



**How does semaglutide compare to other GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors in terms of efficacy and mechanisms of action on glycemic control, lipid metabolism, and cardiovascular outcomes in patients with type 2 diabetes?**

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## Contents

Abstract.....	3
Introduction.....	4
Methods and Analysis.....	5
Discussion.....	8
Conclusion.....	10
Bibliography.....	11

## **Abstract**

This scientific literature review investigates the multifaceted impacts of semaglutide on glucose metabolism, lipid profiles, and cardiovascular health, comparing its efficacy and mechanisms of action with other GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors. Semaglutide, a GLP-1 receptor agonist, has shown significant promise in managing type 2 diabetes by improving glycemic control and promoting weight loss. We explore how semaglutide facilitates HbA1c reduction, modulates triglyceride levels, and influences lipoprotein profiles, and examine factors that affect the drug's efficacy, including insulin resistance, genetic variations, hormonal imbalances, gut microbiota composition, psychological and behavioral factors, metabolic adaptations, and concomitant medications. Finally, the mechanisms by which semaglutide indirectly supports muscle protein synthesis, energy expenditure, and appetite regulation, contributing to its overall efficacy in weight management and metabolic health are discussed.

## **Keywords**

Semaglutide, GLP-1 receptor agonists, insulin resistance, weight loss, SGLT2 and DPP-4 inhibitors, glycemic control, lipid metabolism

## Introduction

Insulin stands as a quintessential hormone vital for orchestrating glucose metabolism and maintaining metabolic homeostasis in vertebrates. Insulin synthesis primarily transpires within the  $\beta$ -cells of the pancreatic islets of Langerhans, where it is initially produced as a precursor molecule, proinsulin. Proinsulin undergoes enzymatic cleavage within secretory vesicles, yielding mature insulin and the C-peptide fragment. Upon secretion into the bloodstream, insulin binds to its cognate receptor, the insulin receptor (IR), located on the surface of target cells. The interaction between insulin and the IR initiates a signaling cascade, culminating in cellular responses pivotal for glucose uptake, glycogen synthesis, lipogenesis, and protein synthesis. Insulin promotes glucose uptake by facilitating the translocation of glucose transporter proteins, such as GLUT4, to the cell membrane, thereby enhancing glucose uptake into cells, particularly muscle and adipose tissue; it also regulates lipid metabolism by promoting the uptake of circulating fatty acids into adipocytes for storage as triglycerides. In individuals with type 2 diabetes, insulin resistance or deficiency can lead to impaired glucose uptake and utilization, resulting in elevated blood glucose levels. It can also result in lipolysis (breakdown of stored fat) leading to elevated circulating levels of free fatty acids and a range of complications, including damage to blood and nerves.

Understanding the interplay between semaglutide and insulin provides insights into their combined therapeutic benefits in managing type 2 diabetes mellitus, offering a multifaceted approach to glucose control and weight management. Semaglutide, as a synthetic analog of glucagon-like peptide-1 (GLP-1), possesses a complex molecular structure comprising 191 amino acids, designed for enhanced stability and prolonged activity. This structural resemblance to native GLP-1 enables semaglutide to engage with GLP-1 receptors, a class of G-protein-coupled receptors (GPCRs) distributed across various tissues including pancreatic  $\beta$ -cells, gastrointestinal tract, brain, and adipose tissue. Upon binding to GLP-1 receptors, semaglutide initiates a cascade of intracellular events, culminating in the activation of downstream signaling pathways. One notable effect of semaglutide is its ability to stimulate insulin secretion from pancreatic  $\beta$ -cells, a crucial step in glucose homeostasis. This insulintropic effect of semaglutide is essential for promoting glucose uptake into cells and reducing blood glucose levels. Additionally, semaglutide inhibits glucagon release from pancreatic  $\alpha$ -cells, further contributing to its glycemic control properties. Moreover, semaglutide-induced activation of GLP-1 receptors elicits effects such as delayed gastric emptying and increased satiety. By slowing down the emptying of the stomach and promoting feelings of fullness, semaglutide helps to reduce food intake and aids in weight loss efforts. These multifaceted actions collectively underscore semaglutide role in enhancing glycemic control and promoting weight loss in individuals with type 2 diabetes mellitus.

