Dean&Francis
ISSN 2959-409X

Analysis of the Mechanism of Action and Therapeutic Efficacy of Semaglutide in the Treatment of Type 2 Diabetes Mellitus

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Abstract:

How to control Type 2 Diabetes Mellitus (T2DM) has been one of the most important current health issues which should be given priority to. Against this background, Semaglutide has created a new breakthrough point for this predicament: while protecting the cardiovascular system and liver, it controls the patient's blood glucose level through two pathways. This article focuses on analyzing the mechanism of action of semaglutide and explores its current shortcomings. As a glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide achieves both blood sugar lowering and weight loss via a multifaceted mechanism. In the field of T2DM treatment, large-scale clinical trials have confirmed that semaglutide not only has a strong hypoglycemic effect, but also lowers risk of hypoglycemia and clearly protect the cardiovascular, and has become the first-line choice for patients with cardiovascular diseases or high-risk factors. Future research should focus on a more comprehensive evaluation of the drug's safety, while also emphasizing its clinical benefits.

Keywords: Type 2 diabetes mellitus; semaglutide; blood sugar.

1. Introduction

Data shows that the number of global diabetes patients has reached 643 million, among which T2DM accounts for as high as 90%. T2DM has become one of the major non-communicable diseases causing death. Data from 2021 shows that diabetes directly or indirectly led to the death of approximately 6.7 million adults. The incidence of diabetes is on the rise along with the obesity rate. Most patients with T2D also have the problem of obesity that endangers their health, and this phenomenon is particularly prominent among the youth. At present, for people who have not been clearly diagnosed with T2D, the mainstream approach is to lose weight through diet to control blood sugar, while for those who have been diagnosed with T2DM, medication is used to control blood sugar.

T2DM is a chronic metabolic disorder whose core pathological features include insulin resistance (IR) and progressive impairment of pancreatic Beta cell function. It has multiple pathogenic mechanisms, different physiological and environmental factors can

ISSN 2959-409X

all have an impact on it. Research has demonstrated that the most significant pathological mechanism is the decline of pancreatic ß -cell function and IR [1]. Dysfunction of pancreatic islet cells can lead to the inability of cells to secrete sufficient insulin, while the excessive secretion of glucagon by α cells is not inhibited. The combined effect of the two causes abnormal elevation of blood sugar, making it impossible to maintain normal blood sugar levels. Insulin inhibition blocks the exact breakdown and utilization of blood glucose, upregulates hepatic glucose output, and reduces glucose assimilation, eventually resulting in hyperglycemia. In addition, chronic inflammation and abnormal function of adipose tissue are also involved in the pathogenesis of T2DM. Genetic susceptibility and environmental factors increase the risk of T2DM.

At present, the first-line drugs for diabetes include metformin, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, etc. However, these drugs are not without flaws. Evidence shows that lower doses of metformin exposure can lead to changes in the expression of endocrine disruption-related genes [2]. Semaglutide, as a breakthrough in new research, is currently a popular drug, and its status has also risen accordingly. However, despite the increasingly widespread clinical application of semaglutide, issues such as its long-term safety and differences in efficacy among different populations still need to be explored and studied. Existing literature often focuses on its simple aspects of lowering blood sugar or losing weight, and integrative analysis is still relatively lacking.

This paper provides an overview of semaglutide, covering its mode of action, molecular structure, clinical evidence among others. of semaglutide, and explore its future development direction in T2DM, so as to provide a reference basis for rational clinical drug use and subsequent research. The core mechanism of semaglutide in the treatment of T2DM lies in simulating the function of the GLP-1 hormone, promoting insulin secretion and inhibiting glucagon release by activating related receptors [3].

2. The molecular mechanism of semaglutide in the treatment of T2DM

2.1 molecular mechanism

Semaglutide ($C_{187}H_{291}N_{45}O_{59}$) is composed of 31 amino acids in 17 kinds. Among them, the lysine of semaglutide contains a modified structure of C18 adipic acid, and there is also an interarm modification composed of glutamic acid and 2-(2-(2-aminoethoxy) ethoxy) acetic acid dimer between this modified structure and the lysine. When synthesizing semaglutide, the main chain of the polypeptide and the side chain containing C18 adipic acid are usually synthesized separately, and then spliced. The entire molecule is composed of multiple fragments.

