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# Semaglutide For Weight Loss: A Literature Review

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**A B S T R A C T**

Obesity and overweight are chronic diseases that increase the risk of diabetes, cardiovascular diseases, and malignancies. Sustainable weight loss is the main goal in preventing diabetes and obesity-related complications. Although diet and exercise interventions are effective, long-term adherence is difficult. Glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide have been approved for weight management and have shown benefits in glycemic control and reducing cardiovascular events. This review discusses the effectiveness of semaglutide for weight loss and its potential as an anti-obesity drug. A scoping review was conducted by searching studies from 2018 to 2024 in the PubMed and Google Scholar databases. Systematic review and meta-analysis study designs on using semaglutide in managing obesity and overweight were included. The literature selection reporting flowchart was summarized according to PRISMA. Current evidence indicates that weekly subcutaneous semaglutide effectively reduces weight in overweight and obese individuals without diabetes, with non-serious side effects, although gastrointestinal effects somewhat reduce its comfort of use. The addition of semaglutide is expected to provide more anti-obesity therapy options and support precision medicine in obesity management.

Keywords: Obesity, Overweight, Semaglutide, Glucagon-like peptide-1

## 1. Introduction

Obesity and overweight are prevalent chronic conditions that significantly increase the risk of various health complications, including type 2 diabetes, cardiovascular diseases, and certain types of cancer. The global rise in obesity rates has highlighted the need for effective weight management strategies.[1,2] While effective, traditional approaches such as diet modification and increased physical activity often face challenges in achieving long-term adherence and sustained weight loss.[3]

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has recently emerged as a promising pharmacological choice for weight management. Initially developed for the treatment of type 2 diabetes, semaglutide has demonstrated significant efficacy in promoting weight loss in both diabetic and non-diabetic individuals. By mimicking the action of the naturally occurring hormone GLP-1, semaglutide enhances reduces appetite, insulin secretion, and slows gastric emptying, contributing to reduced calorie intake and subsequent weight loss.[3,4] Clinical trials have shown that weekly subcutaneous injections of semaglutide result in substantial weight reduction and improvement in cardiometabolic parameters. These benefits, combined with a relatively favorable safety profile, have led to the approval of semaglutide for chronic weight management in several countries.[5,6]

Given the substantial impact of obesity on public health and the promising results seen with semaglutide, further exploration of its efficacy and potential as an anti-obesity medication is warranted. This narrative review discusses the effectiveness of weight loss from semaglutide and its potential as an anti-obesity medication.

## 2. Methods

A literature review was conducted by searching studies published from 2018 to 2024 in the PubMed and Google Scholar databases. The search terms used were combinations of "semaglutide," "glucagon-like peptide-1," "obesity," "overweight," and "weight loss." Reference lists of relevant papers were also screened to identify studies for inclusion. Systematic reviews and meta-analyses on using semaglutide in managing obesity and overweight were included in this review. A flow diagram of literature selection was summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Review (PRISMA-ScR).

## 3. Results

### *3.1 Literature Search*

Figure 1 summarizes the literature search process in this study. From the two selected databases, 113 studies were identified. After removing duplicates and excluding studies not relevant to the study's objectives, fifteen studies were screened according to the study's objectives. Seven papers met the criteria, but two were narrative reviews, resulting in five systematic reviews and meta-analyses presented in this literature review. The range of years covered in the literature was from 2022 to 2024.