By stimulating insulin secretion and enhancing insulin sensitivity, GLP-1 receptor agonists like semaglutide, liraglutide, and exenatide help improve glucose metabolism and lower blood glucose levels. This can indirectly influence weight loss by reducing hyperglycemia-associated complications such as polyuria and polydipsia, which can contribute to weight loss. GLP-1 receptor agonists, by improving insulin sensitivity and reducing insulin resistance, may help normalize lipid metabolism and reduce circulating levels of free fatty acids. This can contribute to improved lipid profiles and potentially facilitate weight loss. Another category of substances with catalytic properties which affect glucose and lipid metabolism include SGLT2 and DPP4 inhibitors. These function by blocking the sodium-glucose co-transporters and by degrading the incretin hormones, respectively.

## Methods and Analysis

The multifaceted impacts of semaglutide on glucose metabolism, lipid profiles, and cardiovascular health, and the comparison of the efficacy and mechanisms of action with other GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors was analyzed in peer-reviewed literature; the significant findings are summarized in Table 1.

	Author, Date	Purpose of study	Methodology	Major findings
1	Nissen, et al. (2005)	To compare sitagliptin, dapagliflozin, or lobeglitazone as “controls” in patients with type 2 diabetes	Clinical study of three groups of medications over a 2-year period.	All three drugs displayed good glucose lowering efficacy.
2	Zinman, et al. (2015)	The effects of inhibitor Empagliflozin on mortality in type 2 diabetes patients.	Clinical study of 7020 patients over 3.1 years	Patients with type 2 diabetes had a lower rate of cardiovascular disease symptoms and death with treatment.
3	Neal, et al. (2017).	The effects of Canagliflozin on cardiovascular diseases	Clinical trial of 200 patients over 3.6 years	Significantly lower rates of death or non-fatal implications from cardiovascular disease.
4	Wiviott, et al. (2019).	The effects of selective inhibitor (Dapagliflozin) on sodium-glucose cotransporter	Clinical study of 17,160 patients with type 2 diabetes with risk of ACD over 4.2 years	Treatment did not result in a higher or lower rate of MACE than placebo.
5	Cefalu, et al. (2016)	The effects of several catalytic substances (SGLT2 inhibitors) on type 2 diabetes	Literature review paper	It is unlikely that the reduction of cardiovascular mortality can be explained by SGLT2 inhibitors.
6	DeFronzo, et al. (2017).	The effects of SGLT2-1 on glucose homeostasis	Literature review paper	The beneficial effects beyond glycemic control and include renal glucose reabsorption, which reduces blood pressure, and lowers glucose toxicity.
7	Holman, et al. (2017)	The effects of adding once weekly treatment of Exenatide to usual care in patients with type 2 diabetes	Clinical trial of 14,752 patients over 3.2 years	No significant effect of Exenatide on type 2 diabetes patients.
8	Scheen (2018)	To compare the effects of DPP4 inhibitors on hemoglobin indices with TSD and SU	Literature review paper	DPP4 inhibitors were less effective than GLP-1 receptor agonists for reducing hemoglobin indices and body weight but are easier and

				cheaper.
<b>9</b>	Zinman et al. (2019).	To investigate the efficacy and safety of semaglutide when added to SGLT2 inhibitor therapy in patients with inadequately controlled type 2 diabetes	Global clinical trials in 61 centers, 6 countries: 302 adult patients with type 2 diabetes	Adding semaglutide to SGLT2 inhibitor therapy significantly improves glycemic control and reduces body weight and is well tolerated.
<b>10</b>	Pratley et al. (2018)	To compare the effects of semaglutide with dulaglutide in patients with inadequately controlled type 2 diabetes	Clinical trial in 194 hospitals/clinics in 16 countries: 1201 adult patients over 5 months	At low and high doses, semaglutide was superior to dulaglutide in improving glycemic control and reducing body weight.
<b>11</b>	Frias et al (2021)	The efficacy and safety of once-weekly Tirzepatide as compared with semaglutide	40-week clinical trial on 1879 patients with type 2 diabetes, average age of 56.6 years	Tirzepatide was superior to semaglutide with respect to glycated hemoglobin level.