In simple terms, semaglutide mimics the structure of GLP-1 in the human body but differs from it, which prevents the drug from being rapidly degraded in the body and prolongs its efficacy. Research has found that in the structure of semaglutide, there are three important structural modifications: α-aminobutyric acid (Aib) at position 8, and arginine (Arg) at position 34. The lysine at position 26 of the original GLP-1 was acylated by a link-functional group with an 18-carbon fatty acid. It is precisely these three important chemical structural modifications that enhance the efficacy of semaglutide and extend its half-life [4].

Semaglutide is a GLP-1 receptor agonist (RA) that uses the same pathway as insulin. It mainly exerts its hypoglycemic effect by regulating pancreatic cells. First, it binds to G-protein receptors in the cells, then motives adenylate cyclase, which increases the intracellular level of cyclic adenosine monophosphate (cAMP) and activates guanine nucleotide exchange factors. Studies have shown that semaglutide mainly transmits two islet pathways through A CAMP-dependent protein kinase A mechanism [5]. On the one hand, it specifically binds to and activates the GLP-1 receptor on the pancreatic ß - cell membrane, activates the PI3K/PKA/mTOR route, and subsequently the hypoxia-inducible factor 1 (HIF-1) is followed, increasing the secretion of glucose-dependent insulin.

It elevates intracellular adenosine triphosphate (ATP) levels, thereby closing ATP-sensitive potassium channels and depolarizing the cell membrane. Depolarizing the cell membrane causes a sharp increase in intracellular cAMP levels and a large influx of calcium ions, thereby triggering exocytosis in insulin-containing vesicles and efficiently promoting insulin release. At the same time, it can also significantly inhibit the secretion of glucagon by pancreatic alpha cells, directly blocking the glycogenolysis and gluconeogenesis pathways in the liver, thereby greatly reducing the liver's output of glucose into the blood. It achieves stable and significant blood sugar control through a molecular synergistic mechanism that promotes insulin secretion and inhibits liver sugar production.

2.2 Animal experimental model confirms the effect of lowering blood sugar

The hypoglycemic effect of semaglutide has also been confirmed in clinical mouse experiments: Using mice as models, high-fat diet-induced obese mice (DIO mice) were established as the experimental group and normal mice as the control group. They were orally administered semaglutide at a dose of 0.23 mg/kg, which is equivalent

to the human dose (14 mg), to rapidly reduce blood sugar in DIO mice for 3 days. The drug is slightly more potent at 0.7 mg/kg (42 mg). It can be seen from this that oral semaglutide in combination with the human protocol and dosage can rapidly lower blood sugar, most food consumption, along with persistent inhibition of both feeding and body weight of DIO mice [6].

Meanwhile, other animal models have also been used to research the mechanism of action of semaglutide. A 12-week-old Diabetes (db/db) mouse model was established and treated with semaglutide for four weeks. Oral glucose tolerance tests and immunofluorescence evaluations were conducted to assess the effect of semaglutide on glucose clearance ability and pancreatic β cells [7]. The test group had their weight, fasting blood glucose and insulin levels measured weekly. The research results indicate that after a four-week course of treatment, although the pancreatic β cells failed to reverse their dedifferentiation, blood glucose levels decreased and insulin levels increased. It can be seen that semaglutide's effect in lowering blood glucose is not related to the change in cell ß identity.

Semaglutide has become a first-line drug not only because of its excellent blood sugar control ability, but also because of its protective effect on the cardiovascular system. The following animal model experiment investigated the effect of semaglutide on mouse cardiomyocytes. An 8-week-old diabetic mouse model was established and directly treated with semaglutide to study its effect on cardiomyocytes [8]. Monitoring revealed elevated phosphorylation levels of the AMP-activated protein kinase (AMPK) and unc-51-like autophagy-activating kinase 1 (ULK1), along with improved morphology of cardiomyocytes in db/db mice. It can be seen that semaglutide directly protects cardiomyocytes from damage caused by high glucose by promoting AMPK-dependent ATP-production and ULK1-mediated mitochondrial absorption.