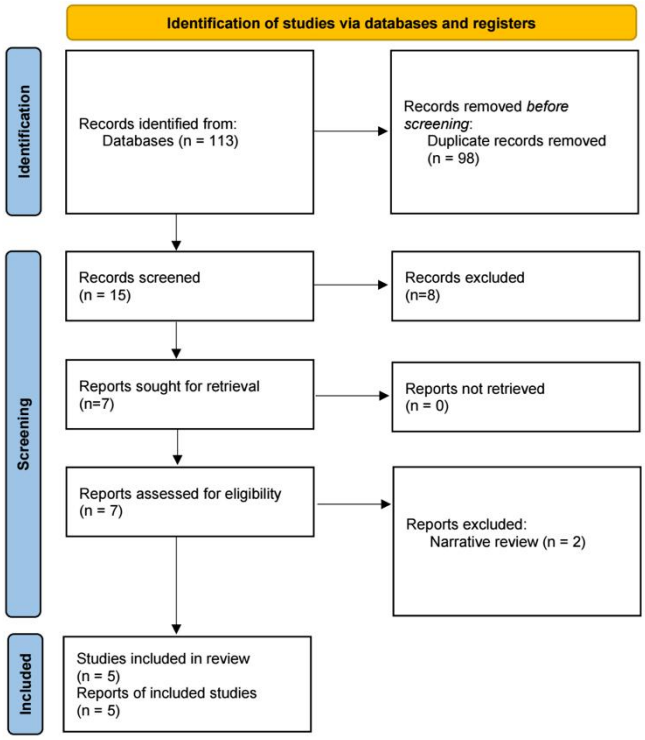


Figure 1. Literature Search

### *3.2 Semaglutide's Pharmacokinetics and Pharmacodinamic*

Clinical use of GLP-1 is hindered by its short half-life in circulation, approximately 1 to 2 minutes, due to proteolytic degradation by the enzymes dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP).[7] Liraglutide, the first-generation GLP-1 receptor agonists, are less vulnerable to enzymatic degradation. Acylation and binding to albumin are key features that extend liraglutide's half-life. Albumin has a half-life of several weeks, so increasing the binding affinity of GLP-1 receptor agonists with albumin can significantly prolong their half-life based on renal elimination. However, a major risk of increasing albumin binding affinity is that the free active fraction will dramatically decrease, reducing in vivo potency and requiring higher doses to achieve efficacy.[8] Therefore, a challenge in developing semaglutide is to ensure that the drug is effective at reasonable dosing and frequency while remaining reversibly bound to albumin with sufficient affinity to prolong its half-life.

Liraglutide has a half-life of 11 to 15 hours after subcutaneous administration, making it suitable for once-daily dosing.[9] There is a strong relationship between the pharmacokinetic and pharmacodynamic properties of GLP-1 receptor agonists, as short-acting GLP-1 receptor agonists significantly delay gastric emptying. In contrast, long-acting drugs, with more than 24 hours of pharmacological exposure, are characterized by better glucose-lowering effects and lower impacts on gastric emptying.[10]

Next-generation GLP-1 receptor agonists are primarily designed as once-weekly dosing. Albiglutide and dulaglutide have a half-life of 5 days, while exenatide, given once a week, has a half-life of 2 weeks. The development of once-weekly subcutaneous semaglutide is encouraged to optimize further metabolic effects, as albiglutide, dulaglutide, and exenatide were less effective than liraglutide in weight loss.[4,11,12] However, albiglutide was withdrawn from the market in 2018 due to economic reasons. Taspoglutide, another once-weekly GLP-1 receptor agonist, has an elimination half-life of 85 hours,

and associated with an increased incidence of hypersensitivity reactions and gastrointestinal side effects, making it clinically unacceptable and resulting in the discontinuation of Phase III clinical trials in 2010.[4,13]

An essential design criterion for semaglutide is keeping its chemical structure close to native GLP-1, minimizing unnecessary amino acid changes to avoid triggering immunogenic responses, a concern observed with exenatide and taspoglutide—semaglutide boasting a longer half-life than liraglutide. Modifications to semaglutide's chemical structure from native human GLP-1 include two amino acid substitutions: alanine to alpha-amino isobutyrate acid at position eight and lysine to arginine at position 34. Additionally, lysine at position 26 undergoes acylation with a linker containing a glutamic acid residue and a diacyl C-18 fatty acid side chain. The substitution at position 8 increases semaglutide's resistance to degradation by DPP-4. The linker enhances the binding of semaglutide to albumin. The substitution at position 34 prevents the C-18 fatty acid diacyl from binding at this position, confining this binding to the sole remaining lysine in semaglutide's structure. These structural adjustments prolong semaglutide's half-life. When administered subcutaneously, semaglutide's half-life is approximately 183 hours in individuals with normal kidney function, 201 hours for those with moderate kidney dysfunction, and 221 hours for those with severe kidney failure.[4,14]

