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Evaluation of the Safety and Efficacy of Semaglutide

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Abstract. Obesity and the type 2 diabetes (T2D) epidemic are now becoming one of the most severe issues of the 21st century in terms of the global population health. Poor compliance, adverse reactions, and inconsistent effectiveness are the limitations of traditional treatments that include lifestyle interventions, medications, and surgery. GLP-1 receptor agonist (GLP-1 RA) semaglutide is a hot topic in recent studies and clinical practice, with broad indications, long half-life, and good safety profile. A large number of clinical trials have shown that semaglutide has dual therapeutic effects of glycemic control and weight loss, and that it enhances insulin secretion, inhibits glucagon, retards gastric emptying, and reduces appetite by central mechanisms. Moreover, it has shown possible clinical advantages in cardiovascular protection and in enhancing renal functioning. Nevertheless, semaglutide is linked to adverse reactions, the majority of which are gastrointestinal symptoms, including nausea, vomiting, and diarrhea. It can also lead to gallbladder issues, elevated heart rate and predisposed hypoglycemia in case of using it with insulin or sulfonylureas. Long-term use also warrants vigilance for rare but serious adverse events such as pancreatitis, retinopathy, and renal damage. There are patients who regain weight following withdrawal of treatment. Future research ought to investigate further its GLP-1R-independent actions, including the regulation of hepatic lipid metabolism, neuroprotection, and inhibition of myocardial fibrosis, and maximize the dosage, minimize adverse reactions, and attain individualized precision therapy, which will increase its value in clinical use.

Keywords: Semaglutide, type 2 diabetes, glucagon-like peptide-1.

1. Introduction

The global prevalence of obesity and diabetes has became one of the most severe piblic health challenges of the 21st century, with the obesity rate demonstrating a potential increase from 36% in2000,to 50% in 2030 as predicted, covering nearly 3 billion people [1].In2024,the number of adult diabetes patients aged20 to79 worldwide will reach 589million which is expected to rise to853 million by 2050 [2].Obesity is a primary risk factor for type 2 diabetes (T2D), and approximately 55% of premature deaths from T2D are associated with obesity and patients with T2D are at a high risk of cardiovascular diseases such as coronary heart disease, stroke, and peripheral vascular diseases ,seriously endangering the patients' lives [2,3]. Traditional modalities of T2D and obesity encompass lifestyle interventions pharmacological therapies, and surgical procedures. However,

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conventional treatment regimens are fraught with challenges such as difficulty in long - term adherence, gastrointestinal reactions, postoperative complications, or unstable weight - loss outcomes [4]. The considerable incidence and prevalence of obesity and type 2 diabetes mellitus (T2DM), together with their associated comorbidities, complications, and the inherent limitations of current therapeutic modalities, underscore an urgent need for innovative treatment strategies. The clinical use and research of semaglutide thus provide a new potential way which could help correct this problem. As a glucagon-like peptide-1 (GLP -1) receptor agonist (RA), semaglutide has become a subject of particular attention in modern clinical studies due to its wide range of therapeutic indications, half-life, and its good safety profile. Semaglutide had important effects to reduce blood glucose levels and promote weight loss in the SUSTAIN series of randomized controlled trials.Moreover, the cardiovascular protective benefits of semaglutide have also been confirmed in studies such as LEADER, SUSTAIN-6 and PIONEER-6 [5]. While semaglutide demonstrates favorable efficacy in managing T2D and obesity, it concurrently presents adverse effects that have to be taken into consideration.

The common adverse reactions in clinical applications of semaglutide are primarily concentrated in the gastrointestinal system, mainly manifested as nausea, diarrhea, vomiting, etc. Over half of the patients showed improvement after discontinuing the drug and receiving symptomatic treatment [6]. It also significantly increases the risks of pancreatitis, gastroparesis and intestinal obstruction [7]. The issue of mass loss has also been observed in recent studies [8]. This article will systematically evaluate the safety and efficacy of semaglutide in treating obesity and T2D by reviewing and analyzing previous literature. This study is conducive to optimizing clinical decisions, enhancing patient medication safety; providing important reference data for drug surveillance and regulatory agencies; promoting the development of individualized treatment; laying the foundation for future related research.

