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UPDATES ON SAFETY AND EFFECTIVENESS OF SEMAGLUTIDE IN WEIGHT LOSS AMONG OBESE PATIENTS WITHOUT DIABETES: A SYSTEMATIC REVIEW

Dr. Nada Zainalabden Tawfeeq[1], Khalil Ibrahim Bo grain[2], Amal Abdullah Alhayek[3], Fatimah Mossa Alahmad[4], Hawra Mohammed Bu hulayqah[5], Zainab Abdulrzzak Aldajani[6], Sakainh Waleed Abdraboh[7], Yara Waleed Alsaeed[8], Sara Abdullah Alali[9], Hawraa Ayesh Al-Ibrahim[10], Maryam Abdulmonem Bukhamsin[11]

[1] Pharmaceutical Chemistry, KSA, [2] Family Medicine Specialist, PHC Alahsa, KSA, [3] Imam Abdulrahman bin Faisal University, KSA,[4] Imam Abdulrahman bin Faisal University, KSA, [5] Imam Abdulrahman bin Faisal University, KSA, [6] Imam Abdulrahman bin Faisal University, KSA, [7] Imam Abdulrahman bin Faisal University, KSA, [8] Imam Abdulrahman bin Faisal University, KSA, [9] Imam Abdulrahman bin Faisal University, KSA, [10] Imam Abdulrahman bin Faisal University, KSA, [11] Imam Abdulrahman bin Faisal University, KSA

Abstract

Objectives: *to conduct a critical assessment and provide an overview of the most recent research on Semaglutide's safety and efficacy in helping obese individuals without diabetes lose weight.*

Methods: *1323 pertinent papers were found after a comprehensive search across four databases. The search produced 511 publications after eliminating duplicates using Rayyan QCRI and screening for relevancy. Of these, 115 full-text articles were examined, and 5 of them satisfied the requirements for evidence synthesis.*

Results: *Less than half of the 27,620 patients in the 5 trials we examined were female (8143, 29.5%). Additionally, emaglutide has been shown to significantly lower cardiovascular event rates in obese patients, which may indicate possible cost savings associated with obesity-related health issues.*

The drug has also emerged as an effective add-on treatment for post-bariatric patients, ensuring prolonged benefits of up to one year regardless of demographic influences. Semaglutide further increases exercise capacity and induces weight loss and improved physical function in heart failure patients compared to placebo. Additionally, it helps non-diabetic individuals at risk lose a significant amount of weight, which lowers the risk of serious cardiovascular events.

Conclusion: *Semaglutide was found to be safe and effective for the management of obesity; its benefits transcend mere weight loss to an improvement in cardiovascular outcomes and the maintenance of weight loss post-surgery. The uniform efficacy across such a diverse range of patients makes this drug a potential key in the management of obesity and its related chronic diseases. Future studies will be required to look at deficiencies in the current body of literature, long-term safety, and optimization of dosing for maximum benefit. Clinically, Semaglutide may not only improve health outcomes for an individual but also reduce the healthcare burden of obesity and cardiovascular diseases.*

Keywords: *Ozempic; Semaglutide; obesity; weight loss; Systematic review.*

Corresponding author:
Dr. Nada Zainalabden Tawfeeq,
Pharmaceutical Chemistry, KSA

QR CODE

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INTRODUCTION

In recent years, the prevalence of obesity has reached epidemic proportions globally, prompting a significant demand for effective weight management solutions. In 2016, more than 1.9 billion adults were classified as overweight, with over 650 million categorized as obese. Childhood obesity is also a concern, affecting an estimated 39 million children under 5 years old in 2020. In the U.S., the CDC reported an obesity prevalence of approximately 42.4% in 2017-2018, reflecting a troubling upward trend associated with various health conditions, including type 2 diabetes and cardiovascular disease.[1] Of them, the drug Semaglutide has attracted a lot of interest, mostly because of its potential to help people with obesity or overweight issues lose weight. Semaglutide was first licensed to treat type 2 diabetes (T2D), but because of its ability to help people lose weight, it is now being investigated as a potential therapy for obesity.[2]

