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REVIEW PAPER

The pleiotropic effects of liraglutide in obesity-linked diseases

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ABSTRACT

Introduction and aim. Obesity, defined by a BMI ≥30 kg/m^2, is a global epidemic associated with increased mortality rates and an increased prevalence of chronic diseases. Such diseases include type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and polycystic ovary syndrome (PCOS), besides several mental health disorders. Liraglutide, a glucagon-like peptide 1 (GLP-1) analogue, is widely recognized for its efficacy in glycemic control and weight loss and this review aims to explore the pleiotropic effects of liraglutide in obesity-related diseases.

Material and methods. Literature search was performed between 2022 and 2024 using the following databases: PubMed (MEDLINE) and Google Scholar. The comprehensive review of the literature focused on the action of liraglutide on NAFLD/NASH, CVD, mental disorders, and PCOS. A qualitative synthesis of the data focusing on efficacy of liraglutide in obesity-related disease outcomes was performed.

Analysis of the literature. Liraglutide improves metabolic outcomes by promoting weight loss, reducing appetite, and improving glycemic control. In NAFLD/NASH, liraglutide reduces intrahepatic fat, liver fibrosis, and inflammation that strongly relate to the degree of weight loss. The LEADER trial showed its cardiovascular benefits in terms of reducing all-cause mortality and major cardiovascular events in patients with T2DM, although its chronotropic effects may pose risks in patients with heart failure. In women with PCOS, liraglutide reduces hyperandrogenism, insulin resistance, and body weight, and thus has even more favorable effects compared with metformin. Liraglutide also counteracts antipsychotic-induced weight gain and improves metabolic markers in patients with severe mental disorders.

Conclusion. Liraglutide demonstrates significant pleiotropic effects apart from weight reduction, including improved hepatic metabolism, cardiovascular protection, and better outcomes in PCOS and mental health. While semaglutide and tirzepatide may offer enhanced efficacy, liraglutide remains a promising therapeutic option for managing obesity and its related comorbidities.

Keywords. cardiovascular disease, liraglutide, mental disorders, obesity, polycystic ovary syndrome

Introduction

Obesity, is a condition characterized by excessive body weight and fat deposition in tissues and organs, defined by a body mass index (BMI)≥30 kg/m^2, with a BMI of 25–29.9 kg/m^2 classified as overweight.[1] It is affected by high incidence of chronic comorbidities, including metabolic disorders (type 2 diabetes (T2DM), hyperlipidemia, non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH), metabolic syndrome (MetS), cardiovascular diseases (CVD), chronic kidney

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disease (CKD), polycystic ovary syndrome (PCOS), obstructive sleep apnea (OSA) as well as it is a major risk factor for cancers.[2] Sometimes neglected, but equally significant, mental health issues such as depression and anxiety are also linked to this condition. Overweight individuals tend to overestimate the width of their own body shape, which leads to greater subjective dissatisfaction with their body appearance.[3] Over the last 30–40 years, obesity rates have surged, particularly in developed countries, exacerbated by the COVID-19 pandemic, especially in youth.[4] Projections suggest that by 2030, 38% of the global population will be overweight and 20% obese making it one of the most frequent diseases of humanity.[5] Obesity and its related comorbidities are associated with healthcare costs approx. 20% higher than compared to normal-weight individuals, amounting to $2 trillion worldwide. Obesity is currently a major public health concern affecting over 600 million adults and 100 million children globally. Diseases related to overweight and obesity result in substantial economic losses and serve as a factor reducing workforce productivity.[2,6]

Obesity is considered as a chronic metabolic disease that arises from a complex interplay of genetic, environmental, socioeconomic, behavioral, and psychological factors (Fig. 1). A key contributor is an imbalance between caloric intake and expenditure, both regulated by the hypothalamus, particularly the arcuate nucleus. Appetite is suppressed by pathways involving proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), while neuropeptide Y (NPY) and agouti-related peptide (AgRP) stimulate hunger. Thus, NPY/AgRP neurons of arcuate nucleus stimulate feeding and inhibit satiety, while POMC/CART neurons stimulate satiety and inhibit feeding. Both groups of neurons are regulated in part by leptin. Signals from peripheral tissues include long-term energy regulation mediated by leptin and insulin and short-term satiety are regulated by gastrointestinal hormones like secretin, glucagon-like peptide 1 (GLP-1) and cholecystokinin.[7] A deficiency in leptin signaling, either via leptin deficiency or leptin resistance, leads to overfeeding and may account for some genetic and acquired forms of obesity. Equally important factor is ghrelin, secreted during fasting and promoting appetite via NPY/AgRP stimulation.[7,8]

There is large body of evidence that genetic factors play a particular role and interact with environmental factors to produce obesity. Genetic factors contribute to 40-70% of obesity cases within families and twins.[9] However, genetic and environmental factors overlap, as a healthy lifestyle can significantly reduce the effect of genetic factors. More than 300 loci have been associated with obesity, though their individual effects on BMI are small (<5%).[9,10] Additionally, familial lifestyle factors further amplify genetic risks, with a threefold increase in obesity risk in case of one obese parent and a tenfold increase if both parents are obese.[11,12] Monogenic obesity involves mutations in genes responsible for satiety and hunger regulation including POMC, MC4R, and leptin, leading to inadequate satiety signaling.[9,10,13] Polygenic obesity, in contrast, results from the interaction of multiple gene polymorphisms.[14] Epigenetic modifications, influenced by environmental factors, also play a role. Histone modifications, for example, regulate adipogenesis-related genes like PPARγ.[15] DNA methylation patterns of leptin and adiponectin correlate with LDL levels and obesity risk.[16] Russo et al. demonstrated that elevated specific miRNAs in children are strongly linked to increased BMI.[17] Intriguingly, gut microbiota dysbiosis in obesity alters the Bacteroidetes-to-Firmicutes ratio, potentially increasing pathogenic variants and affecting microbial metabolites like short-chain fatty acids (SCFA). SCFAs regulate satiety, lipogenesis, and glucose homeostasis, with obese patients showing higher fecal SCFA concentrations.[18-20]

