Editorial: Treatment with Dual Incretin Receptor Agonists to Maintain Normal Glucose Levels May Also Maintain Normal Weight and Control Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)

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Abstract
Worldwide, metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common chronic liver disease. MAFLD is associated with insulin resistance, type 2 diabetes mellitus (T2DM), obesity, hypertension, and dyslipidemia. Early diagnosis and management are vital to improving hepatic and cardiometabolic outcomes. Dietary change, weight loss, and structured exercise are the main treatment approaches for fatty liver disease. Since 2010, several investigational drug treatments failed to achieve regulatory approval due to mixed and unsatisfactory results. Although glucagon-like peptide 1 receptor agonists (GLP1-RAs) showed initial promise as therapeutic agents, metabolic liver damage can recur after monotherapy cessation. Dual incretin receptor agonists target the receptors for glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP). Importantly, on May 13, 2022, the US Food and Drug Administration (FDA) approved tirzepatide as the first dual GLP-1 and GIP receptor agonist for the treatment of T2DM. Dual incretin receptor agonists induce weight loss and enhance hepatic lipid metabolism and systemic insulin sensitivity. Insulin resistance and hepatic steatosis are the main contributors to the development of MAFLD. Treatment with dual incretin analogs reduces hepatic steatosis, lobular inflammation, liver cell damage, fibrosis, and total liver triglyceride levels. The availability of dual incretin receptor agonists for patients with MAFLD may result in weight control, normalizing insulin sensitivity, and reducing or even reversing metabolic dysfunction and liver damage. This Editorial aims to provide an update and discuss how treatment with dual incretin receptor agonists may maintain normal glucose levels and weight and control MAFLD.

Keywords: Incretin • Fatty Liver • Non-Alcoholic Fatty Liver Disease • Insulin Resistance • Editorial
are vital to improving liver and cardiometabolic outcomes and reducing the health care burden of MAFLD [7]. Currently, the latest international guidelines recommend dietary change, weight loss, and structured exercise intervention as the cornerstone of therapy in the absence of regulatory-approved drug treatments [7].

Since 2010, several investigational drug treatments have failed to achieve regulatory approval due to mixed and unsatisfactory results. For example, the results from the Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis (PIVENS) trial (NCT00063622), resulted in pioglitazone and vitamin E being considered as possible adjuvant therapies to lifestyle, dietary changes, and weight loss [8]. However, later studies, including a clinical trial (NCT02970942), found this therapy to have unsatisfactory results [9]. The search for treatments to reduce hepatic steatosis, liver injury, and metabolic and cardiovascular risk has resulted in several clinical trials of new drugs [10]. Notably, elafibranor, cenicriviroc, simtuzumab, selonsertib, volixibat, aldafermin, obeticholic acid, lanifibranor, resmetirom, iraglutide and semaglutide were all studied, as well as developments in bariatric surgery to treat obesity, T2DM, and MAFLD [11].

Currently, weight loss and reduced hepatic insulin resistance are the most useful and promising approaches to managing MAFLD [11]. A recent systematic review and network meta-analysis included randomized controlled trials involving patients with non-alcoholic fatty liver disease (NAFLD) [11]. Meta-analysis data showed that for every 1% reduction in body mass index (BMI), the NAFLD activity score (NAS) was reduced by 1.3% (β=1.28%; P<0.01) and a 1% reduction in the homeostatic model assessment of insulin resistance (HOMA) index reduced the NAS by 0.3% (β=0.31%; P<0.001) [11].

In 2016, the findings from the liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN) phase 2 trial (NCT01237119) were published [12]. The basis for the LEAN trial was that glucagon-like peptide 1 receptor agonist drugs (GLP-1RAs) could be expected to reduce hepatic steatosis since they reduce body weight and reduced insulin resistance. The 72-week phase 2 LEAN trial included 52 patients with biopsy-proven steatohepatitis who were treated with liraglutide at doses of 1.8 mg daily for 48 weeks and weekly semaglutide with subcutaneous doses of 0.1, 0.2, or 0.4 mg [12]. The findings showed efficacy in MAFLD, improved resolution of steatohepatitis, and reduced progression to fibrosis compared with placebo [9,12].