Renal excretion is the primary route for eliminating semaglutide administered subcutaneously, though smaller amounts are also excreted in the feces. Before excretion, semaglutide undergoes metabolism, including cleavage of fatty acid side chains, beta-oxidation, and peptide backbone. In plasma, about 70% to 80% of semaglutide remains intact from the total dose administered. For intact semaglutide excretion, only 3% of the administered dose is detected in urine, and none is found in feces. The metabolism of semaglutide is mainly facilitated by neprilysin (NEP), which is less active on semaglutide than liraglutide and native GLP-1. NEP is primarily located in the kidneys. The role of dipeptidyl peptidase-4 (DPP-4) in the degradation of semaglutide has not been fully explored, but minimal involvement is anticipated due to the presence of alpha-amino isobutyric acid at position 8, which reduces DPP-4-mediated degradation.[3,4]

Factors such as race, gender, age, ethnicity, liver disorders, kidney disease, and injection site do not significantly affect subcutaneous semaglutide pharmacokinetics.[15] In clinical studies, once-weekly subcutaneous semaglutide has shown similar effectiveness and safety profiles in elderly and non-elderly patients, as evidenced by data from the SUSTAIN 1 to 5 trials. Additionally, pharmacodynamic and pharmacokinetic responses and safety profiles were similar between healthy Caucasian and Japanese individuals in randomized trials. The pharmacokinetics, safety, and tolerability of oral semaglutide remain consistent in patients with varying degrees of kidney or liver impairment, indicating that no dose adjustments are necessary based on kidney or liver function.[16–20]

Population pharmacokinetic analyses of once-weekly subcutaneous semaglutide treatment have shown a negative correlation between semaglutide exposure and body weight. The efficacy of semaglutide in lowering glycated hemoglobin (HbA1c) and promoting weight loss increases with higher doses (e.g., 1.0 mg compared to 0.5 mg).[21] Gastrointestinal side effects, associated with higher doses, can be mitigated by gradually increasing the dose. Regarding immunogenicity, once-weekly exenatide has been linked to higher antibody formation, possibly due to lower sequence identity with native GLP-1. In contrast, the percentage of patients developing antibodies is 9% for liraglutide, 3% for albiglutide, and 2% for dulaglutide. About 4% of patients treated with once-weekly semaglutide develop antibodies against the drug, whereas no antibodies were reported in patients receiving once-daily semaglutide at doses of 0.05 to 0.4 mg. These antibodies do not neutralize semaglutide or endogenous GLP-1 in vitro.[4] These antibodies do not have neutralizing effects in vitro on semaglutide or endogenous GLP-1.

### *3.3 Mechanism of Anti-obesity Action of Semaglutide*

Semaglutide operates through several mechanisms to combat obesity. It triggers the secretion of insulin from pancreatic beta cells and reduces the production of glucagon from pancreatic alpha cells, actions that are dependent on glucose levels. By doing so, semaglutide effectively lowers plasma glucose levels during fasting and after meals. Another significant effect of semaglutide is its ability to delay gastric emptying following administration.[22]

In addition to its glucose-lowering effects, semaglutide has been observed to induce weight loss. Studies, such as those conducted by Blundell et al., have delved into the mechanisms underlying semaglutide-induced weight reduction. Specifically, when administered subcutaneously once weekly over 12 weeks (with a titration regimen of 0.25 mg for the first four weeks, 0.5 mg for the next four weeks, and 1.0 mg for the final four weeks), semaglutide led to a more significant decrease in body weight (−5.0 kg) compared to placebo (+1.0 kg) in individuals with obesity who did not have type 2 diabetes and were allowed to eat freely.[5]

The weight loss observed with semaglutide treatment was associated with a lower energy intake during subsequent meals following a standard breakfast, resulting in an overall reduction in total ad libitum energy intake. Importantly, this decrease in energy intake was not attributable to any effect on resting metabolic rate but rather to the suppression of appetite. Semaglutide-treated individuals reported reduced feelings of hunger, decreased food cravings, and diminished preference for high-fat foods. Furthermore, semaglutide improved meal control and portion size among participants.[4,5]

