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Long-term Safety Profile of Semaglutide in the Management of Type 2 Diabetes and Obesity

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Abstract:

Diabetes and obesity are major global health concerns, often leading to serious complications such as heart disease and premature death. Recent progress in treatment has underscored the effectiveness of GLP-1 receptor agonists, like semaglutide, in improving blood sugar levels and aiding weight loss. Semaglutide has demonstrated significant benefits in managing both T2DM and obesity. However, its long-term safety remains largely unexamined. This study aimed to assess the safety profile of semaglutide, focusing on common side effects like gastrointestinal issues, gallbladder disease, and the potential risk of pancreatitis. It also examined how factors such as varying dosages, methods of administration, and patient characteristics influenced these side effects. The results showed that semaglutide was generally well tolerated, though gastrointestinal side effects were dose-related, and rare complications like pancreatitis require further investigation. While the study provides valuable insights for future research, more long-term data is necessary, particularly for patients with multiple health conditions. Future studies should prioritize these groups and investigate the mechanisms behind rare but serious side effects.

Keywords: Semaglutide; Type 2 diabetes; obesity.

1. Introduction

Around 37 million Americans are living with diabetes, which leads to more than twice the medical costs and a 60% higher risk of early death. Diabetes also raises the chances of developing other conditions, such as heart disease, stroke, and kidney problems. Obesity, especially excess fat around the abdomen, greatly increases the risk of type 2 diabetes (T2DM), although losing weight can help lower this risk. Recently, new medications have been approved that not only improve blood sugar control and support weight loss but also offer cardiovascular and kidney benefits. The American Diabetes Association now recommends treatments like glucagon-like peptide-1 receptor agonists (GLP-1RAs) and SGLT2 inhibitors for patients at higher risk of heart disease, heart fail-

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ure, or chronic kidney disease[1].

Semaglutide, a GLP-1RA, has garnered significant attention in recent years, especially for its effectiveness in treating T2DM and obesity. As a GLP-1RA, semaglutide is highly effective at improving blood sugar control and has been approved worldwide in its injectable form. A major advancement is the development of an oral version of semaglutide (Rybelsus®), the first oral GLP-1RA, which has been approved in both Europe and the USA [2]. Among the GLP-1RAs currently used for diabetes treatment, semaglutide at a 1.0 mg dose has shown the most pronounced weight loss effect in patients with T2DM [3].

GLP-1, produced by enteroendocrine cells in the gut, plays a key role in regulating blood sugar during meals by boosting insulin secretion and reducing glucagon release. It also slows gastric emptying and reduces food intake, helping to optimize nutrient absorption while limiting weight gain. These combined effects make GLP-1RAs particularly effective for managing T2DM and obesity [4].

Since the approval of semaglutide, numerous clinical trials and real-world studies have evaluated its safety and efficacy in patients with T2DM and obesity. Studies generally show that semaglutide significantly lowers blood sugar levels, promotes weight loss, and reduces cardiovascular risk. For example, one trial showed that in overweight or obese adults, weekly injections of a higher dose of semaglutide led to significantly greater weight loss than a lower dose or placebo group. More than two-thirds of patients achieved significant weight loss after receiving this high-dose treatment. Additionally, many patients who received the high dose achieved target blood glucose levels. This dose also improved cardiometabolic health markers, with a safety profile consistent with other similar drugs [3].

Additionally, another series of clinical trials showed that weekly injections of semaglutide (trade name Ozempic®) can effectively lower blood glucose levels in patients with T2DM. Results from these trials showed that treatment with semaglutide led to statistically significant reductions in blood glucose. In conclusion, semaglutide showed good efficacy and safety in the treatment of T2DM and obesity [5].

As semaglutide is studied in depth, more and more patients are beginning to benefit from this treatment. In addition to lowering blood sugar and reducing weight, semaglutide may also improve patients‘ quality of life. For example, many patients report that their mobility and overall health have improved as their weight has decreased. This not only has a positive impact on personal health, but may also reduce medical expenses caused by chronic diseases. Future research will continue to explore the long-term effects of semaglutide and its potential application in other metabolic diseases, providing patients with more comprehensive treatment options.

