver steatosis in subjects with NAFLD, using non-invasive MRI methods after 24 wk, 48 wk, and 72 wk of treatment. Significant improvement in liver steatosis was found, accompanied by improvements in liver enzymes and metabolic parameters. In addition, more

participants receiving semaglutide achieved > 15% reduction in liver stiffness compared to placebo, although the difference was not significant^[71].

For now, only two RCTs were conducted with GLP-1 RAs in patients with biopsy-proven NASH, the already mentioned liraglutide^[29] and semaglutide. A 72-wk phase 2 trial evaluated the effect of semaglutide on the histologic resolution of NASH in patients with biopsy-proven NASH and fibrosis. Patients were randomized to receive 0.1 mg, 0.2 mg, or 0.4 mg once daily semaglutide or placebo. The semaglutide 0.4 mg was superior to placebo regarding NASH resolution without worsening liver fibrosis. However, a significant between-group difference in improving at least one fibrosis stage was not shown^[70]. A much longer duration may be required for improvements in the fibrosis stage to become apparent, especially since most patients in the current study had advanced fibrosis. The most reported adverse events were gastroenterological disorders (nausea, constipation, decreased appetite, vomiting, and abdominal pain), which are already known from RCTs and real-world data. They were dose-dependent and mainly occurred during the dose-escalation period in the first 20 wk of the trial.

Semaglutide is a promising treatment for patients with NASH. Additional studies are needed to evaluate the optimal dosage and formulation for MAFLD treatment. The approved doses of injectable semaglutide for treatment of T2DM are 0.5 mg and 1.0 mg once weekly and for obesity 2.4 mg once weekly, which is different from the 0.1 mg, 0.2 mg, and 0.4 mg doses used in the previously mentioned study. Future dedicated trials enrolling MAFLD patients to receive subcutaneous semaglutide 2.4 mg and development of oral semaglutide for treatment of obesity, almost an inseparable condition from MAFLD, is holding promise as a new therapeutic option.

CONCLUSION

THE FUTURE IS... (BRIGHT)

Semaglutide efficacy in the treatment of NASH was undoubtedly confirmed in the recent RCT in patients with and without T2DM. Even though improvement in the fibrosis stage was not shown in this study, a longer duration of treatment may be

needed, especially for advanced-stage fibrosis. Furthermore, ⁴ semaglutide is currently the only GLP-1RA available in an injectable and oral formulation. Thus, the dosage and formulation of semaglutide in NASH treatment need to be further established. Given its definite potency, it is a promising drug for the treatment of NASH, offering the benefit of the choice of the formulation to best suit individual patients' preferences.

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