Unlike the weight loss mechanisms of native GLP-1, which primarily involve peripheral actions such as delaying gastric emptying and affecting intestinal motility through activation of gastric mechanoreceptors and vagal nerve signaling to the brainstem's solitary tract nucleus, semaglutide's effects on appetite suppression may involve relevant central mechanisms, particularly within the hypothalamus. Studies on long-acting GLP-1 receptor agonists like liraglutide have demonstrated that their efficacy in promoting weight loss is largely mediated through central mechanisms, including the activation of proopiomelanocortin neurons and regulation via cocaine- and amphetamine-regulated transcript in the arcuate nucleus of the hypothalamus.[23]

Moreover, observations from the SUSTAIN trials indicate that individuals experiencing nausea or vomiting while on semaglutide treatment tended to achieve more pronounced weight loss compared to those without such symptoms. This suggests that nausea or vomiting might indirectly contribute to the weight loss induced by semaglutide. However, mediation analyses have shown that only a small fraction (0.07-0.5 kg) of the total weight loss can be attributed to these gastrointestinal side effects. The weight reductions observed with semaglutide were notably significant, ranging from approximately 2.5 to 5.7 kg and 2.0 to 7.9 kg with doses of 0.5 mg and 1.0 mg, respectively.[24]

The mechanisms behind semaglutide's weight loss effects highlight its multifaceted approach through glucose regulation, appetite suppression, and potential central nervous system modulation, making it a promising therapeutic option in managing obesity among individuals with or without type 2 diabetes

### *3.4 Semaglutide Eficacy*

Five systematic reviews and meta-analyses have demonstrated the effectiveness of semaglutide for weight loss in overweight or obese patients without diabetes. Gao et al. (2022) found that semaglutide positively impacted blood pressure, C-reactive protein, and lipid profiles, albeit with higher gastrointestinal side effects compared to placebo, which were consistent, reliable, and dose-dependent.[6] Moiz et al. (2024) reported significant body weight reduction, with 33.4% of users achieving ≥20% weight loss versus 2.2% with placebo, noting mostly mild and transient gastrointestinal side effects.[25]

Arastu et al. (2022) validated the clinical efficacy of semaglutide, showing an average weight reduction of -11.62 kg.[26] Kommu and Berg (2024) confirmed substantial decreases in body weight, absolute weight, and waist circumference but highlighted increased gastrointestinal side effects and higher discontinuation rates.[27] Lastly, Smith et al. (2022) indicated that semaglutide 2.4 mg achieved greater weight loss over 52 weeks and a higher likelihood of ≥5% weight loss at 12 weeks than all other treatments.[28] Collectively, these studies suggest that semaglutide is an effective weight loss treatment for overweight and obese patients, though gastrointestinal side effects may necessitate discontinuation in some cases.

**Table 1. Summary of The Study**

| Author | Year | Study Design | Results | Recommendation |
|---|---|---|---|---|
| Gao et al. | 2022 | Systematic Review and Meta-analysis | Semaglutide demonstrated beneficial effects on blood pressure, C-reactive protein, and lipid profiles but also showed a higher incidence of adverse effects than placebo, primarily involving gastrointestinal reactions. These results were consistent, reliable, and dose-dependent. | Semaglutide shows good effectiveness in weight loss and an acceptable level of safety for obese or overweight patients without diabetes. |
| Moiz et al. | 2024 | Systematic Review and Meta-analysis | Semaglutide significantly reduced body weight compared to placebo, with 33.4% of users achieving ≥20% weight loss versus 2.2% with placebo. Gastrointestinal side effects were more common with semaglutide but were mostly mild and transient. | Semaglutide is effective for sustained weight loss in overweight/obese patients and those without diabetes. |
| Arastu et al. | 2022 | Systematic Review and Meta-analysis | Patients who were given semaglutide treatment experienced a significant decrease in average body weight, namely -11.62 kg (95% CI: -13.03-(-10.21); P < 0.00001). | The clinical efficacy of semaglutide for the treatment of obesity in the adult, non-diabetic population has been validated |
| Kommu et al. & Berg et al. | 2024 | Systematic Review and Meta-analysis | Semaglutide led to significant reductions in body weight, absolute weight, and waist circumference but was associated with increased gastrointestinal side effects like nausea, vomiting, diarrhea, and constipation. Serious adverse events were insignificant, though | Once-weekly subcutaneous semaglutide can significantly reduce body weight without risk of serious side effects when compared with placebo, in overweight or obese patients without DM. However, gastrointestinal side effects predominate with semaglutide, which may result in |