However, as the use of semaglutide has expanded, certain safety concerns have emerged. Common side effects include gastrointestinal issues, such as nausea, vomiting, and diarrhea, along with gallbladder disease and, in rare cases, acute pancreatitis. Additionally, some studies suggest an increased risk of pancreatitis with GLP-1-based therapies. These findings also raise concerns about the potential long-term effects of these medications, including the possible risk of promoting pancreatic cancer [5,6].

While semaglutide‘s effectiveness in treating T2DM and obesity is well-established, a thorough evaluation of its long-term safety remains essential. As treatment durations increase and a wider range of patients begin using the medication, new safety concerns may emerge. Therefore, a systematic assessment of semaglutide’s safety profile, particularly across diverse patient populations, is crucial for guiding clinical practice and optimizing therapeutic strategies.

This study aims to evaluate the safety of semaglutide in the management of T2DM and obesity. The specific objectives include: 1) reviewing existing literature to analyse the common adverse effects of semaglutide and their underlying mechanisms; 2) exploring how different doses, administration methods, and treatment durations impact safety; 3) assessing the safety of semaglutide in specific populations (such as the elderly and those with cardiovascular conditions); and 4) summarizing long-term safety data and offering recommendations for future research. By addressing these goals, this study aims to provide clinicians with more comprehensive safety information, enabling them to make better-informed decisions when using semaglutide to treat T2DM and obesity.

2. Mechanism of Action

2.1 GLP-1: Biological Functions and Related Pathways

2.1.1 Biological functions of GLP-1:

GLP-1 is a hormone secreted by intestinal L cells, released rapidly after eating, and may be regulated by the nervous system. This hormone is mainly produced by cells in the colon and terminal ileum. GLP-1 can promote the secretion of insulin by pancreatic β cells while inhibiting the release of glucagon by α cells. In addition, it can suppress appetite and delay gastric emptying, thereby increasing satiety and reducing food intake. GLP-1 plays an important role in regulating blood sugar and body weight. However, its direct application is limited because it exists in the body for a very short time (only 1 to 2 minutes).

In order to prolong the duration of action, scientists have developed a variety of GLP-1 analogs, which have been widely used to treat T2DM. These analogs are usually used by subcutaneous injection and may cause gastrointestinal adverse reactions such as nausea, vomiting and diarrhea, but the symptoms usually decrease with longer use [7,8].

With the successful application of GLP-1 analogs in the treatment of obesity, researchers are constantly exploring its potential for other health problems. Recent studies have shown that GLP-1 analogs may help improve heart health, liver problems, and endocrine disorders in women. In addition, in order to reduce the inconvenience of frequent injections, scientists are also developing GLP-1 drugs that can be taken orally. These new advances not only increase the scope of application of GLP-1 drugs, but also provide more options and possibilities for the management of chronic diseases. In the future, GLP-1 drugs are expected to become an important treatment for a variety of health problems [8].

2.1.2 Pathways Related to T2DM:

GLP-1 primarily enhances insulin secretion at elevated glucose concentrations, such as those observed after a meal (>5 mM), which makes it less likely to cause hypoglycemia compared to other glucose-lowering agents. The detailed mechanisms underlying this action remain partially understood, but it is well-documented that GLP-1 promotes mitochondrial ATP production in a glucose-dependent manner, facilitating the opening of voltage-dependent Ca^{2+} channels. Additionally, GLP-1 increases intracellular cAMP levels, which then mobilizes intracellular Ca^{2+} stores through activation of the cAMP-binding protein Epac and protein kinase A (PKA) pathways [9].

Furthermore, GLP-1 supports insulin biosynthesis by promoting insulin gene expression through the upregulation of Pdx1. Other transcription factors, including NFAT and CREB, are also involved in this regulatory process. By increasing insulin synthesis and storage, GLP-1 ensures a sustained capacity for insulin release, which helps maintain optimal glucose homeostasis and reduce the risk of complications in T2DM [9].

2.1.3 Regulation of blood glucose levels and its clinical relevance in T2DM patients

GLP-1 and GIP are incretin hormones that play a crucial role in stimulating insulin secretion following an oral glucose load, a process often impaired in individuals with T2DM. Both hormones are rapidly inactivated by DPP-4. Pharmacologically elevated levels of GLP-1 can help restore insulin secretion, slow gastric emptying, and reduce glucagon production from pancreatic α-cells when blood glucose levels are high. Additionally, GLP-1RAs reduce pancreatic β-cell apoptosis and encourage their proliferation [10].

