Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Semaglutide as a Novel Therapeutic Agent for Obesity and Type 2 Diabetes

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Abstract. Obesity and type 2 diabetes are becoming more common around the world, creating serious health and economic challenges. There is a growing need for treatments that are not only effective but also safe and easy to use over a long period. In recent years, a group of drugs called glucagon-like peptide-1 agonists （GLP-1RA） has gained attention for their ability to lower blood sugar and support weight loss. One of the most promising of these drugs is semaglutide, which has shown strong results in both clinical studies and real-world use. However, some parts of how semaglutide works in the body are still not fully understood, especially its effects in different groups of people and over many years of treatment. This article reviews semaglutide’s development, including how scientists changed its structure to make it last longer in the body and resist breakdown. It explains how semaglutide works to lower blood glucose, reduce appetite, and help with weight loss by acting on both the pancreas and the brain. It also compares semaglutide to other similar drugs and explains why it is more effective and widely used. These findings help researchers better understand semaglutide and how it could lead to better treatments for metabolic diseases. Still, future studies should explore its long-term safety, how it works in different patients, and how it could be combined with other therapies to improve results.

Keywords: Semaglutide; GLP-1 receptor agonists; obesity.

1. Introduction

The World Health Organization (WHO) has pointed out a worldwide obesity epidemic by considering the body mass index (BMI). It is reported by WHO that around 16% adults worldwide have been diagnosed as obese with BMI index larger than 30 (around 890 million) and over 2.5 billion adults are overweight [1]. According to the researchers, in the United States, over 20% of the adults are obese. Obesity might drive diabetes, cardiovascular diseases (CVDs), cancer, and largely increase healthcare costs. The severe situation raises people’s concern about weight control, thus making eliminating obesity turns out to be an urgent goal for global health [1].

Scientists have been working on simple and accessible treatments for the metabolic diseases to fix the global burden. Among them, Metformin, a first-line medication for type 2 diabetes (T2DM), was serendipitously been found to be efficient in weight loss. However, Metformin might cause gastrointestinal side effects which were observed in more than half of the users [2]. A newer medication, semaglutide alternatively acts on glucagon-like peptide-1 (GLP-1) receptors as a long-acting GLP-1 receptor (GLP-1R) agonist and has been largely used as medication for obesity. The study of GLP-1 began in 1980s since its insulinotropic effect [3,4]. However, the native GLP-1R is not the best choice that the short half-life and rapid dipeptidyl peptidase 4 (DPP-4) enzyme degradation make it unstable for long-term treatment of patients with T2DM. Some researchers who focused on inhibiting DPP-4 to increase half-life found Sitagliptin, a DPP-4 inhibitor [3,5]. However, the DPP-4 inhibitor was proved that it has no effect on weight loss. In the early 1990s, in contrast, Lotte Knudsen from Novo Nordisk modified the GLP-1 peptide by attaching a fatty acid to Lys26 which helps it bind to albumin and prevent it from metabolic degradation, thus prolonging its half-life [6,7]. The innovation further promoted Novo Nordisk to become a pioneer in weight control treatment. Their first product, liraglutide, a GLP-1 derivative with C16 fatty acid attached to Lys26, emerged in 2000. The half-life of liraglutide is about 13 hours, requiring once-daily dosing [4,6].

Clinical trials proved effective in glycemic control and mild weight loss. However, the following side effects make it essential to reduce the dose though the efficacy has reduced sharply. Building on the success of liraglutide, Knudsen teams further modified the molecule by attaching C18 fatty acids to Lys26 via a hydrophilic linker and the mutation in molecule prevents the DPP4 cleavage [7]. The half-life of this molecule is extended to about 7 days and thus semaglutide is created as an ideal weight loss medication.

Semaglutide shows great potential in treating obesity, but more research is still needed. This article covers the composition and mechanism of semaglutide, the clinical trials including effectiveness and side effects, and what challenges remain. The health and global significance including business and economic sides are also mentioned. The goal is to help researchers to better understand the drug and improve future treatments for metabolic diseases.

