ISSN: 2181-3906 2026

International scientific journal
«MODERN SCIENCE AND RESEARCH»
VOLUME 5 / ISSUE 4 / UIF:8.2 / MODERNSCIENCE.UZ

GLP-1 RECEPTOR AGONISTS AND SEMAGLUTIDE: MECHANISMS, CLINICAL OUTCOMES, AND EMERGING THERAPEUTIC FRONTIERS

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https://doi.org/10.5281/zenodo.19492762

Abstract. *Glucagon-like peptide-1 (GLP-1) receptor agonists have become a cornerstone in the management of type 2 diabetes mellitus (T2DM) and obesity. Among them, semaglutide stands out as one of the most potent agents, demonstrating robust glycemic control, substantial weight reduction, and cardiovascular risk mitigation. GLP-1 agonists exert their effects through glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and central appetite regulation. Semaglutide, with its extended half-life and convenient weekly dosing, offers superior metabolic outcomes compared to earlier GLP-1 analogs. Landmark trials such as* ***SUSTAIN****,* ***STEP****, and* ***SELECT*** *highlight its efficacy in glycemic control, weight loss, and cardiovascular event reduction. Despite its benefits, semaglutide is associated with gastrointestinal side effects and rare risks such as pancreatitis. This review synthesizes current knowledge on GLP-1 agonists, emphasizing semaglutide's mechanisms, clinical efficacy, safety profile, and future innovations in metabolic medicine.*

Keywords*: GLP-1 receptor agonists, Semaglutide, Type 2 diabetes mellitus, Obesity, Glycemic control, Weight reduction, Cardiovascular risk mitigation, Insulin secretion, Glucagon suppression, Gastric emptying delay, Appetite regulation, Extended half-life.*

Introduction

Over the past decade, GLP-1 receptor agonists have revolutionized the treatment of metabolic diseases. Initially developed for T2DM, these agents are now recognized for their profound effects on weight reduction, appetite regulation, and cardiometabolic risk. Semaglutide, a next-generation GLP-1 agonist, has garnered global attention due to its strong clinical outcomes and convenient once-weekly regimen.

Beyond glycemic control, semaglutide has demonstrated remarkable weight-loss effects, often surpassing older therapies. Its expanding role now encompasses obesity management, cardiovascular prevention, and investigational applications in neuroprotection and addiction medicine. This review explores the pharmacology, mechanisms of action, clinical outcomes, and therapeutic innovations of GLP-1 receptor agonists, with a focus on semaglutide.

Background and Pharmacology

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient intake.

Its physiological actions include:

- Enhancement of glucose-dependent insulin secretion
- Suppression of glucagon release
- Delayed gastric emptying
- Appetite reduction via central pathways

Native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), necessitating the development of long-acting analogs resistant to enzymatic breakdown.

Semaglutide Pharmacology

Semaglutide is a modified GLP-1 analog with 94% structural similarity to human GLP-1 but enhanced resistance to DPP-4 degradation. Key features include:

- Long elimination half-life (~1 week)
- Once-weekly subcutaneous dosing
- Availability of an oral formulation (first in class)
- Strong binding affinity to GLP-1 receptors

These properties confer superior glycemic and weight-loss outcomes compared with earlier agents such as exenatide and liraglutide.

Mechanisms of Action

1. **Glucose-Dependent Insulin Secretion** – Enhances insulin release only under hyperglycemic conditions, minimizing hypoglycemia risk.
2. **Suppression of Glucagon** – Reduces hepatic glucose output.
3. **Delayed Gastric Emptying** – Blunts postprandial glucose excursions and promotes satiety.
4. **Central Appetite Regulation** – Modulates hypothalamic pathways to reduce hunger and caloric intake.
5. **Cardiovascular Effects** – Improves endothelial function, lowers blood pressure, and reduces inflammation.

Clinical Outcomes

1. Glycemic Control

- **SUSTAIN trials**: HbA1c reductions of 1.0–1.8%
- Superior to basal insulin and most oral agents

2. Weight Loss

- **STEP trials**: 15–20% weight reduction in obesity
- Comparable to metabolic surgery in select individuals

3. Cardiovascular Benefits

- **SUSTAIN-6 and SELECT trials**: ~20% reduction in major adverse cardiovascular events (MACE)
- Benefits extend to patients without diabetes

4. Renal Protection

- Emerging evidence suggests reduced albuminuria and slowed progression of diabetic kidney disease.