These medications typically result in an average weight loss of 2.9 kg, lower blood pressure, and reduced total cholesterol levels. Cardiovascular benefits associated with GLP-1RAs include improved left ventricular function, increased coronary blood flow, and reduced infarct size. Moreover, GLP-1 enhances muscle glucose uptake, decreases hepatic glucose production, provides neuroprotection, and promotes satiety. GLP-1 analogs have shown the ability to lower hemoglobin A1c by approximately 1% and reduce all-cause mortality in patients with T2DM [10]. The American Diabetes Association (ADA) recommends high-dose Dulaglutide, Semaglutide, and Tirzepatide (a GIP/GLP-1 combination) as highly effective options for achieving glycemic control, in conjunction with insulin therapy and other combination treatments [10].

2.1.4 Pathways Related to Obesity

The exact mechanism underlying reduced GLP-1 secretion in obesity remains unclear. Ranganath et al. [11] suggest that elevated levels of plasma non-esterified fatty acids (NEFA) may contribute to this reduction, as increased fasting and postprandial NEFA levels could impair GLP-1's insulinotropic and appetite-suppressing effects.

In the central nervous system, proglucagon-derived peptides play an important role in neurons of the nucleus tractus solitarius. The nucleus tractus solitarius serves as a bridge between the brainstem and hypothalamus and is involved in the regulation of energy balance. Studies have shown that GLP-1, GLP-2 and oxyntomodulin can effectively reduce food intake through central administration in mice. This finding suggests that interventions targeting these neural pathways may be an effective strategy to reduce food intake and increase energy expenditure. Specifically, peptides such as GLP-1 and GLP-2 can affect hunger and appetite, thereby regulating overall energy intake. In animal experiments, the application of these substances showed significant effects on inhibiting food intake, which provides important clues for the future development of new drugs to treat obesity and related metabolic diseases. In addition, neurons in the nucleus of the solitary tract are not only regulators of energy balance, but may also affect mood and behavior through connections with other brain areas, further affecting eating habits. Both GLP-1 and its receptor are expressed in hypothalamic feeding centers and other brain regions, where they directly influence appetite regulation and promote weight loss [12].

GLP-1 slows gastric emptying, reduces gastric acid secretion, and inhibits gastric and duodenal peristalsis via vagal inhibition, contributing to reduced appetite and triggering

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the ileal brake effect. By significantly delaying gastric emptying, GLP-1 affects the distribution of meals and slows nutrient absorption. Exogenous GLP-1 has been shown to produce dose-dependent effects on gastric motility in healthy, diabetic, and critically ill patients, whereas endogenous GLP-1 has a more moderate impact. GLP-1RAs, such as exenatide and liraglutide, also slow gastric emptying, aiding in glucose management. However, the extent of this effect may vary depending on baseline gastric motility. While the development of GLP-1 analogs and DPP-4 inhibitors has improved diabetes treatment, DPP-4 inhibitors have shown minimal effects on gastric emptying [13].

In addition, the GLP-1 analog liraglutide has been shown to stimulate thermogenesis in brown adipose tissue and promote the browning of white fat. This process helps improve the body‘s efficiency in the use of fat and glucose while reducing lipid content. Studies have shown that these effects are mainly mediated through key signaling pathways such as AMPK and SIRT1.

In summary, GLP-1 is an incretin hormone that plays an important role in regulating glucose metabolism and energy balance. After eating, the intestinal L cells will rapidly secrete GLP-1, a process that is glucose-dependent and aims to stimulate the release of insulin from pancreatic β cells while inhibiting the secretion of glucagon from α cells. In addition to these basic functions, GLP-1 also has the effects of suppressing appetite, delaying gastric emptying, and reducing calorie intake, making it a potentially effective target for the management of T2DM and obesity.

Due to the short half-life of GLP-1, scientists have developed a series of GLP-1 analogs to prolong its biological activity. These analogs can not only improve blood sugar control in patients with T2DM but also help with weight loss and cardiovascular health. More importantly, the effects of GLP-1 analogs on the central nervous system enhance satiety, thereby reducing food intake. Studies have also found that GLP-1 may play a broader role in energy homeostasis by promoting thermogenesis and browning of white adipose tissue, and is expected to play an important role in the treatment of obesity management in the future.

