

THE SEMAGLUTIDE TREATMENT EFFECT IN PEOPLE WITH OBESITY: A REVIEW

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ABSTRACT

Background: Over 200 consequences, such as type 2 diabetes, cardiovascular disease, and shortened life expectancy, are linked to obesity, a chronic worldwide health issue. The effectiveness of current pharmaceutical weight-management treatments has been found to be limited. A glucagon-like peptide-1 (GLP-1) receptor agonist called semaglutide has shown promise as a therapy for overweight and obesity. **Methods:** Evidence from the Semaglutide Treatment Effect in People with Obesity is compiled in this review. We conducted a structured narrative review to summarize the current evidence on glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with obesity. Relevant studies were identified through a comprehensive search of PubMed, Embase and Scopus, using the keywords GLP-1 receptor agonists, semaglutide, safety, adverse events and obesity. **Conclusion:** Semaglutide 2.4 mg used once a week is a safe and efficient way for adults who are overweight or obese to manage their weight over time. Its strong effectiveness, cardiometabolic advantages, and manageable safety profile make it a revolutionary pharmaceutical treatment for obesity.

INTRODUCTION

Obesity is a chronic disease and global public health condition defined by a body mass index (BMI) of ≥ 30 kg/m² for White, Hispanic, and Black individuals and ≥ 25 kg/m² for Asians.^[1-4] obesity can increase insulin resistance, hypertension and dyslipidemia.^[5] It is associated with more than 200 complication of morbidity and mortality, like type 2 diabetes (T2D), obstructive sleep apnoea (OSA), cardiovascular disease (CVD), osteoarthritis, and some cancers and the 4 million obesity-related deaths worldwide in 2015.^[6,7,8] recently, obesity has been associated to increased numbers of hospitalizations, the need for mechanical ventilation, and death in persons with coronavirus disease 2019 (Covid-19).^[9,10] In England, about 27% of men and 29% of women were reported to be living with obesity in 2019.^[11] According to World Health Organization (WHO) indicate that 59% of adults and almost one in three children (29% of boys and 27% of girls) in Europe are overweight or living with obesity.^[12] recent WHO, the prevalence of obesity in the Europe is higher than in any other WHO region except for America, and is among the leading causes of death and disability in this region. Of note, while obesity has been

a health issue in high-income countries for many years, the greatest rise in its incidence is now seen in low- and middle-income countries.^[13] The quality of life (QOL) of people with obesity or overweight is often impaired and their lifespan significantly reduced.^[14] A high BMI is linked with decreased life expectancy of up to 10 years compared with those with healthy BMI and, for every 5 kg/m² BMI increment above the range of 22.5–25.0 kg/m², overall mortality is increased by 30%.^[15] In addition to the individual burden, the economic cost associated with obesity should also be noted. The estimated total cost of high BMI to health services worldwide is US\$990 billion per year, which represents 13.2% of total healthcare expenditure.^[13] However, the use of available medications remains limited by modest efficacy, safety concerns, and cost.^[14]

Semaglutide is a drug that has been making waves in the medical community due to its potential to help obese patients manage their weight. It is an injectable glucagon-like peptide-1 (GLP-1) analogue that is approved, at doses up to 1 mg administered subcutaneously once weekly, for the treatment of type 2 diabetes in adults and for reducing the risk of

cardiovascular events in persons with type 2 diabetes and cardiovascular disease. Semaglutide is one of five weight-loss drugs that have been approved. It is receiving a lot of interest in the medical community because of its potential to help obese people control their weight. The maximum dosage of this injectable glucagon-like peptide-1 (GLP-1) analogue is 1 mg given once weekly by subcutaneous injection. It is approved for use in the treatment of adult patients with type 2 diabetes and in reducing the risk of cardiovascular events in individuals who have both type 2 diabetes and cardiovascular disease.^[16] Semaglutide induced weight loss in persons with type 2 diabetes and in adults with obesity who were participants in a phase 2 trial.^[17-18] Once-weekly subcutaneous semaglutide 2.4 mg is being evaluated in individuals who are overweight or obese as part of the Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial development program. Once-weekly subcutaneous semaglutide 2.4 mg has been licensed in Canada, Europe, the UK, and the USA for the chronic control of weight in individuals who are overweight (with weight-related comorbidities) or obese based on findings from the STEP trials.^[19-22] A naturally occurring hormone called GLP-1 is released in response to food consumption and aids in controlling hunger and blood sugar levels. As a GLP-1 receptor agonist, semaglutide 2.4 stimulates the body's GLP-1 receptors. In doing so, it decreases hunger, slows down stomach emptying, and boosts insulin secretion. As a result, eating less food and feeling more satisfied or full is the result.^[23-24-25]