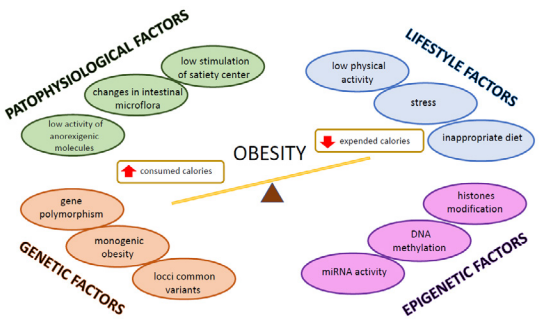

Fig. 1. The interplay between diverse factors leading to obesity – the interaction of multiple biological, environmental, and lifestyle influences

Better comprehension of the mechanisms driving obesity is crucial for developing pharmacological treatment strategies. Currently, lifestyle modification, which includes a balanced diet, physical activity, and behavioral therapy, remains the primary intervention, often yielding successful outcomes.[21] The choice of antiobesity pharmacotherapy depends upon medication efficacy and side effects, individual contraindications, comorbidities, and preferences, as well as insurance coverage and "out-of-pocket" costs. Available medications include lorcaserin, phentermine-topiramate and phentermine (as a single agent), orlistat, naltrexone-bupropion, tirzepatide, semaglutide, liraglutide, and setmelanotide, an MCR4 agonist reserved for a subset of POMC and leptin receptor-deficient patients.[22] Notwithstanding, patients with a BMI >30 or BMI >27 with comorbidities who do not achieve sufficient benefits from lifestyle changes or drug therapy may require surgical intervention. For individuals with severe obesity (BMI >40 or BMI >35 with

comorbidities), bariatric surgery is particularly recommended.[23] Recently, significant effectiveness in lowering body weight has been demonstrated by GLP-1 analogs. These are anti-diabetic drugs, which show additional beneficial effects in delaying gastric emptying or suppressing appetite. In 2014 U.S. Food and Drug Administration approved liraglutide to treat obesity, semaglutide in 2021, and in November 2023 tirzepatide which additionally affects the glucose-dependent insulinotropic polypeptide receptor (GIP) (Fig. 2).[24]

Aim

The aim for conducting a review of the pleiotropic effects of liraglutide lies in the growing popularity and increasing body of research highlighting its multifaceted role in improving health outcomes beyond glycemic control. Further studies demonstrated its potential to influence other organs and systems. The current review addresses liraglutide's pleiotropic effects, the therapeutic implications, and future directions of this research area. Our findings may enhance clinical decision-making and point future research towards the optimization of liraglutide use in a wide spectrum of metabolic and cardiovascular diseases as well as other chronic diseases. The current paper will discuss the therapeutic potential of liraglutide in the treatment of mental disorders, NAFLD/NASH, PCOS, and cardiovascular diseases in obesity.

Material and methods

Literature search was performed between 2022 and 2024 using the following databases: PubMed (MEDLINE) and Google Scholar. A literature review of articles published between 2010 and 2024 was performed. Key search terms used to identify relevant research included "Liraglutide", "Treatment of obesity", "Diseases caused by obesity", "GLP-1 receptor agonists", "Liraglutide cardiovascular risk", "Liraglutide and NAFLD", "Liraglutide and PCOS", "Liraglutide and psychopathology", "Liraglutide, clinical trial, obesity treatment", and "Liraglutide and Semaglutide in treatment of Obesity." All relevant studies were included embracing clinical trials (phase 2, 3, or 4) evaluating the effects of liraglutide on obesity and obesity-related diseases, randomized control trials, observational studies, meta-analyses and systematic reviews, animal experiments, studies that report outcomes related to obesity management (weight reduction, body mass index) and comorbid conditions such as NAFLD, cardiovascular disease, PCOS, mental disorders, researches that includes data on the mechanism of action, safety profiles, and efficacy of liraglutide. Studies that do not directly assess liraglutide as a primary intervention, studies with incomplete data or lacking rigorous methodological standards were excluded. Data was extracted independently by four reviewers, using a standardized data extraction form. A qualitative synthesis of the data conducted, focusing on efficacy of liraglutide in weight loss and obesity-related disease outcomes, comparison of liraglutide with other obesity treatments (pharmacological agents and lifestyle interventions), safety and tolerability of liraglutide, including common and rare side effects.

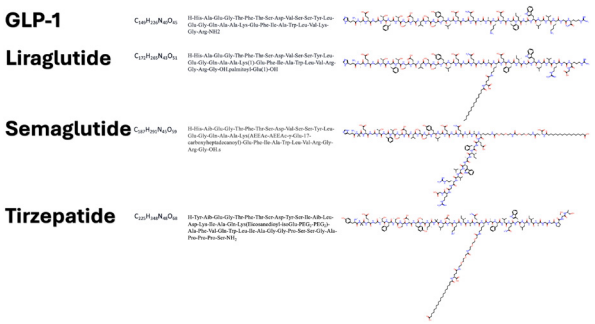

Fig. 2. Visual comparison of the amino acid sequences, chemical structures, and molecular formulas of GLP-1, liraglutide, semaglutide, and tirzepatide, data taken from PubChem (https://pubchem.ncbi.nlm.nih.gov, accessed November 2024), the illustrations were created using RDKit (https://www.rdkit.org) software based on SMILE formulas and the cairosvg library

Analysis of the literature

Liraglutide – mechanism of action

Throughout the development of liraglutide, modifications such as the addition of fatty acid chains to the original GLP-1 structure were made to optimize its properties, including high receptor potency and favorable pharmacokinetics for once-daily dosing (Fig. 2). Liraglutide shares 97% homology with endogenous human GLP-1 and has a prolonged half-life of 13 hours compared to 1.5-2 minutes of endogenous GLP-1 due to resistance to inhibitors of dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases degradation, possibly due to reversible binding to albumin or direct steric hindrance. Liraglutide activates GLP-1 receptors (GLP-1R) in various locations, including the brain, where it induces satiety and reduces food intake by activating subcortical areas.[25,26] These receptors are found in the nodose ganglion of abdominal vagal afferent nerve fibers, which terminate in the nucleus tractus solitarius in the brainstem. Signals are then transmitted to the hypothalamus and forebrain regions through ascending second-order neurons. Additionally, GLP-1R are in areas of the CNS such as the parietal cortex, hypothalamus, and medulla, where they modulate desirable food signals in humans.

