INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Role Of Semaglutide in The Treatment of Obesity

Harshit kumar*, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh, Gaurav Hastir

St. Soldier Institute of Pharmacy, Lidhran Campus Behind NIT (R.E.C) Jalandhar – Amritsar Bypass Nh-1, Jalandhar 144011, Punjab, India.

ARTICLE INFO

Published: 29 July 2026
Keywords:
Semaglutide, Treatment of Obesity, chronic and multifactorial metabolic disorder
DOI:
10.5281/zenodo.21673207

ABSTRACT

Obesity is a chronic and multifactorial metabolic disorder associated with substantial morbidity, mortality, and an increasing global healthcare burden. The growing prevalence of obesity and its associated comorbidities, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and certain cancers, has highlighted the urgent need for effective long-term therapeutic approaches. Although lifestyle modification, including dietary control and physical activity, remains the foundation of obesity management, maintenance of long-term weight loss is often challenging because of poor adherence and physiological adaptations that promote weight regain.Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a significant pharmacological advancement in obesity treatment. Semaglutide is administered as a once-weekly subcutaneous injection, with dose escalation from 0.25 mg to a maintenance dose of 2.4 mg weekly for chronic weight management. This review summarizes the pathophysiology of obesity and discusses the therapeutic role of semaglutide in weight management. Semaglutide exerts its anti-obesity effects through multiple mechanisms, including appetite suppression, delayed gastric emptying, reduced caloric intake, and improvement in glucose homeostasis. Activation of GLP-1 receptors within the hypothalamus and gastrointestinal tract enhances satiety and decreases food intake, thereby promoting sustained weight reduction.Clinical studies have demonstrated that semaglutide produces significant and sustained reductions in body weight in individuals with and without type 2 diabetes mellitus. In addition to weight loss, semaglutide therapy improves several cardiometabolic risk factors, including insulin resistance, blood pressure, lipid profile, and inflammatory markers. Its prolonged half-life and convenient once-weekly dosing schedule further contribute to improved patient adherence and therapeutic effectiveness Despite its clinical benefits, semaglutide therapy is associated with adverse effects that are predominantly gastrointestinal in nature, including nausea, vomiting, diarrhea, and

***Corresponding Author:** Harshit kumar
Address: *St. Soldier Institute of Pharmacy, Lidhran Campus Behind NIT (R.E.C) Jalandhar – Amritsar Bypass Nh-1, Jalandhar 144011, Punjab, India..*
Email ✉: hk7339223@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

constipation. However, these adverse effects are generally mild to moderate and manageable with gradual dose escalation. Overall, current evidence suggests that semaglutide represents an effective non-surgical therapeutic option for long-term obesity management. Further research focusing on long-term safety, personalized treatment strategies, and combination therapies may its future clinical application in obesity and related metabolic disorders

INTRODUCTION

Obesity is a chronic and multifaceted disease characterized by excessive deposition of adipose tissue or fat which affects overall health. It cause a negative impact on health and raises the rise of serious illness and early death. Obesity is risk factor for multiple set of disease involve cardio vascular disease, kidney disease, type 2 diabetes and other several types of cancer. Clinically obesity is defined adults who have a body mass index (BMI) of 30kg/m² are considered as obese and those who have BMI b/w 25.0 to 29.9kg/m² are considered as overweight.[1,2] Globally the frequency of obesity is rising and raising the concerns of health risk problems connected to this growing issue. Last 50 years obesity prevalence has to increase suddenly on globaly. Obesity or overweight cause more death then underweight. In 2021, 2.11 billion peoples (Male+ female) are affected by obesity or overweight.Globally 2.5 billion adults (18+) were overweight in 2022. Compared to 1990 obesity prevalence increased by 155% in male and 104% in female. Obesity affect about 3.88 billion adults predicted 2050 [3,4].

The obesity in India is increasing quickly and has become a major contributor to the worldwide problem of overweight. According to current estimates approximately 135 million people in India are affected from obesity which highlighting is a serious public health concern. According to the Indian National family health survey-4 obesity prevalence increased significantly over the past 10 years. The percentage of obese women aged 15–49 years increased from 13% to 21% between 2005–2006 and 2015–2016 while the prevalence of obesity among men in the same age range increased from 9.3% to 19%(5).