An injectable drug called Semaglutide functions similarly to glucagon-like peptide-1 (GLP-1), a hormone that controls hunger and glucose metabolism. It functions by decreasing stomach emptying, generating a sense of fullness, inhibiting glucagon release, and enhancing insulin secretion.[2] The medication is typically administered once weekly, and its initial indication was for improving glycemic control in adults with T2D. However, researchers soon discovered the collateral effect of weight loss, which has led to extensive studies into its potential use in non-diabetic individuals struggling with obesity.[3]

The STEP (Semaglutide Treatment Effect in People with Obesity) trial series was a crucial investigation that demonstrated Semaglutide's efficacy for weight loss. Semaglutide was administered to patients in these trials who were overweight or obese but did not have diabetes while adhering to lifestyle changes.[4] Over a 68-week period, participants in the 2021 STEP 1 trial lost an average of 14.9% of their body weight, which was much more than the 2.4% average weight reduction of those taking a placebo. Significant weight loss was also demonstrated by other STEP series trials, with some people losing more than 20% of their total weight.[5]

Together, these studies showed that Semaglutide improves cardiovascular risk factors and general metabolic health in addition to facilitating significant weight loss. The results indicate that Semaglutide can be a potent weight control strategy when paired with lifestyle modifications, especially for people who have had trouble with conventional weight loss techniques.[4]

Like all medications, Semaglutide is associated with a range of potential side effects. According to clinical trials, gastrointestinal side effects such as nausea, vomiting, diarrhea, and constipation were the most frequently observed. Even though these symptoms usually go away with time, some people may find them unpleasant. Other less frequent but potentially dangerous adverse effects include allergic responses, renal damage, and pancreatitil.[5]

Importantly, there is also concern regarding the risk of diabetic retinopathy, especially among patients with a history of this condition. The data indicated an increased risk of vision problems in individuals with pre-existing retinopathy who received Semaglutide; hence, careful monitoring of eye health is advised.[2] The long-term safety profile of Semaglutide is still being assessed, but available evidence suggests that the benefits, particularly regarding weight loss and metabolic health, may outweigh the risks for many individuals, especially those with significant obesity-related health complications.[6]

The use of Semaglutide for weight loss raises important considerations that healthcare providers must address. It is essential to ensure that patients are adequately informed about the medication's potential benefits and risks. Given the lifestyle changes that should accompany pharmacotherapy, a comprehensive approach that includes dietary counseling, exercise recommendations, and ongoing behavioral support enhances the likelihood of sustained weight loss and overall success.[7]

Furthermore, patients need to be screened for contraindications and comorbidities before initiating treatment. Semaglutide is not appropriate for everyone; for instance, people who have a personal or family history of multiple endocrine neoplasia syndrome type 2 or medullary thyroid cancer should not use the drug .[5]

Semaglutide's rise as a weight-loss tool highlights a change in thinking about how to treat obesity. Obesity, once thought to be a lifestyle problem, is now more widely acknowledged as a complicated, multifaceted illness that needs medical attention. The effectiveness of Semaglutide in promoting weight loss presents a viable option for individuals struggling to achieve a healthy weight through dietary and behavioral changes alone.[7]

However, it is crucial for patients and healthcare providers to engage in shared decision-making when considering Semaglutide or any weight loss

medication. The person can make an informed decision on Semaglutide's role in their weight management journey if they have a complete grasp of their health status, goals, and potential adverse effects.[8]

Despite the vast literature coverage of Semaglutide in weight loss, it has numerous limitations that have created a dire need to review this topic anew. Previous studies often report short-term efficacy, leaving gaps in understanding the long-term safety profile and sustainability of weight loss with the drug. In addition, most reviews do not comprehensively assess real-world data but rely much on clinical trials within controlled settings that may be devoid of diverse patient populations. Besides, too few comparative analyses with alternative treatments for weight loss allow a complete judgment about the relative efficiency of Semaglutide. The current review covers those lacunas in a greater synthesis of evidence, setting clearer directions for clinicians and policymakers as regards its role in the management of obesity.
This systematic review's main objective is to critically assess and compile the most recent research on Semaglutide's safety and efficacy in helping obese people without diabetes lose weight.