2. Target and mechanism of action

2.1. GLP-1

GLP-1 is a 31-amino-acid peptide hormone secreted by intestinal L cells, derived from the post-translational processing of the proglucagon gene. It exists in two bioactive forms: GLP-1(7–37) and GLP-1(7–36)-amide.Its secretion is regulated by nutrient intake, particularly through activation by glucose and lipids, and modulates gastrointestinal motility via the ileal brake mechanismGLP-1 regulates blood glucose levels by stimulating insulin secretion, suppressing glucagon release, and delaying gastric emptying [9].

2.2. Structure

Semaglutide is a GLP-1 RA exhibiting 94% structural homology with native GLP-1. This peptide compound consists of 31 amino acids linked via peptide bonds with an attached fatty acid side chain. Through molecular modifications from the native GLP-1 structure: 1) The alanine at position 8 has been substituted with α-aminoisobutyric acid to enhance resistance to dipeptidyl peptidase-4 (DPP-4) degradation; 2) A C-18 fatty diacid side chain with glutamic acid as spacer is conjugated to the lysine at position 26, thereby increasing albumin binding affinity, reducing renal clearance, and prolonging plasma half-life; 3) The lysine at position 34 is replaced by arginine to prevent misalignment of the C-18 fatty acid chain and improve side chain stability [10].

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2.3. Impact on metabolic processes

GLP-1 RA exert glycemic control and weight reduction effects by mimicking the physiological actions of GLP-1.

The GLP-1R, a G protein-coupled receptor (GPCR), is predominantly distributed in tissues including pancreatic β-cells, the gastrointestinal tract, central nervous system, and cardiovascular system. GLP-1R agonists bind to GLP-1Rs and subsequently activate intracellular signaling pathways, thereby modulating multiple physiological functions. Upon activation of the GLP-1R, adenylate cyclase (AC) activity is stimulated, thereby elevating intracellular cyclic adenosine monophosphate (cAMP) concentrations. cAMP subsequently activates protein kinase A (PKA), which phosphorylates multiple target proteins and participates in the regulation of insulin secretion.In pancreatic β-cells, the activation of PKA facilitates the closure of potassium channels, induces membrane depolarization, and enhances calcium influx, ultimately promoting insulin secretion. cAMP can also exert its effects through the exchange protein directly activated by cAMP (Epac)-dependent pathway, wherein Epac plays a crucial role in modulating insulin secretion and cellular survival. Furthermore, GLP-1 RAs can also inhibit the activity of phosphodiesterase (PDE), thereby reducing cAMP degradation and consequently enhancing the cAMP signaling pathway [11]. GLP-1 RAs significantly enhance insulin secretion from pancreatic β-cells through activation of the cAMP signaling pathway, demonstrating glucose concentration-dependent characteristics. This pharmacological property ensures that their insulinotropic effect becomes clinically relevant only during elevated blood glucose levels, thereby substantially mitigating the risk of iatrogenic hypoglycemia. Furthermore, these agonists exhibit the ability to suppress glucagon secretion from pancreatic α-cells, consequently reducing hepatic glucose output and contributing to additional glycemic control [12]. GLP-1 RAs regulate blood glucose levels by activating GLP-1R through mechanisms including insulin secretion stimulation, glucagon level reduction, gastric emptying delay, satiety enhancement, and appetite suppression.

3. Efficacy

3.1. Application status

At present, the mechanism of action of semaglutide is widely recognized as a cornerstone of metabolic therapy, exhibiting a trend toward diversification and integration. As elucidated by Liu & Luo, its therapeutic applications have expanded from T2D and obesity to a broader disease spectrum [13]. The core mechanism lies in the GLP-1 RA-triggered cascade effects, which not only modulate pancreatic endocrine function but also engage multiple organ systems (e.g., brain, heart, and gastrointestinal tract), enabling the therapy to address diverse pathological conditions.

In T2D management, the mechanism ensures improved glycemic homeostasis through a glucose concentration-dependent approach, mitigating risks associated with conventional therapies. Concurrently, its weight management mechanism, mediated by appetite suppression and delayed gastric emptying, constitutes a distinct advantage in obesity treatment. This dual-mechanism integration represents a pivotal innovation, distinguishing semaglutide from earlier GLP-1 analogs (e.g., liraglutide), as its optimized half-life and enhanced bioavailability (particularly in oral formulations) reinforce sustained and consistent therapeutic effects.