2.2 Semaglutide‘s Mechanisms of Action

Prolonging the action time of GLP-1 is one of the important pharmacological strategies for treating diabetes and obesity. Currently, GLP-1RAs, such as semaglutide and liraglutide, are FDA-approved for the management of T2DM and long-term weight control. The design of semaglutide is based on natural GLP-1, and its amino acid sequence is highly homologous to the natural peptide. By modifying it at specific positions, semaglutide can significantly reduce the risk of degradation by the DPP-4 enzyme, thereby extending the duration of its efficacy.

Semaglutide activates the intracellular cAMP and PKA signaling pathways by binding to the GLP-1 receptor. This process promotes insulin release from pancreatic beta cells and inhibits glucagon secretion from pancreatic alpha cells. In addition, these signaling pathways are involved in appetite regulation and delayed gastric emptying, and even have the potential for cardiovascular protection [14].

Regarding the mode of administration, the bioavailability of subcutaneous semaglutide is significantly higher than that of the oral form. Subcutaneous administration enables peak plasma concentrations to be reached within a short period of time and to reach a steady state within a few weeks. Due to the limitations of its peptide structure, the bioavailability of oral semaglutide is low, but it can be improved after using absorption enhancers. Different administration methods also have different distribution and metabolic characteristics in the body, and subcutaneous administration has a larger distribution volume [14].

The metabolism of semaglutide in the body is mainly completed through proteolysis and β-oxidation. The elimination half-life is long, and the duration of the drug in the blood allows it to exert a lasting effect during treatment. In terms of excretion, semaglutide is mainly excreted through urine and feces, which shows its potential clinical value in the management of T2DM and obesity [14].

In summary, semaglutide, as a GLP-1 receptor agonist, shows significant potential in the treatment of T2DM and obesity due to its prolonged duration of action and effective insulin secretion-promoting effect. Through specific amino acid modifications, semaglutide not only improves bioavailability, but also optimizes its resistance to DPP-4 enzyme, thereby extending the duration of action. Additionally, its role in regulating appetite, delaying gastric emptying, and providing cardiovascular protection makes it a versatile treatment option. With a deeper understanding of the GLP-1 pathway, semaglutide and its analogs are expected to provide patients with more effective treatment options to help improve blood sugar control and weight management. Future research can further explore its efficacy and safety in different populations and provide more basis for clinical application.

3. Clinical Progress

3.1 T2DM: Application, Efficacy, and Side Effects

3.1.1 Clinical trial data on the use of Semaglutide in T2DM treatment.

The Semaglutide Unabated Sustainability in Treatment of T2DM [SUSTAIN] clinical program consists of a series of Phase III trials aimed at evaluating the efficacy and safety of semaglutide in various patient populations. These trials spanned six key studies, primarily focusing on changes in HbA1c levels from baseline to the end of each trial, with durations ranging from 30 to 56 weeks. Participants included drug-naive patients, those on metformin or other oral antidiabetic medications, and patients using insulin. Semaglutide was tested against placebos, DPP-4 inhibitors, other GLP-1RAs, and long-acting insulin. In each comparison, semaglutide consistently showed significant reductions in HbA1c levels.

3.1.2 Evaluation of efficacy: blood glucose control, improvement in insulin sensitivity, etc.

Semaglutide, when administered at a 0.5 mg dose, effectively reduced fasting plasma glucose (FPG) and postprandial glucose (PPG) in some studies. However, the 1.0 mg dose consistently demonstrated reductions in both FPG and PPG across all trials. Beyond its glucose-lowering effects, semaglutide also improved beta-cell function, as shown by increased fasting C-peptide levels and decreased glucagon levels. Insulin sensitivity was enhanced, with improvements in HOMA-B and reductions in HOMA-IR observed in the SUSTAIN 1–3 trials.

Additionally, semaglutide led to significant weight loss, with reductions ranging from 3.5 to 6.5 kg, depending on the dose and the specific trial. Other benefits included reductions in systolic blood pressure (ranging from 2.4 to 6.3 mm Hg) and improvements in lipid profiles in some studies, although a slight increase in pulse rate was noted.