2. Mechanism of Action of GLP-1

GLP-1 is a natural incretin hormone which is secreted by L-cells in the distal intestines [4]. GLP-1 plays a crucial role in regulating postprandial glucose levels through multiple synergistic mechanisms that help restore and maintain glucose homeostasis. These effects are especially beneficial in individuals with T2DM and obesity, where their endogenous glucose regulation abilities are weak. One of the most significant properties of GLP-1 is the insulinotropic effect that it only secretes glucose-dependent insulin when blood glucose level increases in response to food intake. It acts via the GLP-1R on pancreatic β-cells [4]. This receptor-ligand interaction triggers a signalling pathway via the stimulatory Gαs subunit, which activates adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) levels [4]. The rise in cAMP then activates protein kinase A (PKA) and the exchange protein directly activated by cAMP (EPAC) [8,9]. These pathways converge to enhance insulin gene transcription, stabilize insulin mRNA, and increase insulin granule exocytosis by facilitating membrane depolarization and promoting calcium ion (Ca^{2+}) influx through voltage-gated calcium channels [7]. This glucose-dependent mechanism ensures that insulin is secreted only in the presence of elevated blood glucose, minimizing the risk of hypoglycemia often associated with traditional insulin secretagogues.

In addition to enhancing insulin secretion, GLP-1 also has the anti-glucagonotropic effect, which suppress the glucagen secretion to further contribute to its glycaemic benefits. Although GLP-1R is not prominently expressed on α-cells, GLP-1 indirectly inhibits glucagon secretion through its action on δ-cells. With GLP-1 stimulation, δ-cells release somatostatin, which then acts on α-cells via somatostatin receptor subtype 2 (SSTR2) to suppress glucagon release. Reduced glucagon levels further decrease hepatic glucose production, thereby contributing to the control of both fasting and postprandial blood glucose levels.

The dual glucose-dependent abilities of GLP-1 to stimulate insulin and suppress glucagon, combined with its effects on slowing gastric emptying and reducing appetite through central nervous system pathways, has made it an attractive candidate for therapeutic intervention for T2DM and obesity.

3. Limitations of GLP-1 and Mechanism of Semaglutide

Although endogenous GLP-1 plays an important role in maintaining glucose homeostasis and regulating energy balance, its clinical utility is significantly limited by its rapid degradation and extremely short half-life of 1–2 minutes. This instability is primarily due to enzymatic cleavage by DPP-4, a prevalent serine protease that inactivates GLP-1 by removing two amino acids from its N-terminus, reducing its activity. Additionally, GLP-1 is rapidly removed from the bloodstream through renal filtration, further limiting its duration of action. These limitations prevent native GLP-1 from reaching or sustaining effective therapeutic concentrations in vivo.

To address this, semaglutide was developed as a long-acting GLP-1R agonist with improved structural and pharmacokinetic properties [10]. It contains a substitution at position 8 with a DPP-4-

resistant amino acid, α-aminoisobutyric acid, which blocks enzymatic cleavage. Furthermore, it is acylated with a C18 fatty acid chain that binds to albumin, protecting it from renal clearance and extending its half-life to about one week, thus allowing convenient once-weekly dosing (Figure 1).