Activation of GLP-1R in both the PNS and CNS increases feelings of fullness and reduces food intake. This reduction is mediated by stimulation of POMC neurons and inhibition of NPY/AgRPneurons, decreasing hunger. These effects are also linked to the mesolimbic sys-

tem, where food-induced reward signals are reduced, leading to a decrease in food-seeking behavior. Liraglutide is also reported to slow 1-hour gastric emptying.[27] In a study by van Can and colleagues, it was found that 5-hour gastric emptying was equivalent for liraglutide 1.8 mg and 3 mg and liraglutide versus placebo.[27] However, reductions in 1-hour gastric emptying of 23% with liraglutide 3 mg (p=0.007) and 13% with 1.8 mg (p=0.14) versus placebo were observed. Additionally, liraglutide 3 mg improved postprandial glycemia more than liraglutide 1.8 mg, although both doses similarly increased satiety, reduced hunger, and decreased energy intake by approximately 16%.

Liraglutide at doses up to 1.8 mg is approved for the treatment of T2DM under the name Victoza.[28] It is indicated as an adjunct to diet and exercise for glycemic control in patients aged ≥10 years with T2DM and to reduce the risk of major adverse cardiovascular events in adult patients with T2DM and established CVD. The maximum recommended dose for effective glycemic control in both age groups is 1.8 mg. Another formulation, Xultophy, combines liraglutide with insulin degludec and is similarly indicated for glycemic control in adult T2DM patients, with a maximum liraglutide dose of 1.8 mg.[29]

Saxenda, a liraglutide formulation at 3 mg, is indicated for weight loss in adult and pediatric patients. Efficacy for chronic weight management at doses below 3 mg has not been established, although pediatric patients may use a reduced maintenance dose of 2.4 mg if 3 mg is not tolerated.[30] Indications for adult patients include an initial BMI of ≥30 kg/m² (obese) or ≥27 kg/m² (overweight) with at least one weight-related comorbidity (e.g., hypertension, T2DM, or dyslipidemia). For pediatric patients aged ≥12 years, indications include body weight over 60 kg and an initial BMI corresponding to 30 kg/m² for adults by international cut-offs. Studies have indicated the safety of short-term liraglutide use in pediatric patients aged 7–11 years, although the drug is not yet approved for this population.[25] Treatment should begin with 0.6 mg, with weekly dose escalation to 3 mg. If a pediatric patient does not experience a BMI reduction of at least 1% from baseline after 12 weeks on the maintenance dose, treatment should be discontinued as further benefits are unlikely. Similarly, in adult patients, treatment should be discontinued if a 4% reduction in baseline body weight has not occurred after 16 weeks.[30]

Side effects

As liraglutide's indications expanded from treating only T2DM to addressing obesity in non-diabetic patients, it is increasingly important to consider adverse reactions in the growing patient population. The most relevant adverse events were collected and shown in Figure 3. Liraglutide doses up to 3 mg are associated with elevated serum lipase and amylase levels, and an increased absolute risk of acute pancreatitis, gallbladder or biliary disease, and gastrointestinal symptoms. The potential cancer-related side effects of liraglutide remain unclear, as various studies yield different outcomes.[31] However, when considering only high-quality studies, a statistically significant increase in cancer risk is observed. There are reports of elevated risks for thyroid, pancreatic, and early breast cancer, although these findings are inconclusive, with breast cancer risk specifically studied only at doses up to 3 mg.[32] Close monitoring of side effects is essential, and the balance between benefits and risks must be carefully evaluated in the context of the patient's long-term health.

The most common side effects of liraglutide are nausea and vomiting, which were the primary reasons for patient dropout in one of the pivotal clinical trials demonstrating liraglutide's effectiveness in obesity management.[33] Vomiting is relatively frequent and dose-dependent, likely due to delayed gastric emptying induced by the drug.[34-36] Other GLP-1 receptor agonists also slow gastric emptying, as this effect appears to be characteristic of the entire class of these medications.[37] This is likely due to the physiological actions of GLP-1 and other incretin hormones in slowing upper GI tract motility. However, the exact mechanism by which GLP-1 affects gastric emptying and satiation remains unclear, though it is hypothesized that CNS GLP-1 receptors may play a more significant role than peripheral GLP-1 vagal receptors in this process.[38,39]

The current liraglutide dose appears to balance efficacy with common side effects. Nonetheless, increasing the dose beyond 3 mg may not be feasible due to these adverse events, even though higher doses might further improve the treatment of obesity-related comorbidities.

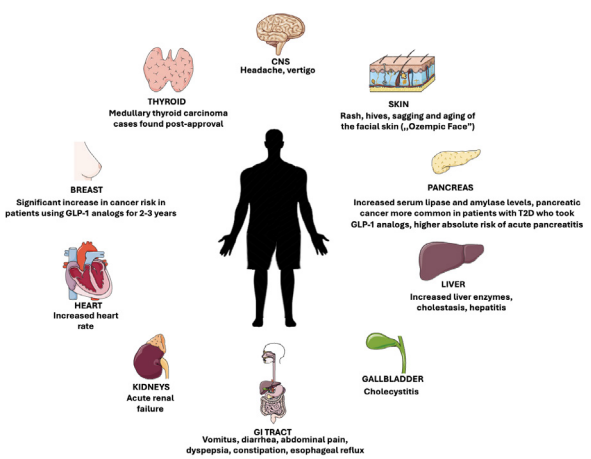

Fig. 3. The overview of the organ-specific adverse effects that may be associated with the use of GLP-1 analogues, this figure is created using Servier Medical Art, licensed under Creative Commons Attribution 4.0 Unported License, https://creativecommons.org/licenses/by/4.0/,

(accessed October 2024)

Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

Nonalcoholic fatty liver disease recently more recognized as metabolic dysfunction–associated steatotic liver disease is the most common liver disease referring to liver steatosis in patients with at least one metabolic risk factor (e.g., obesity, diabetes mellitus, dyslipidemia, hypertension). Recent studies estimate that NAFLD affects 32.4% of the global population, a prevalence that has risen sharply in recent years due to the global epidemics of obesity and type 2 diabetes. In obese patients and those with T2DM, the prevalence of NAFLD reaches 70–80%.[40] In the USA and EU, NAFLD is a leading cause of liver transplantation.[41] During NAFLD, excessive lipid accumulation in the liver (hepatic steatosis) causes hepatocyte damage, leading to liver fibrosis, cirrhosis, end-stage chronic liver disease, or hepatocellular carcinoma.[42] This lipid accumulation also triggers oxidative stress, mitochondrial dysfunction, and inflammation. Severe inflammation and necrosis of hepatocytes characterize NASH, a more severe form of NAFLD that can result in serious multisystem complications. Additionally, insulin resistance (IR) often develops during NAFLD, and patients with NAFLD have a 2–3 times greater risk of developing T2DM. This is accompanied by the increased likelihood of serious cardiovascular diseases, hypertension, dyslipidemia or CKD.[43] A vicious cycle forms, where obesity and T2DM promote the onset and severity of NAFLD/NASH, which in turn worsens the course of obesity and T2DM.

Studies have suggested several mechanisms through which GLP-1 analogues, including liraglutide, may improve the course of NAFLD/NASH, the most likely being their ability to induce weight loss. The degree of weight loss correlates most strongly with a decrease in intrahepatic fat (IHF), more so than with changes in total triglycerides, AST/ALT, or HbA1c levels ($p<0.0001$).[44,45] In patients with poorly controlled diabetes and NAFLD, no significant weight loss resulted in no reduction in IHF despite improvements in other liver parameters, whereas the greatest decrease in IHF was observed in patients with more than 5% weight loss.[45,46] Among the drugs tested for NAFLD/NASH, liraglutide and other GLP-1 analogues have shown the greatest efficacy. Liraglutide has been demonstrated as an independent factor for achieving body weight reduction of more than 5%.[47] In a study of T2DM patients with NAFLD, liraglutide treatment for 24 weeks resulted in greater weight loss (-5.60 kg) compared to metformin (-3.58 kg) or gliclazide (-0.1 kg), with a mean weight loss of 6.4% in the liraglutide group.[46]

In a study by Yan et al., patients with NAFLD and poorly controlled T2DM, previously treated unsuccessfully with metformin, experienced greater average weight loss (-3.6 kg) with the addition of liraglutide (1.8 mg daily for 26 weeks) compared to sitagliptin (-1.7 kg) or insulin glargine (-1.2 kg). Liraglutide also led to the greatest reduction in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in these patients.[48] Guo et al. also demonstrated that liraglutide was more effective than insulin glargine in reducing body weight (-5.1 kg vs -0.9 kg) and VAT (-47 cm^2 vs -16.6 cm^2).[49] A significant decrease in IHF (19–32%) was observed in all these studies. Additionally, Frossing et al. showed that administering liraglutide for 26 weeks to overweight women with PCOS and IR, who are at higher risk of developing NAFLD, resulted in significant reductions in body weight (5.6%), IHF (44%), and VAT (18%), reducing the prevalence of NAFLD by two-thirds ($p<0.01$).[50]

There are also weight-independent mechanisms by which liraglutide and other GLP-1 analogues may positively impact hepatic metabolism in NAFLD/NASH. Several animal studies suggest that GLP-1 plays a key role in regulating hepatic insulin sensitivity, lipogenesis/lipolysis gene expression, mitochondrial function, and endoplasmic reticulum (ER) stress in hepatocytes. Ding et al. first demonstrated that administering exendin-4, a GLP-1 receptor stimulator, to obese mice decreased the expression of lipogenesis-related genes and enzymes, such as stearoyl-CoA desaturase-1 and sterol regulatory element-binding protein 1, while increasing the expression of enzymes involved in fatty acid beta-oxidation, including PPARγ and acyl-coenzyme A oxidase 1.[47] This correlated with reductions in hepatic steatosis, serum ALT levels, HOMA-IR scores, and hepatocyte morphological changes compared to controls.[51] Similar results were found in non-obese NASH mice, where GLP-1 receptor stimulation also reduced hepatocyte inflammation.[52]

In high-fat diet mice with induced NASH, a reduction in GLP-1 receptor expression, PPARγ expression, and PPARα activity was observed. Exenatide (a GLP-1 analogue) stimulation of hepatocytes in vitro increased GLP-1 receptor expression and enhanced PPARγ expression and PPARα activity, improving insulin sensitivity and reducing lipid levels in hepatocytes.[53] Liraglutide also improved metabolic parameters in mice by inhibiting ER stress and reducing hepatocyte apoptosis.[54,55] Additionally, GLP-1 analogues have been shown to reduce lipid accumulation in hepatocytes by enhancing autophagy. In HFD mice and in vitro human hepatocytes, exendin-4 and liraglutide stimulated autophagy protein expression by activating 5'AMP-activated protein kinase (AMPK) and beclin II. Electron microscopy revealed an increased presence of autophagosomes in hepatocytes, correlating with decreased fat vacuoles. *In vivo*, liraglutide improved liver weight and serum lipid profiles.[55,56]

AMPK activation following GLP-1 receptor stimulation in mice also reduced fibroblast growth factor 21 (FGF21) expression, a key factor in liver fibrosis. In T2DM patients treated with pioglitazone, adding exen-

din significantly lowered plasma FGF21 levels and intrahepatic fat (IHF), an effect not observed without a GLP-1 analogue.[57] AMPK phosphorylation is critical for insulin signaling, explaining the reduced insulin resistance seen with GLP-1 analogue use. Exendin-4, *in vitro*, increased AMPK phosphorylation, cAMP concentrations, and phosphorylation of key insulin signaling proteins, such as PDK-1, AKT, and PKC-ƒ, in human hepatocytes.[58] These experimental findings offer promising insights into the therapeutic potential of GLP-1 analogues like liraglutide for NAFLD/NASH. However, this mechanism remains less understood in humans. Some studies do not confirm the presence of GLP-1 receptors in the human liver, suggesting indirect mechanisms behind hepatic lipid reduction.[59,60]