METHODS

PROSERO Registration Number:
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The PRISMA and GATHER criteria were met by the systematic review.

Selection criteria:
Inclusion criteria:

1. Studies including obese patients (BMI ≥25 kg/m²) without a diagnosis of diabetes.
2. Studies assessing the effects of Semaglutide for weight loss.
3. Randomized controlled trials (RCTs), cohort studies, and observational studies.
4. Studies reporting outcomes related to weight reduction, safety, adverse effects, and cardiovascular/metabolic benefits.
5. Articles published in English.
6. Studies with full-text access available for data extraction.

Inclusion criteria:

1. Studies that include diabetic patients or patients with T1D or T2D.
2. Studies evaluating other weight-loss medications or interventions (e.g., lifestyle modifications, bariatric surgery) without semaglutide.
3. Case reports, editorials, letters to the editor, animal studies, and reviews without original data.
4. Studies that do not report weight-loss outcomes or safety-related findings.
5. Non-English studies without available translations.

SEARCH STRATEGY

The PRISMA and GATHER criteria were met by the systematic review. To find pertinent research on Semaglutide's safety and efficacy in helping obese people without diabetes lose weight, a comprehensive search was conducted. Four electronic databases were examined by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed. Included were studies released in 2023–2024. After eliminating duplicates, we uploaded all of the abstracts and titles found by computerized searches into Rayyan. Every text from a paper that satisfied the requirements for inclusion based on its abstract or title was gathered and carefully examined. Two reviewers independently evaluated the appropriateness of the extracted publications and resolved any contradictions through discussion.

Study population—selection

The PICO (Population, Intervention, Comparison, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Obese patients, (ii) Intervention: Semaglutide, (iii) Comparator: Placebo, (iv) Outcome: Effectiveness and safety of Semaglutide.

Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform manner. The data listed below was obtained and noted: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Gender, (vii) Age (viii) Follow-up duration (in weeks), (ix) Obesity cut-of, (x) Mean BMI, (xi) Dosage, (xii) Main outcomes (effectiveness and safety).

Quality review

The selected RCTs underwent a meticulous assessment utilizing the Cochrane Risk of Bias Tool.[9] This framework evaluates the probability of bias across seven key aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and additional potential sources of bias. Each domain's bias level was classified as low, unclear, or high.

Given that residual confounding is a prevalent concern in research within this domain, we employed the ROBINS-I methodology to assess bias susceptibility, as it facilitates a comprehensive analysis of confounding variables. Designed for non-randomized studies, the ROBINS-I instrument is particularly useful for cohort study designs, where individuals subjected to varying staffing levels are observed over time. To ensure objectivity, two independent reviewers appraised the risk of bias for each study, with any discrepancies resolved through consensus discussions.[10]

RESULTS

The specified search strategy yielded 1323 publications **(Figure 1).** 632 articles were assessed using the title and abstract after duplicates (n = 691) were eliminated. Of these, 511 failed to satisfy eligibility criteria, leaving just 115 full-text articles for comprehensive review. A total of 5 satisfied the requirements for eligibility with evidence synthesis for analysis.