The metabolic impact of insulin and the various substances used to treat type 2 diabetes is summarized in Table 2.

<b>Table 2: Overview of the metabolic impact of insulin and medications</b>				
	<b>HbA1c</b>	<b>Triglyceride Levels</b>	<b>HDL and LDL Cholesterol Levels</b>	<b>Weight loss</b>
<b>Insulin</b>	Insulin regulates blood glucose levels, and its effectiveness is reflected in the HbA1c hemoglobin index. Insulin resistance elevates this index.	Elevated insulin levels increase the triglyceride levels in the blood	Elevated insulin levels lower HDL and increase LDL cholesterol levels.	Insulin resistance increases weight gain and increases the difficulty of weight loss.
<b>GLP-1 Receptor: Semaglutide</b>	Semaglutide has been shown to reduce the HbA1c levels in type 2 diabetes patients. It is the most effective of the GLP-1 receptor agonists.	Semaglutide lowers the triglyceride levels and is the most effective of the GLP-1 receptor agonists.	Semaglutide has the relative highest HDL cholesterol content and the lowest LDL cholesterol content.	Semaglutide has been shown to affect the weight loss of patients significantly and positively.
<b>GLP-1 Receptor: Liraglutide/Exenatide/dulaglutide</b>	All three drugs are effective in reducing these levels but not as significantly as semaglutide	All three drugs are effective in reducing these levels but not as significantly as semaglutide	All three drugs are effective in reducing these levels but not as significantly as semaglutide	All three drugs exhibit a positive effect on weight loss but not as significant as semaglutide.
<b>GLP-1 Receptor co-agonist: Tirzepatide</b>	(no data)	Lowers the levels at a higher level than semaglutide.	Tirzepatide lowers the LDL levels and increases the HDL levels and is more effective than semaglutide.	Tirzepatide is more effective in weight loss than semaglutide by enhancing insulin sensitivity
<b>SGLT2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin</b>	These inhibitors lower blood glucose levels by increasing glucose excretion through urine which reduces hemoglobin index, and exhibit beneficial effects on lowering triglyceride levels, increasing HDL and reducing LDL levels, and promoting weight loss.			
<b>DPP-4 inhibitors: sitagliptin, saxagliptin, and linagliptin</b>	These classes of inhibitors work by increasing insulin secretion and decreasing glucagon levels, which help lower the blood glucose levels and reducing the hemoglobin index. Additionally, they contribute to improved lipid profiles and enhancing glycemic control.			

## Discussion

In most cases, semaglutide demonstrates superior efficacy in glycemic control compared to other GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors – it shows a greater reduction in HbA1c and more pronounced weight loss effects. Its mechanism of action involves enhancing insulin secretion, suppressing glucagon release, slowing gastric emptying, and reducing appetite, leading to significant reductions in HbA1c levels and body weight. The GLP-1 coreceptor Tirzepatide demonstrated greater efficiency with respect to metabolic regulation in most patients diagnosed with type 2 diabetes when compared to semaglutide.

Semaglutide effectively lowers triglyceride levels and increases HDL cholesterol, like SGLT2 inhibitors, but these achieve the effects through increased urinary glucose excretion. Both semaglutide and SGLT2 inhibitors contribute to improved lipid profiles and reduced cardiovascular risk. DPP-4 inhibitors, while beneficial in glycemic control by preventing the breakdown of incretin hormones and thereby enhancing insulin secretion and suppressing glucagon, have a less pronounced impact on lipid metabolism and weight loss.

In cardiovascular outcomes, semaglutide has been shown to reduce major adverse cardiovascular events (MACE) more effectively than both SGLT2 and DPP-4 inhibitors. This cardioprotective effect is attributed to its multifaceted actions on glucose and lipid metabolism, as well as its favorable influence on weight reduction and blood pressure.