Summarizing the above animal model experiments, it can be seen that semaglutide can not only efficiently promote insulin secretion and control blood sugar decline through non-reversing ß -cell morphology, but also protect myocardial cells from damage caused by hyperglycemia and prevent end-stage heart failure caused by diabetic cardiomyopathy.

3. Clinical data of semaglutide in the treatment of type 2 diabetes

At present, many clinical trials have been conducted on semaglutide. Based on these clinical results, semaglutide has a clear and significant therapeutic effect on T2DM, which is reflected in its excellent hypoglycemic data. Taking the clinical study SUSTAIN1-5 as an example, the enrolled subjects were T2DM patients who received stable basal insulin treatment but still had poor blood sugar control. A total of 397 patients were included [9]. At 26 weeks of therapy, semaglutide outperformed sodium-glucose cotransporter 2 inhibitors (SGLT2is) in decreasing glycated hemoglobin (HbA1C) levels and weight loss, and at semaglutide 0.5 mg (baseline [MD] mean change difference: -0.4% to -0.8%) and 1.0 mg (mean: The HbA1C level decreased significantly when the range was -0.7 to -1.1%. Compared with SGLT2i, the weight loss of semaglutide 1.0 mg was significantly significant (MD: -0.9 to -2.3 kg). It can be seen that semaglutide is superior to many other drugs in the treatment of IR, such as empagliflozin. According to the PIONEER 2 study, semaglutide was significantly superior to empagliflozin in glycemic control following 52 weeks of therapy. The subsequent SUSTSIN6 further made people aware of the role of semaglutide in cardiovascular protection [10]. Based on the above clinical research results, semaglutide has demonstrated its powerful blood sugar control ability. This drug was effectively able to control blood sugar in the SUDSTAIN1-5 experiments, and its cardiovascular benefits were further confirmed.

4. Controversy and future prospects

Semaglutide, as a drug acting on pancreatic islet cells, its impact on the pancreas is worthy of attention. Across the multiple large-scale clinical trials conducted to date, the incidence of pancreatitis has been consistently low, with no statistically significant difference usually detected between the treatment and control groups. Multicenter analysis showed that the correlation between semaglutide and acute pancreatitis attacks was low but not zero. This large-scale patient analysis found that the hazard ratio (HR) for the risk of pancreatitis complications in the GLP-1 RA group was 0.32 [11].

It is worth noting that semaglutide has received reports of pancreatitis cases one after another since its launch. It not only includes mild acute pancreatitis, but also a few cases of necrotizing pancreatitis and fatal cases. After ruling out common causes of pancreatitis, the symptoms of these patients were relieved after discontinuing semaglutide, while those of some patients relapsed after resuming the medication. This correlation makes it difficult to completely deny the causal relationship between drugs and pancreatitis.

For this controversy, a rational analysis from the perspective of pathophysiology shows that the GLP-1 receptor is not only distributed in pancreatic cells, but also expressed in pancreatic ductal cells and acinar cells. In animal experiments, certain GLP-1RAs have observed the phenom-

ISSN 2959-409X

enon of pancreatic ductal epithelial hyperplasia and acinar cell infiltration. Although there are differences among different drugs, this provides a possible biological basis for the risk of pancreatitis. Therefore, for patients with a relevant past medical history, the use of semaglutide should be particularly cautious. This drawback is also part of the current limitations of semaglutide.

In addition, in the field of weight loss, semaglutide has gained wide recognition. From the perspective of therapeutic effect, this drug can achieve a significant reduction in weight through multiple mechanisms such as central appetite suppression, delayed gastric emptying and energy expenditure regulation. It is particularly worth mentioning that some patients have achieved improvements in metabolic indicators such as blood lipids and blood sugar while losing weight, and the benefits far exceed those of other common weight loss drugs. At present, the combination of semaglutide and metformin has become increasingly mature. Multiple randomized controlled trials indicate that concomitant use of the two agents potentiates semaglutide's efficacy while posing no additional safety concerns [12]. However, semaglutide still has problems such as weight rebound after discontinuation and gastrointestinal discomfort in the early stage of use. These issues indicate that semaglutide is not a so-called all-powerful "miracle drug", and clinical use requires more caution.

