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Original Research Article

# UNLOCKING SEMAGLUTIDE'S POTENTIAL: A GAME-CHANGER IN INSULIN RESISTANCE

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**ABSTRACT**

One of the main characteristics of type 2 diabetes mellitus (T2DM) is insulin resistance, which makes it difficult to maintain glucose homeostasis and avoid complications from the disease. The effectiveness of two well-known pharmaceutical products, semaglutide and exenatide, in treating insulin resistance is compared in this review. Both exenatide and semaglutide, agonists of the glucagon-like peptide-1 (GLP-1) receptor, have shown encouraging outcomes in enhancing glycemic control and lowering cardiovascular risk in individuals with type 2 diabetes. It will also evaluate the effects of each drug on glycemic control, adverse effects, weight loss, cardiovascular outcomes. This review aims to give clinicians and researchers a detailed understanding of the relative advantages and potential considerations when deciding between semaglutide and exenatide in personalised T2DM treatment regimens.

**Keywords:** Type 2 diabetes mellitus, Semaglutide, Exenetide.

## INTRODUCTION

According to estimates from the International Diabetes Federation, the prevalence of diabetes would rise from 10.5% in 2021 to 11.3% by 2030 and 12.2% by 2040.[1] According to Centers for disease control and prevention, more than 38 million Americans have diabetes (about one in ten), and about 90% to 95% of them have type 2 diabetes. Although type 2 diabetes primarily affects those who are 45 years of age and older, it is also increasingly occurring in children, teenagers and young adults. It was observed that T2DM patients had a 15% increased risk of premature death and an approximate 20-year reduced life expectancy.[2]

The emergence of insulin resistance and the insulin resistance syndrome has been linked to a number of factors. These include: 1) genetic abnormalities of one or more proteins of the insulin action cascade 2) fetal malnutrition 3) increases in visceral adiposity. Insulin resistance occurs as part of a cluster of cardiovascular-metabolic abnormalities commonly referred to as "The Insulin Resistance Syndrome" or "The Metabolic Syndrome". Depending on the genetic makeup of the person acquiring the insulin resistance, this cluster of abnormalities may result in the development of type 2 diabetes, accelerated atherosclerosis, hypertension, or polycystic ovarian syndrome.[3] Patients with type 2 diabetes have a greater risk of fragility fractures even if their bone mineral density is higher than that of control people without the disease. Since vertebral fractures are usually asymptomatic, morphometric radiologic assessment should be taken into consideration, particularly in individuals with diabetes.[4]

The U.S. Food and Drug Administration (FDA) approved Ozempic, also known as semaglutide, in 2017 for use in individuals with type 2 diabetes. The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is the most recently approved agent of this drug class, and the only GLP-1RA currently available as both subcutaneous and oral formulation.[5] Exendin-4 is a 39-amino acid peptide produced naturally only in the salivary glands of Gila monster (Heloderma suspectum), a poisonous lizard found in New Mexico and Arizona. It is a

potent and specific agonist of GLP-1R, having actions in all tissues, including β cells in islets of Langerhans that express GLP-1Rs. It has a half-life of around 2.4 hours. As a result, its biological effects are longer-lasting than GLP-1's. Exendin-4 is synthesized for human usage as exenatide, and it is administered via subcutaneous injection (SC).[6,7] In this study, we will compare the efficacy and safety of Semaglutide and Exenatide by reviewing some research studies and articles.

**Review**

This article is a review of the literature. This section will discuss about the pathophysiology of type 2 diabetes, incretin system, mechanism of action of semaglutide and exenatide.

Type 2 diabetes mellitus is a chronic metabolic disorder defined by elevated blood sugar levels (hyperglycemia) brought on by insulin resistance and relative insulin insufficiency. Early identification and treatment are essential to prevent complications and enhancing quality of life.