Despite these discrepancies, clinical trials support liraglutide's efficacy in NAFLD/NASH. In one study, administering liraglutide 1.8 mg to obese NASH patients for 48 weeks resulted in a significantly higher rate of NASH resolution (39%) compared to the control group (2%), as shown by liver biopsy histopathology. Similarly, fibrosis progression was slower in the liraglutide group (9% versus 36%). While no significant changes in serum aminotransferases were observed, modeling indicated significant differences compared to placebo, along with reductions in markers of hepatocyte damage and fibrosis. Patients in the liraglutide group also experienced greater weight loss, HbA1c improvement, and enhanced physical scores in the SF36 questionnaire.[61] Eguchi et al. reported similar results in a study of 26 poorly controlled diabetic patients with elevated ALT levels. Liraglutide therapy (0.9 mg daily for 24 weeks) led to reductions in body weight, BMI, visceral fat area, ALT, AST, GGTP, and HbA1c ($p<0.01$). Liver biopsies in 10 patients after 96 weeks of treatment showed improved NASH activity scores, although the study's small sample size was a limitation.[62] A larger study involving 128 patients with T2DM and NAFLD found that liraglutide significantly reduced AST, ALT, and HOMA-IR levels, unlike insulin glargine and placebo.[49] In contrast, Matikainen et al. found that while liraglutide 1.8 mg for 16 weeks reduced IHF (31% versus 18%) in patients with well-controlled T2DM, it did not affect hepatic de novo lipogenesis or fat oxidation. However, liraglutide did improve postprandial triglyceride levels, VLDL, chylomicrons, glycemia, and apolipoprotein C-III (apoCIII) concentrations, key regulators of postprandial lipid metabolism.[63] Some studies, however, do not confirm liraglutide's benefits on liver parameters. Tang et al. found that in T2DM patients, liraglutide for 12 weeks did not significantly reduce IHF, liver volume, or total liver fat index despite significant reductions in body weight and BMI compared to placebo and insulin.[59] Table 1 summarizes the most important studies on the role of liraglutide in the course of NAFLD/NASH.

Table 1. The effect of GLP-1 treatment in patients and animals on hepatic lipid's metabolism*

Group	Intervention	Effects	Ref.
Patients with T2DM and NAFLD	Liraglutide treatment (1.8 mg per 24–26 weeks)	↓ Body mass ↓ IHF ↓ SAT ↓VAT	46,48, 49
Obese patients with NASH	Liraglutide treatment (0.9-1.8 mg per 24–48 weeks)	↓ Fibrosis progression ↓ NASH activity score	61,62
HFD mice with induced NASH	Liraglutide, exenatide administration	↑ Insulin sensitivity ↓ Lipid levels in hepatocytes	53,54, 55,56

* T2DM – type 2 diabetes mellitus, NAFLD – non-alcoholic fatty liver disease, NASH – non-alcoholic steatohepatitis, HFD – high-fat diet, IHF – intrahepatic fat, SAT – subcutaneous adipose tissue, VAT –visceral adipose tissue

There are notable differences among the aforementioned studies. One key distinction is the duration of liraglutide therapy. In studies where liraglutide was ineffective in reducing IHF and other liver parameters, treatment lasted only 12 weeks. Conversely, studies reporting significant improvements had much longer treatment durations, averaging 24–26 weeks. Additionally, greater reductions in IHF were observed in patients with obesity, poorly controlled diabetes, and concomitant NAFLD, suggesting that liraglutide's effectiveness may be stage-dependent and more pronounced in patients with advanced NAFLD/NASH or exacerbated comorbidities. However, the primary limitation of these studies is the small sample sizes, which constrain the ability to draw definitive conclusions. Despite this, the results offer a promising outlook for the use of liraglutide and other GLP-1 analogues in the treatment of NAFLD/NASH.[64] Figure 4 summarizes the mechanisms of action of liraglutide in NAFLD/NASH.

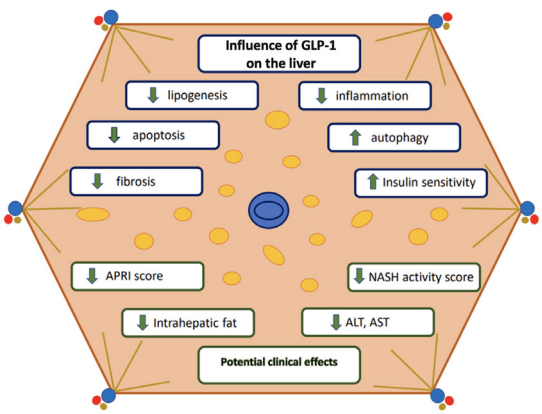

Fig. 4. Mechanisms and potential clinical effects of liraglutide in hepatocytes during NAFLD/NASH through various biological pathways

Cardiovascular disorders

Obesity contributes to CVD and cardiovascular mortality independently of other risk factors.[65] Although

liraglutide is primarily used to lower blood glucose levels, it has been found to offer potential cardiovascular benefits.[66] T2DM is strongly associated with increased cardiovascular risk, and reducing blood glucose levels is generally thought to be beneficial. However, liraglutide also appears to have direct effects on cardiovascular health.[66] One significant way liraglutide may reduce cardiovascular risk is through weight loss, which helps mitigate obesity-related conditions such as dyslipidemia, hypertension, and T2DM, all of which are major CVD risk factors. Liraglutide has been shown to lower blood pressure, improve endothelial function, and reduce inflammation, a key driver of CVD.[67-69] Endothelial dysfunction is a direct contributor to atherogenesis and its subsequent consequences.[70]

The most well-known evidence of liraglutide's cardiovascular effects comes from the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results; NCT01179048), initiated in 2010.[71] The LEADER trial demonstrated significant improvement in patient survival compared to placebo (Hazard ratio=0.78), with a lower rate of death from any cause in the liraglutide group (Hazard ratio=0.85). Although non-fatal stroke and myocardial infarction rates were lower in the liraglutide group, the results were not statistically significant.[71] Other cardiovascular effects observed in the trial included reductions in both systolic and diastolic blood pressure, an increase in heart rate by 3 beats per minute (CI, 2.5 to 3.4), and a lower incidence of composite renal and retinal microvascular events in the liraglutide group.[71]