5. Conclusion

The advent of semaglutide represents a major advance in the therapeutic field of T2DM. As a standalone glucose-lowering agent, it has delivered remarkable efficacy: it acts through multiple parallel glucose-lowering pathways, concurrently regulating pancreatic β-cells and α-cells to maintain glycemic control, and possesses numerous advantages that were unavailable in previous first-line antidiabetic medications, such as cardioprotective and hepatoprotective effects, thereby providing a novel therapeutic option for a large number of patients. Additionally, semaglutide can be used in combination with other agents to enhance overall therapeutic efficacy, and future research can prioritize combination therapy with multiple agents, with the aim of advancing the development from single-target to multi-target medications.

Nevertheless, all medications have dual effects, and semaglutide still has potential associations with adverse events such as pancreatitis. Every relevant clinical case must not be overlooked, the potential adverse effects of semaglutide still warrant careful attention.While further exploring its glucose-lowering potential in future research, greater emphasis should also be placed on evaluating its safety, with the goal of striking a balance between risk reduction and therapeutic efficacy in clinical trials.

References

[1] Mizukami H, Kudoh K. Diversity of pathophysiology in type 2 diabetes shown by islet pathology[J]. Journal of Diabetes Investigation, 2022, 13(1): 6-13.

[2] Niemuth N J, Klaper R D. Low-dose metformin exposure causes changes in expression of endocrine disruption-associated genes[J]. Aquatic Toxicology, 2018, 195: 33-40.

[3] Yang X D, Yang Y Y. Clinical pharmacokinetics of semaglutide: a systematic review[J]. Drug Design, Development and Therapy, 2024, 18: 2555-2570.

[4] Zheng Z, Gao L Y. I am not a miracle drug: a dialogue on semaglutide[J]. University Chemistry, 2025, 40(1): 297-302.

[5] Papakonstantinou I, Tsioufis K, Katsi V. Spotlight on the mechanism of action of semaglutide[J]. Current Issues in Molecular Biology, 2024, 46(12): 14514-14541.

[6] Rakhat Y, Wang L, Han W, et al. Oral semaglutide under human protocols and doses regulates food intake, body weight, and glycemia in diet-induced obese mice[J]. Nutrients, 2023, 15(17): 3765.

[7] Deng Z, Zheng D, Son J, et al. Effect of weight-neutral treatment with semaglutide or tirzepatide on β-cell identity in db/db mice[J]. Acta Physiologica, 2026, 242(1): e70141.

[8] Tian M Y, Yang J Q, Hu J C, et al. Semaglutide administration protects cardiomyocytes in db/db mice via energetic improvement and mitochondrial quality control[J]. Acta Pharmacologica Sinica, 2025, 46(5): 1250-1261.

[9] Goldenberg R M, Steen O. Semaglutide: review and place in therapy for adults with type 2 diabetes[J]. Canadian Journal of Diabetes, 2019, 43(2): 136-145.

[10] Rodbard H W, Rosenstock J, Canani L H, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial[J]. Diabetes Care, 2019, 42(12): 2272-2281.

[11] Nieto L M, Martinez J, Narvaez S I, et al. Glucagon-like peptide-1 receptor agonists use does not increase the risk for acute pancreatitis and is associated with lower complications in patients with type 2 diabetes who develop acute pancreatitis: a multicenter analysis[J]. American Journal of Gastroenterology, 2026, 121(2): 424-431.

[12] Li J, Li K, Liu Z, et al. Efficacy and safety of semaglutide combined with metformin in treating T2DM with overweight or obesity: a systematic review and meta-analysis[J]. American Journal of Translational Research, 2024, 16(8): 3545-3556.