**Pathophysiology of T2DM**

Ethnicity and genetic predisposition play a significant role in the risk of developing type 2 Diabetes mellitus.[8] Type 2 diabetes is a highly heterogeneous polygenic disease.[9] Patients with type II diabetes have two main distinguishable pathophysiological abnormalities. One is the diminished capacity of insulin to affect peripheral tissues. This is known as insulin resistance, and it is widely believed to be the main underlying physiology. Another is the lack of ability of the pancreas to generate enough insulin to offset the effects of insulin resistance is known as beta cell dysfunction.[10]

The "Ominous Octet" of type 2 diabetes was described by Ralph DeFronzo in 2009. Eight pathophysiologic abnormalities lead to glucose intolerance in type 2 diabetes. They include: 1) Impaired insulin secretion. 2) Reduced glucose uptake by muscle. 3) Higher hepatic glucose production. 4) Increased lipolysis causes a day-long rise in plasma FFA levels. Increased plasma FFA levels promote gluconeogenesis, increase hepatic/muscular insulin resistance, and impede insulin secretion.5) Reduced incretin effect. 6) Increased secretion of glucagon by pancreatic alpha cells. Increase in glucagon levels result in inadequate uptake, storage, and disposal of ingested glucose as well as elevated hepatic production of glucose leading to profound hyperglycemia. 7)Increased glucose reabsorption in the kidneys. Normally, 90% of the filtered glucose is reabsorbed by the SGLT2 transporter in the proximal tubule, while the remaining 10% is reabsorbed by the SGLT1 transporter, leaving no glucose in the urine. Cultured human proximal renal tubular cells from type 2 diabetic patients show significantly higher levels of SGLT2 mRNA and protein, as well as a fourfold increase in the uptake of α-methyl-d-glucopyranoside (AMG), a non-metabolizeable glucose analogue. 8) Neurotransmitter dysfunction.[11,12] Figure 1,[13] demonstrates these factors clearly.

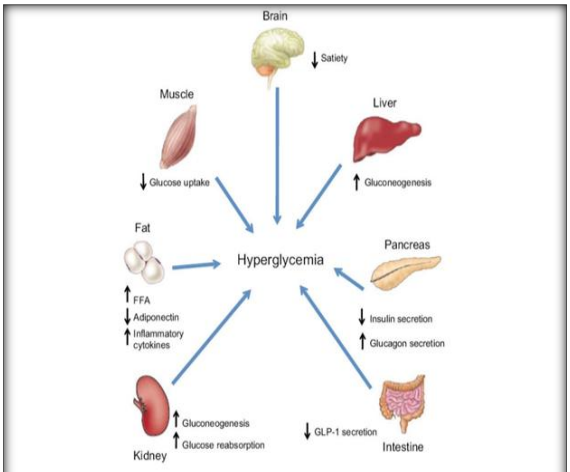


**Figure 1.** Multi-organ and tissue pathophysiology of type 2 diabetes

**Incretin system**

The incretin effect is mainly due to the actions of the gut hormones Gastric inhibitory polypeptide (GIP) and Glucagon-like peptide 1 (GLP-1). These hormones are synthesised in intestinal endocrine cells called K and L cells respectively.[14] K cells are more dense in the duodenum and proximal jejunum, whereas L-cells are more frequent farther distally, and can be found at high densities in the colon.[15] GLP-1 hormone promotes insulin secretion from pancreatic β-cells, decreases glucagon secretion, slows down gastric emptying via inhibition of the efferent vagus, reduces appetite and food intake, inhibits β-cell apoptosis. Whereas GIP increases glucagon as well as insulin secretion, promotes pancreatic β-cell proliferation and inhibits β-cell apoptosis.[16]

Mechanism of action of Glucagon Like Peptide-1 Receptor Agonists (GLP1-RA):

Berman C et al explained about the therapeutic benefits of GLP-1RAs in their study which is demonstrated in Figure 2.[17]