Another hallmark of its current status is the therapy's cross-disease applicability. As outlined by Liu & Luo, deeper insights into the mechanism reveal GLP-1 pathway influences in neuroprotection and cardiovascular systems: GLP-1R activation in brain regions (e.g., hypothalamus and

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hippocampus) may correlate with neuronal survival and cognitive improvement, offering potential therapeutic avenues for neurodegenerative diseases (e.g., Alzheimer's disease) [13]. In cardiovascular contexts, the mechanism indirectly reduces atherosclerosis and heart failure risks by ameliorating metabolic risk factors (e.g., hyperglycemia and obesity-related inflammation), showcasing its multidimensional benefits [13].

This integration reflects the evolution of modern therapeutics—no longer confined to single diseases but rather constructing composite intervention strategies based on shared pathological mechanisms (e.g., insulin resistance and inflammation). For instance, semaglutide's transition from injectable to oral formulations (e.g., Rybelsus®) addresses patient adherence barriers, further optimizing real-world application. Moreover, current mechanistic explorations extend to personalized medicine: studies are evaluating pharmacokinetics in specific patient subgroups (e.g., renal impairment) to refine dosing regimens, ensuring targeted efficacy and safety.

3.2. Clinical applications

In the treatment of obesity, semaglutide combined with lifestyle interventions demonstrates significant weight reduction efficacy. A double-blind, randomized controlled experiment involving 1,961 patients whose BMI is greater than or equal to 30 showed that a weekly 2.4 mg dose of semaglutide achieved an average weight loss of 14.9% ($p<0.001$ vs. placebo). Notably, 86.4% of participants achieved ≥5% weight reduction, compared to only 31.5% in the control group. Furthermore, 69.1% attained ≥10% weight loss versus 12.0% in controls [14].

For T2D patients, semaglutide exhibits substantial weight-loss effects. Clinical trials report mean reductions of 4.3 kg and 6.3 kg with 0.5 mg and 1.0 mg doses respectively, both statistically superior to placebo ($p<0.001$) [2]. This weight reduction positively correlates with improved HbA1c levels [15,16].

Regarding glycemic control, semaglutide significantly enhances diabetes management outcomes. The 1.0 mg dose cohort achieved 79.2% HbA1c <7.0% attainment versus 34.4% with placebo [13], with mean HbA1c reduction of 1.5% [15]. Its mechanisms include glucose-dependent insulin secretion (reducing hypoglycemia risk) [13], glucagon suppression (decreasing hepatic glucose output) [4], and delayed gastric emptying (mitigating postprandial fluctuations) [8].

However, weight rebound may occur post-treatment discontinuation. Meta-analyses indicate approximately two-thirds of lost weight is regained within 20 weeks after cessation, necessitating sustained therapy for maintained efficacy [8]. Patients continuing treatment through 68 weeks preserved ≥10% weight loss [8], with rebound primarily attributed to dysregulated appetite control mechanisms [13,16].

Additionally, semaglutide demonstrates cardiovascular benefits, showing 26% reduced major adverse cardiovascular event risk (HR=0.74, 95%CI 0.58–0.95) [13] through improvements in lipid profiles, blood pressure, and endothelial function [17]. Each 5 kg weight reduction associates with 4.2 mmHg systolic BP decrease [17] and 21% reduction in urinary albumin-to-creatinine ratio, indicating renal protective effects [16].

4. Safety

Multiple randomized controlled trials (RCTs) and systematic reviews indicate that this medication shows association with a spectrum of adverse effects during treatment, ranging from common gastrointestinal symptoms to specific risk events.

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According to a multinational RCT involving overweight/obese patients with T2D mellitus (T2DM), the CagriSema (semaglutide-containing compound) demonstrated an overall adverse event incidence of 74.1%, higher than the placebo group's 69.8%, while the rates of serious adverse events were 2.8% and 1.9%, respectively [18]. Gastrointestinal reactions were the most frequently reported adverse effects, with nausea (17.2%), vomiting (8.8%), diarrhea (12.4%), and constipation (6.9%) occurring significantly more often in the treatment group compared to the placebo group (all <3%). Notably, nausea exhibited dose-dependency and was predominantly observed during the initial treatment phase [19].