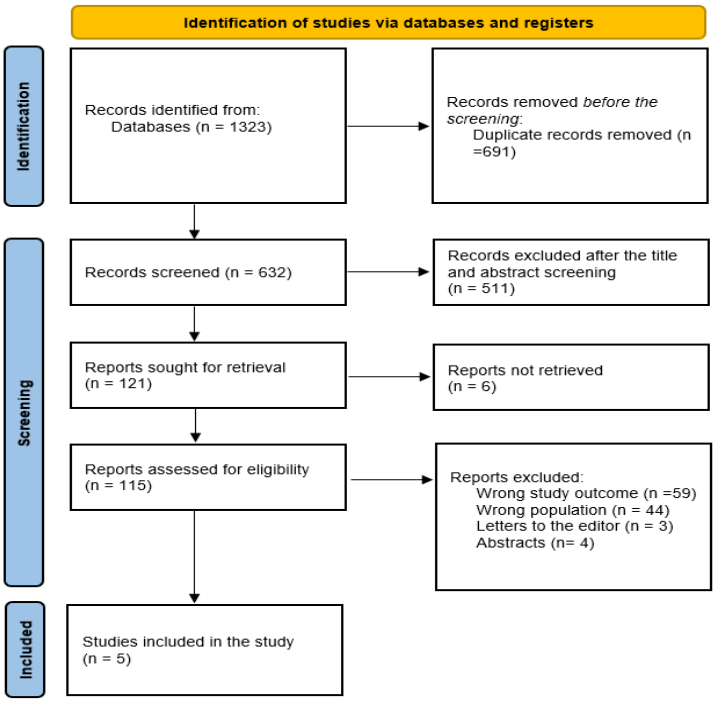


Figure (1): PRISMA flowchart [11]

Sociodemographic and clinical outcomes

Less than half of the 27,620 patients in the 5 studies we included were female (8143, 29.5%). Three of the investigations were RCTs[14-16] and two were retrospective cohorts.[12, 13] Four studies were implemented in the USA [12, 14-16] ,and one in Germany.[13] In cases involving individuals with obesity and an elevated cardiovascular risk profile, Semaglutide appears to contribute significantly to lowering the occurrence obesity.[12] For patients who have undergone bariatric surgery and are facing treatment failure, Semaglutide has been highlighted as a promising adjunct therapy. It seems to offer sustained benefits for up to a year, reinforcing its potential as a long-term intervention in the post-surgical setting. [13] Additionally, Semaglutide has shown marked improvements in weight loss and physical function among individuals with heart failure. These improvements were more substantial when compared to a placebo, indicating Semaglutide's potential in enhancing quality of life through better exercise tolerance and reduced physical limitations.[14]

Another crucial finding is the impact of Semaglutide on weight reduction among people with non-diabetic but at-risk profiles, including those with pre-existing cardiovascular diseases. It effectively decreases the incidence of serious cardiovascular events, highlighting its preventive benefits beyond mere weight management.[15]

The outcomes also suggest that Semaglutide's benefits extend to reducing anthropometric parameters, leading to clinically meaningful weight loss. This effect was consistently superior to placebo in diverse clinical trials, strengthening the evidence for Semaglutide's role as a key agent in weight management, particularly in the context of chronic disease management and prevention.[16]

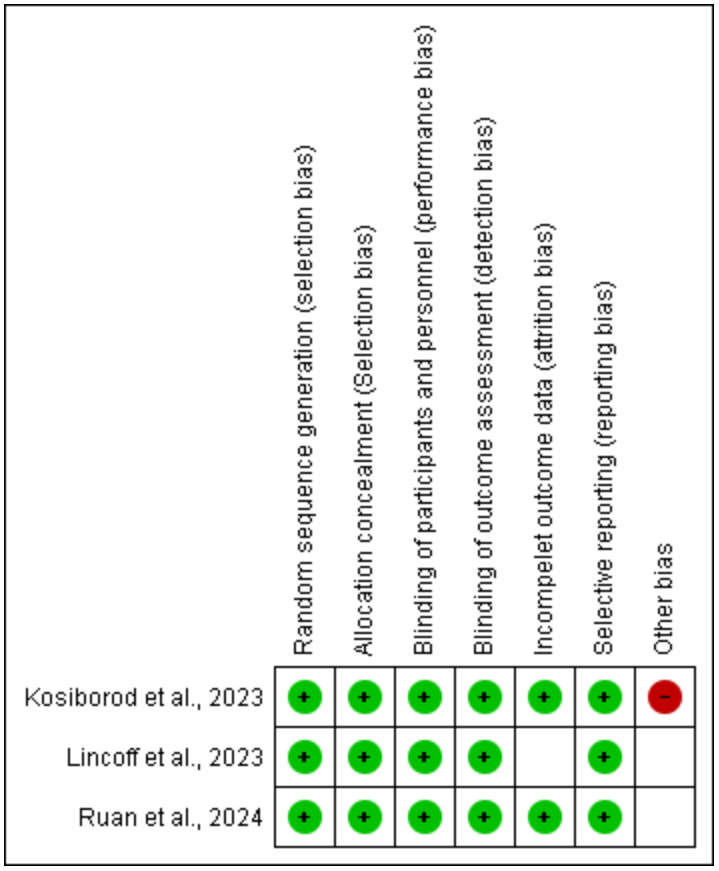
Table (1): Outcome measures of the included studies