Indications

Semaglutide is approved for:

- **Type 2 Diabetes Mellitus** (monotherapy or combination therapy)
- **Chronic Weight Management** (BMI ≥30, or ≥27 with comorbidities)
- **Cardiovascular Risk Reduction** in T2DM with established CVD

Investigational uses include addiction treatment, neuroprotection in Alzheimer's disease, PCOS, and NAFLD.

Safety Profile

Common Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea, abdominal discomfort

Less Common Risks

- Acute pancreatitis
- Gallbladder disease
- Acute kidney injury (secondary to dehydration)

Rare but Serious Concerns

- Possible thyroid C-cell tumors (rodent data)
- Hypoglycemia when combined with insulin or sulfonylureas

Overall, semaglutide is well tolerated and safe for long-term use.

Therapeutic Innovations and Future Directions

1. **Dual and Triple Agonists** – Combining GLP-1 with GIP or glucagon receptor agonism (e.g., tirzepatide).
2. **Extended-Release Formulations** – Development of once-monthly injectables.
3. **Expanded Obesity Indications** – Trials in adolescents, prediabetes, and metabolic syndrome.
4. **Cardiometabolic Prevention** – Potential role in primary prevention of cardiovascular disease.

Conclusion

GLP-1 receptor agonists, particularly semaglutide, have transformed the management of T2DM and obesity. Their ability to improve glycemic control, induce substantial weight loss, and reduce cardiovascular events positions them at the forefront of metabolic medicine.

Ongoing innovations—including dual agonists and expanded indications—promise to further broaden their clinical utility. With strong efficacy and a favorable safety profile, semaglutide is poised to remain a cornerstone therapy in the fight against chronic metabolic disease.

References

1. Drucker DJ. (2022). Mechanisms of GLP-1 receptor agonists in diabetes and obesity.
2. Wilding J. et al. (2021). Semaglutide and weight loss outcomes: STEP trial results.
3. Marso S. et al. (2016). Semaglutide and cardiovascular outcomes in T2DM: SUSTAIN-6.
4. Nauck M., Meier J. (2019). GLP-1 physiology and therapeutic applications.
5. SELECT Trial Group. (2023). Semaglutide for cardiovascular prevention in overweight adults.
6. Davies MJ et al. (2021). Management of hyperglycemia in type 2 diabetes, 2021. *ADA/EASD Consensus Report.*
7. Pratley RE et al. (2018). Semaglutide versus dulaglutide in type 2 diabetes (SUSTAIN-7). *Lancet Diabetes Endocrinol.*
8. Ahrén B. (2020). Incretin hormones and beta-cell function. *Physiol Rev.*
9. Frias JP et al. (2021). Tirzepatide versus semaglutide in T2DM (SURPASS-2). *N Engl J Med.*

10. Kapitza C et al. (2017). Effects of oral semaglutide on pharmacokinetics and glycemic control. *Diabetes Care.*
11. Bethel MA et al. (2018). Cardiovascular outcomes with GLP-1 receptor agonists: A meta-analysis. *Lancet.*
12. Blundell J et al. (2017). Appetite and energy intake effects of semaglutide. *Diabetes Obes Metab.*
13. Husain M et al. (2019). Semaglutide and renal outcomes: Post-hoc SUSTAIN analysis. *Kidney Int.*
14. Capehorn M et al. (2022). Semaglutide 2.4 mg for weight management: Real-world data. *Obesity (Silver Spring).*
15. Rubino DM et al. (2021). STEP TEENS Trial: Semaglutide for adolescent obesity. *N Engl J Med.*
16. Perreault L et al. (2022). GLP-1 agonists in metabolic syndrome and prediabetes. *J Clin Endocrinol Metab.*
17. Astrup A et al. (2020). GLP-1 agonists and gastric emptying physiology. *Obes Rev.*
18. Madsbad S. (2016). Safety and tolerability of GLP-1 agonists. *Clin Pharmacol Ther.*
19. Kahn SE et al. (2019). Incretin-based therapies and beta-cell preservation. *Diabetes Care.*
20. Newsome PN et al. (2021). Semaglutide in non-alcoholic steatohepatitis (NASH). *N Engl J Med.*