Semaglutide 2.4mg is a revolutionary new treatment for overweight and obesity. It is a FDA-approved medication that is designed to help people lose weight by suppressing their appetite. The medication is administered through an injection that can be taken once weekly. It is available in two doses, 0.5 mg and 1.0 mg, and is prescribed to patients with type 2 diabetes mellitus to improve glycemic control, semaglutide 0.5 mg and 1.0 mg have been shown to reduce cardiovascular events in persons with type 2 diabetes. and oral semaglutide in doses up to 14 mg is also approved for diabetes.^[26] US Food and Drug Administration (FDA) for chronic Weight loss management, consisting orlistat (a lipase inhibitor), phentermine-topiramate, naltrexone-bupropion (neurotransmitter agonists and reuptake inhibitors), liraglutide, and recently, semaglutide; the latter two are glucagon-like peptide-1 receptor agonists [GLP-1 RAs].^[27-28]

How does Semaglutide 2.4mg work?

A ground-breaking medicine for obesity and overweight is semaglutide 2.4 mg. It is a prescription medication that has been shown to help people lose weight. The injectable medication semaglutide 2.4 mg functions by imitating glucagon-like peptide-1 (GLP-1), a hormone that the body naturally produces. By telling the brain when a meal is complete, GLP-1 helps control appetite. Semaglutide 2.4 mg reduces hunger and increases

feelings of fullness by stimulating the brain's GLP-1 receptor. As a result, fewer calories are consumed, which eventually leads to weight loss. Semaglutide 2.4mg also slows down the movement of food through the digestive system, which can help regulate blood sugar levels. This drug is intended for patients who have a BMI of 30 or higher, or a BMI of 27 or higher with at least one weight-related health condition, such as type 2 diabetes. It is important to note that Semaglutide 2.4mg should only be used in conjunction with a healthy diet and exercise program.^[29-30]

Following food consumption, intestinal L-cells quickly release GLP-1 into the bloodstream, where it mediates its actions by activating the GLP-1 receptor, which is distributed throughout the body, including the brain, pancreas, and the GIT.^[31-32]

Multiple meta-analyses and systematic reviews conducted between 2019 and 2024 consistently demonstrate the efficacy of semaglutide in reducing body weight, body mass index (BMI), waist circumference (WC), and improving cardiometabolic risk factors in patients with obesity and type 2 diabetes (T2D). Early evidence (Mishriky *et al.*, 2019; Lingvay *et al.*, 2020) established semaglutide's superiority over other incretin-based therapies and empagliflozin for HbA1c and weight reduction, albeit with a higher frequency of gastrointestinal (GI) adverse events. Subsequent analyses (Zhong *et al.*, 2022; Arastu *et al.*, 2022; Gao *et al.*, 2022; Smith *et al.*, 2022; Tan *et al.*, 2022) confirmed significant weight loss in both diabetic and non-diabetic populations, with mean reductions of 10–12 kg and improvements in BMI, WC, and metabolic risk markers, though consistently reporting increased rates of nausea, vomiting, diarrhea, and treatment discontinuation.

More recent studies (Patoulis *et al.*, 2023; Zhang *et al.*, 2023; Hu *et al.*, 2023) highlighted semaglutide's robust efficacy for glycemic control and weight loss across diverse populations, with optimal outcomes at doses ≥ 2.0 mg weekly, particularly when combined with lifestyle modification. Large pooled analyses in 2024 (Qin, Müllertz, Dorneles, Moiz, Zhang, Wen, Kommu & Berg) further reinforced these findings, showing clinically meaningful weight loss of 11–15% and substantial proportions of patients achieving ≥ 5 –20% weight reduction. Importantly, semaglutide remained well tolerated overall, with GI side effects typically dose-dependent and transient, though discontinuation rates were higher compared to placebo or other GLP-1RAs. Comparative evidence suggests that tirzepatide may provide greater reductions in HbA1c and body weight than semaglutide, but both agents carry a similar burden of GI adverse events. Collectively, the evidence positions semaglutide, particularly the 2.4 mg once-weekly dose, as a highly effective pharmacologic option for sustained weight loss and metabolic improvement in both diabetic and non-diabetic populations, with a predictable and manageable safety profile.^[33] (Table no.1)

Table 1: Effects of semaglutide treatment on body weight: a meta-analysis of studies, ordered chronologically.