The increase in heart rate may be explained by the presence of GLP-1R expression in all four heart chambers and the sinoatrial node.[72] Liraglutide may directly affect the cardiac conduction system, but studies in mice suggest that it exerts complex chronotropic effects, likely through inhibition of vagus nerve impulses, increasing sympathetic influence on the heart's autonomic system.[73] This is critical in liraglutide treatment because it could elevate heart workload, leading to potential complications, including death. A post-hoc analysis of the FIGHT trial revealed that liraglutide increased the risk of arrhythmias and other cardiovascular adverse events in patients with heart failure and reduced ejection fraction.[74]

Randomized controlled trials, such as the LIVE study, suggest that liraglutide significantly increases heart rate in patients with sinus rhythm, with a reported rise of 8 ±9 beats per minute compared to placebo. This effect was not observed in patients without sinus rhythm or after beta-blocker treatment.[25] While this study indicated that the heart rate increase did not elevate the risk of cardiovascular events compared to placebo, other research linked to the LIVE trial highlighted a higher risk of these events in the chronic heart failure population.[25-75] Understanding the chronotropic effects of liraglutide is crucial due to the increased risk of arrhythmias. However, it was shown that liraglutide does not cause clinically relevant increases in QTc interval, alleviating concerns about QTc prolongation.[76] Additional clinical trials have confirmed significant reductions in major adverse cardiovascular events and even all-cause mortality in patients with diabetes treated with liraglutide.[77,78]

Table 2. Liraglutide's effects on cardiovascular outcomes in various patient groups

Group	Intervention	Effects	Ref.
Patients with T2DM	Liraglutide treatment (1.2-1.8 mg/day for 24-36 months)	↓ Major cardiovascular events ↓ All-cause mortality	66, 71, 77
Patients with T2DM and high cardiovascular risk	Liraglutide treatment (1.8 mg/day for 36 months)	↓ Cardiovascular death, ↓ Hospitalizations for heart failure	71, 74
Obese patients with CVD risk	Liraglutide treatment (1.8 mg/day for 52 weeks)	↓ Blood pressure ↓ Inflammation markers ↑ Endothelial function	66, 68, 69
Patients with heart failure and reduced ejection fraction	Liraglutide treatment (1.8 mg/day for 48 weeks)	↑ Heart rate ↑ Risk of arrhytmias No significant change in QTc interval	73, 74, 76

* T2DM – type 2 diabetes mellitus, CVD – cardiovascular disease

Polycystic ovary syndrome

PCOS is the most common endocrine disorder in women of reproductive age, affecting up to 18% of women based on the Rotterdam criteria, though prevalence estimates range from 2.2% to 26%.[79] Women with PCOS have up to a threefold higher prevalence of obesity compared to women without the syndrome.[80] Up to 70% of women diagnosed with PCOS also present with dyslipidemia, hyperinsulinemia, and IR, all of which increase the risk of developing T2DM. Additionally, these women face an elevated risk of endometrial carcinoma.[81] Obesity exacerbates PCOS symptoms, creating a vicious cycle.[82]

The pathogenesis of PCOS is complex, with no single factor fully accounting for the syndrome. Ovarian theca cells synthesize androgens in response to luteinizing hormone (LH) stimulation. Studies show that ovarian theca cells in women with PCOS are more efficient at converting androgenic precursors to testosterone compared to healthy theca cells. Moreover, women with PCOS have lower levels of progestins, which normally slow the pulse frequency of gonadotropin-releasing hormone (GnRH). The resulting acceleration in GnRH pulse frequency leads to overproduction of androgens.[83] Hyperinsulinemia, a consequence of insulin resistance, is a key driver in the pathogenesis of PCOS and hyperandrogenism. Insulin works synergistically with LH to increase androgen synthesis and inhibits the production of sex-hormone binding globulin, increasing free testos-

terone levels.[83]

Insulin resistance not only exacerbates PCOS but also raises the risk of glucose intolerance, diabetes, lipid abnormalities, and macrovascular disease.[83] Women with PCOS face a CVD risk like those with metabolic syndrome, as both syndromes share insulin resistance as a central pathogenic factor.[83]

Obesity is present in up to 70% of women with PCOS, with visceral adiposity often indicated by increased waist circumference and waist-to-hip ratio.[83] Normalizing insulin levels in these women is associated with the resolution of many metabolic abnormalities.[83] Therefore, in addition to weight loss, reducing hyperandrogenism and alleviating all PCOS symptoms are essential for improving IR.[84] Lifestyle modifications, such as physical activity and a low-carb diet, are the first-line treatments but are often reported to have limited efficacy.[85] As a result, pharmacotherapy is frequently employed to enhance weight loss and better manage clinical symptoms.[86] For weight management, metformin combined with lifestyle changes is recommended for treating PCOS. Studies show that it improves menstrual cycles, glucose levels, and adiposity in women with PCOS. Metformin also alleviates IR and improves the lipid profile, although these effects are generally mild to moderate. However, there is increasing evidence that GLP-1 receptor agonists are more effective than metformin in treating obesity in women with PCOS.[87]

GLP-1 receptor agonists stimulate endogenous insulin secretion in response to meal ingestion and inhibit glucagon secretion. Additionally, they suppress appetite, leading to changes in eating patterns, a benefit not observed with other T2DM treatments.[88] A daily dose of 3 mg liraglutide combined with lifestyle modifications has been shown to reduce body weight by 5–10%. Studies also show that liraglutide is effective for weight reduction in women with PCOS, both as monotherapy and in combination with metformin.[89]

Furthermore, higher doses of liraglutide (3 mg) have shown better outcomes compared to lower doses combined with metformin.[90]

A 32-week trial demonstrated that participants taking 3 mg liraglutide lost at least 5% of their body weight. Additionally, the free androgen index significantly decreased in the liraglutide group, while it slightly increased in the placebo group.[83] In a study by Niafar et al., BMI decreased significantly by 1.65 kg/m² after 3 months of liraglutide treatment, although waist circumference and fasting insulin levels did not change significantly. However, serum testosterone decreased, suggesting that GLP-1 receptor agonists may affect overall obesity rather than abdominal obesity.[91] In another study by Jensterle Sever et al., using a 1.8 mg liraglutide dose, 19 obese women with PCOS were recruited, and 13 completed the study. After six months, weight was reduced by 3.0±4.2 kg.[88] A lower dose of liraglutide (1.2 mg) over 12 weeks also showed a reduction in weight (3.8±0.1 kg) and significant reductions in waist circumference and visceral adipose tissue mass.[91-93]