Study ID	Study Design	Country	Sociodemographic	Follow-up (weeks)	Obesity (kg/m^2)	Mean BMI	Dosage	Main outcomes
Wong et al., 2023[12]	Retrospective cohort	USA	Cases: 655 Mean age: 47 Females: 498 (76%)	NA	≥30	38±6.5	NM	Semaglutide treatment may significantly lower the prevalence of obesity and CVD events, which could have a significant influence on related medical expenses.
Lautenbach et al., 2023[13]	Retrospective cohort	Germany	Cases: 29 Mean age: 48.5 Females: 24 (82.8%)	48	≥30	50.4 ± 9.5	During the first four weeks, semaglutide was administered at a dose of 0.25 mg weekly; depending on the patient's tolerance, the dosage was increased to 0.5 mg weekly.	This study supports the notion that adjunct medication is a safe and efficient means of treating post-bariatric treatment failure, regardless of the kind of surgery or sex. Semaglutide treatment has long-lasting benefits for post-bariatric patients for up to 12 months after BS.
Kosiborod et al., 2023[14]	RCT	USA	Cases: 529 Mean age: 69 Females: 297 (56.1%)	52	≥30	33.7–41.4	Semaglutide 2.4 mg weekly	In patients with obesity and heart failure with intact ejection fraction, semaglutide (2.4 mg) was more effective than a placebo in improving exercise function, weight loss, and symptom and physical limitation reductions.
Lincoff et al., 2023[15]	RCT	USA	Cases: 8803 Mean age: 61.6 Females: 2448 (27.8%)	38.6	≥25	33.3±5	Semaglutide at a dose of 2.4 mg	People with preexisting cardiovascular disease who were overweight or obese and took 2.4 mg of weekly subcutaneous semaglutide were less likely to die from cardiovascular causes, have a nonfatal myocardial infarction, or have a nonfatal stroke than those who took a placebo. not have diabetes.
Ruan et al., 2024[16]	RCT	USA	Cases: 17,604 Mean age: 61.6 Females: 4876 (27.7%)	208	≥30	NM	Weekly subcutaneous semaglutide 2.4 mg	Semaglutide produced clinically significant weight loss and improvements in anthropometric measurements when compared to a placebo.

NM=Not-mentioned

Table (2): Risk of bias assessment using ROBINS-I

Study ID	Bias brought on by confusion	Bias in the selection of participants into	Prejudice in how interventions are categorized	Bias brought on by departures from the planned interval	Bias brought on by incomplete data	Inaccuracy in outcome measurement	Bias in the selection of reported result	Overall bias
Wong et al., 2023 [12]	Mod	Mod	Low	Low	Low	Low	Low	Low
Lautenbach et al., 2023 [13]	Mod	Mod	Low	Low	Low	Mod	Low	Moderate


Random sequence generation (selection bias)
Allocation concealment (Selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incompelet outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Kosiborod et al., 2023
Lincoff et al., 2023
Ruan et al., 2024