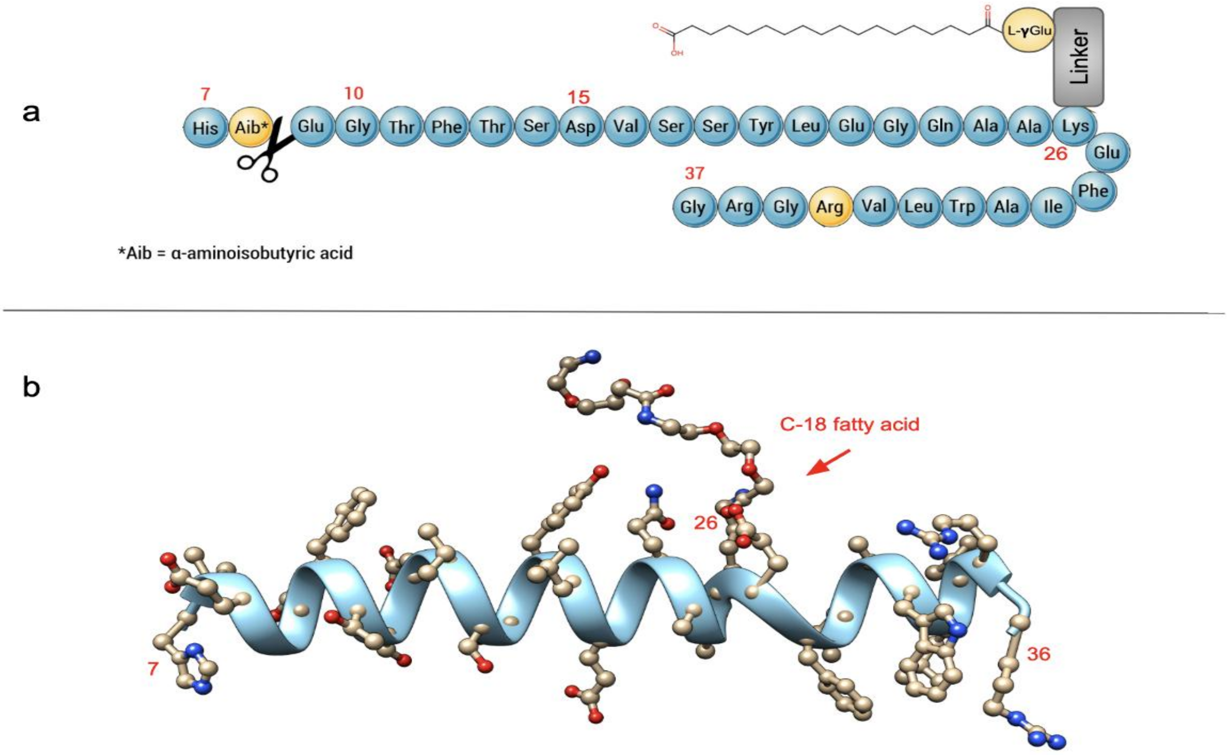

Fig. 1 2D and 3D structures of semaglutide.

a. The amino acid sequence (residues 7–37, from PubChem) is based on Knudsen and Lau, with modifications in yellow and the DPP-4 cleavage site marked by scissors [8].

b. 3D structure. The C18 fatty acid chain is partially disordered. Only semaglutide atoms are shown; receptor and G-protein chains are hidden for clarity [11].

Functionally, semaglutide mimics native GLP-1 by activating GLP-1Rs on pancreatic β-cells to enhance glucose-dependent insulin secretion through the cAMP–PKA–EPAC signaling pathway. It also suppresses glucagon release via somatostatin-mediated inhibition of α-cells. Beyond glycaemic control, semaglutide reduces appetite by acting on the hypothalamus and brainstem, leading to decreased food intake and sustained weight loss. These enhancements make semaglutide a powerful therapeutic agent that effectively overcomes the pharmacological limitations of endogenous GLP-1 while preserving and amplifying its metabolic benefits in the treatment of T2DM and obesity.

In addition to these properties, semaglutide initiates a canonical Gαs-mediated signaling cascade via GLP-1R activation, triggering adenylate cyclase and increasing intracellular cAMP. This stimulates PKA and exchange protein activated by cAMP (EPAC2), which enhance insulin gene transcription and secretion via calcium influx and membrane depolarization [4].

Moreover, semaglutide engages non-canonical metabolic pathways such as PI3K/AKT and mTOR through EPAC2, contributing to β-cell survival and reduced apoptosis. In peripheral tissues, it enhances glucose uptake via GLUT4 translocation by cAMP–PKA–AKT and AMPK/SIRT1 signaling, improving insulin sensitivity. It also indirectly inhibits glucagon secretion by stimulating somatostatin release from δ-cells, suppressing α-cell activity via somatostatin receptor-2 (SSTR2), thus reducing hepatic glucose production and aiding fasting glucose control.

Semaglutide's central actions further differentiate it from traditional glucose-lowering agents. In the hypothalamus and brainstem, it modulates neuropeptide pathways, downregulating orexigenic signals and upregulating anorexigenic responses to promote satiety [12]. This central effect, coupled with slowed gastric emptying, supports significant and sustained weight loss. Structural insights from cryo-EM show that semaglutide-bound GLP-1R maintains similar binding modes to native GLP-1 but with unique receptor conformations that may enhance receptor signaling duration and trafficking, contributing to its therapeutic durability.

4. Chemical Structure and Formulation

As mentioned before, to resist enzymatic degradation by dipeptidyl DPP-4, the native alanine at position 8 is substituted with the non-natural amino acid α-aminoisobutyric acid (Aib), effectively preventing DPP-4-mediated cleavage at the N-terminus [10]. In addition, Lys26 is site-specifically acylated via a γ-glutamic acid spacer and a dual OEG (oligoethylene glycol) linker to a C18 fatty diacid, allowing high-affinity reversible binding to serum albumin [13]. This albumin association shields the peptide from proteolytic enzymes, slows renal elimination, and facilitates a prolonged plasma half-life. Further structural refinement includes the substitution of Lys34 with arginine to eliminate unintended acylation sites and promote molecular integrity.