Some studies suggest that the weight loss response to GLP-1 agonists may vary among obese patients, with those without diabetes and with a higher BMI experiencing greater weight loss than patients with diabetes and lower BMI. Genetic variability in GLP-1 receptor function, such as single nucleotide polymorphisms, may influence the efficacy of GLP-1 receptor agonists.[94] In a study by Jensterle et al., 57 women with PCOS and obesity were treated with 1.2 mg liraglutide for 12 weeks. On average, participants lost 3.96±3.24 kg, BMI decreased by 1.44±1.22 kg/m², waist circumference reduced by 3.31±4.13 cm, and VAT decreased by 7.10±18.76 cm².[94] Notably, 35% of these women showed a stronger response, losing around 5% of their weight, while others lost less (Table 3).

Table 3. Comparison of results of different studies concerning liraglutide in PCOS and obesity treatment

Study	PreT weight (kg)	PostT weight (kg)	PreT BMI (kg/m²)	PostT BMI (kg/m²)	PretT WC (cm)	PostT WC (cm)	PreT WHR	PostT WHR	Dose (mg)
Elkind-Hirsch et al.[84]	111 ±2.8	104.7 ±2.9	41.6 ±1.1	39.1 ±1.1	111 ±2.2	101 ±2	0.85 ±0.01	0.81 ±0.01	3
Kahal et. al.[95]	102.1	99.1	37.9	36.9	112	110.9	–	–	1.8
Jensterle Sever et al.[93]	108 ±15.1	105 ±13.8	39.3 ±4.2	37.9 ±4.0	124.9 ±9.9	121.7 ±9.6	–	–	1.2
Jensterle et al.[94]	102.1	96	38.7	35.8	118	111	–	–	1.2

* PreT – preatreatment, PostT – posttreatment, WC – waist circumference, WHR – waist hip ratio

Treatment of obesity in patients with mental disorders

Compared to the general population, patients with mental disorders are two to three times more likely to be overweight or obese, which is associated with increased morbidity and higher mortality due to CVD.[96] Antipsychotic medications like clozapine and olanzapine contribute to weight gain, elevated serum glucose, cholesterol, and triglycerides, primarily through mechanisms involving increased appetite and delayed satiety signaling. For individuals with severe mental illnesses, such as schizophrenia, antipsychotic treatment is often lifelong, as discontinuation increases the risk of psychotic relapse.[97] However, implementing lifestyle interventions is challenging in this population, and even short-term interventions tend to have a minimal impact on reducing BMI. Long-term efficacy of lifestyle changes is also limited, highlighting the need for additional pharmacological support. Currently, orlistat is the only licensed drug for managing obesity in these patients, but its long-term use is limited due to high discontinuation rates and limited clinical value.[96,97]

Using the GLP-1 receptor agonists was, however,

limited in this group of patients, due to concerns highlighted by Icelandic medicines agency following the reports of suicidal thoughts and self-injury.[98] The review of available data made by European Medicines Agency's (EMA) safety committee, the Pharmacovigilance Risk Assessment Committee published on 12th of April 2024, has concluded that the gathered evidence does not support a casual association between the GLP-1 receptor agonists, including liraglutide, and suicidal and self-injurious actions or thoughts.[99] This review incorporates the recent study made by Wang et al. published in Nature Medicine on 5th of January 2024 on "Association of semaglutide with risk of suicidal ideation in a real-world cohort" which found the risk of incident and recurrent suicidal ideation to be lower in comparison to the group of non-GLP1R agonist anti-obesity medications. Those results were consistent across sex, age and ethnicity stratification and replicated in both the group of overweight or obese patients and ones with T2DM.[100]

Thus, the GLP-1 receptor agonists still offer a promising alternative to achieve clinically significant weight loss in this population, as will be discussed in the following paragraphs.

In a qualitative sub-study by Barnard-Kelly et al., interviews with patients who had undergone liraglutide treatment at a 3 mg dose reported improved quality of life and minimal side effects.[96] The randomized clinical trial by Larsen et al. demonstrated significant weight loss with liraglutide (1.8 mg) compared to placebo after 16 weeks, with a mean weight loss difference of -5.3 kg (95% CI, -7.0 to -3.7 kg).[97] This trial included 103 overweight or obese patients with prediabetes and schizophrenia spectrum disorders treated with clozapine or olanzapine. Compared to placebo, liraglutide significantly reduced waist circumference (-4.1 cm; 95% CI, -6.0 to -2.3 cm), BMI (-1.8; 95% CI, -2.4 to -1.3), systolic blood pressure (-4.9 mmHg; 95% CI, -9.5 to -0.3 mmHg), total cholesterol (-19.3 mg/dL; 95% CI, -30.9 to -7.7 mg/dL), and LDL cholesterol (-15.4 mg/dL; 95% CI, -23.2 to -7.7 mg/dL). Liraglutide also reduced visceral fat and total body fat, as evaluated by DXA scans.[97] In a study conducted by Whicher et al., which was a pilot-randomized, double-blind, placebo-controlled trial, 47 participants were randomized to intervention with liraglutide 3 mg and placebo.[101] Patients were overweight or obese with at least one weight-related consequence such as dysglycaemia (prediabetes or T2DM), hypertension, dyslipidemia, or OSA. Eligible participants were aged from 18 to 75 years and had diagnoses of schizophrenia, schizoaffective disorder, or first-episode psychosis and had been prescribed antipsychotic medication for at least 1 month. 79% of randomized patients completed the trial. Intention-to-treat analysis was performed on 15 intervention participants and 19 control participants. Participants in the liraglutide group lost a mean of 5.7±7.9 kg (4.5%; 95% CI -8.3% to -0.8%) after six months compared with no significant (0.3±5.7 kg [0.0%; 95% CI -2.5% to 3.1%]) weight change in the placebo group (treatment difference -6.0 kg, p=0.015). BMI, waist circumference, and HbA1c were reduced in the intervention group. Furthermore, 53% of those who completed the trial on the trial medication in the liraglutide treatment group lost 5% or more of their body weight in comparison to 10% of the placebo participants (p=007).[101] In the systematic review of licensed weight-loss medications in treating antipsychotic-induced weight gain and obesity in schizophrenia and psychosis carried out by Lee et al. authors reviewed three RCTs (two liraglutide, one naltrexone-bupropion), one unpublished open-label trial (naltrexone-bupropion), and seven observational studies (five liraglutide, one semaglutide, one multiple WLMs).[102] In regard to liraglutide, a meta-analysis was conducted for RCTs previously mentioned, carried out by Larsen et al., and by Whicher et al., giving in a total of 131 participants. Findings were statistically significant ($p<0.05$) for improvement in weight, BMI, waist circumference, glycated in (HbA1c), total cholesterol, and LDL favoring the liraglutide intervention over placebo. However, the difference in systolic blood pressure was not found to be statistically significant. These findings were supported by the observational studies reviewed by the authors, which found liraglutide intervention beneficial and significant.[102]