| | | | | |
|---|---|---|---|---|
| | | | discontinuations due to side effects were higher. | discontinuation of treatment. |
| Smith et al. | 2022 | Systematic Review and Meta-analysis | Semaglutide 2.4 mg resulted in greater weight loss over 52 weeks and a higher likelihood of achieving ≥5% weight loss at 12 weeks than all other treatments. | In a network meta-analysis, semaglutide 2.4 mg effectively achieved ≥5% weight loss across all glucose tolerance groups compared to active comparators, making it a valuable treatment for overweight and obesity. |

### *3.5 Safety of Semaglutide*

Semaglutide, like other GLP-1 agonists, is generally well-tolerated, with gastrointestinal disturbances such as nausea, vomiting, diarrhea, constipation, and dyspepsia being the most common adverse effects. These effects are typically dose-dependent, transient (especially during the initial two weeks of treatment initiation), and generally mild to moderate in severity. Mild hypoglycemia induced by semaglutide is infrequent, while severe hypoglycemia occurs even less commonly. Additional reported side effects in patients treated with semaglutide include headache, nasopharyngitis, influenza virus infections, and elevated levels of pancreatic lipase, though these occur less frequently than gastrointestinal symptoms.[29]

Clinical trials have not shown an increased risk of pancreatitis or pancreatic cancer associated with the use of GLP-1 receptor agonists, including semaglutide. However, isolated cases of acute pancreatitis have been reported with semaglutide, necessitating careful consideration of these findings. There is also a slightly elevated risk of cholecystitis associated with treatment, which requires further investigation.[20,30]

Semaglutide has been observed to increase heart rate, although this effect is not dose-dependent and lacks clinical significance. The rise in heart rate induced by both liraglutide and semaglutide does not diminish the cardiovascular benefits associated with GLP-1 receptor agonist therapy. Nevertheless, an elevated heart rate has historically been linked to increased overall mortality and cardiovascular risks, underscoring the need for ongoing evaluation of the long-term implications of this pharmacological effect.[31]

Results from the SUSTAIN 6 trial indicated a 76% heightened risk of diabetic retinopathy complications (such as blindness, vitreous hemorrhage, and conditions necessitating photocoagulation or intravitreal therapy) in patients treated with semaglutide compared to those on placebo. It is important to note that other SUSTAIN trials have also reported incidences of retinopathy in patients receiving semaglutide. Rapid reductions in blood glucose levels may exacerbate retinopathy, potentially contributing to these findings, although further evidence is required to elucidate this safety concern fully.[4,29]

The risk of discontinuing semaglutide due to gastrointestinal side effects, such as nausea, is comparable to that of other GLP-1 receptor agonists. A meta-analysis has suggested that patients treated with semaglutide experience less nausea than those treated with other GLP-1 receptor agonists. Regarding pharmacokinetics, semaglutide does not necessitate dosage adjustments in patients with impaired kidney or liver function or in those concurrently receiving medications like warfarin, digoxin, atorvastatin, or metformin.[32] Continued vigilance and research are essential to further delineate the safety profile of liraglutide, particularly in long-term use and specific patient populations

## 4. Conclusion

Semaglutide is a promising therapy for the management of obesity and overweight. It offers substantial weight loss benefits and improvements in cardiometabolic health. Its once-weekly dosing regimen and favorable safety profile make it an attractive option for patients struggling with obesity. However, ongoing research is needed to fully understand the long-term implications of semaglutide therapy, including its effects on cardiovascular outcomes and other health parameters.

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