. The key element of managing obesity continues to be lifestyle modification, which includes food adjustments and increased physical activity. Even though these treatments may result in short-term weight loss but their long-term efficacy is frequently restricted. Long-term weight loss is often undermined by poor adherence and physiological changes including decreased energy consumption and increased appetite, which eventually lead to weight return(6). The most successful treatment for extreme obesity at current time is bariatric surgery, which has also shown significant benefits in decreasing the conditions associated with obesity. However, the need for lifelong nutritional monitoring, perioperative risks, high costs, and limited availability limit its wide use. Also, a large number of people are either unable to have surgical operations done on them and they are not qualified for surgical treatment. Due to issues with safety, poor tolerance, or lack of efficacy, pharmacological treatments for obesity have generally shown limited long-term benefit. All of these drawbacks point to the unfilled demand for sustainable, safe, and efficient pharmaceutical approaches that can help people to lose weight over a long period while addressing the biological causes of obesity(6,7).A complicated neuroendocrine network that includes the gastrointestinal tract, peripheral metabolic organs, and the central nervous system controls body weight. Incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted by the gastrointestinal tract in response to food intake. These hormones are crucial for controlling hunger and maintaining glucose levels after eating. GLP-1 has produced a lot of interest among these hormones because of its broad and significant metabolic effects(7,8). GLP-1 works

by attaching itself to receptors that appear in the pancreatic β-cells, the gastrointestinal tract, and parts of the brain that control appetite. In order to decrease calorie intake, it increases glucose-dependent insulin secretion, inhibits glucagon release, delay stomach emptying time, and encourages satiety. Obesity may be associated with improper appetite control and higher daily calorie intake because of indications of defective incretin signalling in obese people, specifically decreased GLP-1 production and receptor activity(8,9). Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA). It was first developed to treat type 2 diabetes mellitus because of its strong glucose-lowering properties (10). Semaglutide decreases hunger and energy intake while simultaneously improving glycaemic management by activating GLP-1 receptors in central and peripheral tissues(11).Various independent clinical trials have shown that semaglutide medication leads to much higher weight loss then compared to a placebo. It's advantages seen in both people with or without type 2 diabetes [12]. Semaglutide therapy is related to improvements in cardiometabolic risk factors such as blood pressure, lipid parameters, and insulin sensitivity along with weight loss.

2.. Pathophysiology of obesity

Obesity is a chronic metabolic condition defined by a sustained positive energy balance wherein caloric consumption consistently surpasses energy expenditure. This continuous imbalance causes an abnormal accumulation of adipose tissue and triggers metabolic problems associated with obesity. The etiology of obesity is complex that includes abnormal adipocyte proliferation and chronic inflammation both which contribute to systemic metabolic dysfunction, including insulin resistance and chronic inflammation.(14).

A. Energy imbalance and adipose tissue dysfunction

Obesity is fundamentally driven by a chronic positive energy balance in which caloric intake consistently exceeds energy expenditure. Importantly, this imbalance reflects dysregulation of energy homeostasis rather than voluntary overconsumption alone. Energy balance is governed by a complex interaction of genetic susceptibility, environmental influences, behavioral factors, and neuroendocrine control mechanisms (15). The hypothalamus serves as the primary integrative center, processing peripheral metabolic signals such as leptin, insulin, and gut-derived hormones to regulate appetite and energy expenditure (16). Within the arcuate nucleus, neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons stimulate food intake, whereas pro-opiomelanocortin (POMC) neurons promote satiety and increase thermogenesis (17).

In obesity, chronic nutrient excess leads to central leptin resistance and impaired insulin signaling, weakening the feedback systems that normally suppress appetite and maintain body weight stability . This disruption promotes persistent hyperphagia, reduced adaptive thermogenesis, and altered metabolic efficiency. Over time, even a modest but sustained caloric surplus drives adipocyte hypertrophy, progressive adipose tissue expansion, and gradual weight gain . Thus, obesity represents a state of impaired neuroendocrine regulation of energy balance rather than a simple excess of caloric intake(18).

B. Role of hypothalamus and appetite regulation

The hypothalamus plays a vital role in the regulation of appetite levels, energy balance, and body weight. It regulates brain responses that affect eating habits and energy expenditure. Within the hypothalamus, the arcuate nucleus (ARC) involves two primary groups of neurons that produce opposing effects on food intake. The

first category consist of neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons which increase hunger and increase food intake. Pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) of the hypothalamus are the primary neurons that oppose the effects of NPY and AgRP neurons., the pro-opiomelanocortin (POMC) neurons produce anorexigenic peptides such as α-melanocyte-stimulating hormone (α-MSH), which reduce hunger and increase energy consumption. The balance between orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) neural pathways in the hypothalamus is maintaining energy homeostasis(18,19).

The hypothalamus receives feedback signals about the nutritional and metabolic state from peripheral hormones. , insulin and leptin, which are released by adipose tissue, act on hypothalamic neurones to stimulate POMC neurones and inhibit NPY/AgRP activity, which decreases food intake and increases satiety. During fasting, the stomach releases the hormone ghrelin into the bloodstream. Ghrelin acts as an orexigenic (appetite-stimulating) hormone by crossing the blood-brain barrier and directly bind to the growth hormone secretagogue receptor (GHS-R) on Neuropeptide Y/Agouti-Related Peptide (NPY/AgRP) neurons. The central nervous system is able to manage both short-term eating habits and long-term body weight regulation because both hormone signals merge on hypothalamic circuits(20,21,22).