There is currently limited data available on this subject, highlighting the need for additional studies. Table 4 summarizes the key findings of the studies discussed above while indicating the type of the study. Authors believe that, priority should be given to conducting more randomized clinical trials, as only two on liraglutide treatment have been published thus far. Furthermore, despite the current stance of the EMA, reports of suicidal thoughts or self-injury suggest the necessity for further research into the potential risks of these outcomes in patients treated particularly with liraglutide.

Table 4. Summary of key findings from studies on liraglutide's effects in patients with psychotic disorders, overweight or obese

Group	Intervention	Key outcomes	Ref.
Overweight/obese patients with schizophrenia, schizoaffective disorders or first episode psychosis	Liraglutide 3 mg vs placebo for 6 months	Improved quality of life, minimal side effects, weight loss reductions in BMI, waist circumference, HbA1c	96, 101
Overweight/obese patients with prediabetes and schizophrenia spectrum disorders on clozapine or olanzapine	Liraglutide 1.8 mg vs placebo for 16 weeks	Significant weight loss, reduced waist circumference and BMI, systolic blood pressure, total cholesterol, LDL, visceral fat, and total body fat	97
Review of participants with a diagnosis of a psychotic disorder from RCTs, and observational studies	Liraglutide, semaglutide, naltrexone-bupropion	Significant improvements in weight, BMI, waist circumference, HbA1c, total cholesterol, LDL, no significant effect on systolic blood pressure	102

Future directions

Obesity-related diseases are currently one of the main denominations of medicine. The action of liraglutide and other GLP-1 analogues described above have a positive effect on the course of diseases. In NAFLD/NASH, liraglutide has a protective effect on hepatocytes, reduces inflammation, fibrosis, apoptosis and lipid deposition. In patients with NAFLD and T2DM used for at least 24 weeks, it led to a significant reduction in IHF, liver parameters AST and ALT. It resulted in a significant weight loss (more than 5%) which is the most important indicator of a slower progression of NAFLD. Liraglutide has a significant impact on the cardiovascular system. The use of liraglutide in obese patients was associated with limitation in the cardiovascular mortality rate in clinical trials, though it could be dangerous in patients with developed chronic heart failure most presumably due to increase heart rate. Treatment with liraglutide can be beneficial for patients with severe mental disorders, as it shows effectiveness in reducing the mass gain on the psychiatric drug course, and improvement in the level of factors connected to CVD, without the necessity of using other interventions. There has been a growing interest in GLP-1 agonists as a potential treatment for women suffering from PCOS and obesity. As stated above, studies have shown that use of liraglutide helps with weight loss, as well as it improves hyperandrogenism, insulin resistance and hyperinsulinemia.

An important aspect is a brief comparison of the action and efficacy of liraglutide with semaglutide (GLP-1 analogue) and tirzepatide (GLP-1 and GIP agonist). They are registered for once-weekly subcutaneous administration, which is much more convenient than daily subcutaneous injections of liraglutide. In addition, recent meta-analyses indicate greater efficacy of semaglutide and tirzepatide in reducing body weight. The mean weight loss with tirzepatide 15 mg/week was on average 5.1% greater than with semaglutide 2.4 mg/week and 13% greater than with liraglutide 3 mg/day.[103] The latest randomized control trials from the last 2–3 years confirm that both tirzepatide and semaglutide effectively control glycemia, show beneficial effects on the cardiovascular system, reduced arterial hypertension, lower the level of total cholesterol, reduce the degree of fatty liver disease and fibrosis in the course of NAFLD/NASH.[104,105,106] Semaglutide and tirzepatide have a similar safety profile, the main side effects include gastrointestinal symptoms such as nausea and diarrhea, similar to liraglutide. Further studies are needed to determine which drug is the best for overweight patients with specific obesity-related diseases.

Conclusion

The findings of our study imply the possibility of developing the new indications for GLP-1 analog intervention, particularly for states associated with obesity. That could offer improvement in quality and length of the patients' life.

The obtain results may be applied to create combination therapies for treating certain conditions.

For instance, in the treatment of PCOS, standard pharmacotherapy involves the use of hormonal contraception, metformin, antiandrogenic agents, and infertility treatment. The use of GLP-1 analogs could enhance the principal effects of such drugs. Other applications of liraglutide embrace mental health disorders, such as depression, in which obesity might be both an etiological factor and a consequence. GLP-1 analogs are also likely to reduce the noxious metabolic effects of antipsychotic treatment, though the interaction of liraglutide with such treatments is not yet fully understood.

Future studies, especially about the efficacy of liraglutide in these conditions, should be directed toward meta-analyses or network meta-analyses.

Intriguingly, use of GLP-1 analogs with other antidiabetic drugs, such as SGLT2 inhibitors or DPP-4 inhibitors, represents a promising direction in the pharmacotherapy of obesity. Dual or triple antiobese therapy utilizing these agents could enhance the synergistic effects of treatment ensuring significant results.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

Ethics approval

The study does not involve any human or animal subjects.

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