Author, year [ref]	Sample	Findings	Conclusion
Mishriky <i>et al.</i> , 2019	5 RCTs, 3769 patients (2161 semaglutide, 1608 incretin-based therapy)	Greater reduction in HbA1c and body weight compared to GLP-1RAs/DPP4 inhibitors. Higher GI adverse events (AEs).	Semaglutide leads to higher HbA1c and weight reduction vs. other incretin therapies, but more GI AEs.
Lingvay <i>et al.</i> , 2020	Indirect comparison: OW semaglutide 1 mg vs. OD empagliflozin 25 mg in T2D on metformin	Semaglutide reduced HbA1c (–0.61%) and BW (–1.65 kg) more than empagliflozin.	OW semaglutide provides superior HbA1c and BW reduction compared to empagliflozin.
Zhong <i>et al.</i> , 2022	4 trials, 3447 patients	OW semaglutide superior to placebo for weight change, waist circumference (WC), BMI, and cardiometabolic risk (CMR).	OW semaglutide yields clinically relevant weight loss in overweight/obese adults.
Arastu <i>et al.</i> , 2022	4 RCTs, 2882 participants with BMI ≥ 27	BW reduction –11.62 kg vs. placebo.	Confirms semaglutide efficacy in obesity treatment (non-diabetics).
Gao <i>et al.</i> , 2022	8 RCTs, 4567 patients	Significant BW loss (–10.09%), BMI (–3.71), WC (–8.28 cm). Improved cardiometabolic risk factors but more GI AEs.	Effective in non-diabetic overweight/obese with acceptable safety.
Smith <i>et al.</i> , 2022	SLR of 108 RCTs, NMA of 41 RCTs	Semaglutide 2.4 mg → higher BW reduction and $\geq 5\%$ BW loss odds vs. comparators.	Effective BW loss across all subpopulations.
Tan <i>et al.</i> , 2022	4 RCTs, 3613 non-diabetic obese	BW reduction –11.85%. GI AEs, discontinuation, and serious AEs higher with semaglutide.	Supports use in obesity management, but higher GI risks.
Patoulias <i>et al.</i> , 2023	5 RCTs, 3760 participants	Greater HbA1c reduction (–0.44%), BW (–2.53 kg) vs. GLP-1RAs, but higher GI AEs.	More effective in T2D but with higher GI risk.
Zhang <i>et al.</i> , 2023	13 RCTs, 5838 participants	Significant BW loss (–8.97 kg, –10%), BMI (–3.19), WC (–7.21). Daily > weekly AEs.	Recommend combining with lifestyle; optimal ≥ 2.0 mg OW dosing.
Hu <i>et al.</i> , 2023	17 RCTs, 14,940 T2D patients	HbA1c (–0.97 to –1.36%), BW reduction, better vs. other drugs. GI AEs \uparrow but not severe.	Improves glycaemic control & BW but increases GI SEs.
Qin <i>et al.</i> , 2024	6 RCTs, 3962 overweight/obese	BW reduction –12.2 kg, BMI –4.5, WC –9.4 cm. Improved BP, FBG, CRP, lipids. GI AEs transient.	Effective & safe for sustained BW loss.
Müllertz <i>et al.</i> , 2024	5 studies, 3288 obese non-diabetic	BW –15%, WC –11.4 cm. Mild GI AEs.	OW semaglutide 2.4 mg induces meaningful BW/WC reductions, well tolerated.
Dorneles <i>et al.</i> , 2024	10 RCTs, 22,155 patients	BMI –4.15; more patients achieved 5–15% BW loss. AEs small risk, but GI AEs & discontinuation \uparrow .	OW semaglutide linked to clinically meaningful BW loss.
Karagiannis <i>et al.</i> , 2024	28 RCTs, 23,622 participants	Tirzepatide > semaglutide for HbA1c & BW reduction.	Tirzepatide more effective, but both \uparrow GI AEs.
Moiz <i>et al.</i> , 2024	4 RCTs, 3087 subjects	BW loss –12.3 kg, 33.4% achieved $\geq 20\%$ BW loss vs. 2.2% placebo. GI AEs \uparrow .	Effective in non-diabetic overweight/obese.
Zhang <i>et al.</i> , 2024	10 RCTs, 9541 patients	Oral semaglutide reduced HbA1c, BW, BMI. More GI SEs vs. placebo/controls.	Oral form effective with good safety.
Wen <i>et al.</i> , 2024	9 RCTs, 5445 T2D patients	Greater BW loss vs. liraglutide/dulaglutide; tirzepatide > semaglutide.	Semaglutide effective, but tirzepatide better.
Kommu & Berg, 2024	9 studies, 11,641 semaglutide vs. 10,479 placebo	BW –11.74 kg, WC –9.06 cm. GI SEs: nausea OR 4.06, vomiting OR 4.43, diarrhoea OR 2.10.	Significant BW loss, but more GI SEs, leading to higher discontinuation.