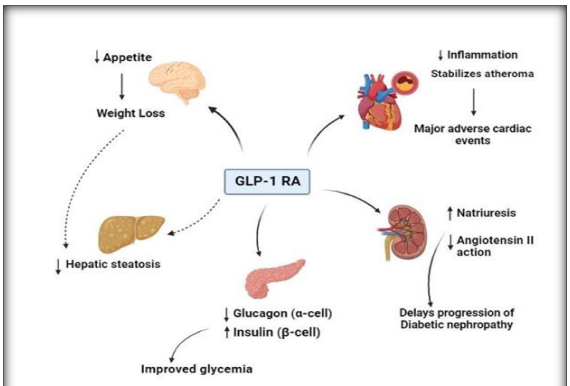


**Figure 2.** Therapeutic benefits of Glucagon like peptide-1 Receptor agonists in obesity, diabetes and diabetes related complications.
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**Semaglutide**

Semaglutide is one of the GLP-1 receptor agonists. It acts by binding to and activating the GLP-1 receptor, it stimulates insulin secretion and lowers glucagon secretion when blood glucose levels are high and slows down gastric emptying. Available orally as 3mg, 7mg, and 14mg tablets (Rybelsus brand). Also available as a once-weekly pre-filled injection pen that is given subcutaneously (Ozempic brand). The injection is given once a week, on the same day each week.

In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among patients receiving placebo, confirming the non-inferiority of semaglutide.[18] Spellman et al summarized the effects of GLP-1 agonists on β-cells and cardiac health based on human and animal trails (Figure 3).[19] Among patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, semaglutide led to significant reductions in heart failure-related symptoms and physical limitations, as well as greater weight loss compared to placebo after one year.[20]

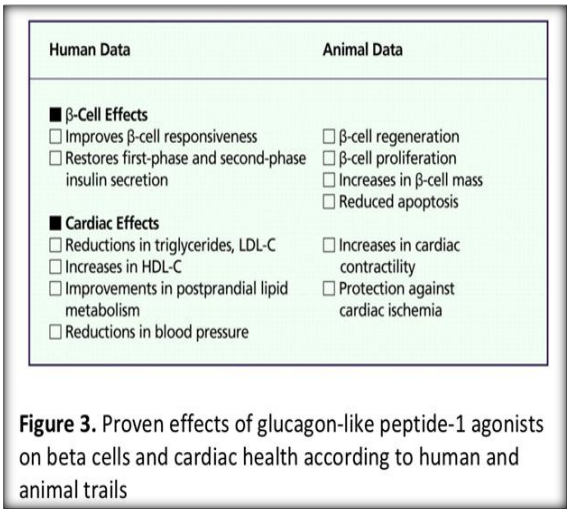


**Figure 3.** Proven effects of glucagon-like peptide-1 agonists on beta cells and cardiac health according to human and animal trails

**Exenatide**

Exenatide also belongs to the class of GLP-1 RAs just like semaglutide. It was approved in 2012 in Europe and the U.S.A. for the treatment of type 2 diabetes (T2D). This drug is only available in subcutaneous injection form. Exenatide improves glycemic control in patients with type 2 diabetes through various mechanisms of action: enhanced glucose-dependent insulin secretion, reduced postprandial secretion of glucagon, slowed gastric emptying, increased satiety, reduced body weight and preserved pancreatic β-cell function.[21-23]

Exenatide shares the majority of the glucoregulatory activities of GLP-1, however unlike GLP-1, it is resistant to in vivo proteolytic degradation by dipeptidyl peptidase-IV and has a much longer elimination half-life.[24] The twice-daily preparation of exenatide (exenatide BID) improves both fasting and postprandial glucose control, achieving A1C reductions of approximately 0.8-1.0% in placebo-controlled trials and 1.0-1.4% in open-label trials.[25-28] Kidneys are the primary route of elimination and metabolic inactivation of exenatide.