3.1.3 Common side effects: gastrointestinal reactions, hypoglycemia risk, etc.

In the semaglutide clinical program, over 8,400 patients with T2DM were evaluated across 8 trials. The rate of discontinuation due to adverse events (AEs) was generally low, ranging from 5% to 13%, except in the SUSTAIN 6 trial, where the discontinuation rate reached 20%, likely due to its longer duration [15]. The most common reasons for discontinuation were gastrointestinal AEs, including nausea, diarrhea, and vomiting. Hypoglycemia rates were low, except when semaglutide was used in combination with insulin or sulfonylureas. No significant increases in calcitonin levels or cancer risk were observed. While semaglutide demonstrated benefits in reducing diabetic nephropathy, it was associated with a higher incidence of diabetic retinopathy, likely due to the rapid reduction in HbA1c levels.

3.1.4 Long-term safety studies and cardi€ovascular risk assessments.

In a randomized trial involving 3,297 patients with T2DM, the study evaluated the effects of the GLP-1 drug semaglutide versus placebo on cardiovascular outcomes over 104 weeks. The results showed that the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was lower in the semaglutide group than in the placebo group, confirming its non-inferiority. In addition, although semaglutide performed well in reducing the risk of kidney disease, it was associated with an increased incidence of complications of diabetic retinopathy. Overall, semaglutide maintained an acceptable safety profile while providing cardiovascular protection. These results support its status as an important option in the treatment of patients with T2DM, while emphasizing the need to pay attention to the risk of retinal complications when monitoring its safety.

3.2 Obesity: Application, Efficacy, and Side Effects

Almost 2,000 adult volunteers with weight-related health issues and a BMI of ≥30 or ≥27 were included in a double-blind trial. A 68-week lifestyle intervention was given to participants along with a weekly semaglutide therapy or placebo, chosen at random. The outcomes of the trial demonstrated that semaglutide medication was clearly superior to placebo and had a considerable positive impact on weight management. While those in the placebo group lost less weight, the great majority of semaglutide recipients successfully lost more weight than their goal weight. Semaglutide improves general bodily function and cardiometabolic health indices in addition to aiding in weight loss [16]. Semaglutide‘s safety was demonstrated in this research, even though a small number of individuals experienced unpleasant side effects like nausea and diarrhea. In most cases, these side effects were minor, temporary, and easily handled. acknowledged. The results offer fresh proof in favor of pharmaceutical weight-management strategies.

In comparisons with other weight loss drugs, semaglutide has shown superior weight loss results. Compared with liraglutide, phentermine/topiramate, and bupropion/naltrexone combined with lifestyle modification, semaglutide had the most significant weight loss effect, with mean weight loss 13.7% lower than baseline, significantly higher effects on other drugs. In direct comparison, semaglutide is superior to liraglutide in terms of weight loss, and both can effectively improve blood sugar and blood pressure levels, but their effects on these parameters relative to other drugs are unclear. Although adverse events were common across all treatments, discontinuation rates due to side effects were relatively low with semaglutide. These

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results indicate that semaglutide has good prospects for weight loss and improving related health indicators, and is worthy of further promotion and application in obesity management.

Through recent trials, this article found that semaglutide not only effectively reduces body weight, but also improves cardiometabolic risk factors and is well tolerated. Compared with other weight loss drugs, semaglutide has a more significant weight loss effect, and when combined with lifestyle intervention, it can help more patients achieve at least 5% weight loss. In addition, despite some minor side effects during treatment, its discontinuation rate is relatively low, further demonstrating its safety. These results provide strong support for semaglutide as an effective treatment option for obesity management, with broad prospects for future clinical applications.

4. Conclusion

This study provides a comprehensive evaluation of the safety profile of semaglutide, a GLP-1RA, used in the treatment of T2DM and obesity. It investigates common adverse effects, such as gastrointestinal symptoms, gallbladder disease, and the potential risk of pancreatitis. The analysis also considers how safety outcomes may vary depending on semaglutide's dosage, route of administration, and patient demographics. The efficacy of semaglutide in improving glycemic control and facilitating weight loss is consistent with its established benefits for patients at elevated cardiovascular risk. The study explores the mechanisms behind semaglutide's effects, emphasizing its role in slowing gastric emptying, reducing appetite, and modulating insulin and glucagon secretion. These combined actions make semaglutide a potent option for managing metabolic disorders.

However, the study also highlights concerns about its long-term safety, particularly regarding pancreatic health, which requires further investigation. Additionally, the potential for variability in patient responses—especially related to baseline gastric motility and pre-existing cardiovascular conditions—underscores the need for personalized treatment approaches. Future research should prioritize long-term safety assessments, particularly in vulnerable populations, such as the elderly and those with pre-existing cardiovascular or renal conditions.

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