In 2021, Dai and colleagues published the findings from a systematic review and meta-analysis to compare the efficacy of GLP1-RAs in patients with MAFLD [13]. This study identified eight randomized controlled trials that included 396 patients with MAFLD [13]. There were 265 patients with MAFLD who had T2DM [13]. GLP1-RA treatment resulted in a significant reduction in hepatic fat, patient waist circumference, alanine aminotransferase (ALT) levels, γ-glutamyl transferase (γGT) levels, fasting blood glucose levels, and hemoglobin A1c (HbA1C) [13]. The studies reviewed showed no serious adverse events, while most gastrointestinal symptoms resolved within two weeks after dose titration [13]. In a further systematic review and meta-analysis of controlled trials conducted by Mantovani and colleagues in 2021, placebo or standard therapy was compared with GLP-1 RAs for a median of 26 weeks [14]. Treatment was associated with significant reductions in the absolute percentage of liver fat content assessed using magnetic resonance imaging (MRI)-based techniques [14]. Treatment with liraglutide and semaglutide reduced serum liver enzyme levels [14]. Also, liver biopsies showed a histologically-confirmed reduction in steatohapatitis without an increase in liver fibrosis [14]. However, despite these promising results, cessation of treatment with GLP1-RAs resulted in the return of hepatic steatosis and abnormal liver function tests [14].

Dual incretin receptor agonists are novel pharmacologic agents that target the receptors for both glucagon-like peptide 1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP) [15]. The gut-derived incretin hormones, GLP-1 and GIP, modulate glucagon secretion, amino acid metabolism, energy expenditure, body weight, and lipid metabolism [15]. GLP-1 inhibits glucagon secretion in hyperglycemic states but not during hypoglycemia or euglycemia [15]. As a result, GLP-1RAs reduce hyperglycemia with little risk of hypoglycemia [16]. In non-diabetics, GIP stimulates glucagon secretion during hypoglycemia and potentiates GLP-1-induced insulin secretion [16]. Also, the action of GIP on glucose metabolism is reduced during hyperglycemic states, which occurs most commonly in patients with T2DM [16]. The enteroinsular axis originates with the activation of enteroendocrine cells in the intestine in response to food intake and ultimately regulates gastric motility, nutrient absorption, blood flow, and food intake [17]. The GIP constituent of dual GIP/GLP-1 receptor agonism is believed to have a central action in promoting GLP-1-induced weight loss and enhanced white adipose tissue function, leading to improved lipid metabolism and systemic insulin sensitivity (Figure 1) [18].

Furthermore, a recently described axis involving the G-coupled receptor GPR119 (GPR119/incretin axis) has been described as a potentially important pathway [19]. The GPR119/incretin axis may have a role in reducing insulin resistance, fat production, and total body mass, appetite reduction, and inhibiting effect on inflammation, potentially reducing the development and outcomes of MAFLD [19]. A further important consideration is the relationship between the incretins and the mechanisms of fibrosis [19]. GIP exerts biological functions through binding to
Its receptor and influences macrophage activation [19]. GLP-1 binds to its receptor to downregulate collagen formation by downregulating the expression of transforming growth factor-beta 1 (TGF-β1) and fibroblast growth factor-21 (FGF-21) in mouse models of steatohepatitis and AMP-activated protein kinase (AMPK) in diabetic pulmonary fibrosis [19]. Therefore, combined treatment with dual incretins in animal models reduced steatohepatitis, lobular inflammation, hepatocyte damage, and liver fibrosis [19].