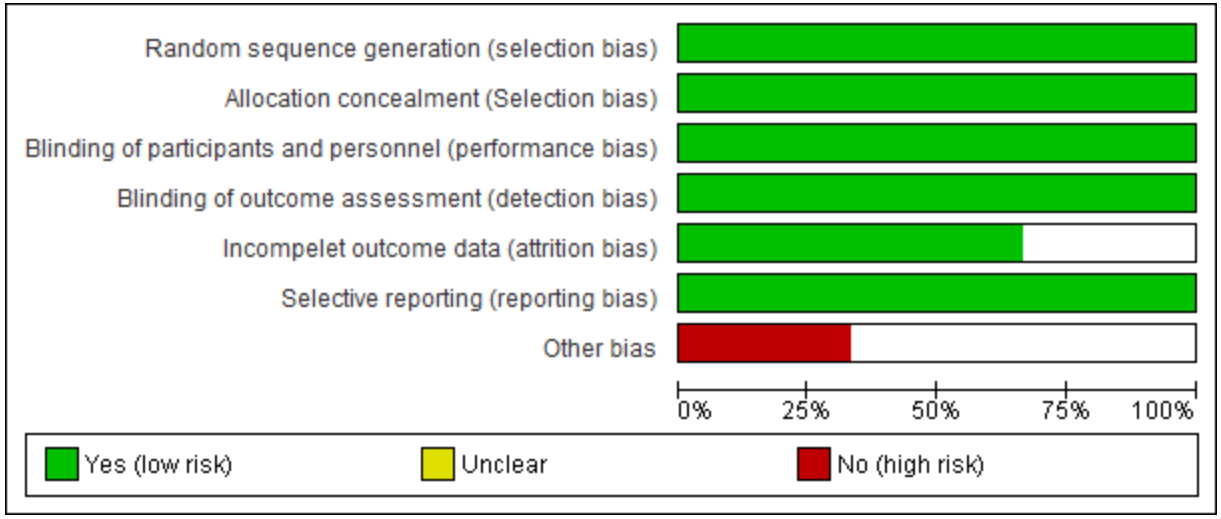


Figure (2): Cochrane risk of bias assessment.

DISCUSSION

The promising role of Semaglutide in the treatment of obesity, cardiovascular health, and weight maintenance following surgery is supported by data from recent research. The results brought to the fore Semaglutide's efficacy as a weight-reducing agent, with benefits extending beyond weight reduction to significant improvements in cardiovascular outcomes.

Most importantly, reductions in obesity-related comorbidities and in cardiovascular events point toward Semaglutide as a dual-purpose intervention that would have an impact both on primary weight management and secondary chronic disease prevention. Evidence so far suggests that Semaglutide is effective across demographic groups and different clinical settings and therefore could be a versatile therapeutic tool for different patient populations.

Deng *et al.* concluded that the clinically significant (≲5%) weight loss that semaglutide therapy produced in obese/overweight persons without diabetes ranged from 48.2% to 88.7%.[17] **Alanazi *et al.*** also found that Semaglutide improves metabolic health indicators in addition to facilitating significant weight loss, improving participants' overall quality of life. Its usage in clinical practice is further supported by its excellent safety profile, which is characterized by a preponderance of mild to moderate adverse effects.[18]
For 30 obese patients, **Blundell *et al.*** conducted two-period crossover studies of once-weekly subcutaneous semaglutide therapy after 12 weeks that were randomized, double-blind, placebo-controlled, and [19]
The individuals were randomly assigned to either the Semaglutide-placebo or placebo-Semaglutide therapy groups throughout two 12-week crossover treatment periods, which were separated by a wash-out interval of five to seven weeks.[19] Semaglutide-induced weight loss was linked to a decrease in appetite, better eating control, fewer food cravings, a relatively higher reduction in body fat than lean body mass, and a decreased preference for fatty, energy-dense meals rather than an increase in energy expenditure.[19]

Our findings included that Semaglutide significantly improves weight loss and physical function in individuals with heart failure, outperforming a placebo. It enhances exercise tolerance and reduces physical limitations, highlighting its potential to improve quality of life.[14,15] Similarly, **Gao *et al.*** found that with adequate safety and high conformity, Semaglutide may successfully enhance the health and quality of life of obese patients by significantly lowering weight and BMI in overweight or obese patients without diabetes. It also has a positive effect on heart-related risk factors like blood pressure, waist circumference, and lipid levels.[5]