**Semaglutide vs Exenatide**

Andrew J et al conducted a 56 week, open label, parallel-group Randomised Clinical Trial (SUSTAIN 3) in which 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomised (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The results showed that mean Hba1c was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER. Mean body weight was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER. Significantly more subjects treated with semaglutide (67%) achieved HbA1c <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%). Free fatty acid, VLDL cholesterol, and triglycerides were improved with semaglutide compared with exenatide ER. Coming to the adverse effects, nausea, vomiting and diarrhoea are reported more in subjects taking semaglutide compared to exenatide ER. Two instances of EAC-confirmed mild acute pancreatitis occurred with semaglutide and three with exenatide ER. Injection-site reactions were more common in exenatide ER-treated patients (22%) than in those treated with semaglutide (1.2%). The study concluded that Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment.[29]

In another study, Fonseca et al conducted post hoc analysis of the SUSTAIN 1-3 trails that included 2432 subjects with T2D. It showed that semaglutide treatment consistently reduced both body weight and insulin resistance(IR) in subjects with T2D. In addition, semaglutide reduced IR across weight change categories with greater weight loss, generally being associated with greater reductions in IR. Weight loss has been shown to be the strongest predictor of improved insulin sensitivity whereas weight regain predicted reduced insulin sensitivity. The results showed that mean body weight across SUSTAIN 1-3 trails (baseline 89.5 to 95.8 kgs) decreased significantly from baseline to end of treatment by 3.7 to 4.3 kgs with semaglutide 0.5mg and 4.5 to 6.1kg with semaglutide 1mg vs 1.9 kg with exenatide ER. Overall insulin resistance decreased by 27.3% to 36% with semaglutide 0.5mg and 32.4% to 45.9% with semaglutide 1mg vs 27.9% with exenatide ER in SUSTAIN 1,2,3 trails ($P<0.05$). Greater reductions in IR were observed with increasing weight loss. The mediation analysis showed that the proportion of effect of semaglutide vs comparator on HOMA-IR mediated by weight loss were as follows: 70% for 0.5mg semaglutide and 34% for 1mg semaglutide in SUSTAIN 1. 80%

for semaglutide 0.5mg and 94% for semaglutide 1mg in SUSTAIN 2, 69% for semaglutide 1mg in SUSTAIN 3.[30]

A study conducted by Rafaella et al explained that the primary pharmacodynamic difference between short-acting exenatide twice daily formulation and long-acting semaglutide once weekly formulation is that short-acting agents primarily delay gastric emptying (lowering postprandial glucose), whereas long-acting agents affect both fasting glucose (via enhanced glucose-dependent insulin secretion and reduced glucagon secretion in the fasting state) and postprandial glucose (via enhanced postprandial insulin secretion and inhibition of glucagon secretion). Other benefits of long-acting GLP-1 RAs include a lesser fluctuations in plasma drug concentrations, improved gastrointestinal tolerability profiles, and simpler, more convenient dosing schedules.[31]

Crabtree TSJ et al have extracted data from the Association of British Clinical Diabetologist (ABCD) nationwide semaglutide audit and prepared for analysis, providing baseline and relevant follow- up data for HbA1c and/or weight. They performed a Statistical analysis in Stata 16 using paired t tests and ANOVA with Bonferroni corrections to compare patients who moved from dulaglutide, liraglutide, and exendin-based GLP-1RA (exenatide) to semaglutide medication. Of 1625 users in the audit, 765 had sufficient data available for analysis. The results included that switching to semaglutide from other GLP-1RAs resulted in statistically significant HbA1c reductions. Patients who switched from exendin-based GLP-1RAs to semaglutide lost significant amounts of weight.[32] After reviewing these studies, we conclude that semaglutide is the superior choice for treating type 2 diabetes compared to exenatide since it is more effective and has better compliance.

## CONCLUSION

Type 2 diabetes is a complex metabolic disorder marked by insulin resistance and hyperglycemia that requires appropriate management strategies to avoid complications and improve quality of life. Among the GLP-1 receptor agonists used in treatment, semaglutide and exenatide stand out because of their functions in improving glycemic control and achieving weight loss. This literature review reveals that semaglutide outperforms exenatide in terms of overall benefits. Semaglutide's once-weekly dosing strategy improves patient adherence, while its higher potency results in more significant HbA1c reductions and weight loss. Furthermore, semaglutide has proven impressive cardiovascular effects, which add to its clinical advantages. While exenatide remains a valuable option with a proven track record, its efficacy and convenience often do not match the robust outcomes achieved with semaglutide. In conclusion, semaglutide is a more effective treatment option than exenatide for most patients with type 2 diabetes.

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