Several clinical studies now support the clinical evidence for the efficacy and safety of dual GLP-1/GIP receptor agonists. In May 2022, the dual receptor agonist tirzepatide was approved by the US Food and Drug Administration (FDA) for glycemic control in patients with T2DM [20]. Tirzepatide is administered subcutaneously and showed a greater reduction in levels of Hba1C when compared with semaglutide, insulin degludec, and insulin glargine [20]. Also, in a 2020 study reported by Hartman and colleagues, tirzepatide was shown to reduce the levels of steatohepatitis-related biomarkers, including pro-C3, K-18, AST, and ALT, and to increase adiponectin levels in a dose-dependent manner [21]. Another study by Pirroin and colleagues in 2021 showed that tirzepatide improved glycemic control, reduced triacylglycerides, reduced markers of insulin resistance, and improved beta cell function by direct pharmacologic effects, rather than by the effects of weight loss alone [22]. In a phase 2b, 26-week trial in T2DM patients, tirzepatide (dual GIP/GLP1 RA) demonstrated superior glucose control and reduction in body weight compared with mono-therapy with the GLP-1RA, dulaglutide (NCT031316874) [23]. The findings from this trial showed that tirzepatide reduced serum glycosylated Hba1C by 1.6%, 2.0%, and 2.4% in the 5 mg, 10 mg, and 15 mg dose groups, respectively, compared with 1.1% for dulaglutide at a dose of 1.5 mg [23]. Also, 48% of patients achieved normoglycemia (Hba1C 5.7%) compared with 2% of subjects treated with dulaglutide [23]. More patients treated with 5 mg, 10 mg, and 15 mg of tirzepatide reached normal body weight targets (<5%, <10%, and <15% weight loss).
loss from baseline, respectively) when compared with dula-
glutide [23]. Reduced appetite was more common with tirz-
epatide, which was consistent with the putative role of GIP to
complement the anorectic action of GLP-1. The incidence of
nausea, diarrhea, and vomiting was similar for tirzepatide at
5 mg and 10 mg to dulaglutide, but higher at the 15 mg dose
for tirzepatide [18,23]. However, GIP appears to have a dose-
related effect on adipose tissue inflammation and may have
anti-atherogenic effects [23,24]. Nitric oxide production pre-
vents vessel obstruction by inhibiting vascular smooth mus-
cle cell proliferation [23,24]. Also, there may be effects that
suppress the inflammatory responses in specific inflammatory
cells and adipocytes [24]. Therefore, the effects of dual incre-
tin receptor agonists may have beneficial effects on managing
comorbidities associated with MAFLD, particularly cardio-
metabolic outcomes.

This overview of the dual function of incretins and the synergic
effects on insulin regulation, hepatic fat content, and fibrosis
has highlighted the importance of conducting further longitudi-
dinal studies. Future studies should primarily evaluate weight
loss, hepatic steatosis, and fibrosis. Recent studies have shown
the early impact of dual incretin receptor agonists on insulin
resistance, obesity, and the metabolic profile, which could be
a solution to prevent or treat MAFLD.

Conclusions
The use and effect of dual incretin receptor agonists for pa-
tients with MAFLD are promising and increase the probabil-
ity of inducing and maintaining normal weight and insulin
sensitivity and reducing or reversing metabolic dysfunction.
Achieving metabolic homeostasis and maintaining a healthy
lifestyle could reduce the likelihood of recurring obesity, ste-
atosis, steatohepatitis, and the hepatic and cardiometabolic
consequences of MAFLD. Ideally, treatment for each patient
should be individualized according to their metabolic state to
identify which therapeutic strategy is most effective. However,
there is a long way to go before establishing precision medi-
cine in the field of metabolic disease. Clinical trials are await-
ed to provide evidence for managing specific patient groups
according to age, gender, comorbidities such as T2DM, car-
diovascular disease, and renal disease, and genetic suscepti-
bility of patient groups according to factors such as ethnicity.

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