The molecular mechanisms and physiological effects of the medications can be summarized:

- **Semaglutide** mimics the endogenous hormone GLP-1 by binding to GLP-1 receptors on pancreatic  $\beta$ - cells, the gastrointestinal tract, and the central nervous system. This binding stimulates insulin release from the pancreas in a glucose-dependent manner while simultaneously inhibiting glucagon secretion, thereby reducing hepatic glucose production. Additionally, semaglutide slows gastric emptying and enhances satiety, leading to reduced food intake and subsequent weight loss. Clinical outcomes for semaglutide include significant reductions in HbA1c levels, effective weight loss, and improvements in lipid profiles. Semaglutide has demonstrated superior efficacy in HbA1c reduction compared to other GLP-1 receptor agonists. This enhanced glucose control, combined with weight loss, makes semaglutide a powerful agent in managing type 2 diabetes mellitus (T2DM). Furthermore, semaglutide has been shown to improve lipid profiles by reducing triglycerides and increasing HDL cholesterol.
- **Liraglutide and exenatide** also act by binding to GLP-1 receptors, exerting similar effects on insulin and glucagon secretion, gastric emptying, and satiety. While these medications are effective in reducing HbA1c levels and promoting weight loss, semaglutide often demonstrates superior outcomes due to its longer half-life and once-weekly dosing regimen. In clinical outcomes, liraglutide and exenatide also show beneficial effects on lipid profiles, with reductions in triglycerides and increases in HDL cholesterol. However, semaglutide may provide more pronounced improvements.
- **Tirzepatide** belongs to the class of peptides known as dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonists. Its molecular function lies in its ability to activate both GIP and GLP-1 receptors, which are crucial in regulating blood sugar levels and appetite. By targeting these receptors, tirzepatide promotes insulin secretion and inhibits glucagon release, leading to improved glycemic control in patients with type 2 diabetes and weight loss. Clinical trials have demonstrated its efficacy in lowering HbA1c levels and reducing body weight, making it a promising therapeutic option for individuals with these conditions.

- **SGLT2 inhibitors** including canagliflozin, dapagliflozin, and empagliflozin, work by blocking the sodium-glucose co-transporter 2 (SGLT2) in the proximal tubules of the kidneys, which reduces glucose reabsorption and increases urinary glucose excretion. This mechanism is insulin-independent, making SGLT2 inhibitors effective even in insulin-resistant individuals. Clinical outcomes for SGLT2 inhibitors include moderate reductions in HbA1c levels, typically around 0.5-1.0%, as well as weight loss due to the calorie loss through urinary glucose excretion. They may also modestly increase LDL cholesterol but improve HDL cholesterol and reduce triglycerides. Importantly, SGLT2 inhibitors have demonstrated significant reductions in cardiovascular events and hospitalizations for heart failure, along with renal protective effects that reduce the progression of diabetic kidney disease.
- **DPP-4 inhibitors**, such as sitagliptin, saxagliptin, and linagliptin, work by blocking the enzyme dipeptidyl peptidase-4 (DPP-4), which degrades incretin hormones (GLP-1 and GIP). This results in prolonged action of incretins, enhancing insulin secretion and inhibiting glucagon release. The effects of DPP-4 inhibitors are glucose-dependent, reducing the risk of hypoglycemia. Clinical outcomes for DPP-4 inhibitors include moderate reductions in HbA1c levels, typically around 0.5-1.0%, and they are generally weight-neutral, making them less beneficial for weight management compared to GLP-1 receptor agonists and SGLT2 inhibitors. Their impact on lipid profiles is minimal, and while they provide cardiovascular safety, they do not offer significant cardiovascular benefits. DPP-4 inhibitors are suitable for use in patients with renal impairment.

## Conclusion

Patients with type 2 diabetes show a significant improvement in blood sugar levels, lipid metabolism, and cardiovascular symptoms when treated with semaglutide. Other types of GLP-1 receptor agonists also show improved results but are not as effective; one GLP-1 receptor co-agonists (ex. Tirzepatide) showed superior improvements in patients. Finally, the SGLT2 and DPP-4 inhibitors were not as effective in improving the symptoms and conditions of patients with type 2 diabetes as compared to semaglutide. Further investigations into the effects of various glucose related medications may lead to a better understanding of the molecular mechanism of insulin resistance.

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