Beyond common gastrointestinal symptoms, semaglutide carries specific risk warnings. Studies reveal a significantly higher incidence of gallbladder-related disorders (cholelithiasis and cholecystitis included) in the treatment group (17.3%) versus placebo (5.1%) [18,19]. Injection-site reactions occurred in approximately 4.1% of cases [19].

It has been confirmed that semaglutide monotherapy in T2DM patients showed an extremely low risk of hypoglycemia. However, when combined with insulin or sulfonylureas, the risk of severe hypoglycemia increased threefold, warranting clinical vigilance [20].

In terms of cardiovascular safety, semaglutide demonstrated a reduced hazard ratio for major adverse cardiovascular events, though it was accompanied by a dose-dependent mean increase in heart rate of ≥4 beats per minute [20].

Special caution is advised when administering semaglutide to specific populations. Among elderly patients (>60 years), the reported incidence of sarcopenia reached 25%, markedly higher than in younger individuals [18]. In Prader-Willi syndrome patients, vomiting occurred in up to 35% of cases, substantially exceeding rates in the general T2DM population [22].

Long-term safety data (≥12 months) for semaglutide indicate pancreatitis, retinopathy, and acute kidney injury incidences of 0.3%, 1.7%, and 0.9%, respectively, underscoring the need for monitoring relevant organ functions during prolonged therapy [21].

5. New target points

Recent studies have demonstrated that semaglutide exerts its effects not only through classical GLP-1R-mediated pathways but also via multiple non-GLP-1R-dependent mechanisms, providing novel mechanistic insights into its multi-organ protective effects. In hepatic tissues, semaglutide significantly reduces lipid deposition and ameliorates pathological manifestations of non-alcoholic steatohepatitis (NASH) by acting on unidentified non-GLP-1R receptors in hepatocytes, thereby offering new perspectives for metabolic liver disease treatment [23,24]. Within the central nervous system, semaglutide improves cerebral insulin resistance through non-canonical receptor pathways and may potentially delay the progression of neurodegenerative disorders for instance Alzheimer's disease [24]. Moreover, this pharmacologic agent exhibits direct cardioprotective properties: by targeting yet-to-be-identified myocardial receptors independent of its glucose-lowering effects, it mitigates oxidative stress and fibrotic processes, thereby expanding its therapeutic potential in cardiovascular diseases. The identification of these receptor-independent pathways not only deepens our understanding of semaglutide's pleiotropic actions but also establishes a foundation for developing novel targeted therapeutic strategies.

6. Conclusion

This article systematically reviews the mechanism of action, clinical efficacy, safety, and novel targets of semaglutide. As a GLP-1 RA, semaglutide mimics the physiological effects of endogenous

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GLP-1, significantly improving insulin secretion, inhibiting glucagon, and delaying gastric emptying. It also suppresses appetite through centrally acting mechanisms, thereby achieving dual therapeutic benefits for glycemic control and weight management. There are multiple clinical trials that have consistently reported semaglutide to induce a significant change in the level of HbA1c and weight loss in patients diagnosed with type 2 diabetes. The agent also has better weight-loss effects in the treatment of obesity, with extra cardioprotective advantages and enhances renal activity. However, recent work points to a number of weaknesses and negative outcomes. The most common side effects are mainly gastrointestinal but include also gallbladder issues, tachycardia, and an increased risk of hypoglycaemia- a factor that is especially relevant in cases of semaglutide co-administration with insulin or sulfonylureas. Some of the complications which have seldom occurred but have serious consequences include pancreatitis, retinopathy, and renal injury, which are raised with long-term use. In addition, weight gain after withdrawal is experienced by some people, therefore, the need to use the maintenance therapy to maintain therapeutic benefits.

Future studies will also shed more light upon the GLP -1R -independent mechanisms of semaglutide, such as its possible effects on the hepatic lipid metabolism, mediation of neuroprotection, and inhibition of myocardial fibrosis. These studies would make it applicable in more metabolic liver diseases, neurodegenerative and cardiovascular diseases. Also, dosing regimens optisation, reduction of adverse reactions, and the search of individual, precision-based treatment options are significant areas of improvement to the clinical utility of semaglutide.

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