Semaglutide is presently available and being studied in an oral formulation, which has demonstrated a notable ability to lower body weight and HbA1c and may make the drug more palatable than the injectable form.[20] Given the results of Semaglutide, researchers are particularly interested in finding out if binding one or more peptide epitopes in conjunction with GLP-1 can lead to greater weight reduction. Among the co-agonists that have shown promising results in the treatment of obesity are GIPR-GLP1R co-agonists, amylin-GLP-1R co-agonists, and glucagon-GLP-1R co-agonists.[21]

The precise mechanism underlying its weight-reducing effects remains uncertain. Research suggests that Semaglutide's interaction with the GLP-1 receptor in the brain may play a role in mediating weight loss. Some studies propose that Semaglutide influences brain regions responsible for appetite regulation through primary and secondary activation, leading to reduced cravings and suppressed hunger.[22]

In support of this, **Gabery *et al.***[23] demonstrated that Semaglutide directly reaches the brainstem, septal nuclei, and hypothalamus, engaging with specific periventricular sites and adjacent ventricles. This interaction triggers c-Fos activation in 10 brain regions, potentially influencing neuronal control of feeding cessation in the lateral parabrachial nucleus.
Although GLP-1RA therapy has been shown to delay gastric emptying for up to an hour post-meal, it does not significantly alter overall gastric emptying. Findings indicate that GLP-1RA therapy is linked to appetite suppression, reduced hunger, decreased preference for calorie-dense foods, modifications in the food reward system, diminished food cravings, and improved dietary regulation. These effects provide substantial evidence supporting the role of GLP-1RA in weight reduction and its mechanism of action.[24]

These findings point to Semaglutide, which may become a new standard element in the therapeutic armamentarium for obesity management, especially in high-risk patients for cardiovascular events. Long-term weight loss and improvement in physical function in heart failure make Semaglutide a potentially desirable choice in comprehensive cardiovascular risk management. For individuals who have had bariatric surgery, Semaglutide may potentially be used as an adjuvant medication to improve outcomes for those who have failed at weight loss surgery. The clinicians may consider Semaglutide

in cases that require sustainable weight management, especially when the other means of intervention have not been quite successful.

Strengths and limitations

These studies reviewed provide a robust analysis across multiple clinical contexts, using diverse populations with a range of methodologies, including RCTs and cohort studies. This diversity supports the generalizability of the findings. The consistency of data regarding benefits from Semaglutide irrespective of patient age, sex, and surgical history further enhances the reliability of these conclusions. Long follow-up in some studies allows for a better understanding of the continued effect of Semaglutide. While the results are encouraging, there are some limitations that need to be considered. A few studies had retrospective cohorts that may introduce a bias in data collection and interpretation. Besides, not all studies had the same dosing regimen; therefore, this might affect the comparability of the various outcomes and limit the possibility to establish a uniform guideline on dosing. Some of the studies did not provide the baseline BMI or the severity of obesity; hence, it limits the degree to which one can assess the overall reach of Semaglutide effects across varied degrees of obesity. Confirmation would require further studies with more homogeneous study designs and standardized dosing protocols.

CONCLUSION

Semaglutide is safe and effective in managing obesity, according to evidence, and it has benefits beyond weight loss, including improved cardiovascular outcomes and maintenance of lost weight post-surgery. Consistent efficacy regardless of patient backgrounds underlines its potential to be a cornerstone in obesity and chronic disease management. With this in view, the direction of future research is needed to overcome such lacunae, study long-term safety, and fine-tune optimum dosing strategy to maximize its benefit profile. Semaglutide's application clinically will be of use not only in improving health outcomes in individuals but also in curbing the health care burden produced by such dangerous companions as obesity and cardiovascular diseases.

ABBREVIATIONS

BMI: body mass index
GIRP: glucose- dependent insulinotropic polypeptides
GLP-1: Glucagon-like peptide-1
RCT: Randomized controlled studies.
T2D: Type 2 Diabetes

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