The following list of acronyms is used: AEs, adverse events; BMI, body mass index; BW, body weight; CFB, change from baseline; Confidence Interval (CI) Cardiometabolic risk factors, or CMRFs; CRP, or CRE, DPP4i, or dipeptidylpeptidase 4 inhibitors; ETD, or estimated treatment difference; GI, gastrointestinal; GLP1RA, glucagonlike 1 receptor agonist; HbA1c, glycated hemoglobin; HRQL, health-related quality of life; FPG, fasting plasma glucose; IPD, patient information MASLD, or steatotic liver disease linked to metabolic dysfunction; WC, waist circumference; WMD, weighted mean difference; RCTs, randomised controlled trials; RR, relative risk; SC, subcutaneous; SLR, systematic literature review; T2D, type 2 diabetes; MD, me and difference; NMA, network metaanalysis; OD, once daily; OW, once weekly.

Adverse Events Associated with GLP-1 Receptor Agonists (GLP-1RAs)

1. Gastrointestinal (GI) Disturbances

Mild to moderate GI side effects (nausea, vomiting, diarrhea, constipation, bloating, reflux, abdominal pain) occur in ~80% of patients in RCTs. They are dose dependent, most frequent during titration, and often improve over time. Real-world surveys show similar rates (nausea 35%, constipation 29%).

2. Gastroparesis & Intestinal Obstruction

Severe GI complications are rare but reported. Pharmacovigilance signals exist for obstruction. A real-world study found higher risks of gastroparesis (HR 3.67) and obstruction (HR 4.22), though criticized for methods. ASA advises withholding GLP-1RAs before surgery due to delayed gastric emptying.

3. Gallbladder & Biliary Disease

Meta-analyses show increased risk of gallbladder/biliary disease (RR ~1.37 overall; higher in weight loss trials RR 2.29). Risk appears dose- and weight loss-related. Real-world studies report modestly higher risks, though results are inconsistent.

4. Pancreatitis & Pancreatic Cancer

Meta-analyses of RCTs show no clear increased risk of pancreatitis or pancreatic cancer. Real-world studies suggest slightly higher pancreatitis rates (4–8/1000 person-years), especially compared to non-GLP-1RA users, but findings remain inconsistent. Some registries suggest reduced pancreatic cancer risk.

5. Thyroid Disorders

Rodent studies raised concerns about thyroid C-cell tumors. FDA contraindicates GLP-1RA in MTC/MEN2, though EMA does not. Meta-analyses suggest a weak association with thyroid disorders (RR 1.28), but real-world studies show no clear link with thyroid cancer.

6. Depression & Suicidality

Despite obesity/T2D being associated with depression, most studies show no increased risk of depression,

suicidality, or self-harm with GLP-1RA use compared to other drugs (HRs close to 1.0).