These modifications collectively confer a terminal half-life of approximately 160 hours (~1 week), enabling once-weekly subcutaneous administration and improving patient adherence relative to shorter-acting GLP-1 receptor agonists. Semaglutide is formulated for both injectable and oral delivery. In the oral formulation, semaglutide is co-administered with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC), which transiently elevates local gastric pH and facilitates transcellular absorption of the intact peptide across the gastric epithelium [14]. Clinical studies have demonstrated that the oral form achieves glycaemic control comparable to injectable semaglutide, offering a valuable alternative for patients seeking non-invasive therapy [4] [14].

Despite its enhanced albumin binding, semaglutide maintains a high binding affinity to the GLP-1 receptor (Kd≈ 0.38 nM), similar to liraglutide, ensuring strong agonist activity with sustained receptor engagement [13]. The optimized structural and formulation features of semaglutide not only extend its pharmacokinetic profile but also enhance pharmacodynamic outcomes, supporting superior glucose control and clinically meaningful weight loss in patients with T2DM and obesity.

5. Clinical Efficacy and Safety

Semaglutide has demonstrated strong clinical efficacy in multiple large-scale trials, both in patients with T2DM and those with obesity. In the SUSTAIN clinical program, semaglutide significantly reduced HbA1c levels and body weight compared to placebo and several active comparators, including other GLP-1R agonists [15]. In non-diabetic individuals with obesity, the STEP trials showed that semaglutide 2.4 mg weekly led to mean weight losses exceeding 15% of body weight, a level of effectiveness comparable to bariatric surgery in some cases. Importantly, these benefits were achieved without a high risk of hypoglycemia, thanks to semaglutide's glucose-dependent mechanism of action [7]. The most common adverse events reported are gastrointestinal, including nausea, vomiting, and diarrhea, which are typically transient and dose-dependent. Serious adverse events are rare, and cardiovascular outcome trials have confirmed semaglutide's safety, with additional benefits in reducing major adverse cardiovascular events (MACEs) in high-risk populations [16].

6. Comparisons and Commercial Landscape

Compared to earlier GLP-1R agonists, semaglutide stands out for its higher efficacy and longer dosing interval, making it a leading option in incretin-based therapies. For example, liraglutide—a once-daily GLP-1 analogue—has been widely used but is now largely outperformed by semaglutide in terms of both blood glucose control and weight loss [7,8]. Other weekly GLP-1 RAs, such as dulaglutide and extended-release exenatide, offer similar dosing convenience, but clinical trials (notably SUSTAIN 7) have demonstrated that semaglutide produces greater reductions in HbA1c and body weight [15].

Semaglutide is marketed under different brand names based on its indication: Ozempic for T2DM, Wegovy for obesity, and Rybelsus for the oral formulation, offering patients a choice between injectable and oral administration [16]. Its clinical success has not only redefined treatment standards for metabolic diseases but has also driven innovation in the field. This includes the development of next-generation incretin therapies like tirzepatide, a dual GLP-1/GIP receptor agonist, underscoring semaglutide's central role in advancing future therapeutic strategies for diabetes and obesity.

7. Conclusion

This article reviewed semaglutide's structure, mechanism, clinical performance, and its growing role in treating obesity and type 2 diabetes. Semaglutide was designed to overcome the limitations of native GLP-1 by resisting DPP-4 degradation and binding to albumin, which extends its half-life. It activates GLP-1Rs to boost insulin, lower glucagon, reduce appetite, and improve insulin sensitivity. It also engages both classical and non-classical pathways to support β-cell function and metabolic control. Clinical trials show strong effects on lowering blood glucose and promoting significant weight loss, with mostly mild and temporary side effects. Semaglutide offers better outcomes than older drugs like metformin and earlier GLP-1 analogues, especially in terms of weight loss. It sets a new standard for metabolic treatments and has paved the way for newer drugs like tirzepatide. Its development is a strong example of how targeted molecular design can lead to real-world success.

There are some limitations in this article as well as it did not cover all patient types, such as adolescents or elderly populations. The long-term safety of semaglutide, especially beyond controlled trials, needs further study. Also, issues like cost, access, and patient adherence were not discussed in detail. Future research should explore semaglutide's long-term effects in broader populations and real-world settings. More work is also needed to understand its brain–gut mechanisms and potential in combination therapies. With further study, semaglutide could support more personalized and effective treatment strategies for metabolic diseases.

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