7. Eye Disorders

SUSTAIN-6 suggested worsening diabetic retinopathy with semaglutide, likely due to rapid HbA1c reduction. Evidence from real-world studies remains conflicting. Recently, GLP-1RAs (notably semaglutide) have been linked to increased risk of non-arteritic anterior ischemic optic neuropathy (NAION), but more research is needed.^[34]

METHODS

We conducted a structured narrative review to summarize the current evidence on glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with obesity. Relevant studies were identified through a comprehensive search of PubMed, Embase and Scopus, using the keywords GLP-1 receptor agonists, semaglutide, safety, adverse events, obesity. Reference lists of key articles and regulatory safety reports from the FDA, EMA, and WHO pharmacovigilance databases were also screened to identify additional studies.

Eligible studies included randomized controlled trials (RCTs), systematic reviews, meta-analyses, large observational or registry-based studies, and pharmacovigilance analyses reporting adverse outcomes related to GLP-1RAs. Case reports, small case series (<10 patients), and studies without relevant safety data were excluded. Evidence from meta-analyses and large RCTs was prioritized.

DISCUSSION

Adults with diabetes or obesity (or overweight with one or more weight-related comorbid illnesses) were identified based on the information above. Semaglutide used in conjunction with a lifestyle modification resulted in an average weight decrease of 14.9% from baseline. This loss was 12.4 percentage points greater than that of the placebo plus lifestyle intervention.^[4] Additionally, 86% of people who took semaglutide lost 5% or more of their baseline body weight, a commonly recognized indicator of a clinically meaningful response, compared to 32% of those who got a placebo.^[35-36-37]

Semaglutide causes weight loss by reducing caloric intake due to decreased hunger, which is believed to be caused by both direct and indirect effects on the brain.^[38-39] Semaglutide-assisted weight loss was associated with better improvements than placebo in terms of cardiometabolic risk factors, such as decreases in blood pressure, glycated hemoglobin levels, lipid levels, and waist circumference; a larger drop from baseline in C-reactive protein, an indicator of inflammation; and a higher percentage of participants experiencing normoglycemia. Given that being overweight or obese severely lowers health-related quality of life, semaglutide

also improved physical functioning as measured by the SF-36 and IWQOLLite-CT.^[40]

The findings suggest that semaglutide may be more effective than a placebo at enhancing blood pressure, weight, cholesterol, and glycaemic management in obese and overweight people. Additionally, more patients in the semaglutide group than in the other placebo group achieved their weight goals. Additionally, semaglutide improves quality of life in relation to health. According to the subgroup analysis, semaglutide's clinically significant effect might have been dose-response related. In terms of safety results, semaglutide medication was linked to higher rates of adverse events and serious adverse reactions (SAEs), particularly gastrointestinal AEs, but not for acute pancreatitis, acute renal failure, or hypoglycemia.^[41]

CONCLUSION

Semaglutide 2.4mg: The Revolutionary Treatment for Overweight and Obesity.

Obesity is a growing concern around the world. As people continue to struggle with their weight, medical professionals are constantly searching for new and innovative ways to help people lose weight and improve their health. One of the most exciting new treatments is the use of Semaglutide 2.4mg. This revolutionary medication has been shown to help people lose weight and keep it off, leading to a healthier and happier life.

In conclusion, semaglutide is a potent glucagon-like peptide-1 (GLP-1) receptor agonist that has shown promising results in the management of overweight or obesity and other comorbid conditions. It works by increasing insulin secretion, decreasing glucagon secretion, and delaying gastric emptying, leading to improved glycemic control.

Semaglutide has a long half-life and is administered subcutaneously once a week, making it a convenient option for patients. It is also associated with weight loss and has shown cardiovascular benefits in clinical trials.

However, like all medications, semaglutide is not without its side effects, which include gastrointestinal disturbances such as nausea and vomiting and abdominal pain.

Overall, once weekly subcutaneously 2.4mg semaglutide has demonstrated efficacy and safety in the management of overweight or obesity with or without diabetes, and its unique pharmacokinetic properties make it a promising option for patients who require additional glycemic control.

We hope you found this article informative and interesting in decoding the mechanism of action and pharmacokinetic properties of Semaglutide. Understanding how this medication works in the body

can be incredibly helpful for individuals with overweight or obesity with or without diabetes or are at risk for developing cardiovascular problems. As always, it's important to consult with your healthcare provider before starting any new medication. We hope that you found this article both educational and helpful in understanding this medication's mechanism of action and pharmacokinetic properties.

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