C. Hormonal regulation (insulin, leptin, ghrelin, GLP-1)

The central nervous sy Insulin, leptin, ghrelin, and glucagon-like peptide-1 (GLP-1) are one of the most significant hormones. they are essential for controlling hunger, satiety, and general energy homeostasis. The anorexigenic pro-opiomelanocortin (POMC) neurones and the orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurones are two of the hypothalamic neuronal circuits that these hormonal signals mainly affect. Peripheral hormones affect consumption of energy, food intake, and a long-term body weight regulation by modifying the activation of various pathways.(23) Pancreatic β-cells produce the peptide hormone insulin which function as a significant central satiety signal to regulating glucose metabolism. In blood insulin can bind to insulin receptors in the hypothalamus after passing through the blood–brain barrier. Insulin inhibits orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurones and stimulates anorexigenic pro-opiomelanocortin (POMC) neurones in the hypothalamus to reduce appetite. Insulin plays an important role in regulating long-term energy balance and controlling body weight through the activation of these neural pathways. Poor insulin signalling in the central nervous system can interfere with controlling appetite and lead to obesity. (24).

Leptin is a hormone mostly produced by adipose tissue that plays a crucial role in long-term energy homeostasis and reflects the amount of body fat stores. It increases energy consumption and decreases appetite by acting on hypothalamic leptin receptors. It stimulat anorexigenic POMC (pro-opiomelanocortin) neurones and suppressing orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurones to reduces food intake.Leptin resistance is a condition where high levels of circulating leptin fail to suppress appetite in individuals with obesity , which interferes with the normal feedback mechanisms involved in weight control. High circulating leptin levels are unable to decrease appetite in many obese persons. (25).

leptin and insulin, ghrelin primarily acts as a hunger-stimulating hormone. It is released primarily by endocrine cells in the stomach, and its circulating levels usually rise during fasting and

fall after eating. Ghrelin activates NPY and AgRP neurones in the hypothalamic arcuate nucleus to enhance food intake and increase appetite. It also associates with other metabolic
hormones to regulate energy balance and feeding behaviour (26).
, intestinal L-cells release the incretin hormone glucagon-like peptide-1 (GLP-1). GLP-1 is important for controlling hunger and fullness to increasing glucose-dependent insulin production. The brainstem and hypothalamus are two areas of the brain where GLP-1 receptors are widely distributed. When these receptors are activated, food intake is decreased, stomach emptying decreases, and feelings of fullness are increased. GLP-1 regulates energy balance and reduces calorie intake through several ways. , GLP-1 receptor agonists, such semaglutide, have been developed and are now commonly used in the pharmacological treatment of obesity.
(27).

D. Inflammation and insulin resistance.
Chronic low grade inflammation is a key characteristics of obesity which also lead significantly to the development of insulin resistance. Overconsumption of energy causes cellular stress, local hypoxia, and metabolic dysfunction by promoting adipocyte hypertrophy and the growth of adipose tissue. The subsequent inflammatory reaction leads to the chronic inflammation linked to insulin resistance and disrupts regular metabolic homeostasis. (28,29).
Increased production of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) is a sign of the inflammatory response in obese adipose tissue. In peripheral tissues such skeletal muscle, the liver, and adipose tissue, these mediators interfere with insulin signalling pathways. As a result, insulin's capacity to control glucose metabolism and promote glucose absorption is reduced and leading to insulin resistance. The accumulation of high quantities of circulating free fatty acids (FFAs) in non-adipose tissues, such as the liver, heart, and skeletal muscle, leads to a pathological condition known as lipotoxicity and cause metabolic dysfunction (30).

3. Mechanism of Action of Semaglutide in Obesity
Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) designed to treat type 2 diabetes mellitus and overweight or obesity. It is structurally similar to endogenous form of GLP-1 and mimics its physiological functions in appetite management, glucose homeostasis and energy balance (31,32). The structural modifications of semaglutide increase the binding affinity for albumin and provide resistance to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) which lead to a long elimination half-life of approximately one week. These pharmacokinetic property make it easy to administer once a week and provide a sustained activation of GLP-1 receptor (33).
The anti-obesity effects of semaglutide are influenced by coordinated actions on the central nervous system (CNS), gastrointestinal tract (GIT) and pancreatic endocrine system. GLP-1 receptors are widely distributed in many tissues such as hypothalamus, brainstem, pancreas and gastrointestinal tract (GIT) (34). The main mechanism for weight loss stimulated by semaglutide is central regulation of appetite. Activation of GLP-1 receptors in the arcuate nucleus of the hypothalamus leads to stimulation of anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurones and inhibition of orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) signalling pathways (35).
This regulation of neuronal activity leads to a decrease in calorie intake. It causes satiety and reduces the feeling of hunger.Beyond its effects on

homeostatic appetite regulation semaglutide impacts mesolimbic reward pathways involved in hedonic eating behaviour. Research in neurobiology has shown that activation of the GLP-1 receptor decreases the activity of brain regions which involved in food craving and reward processing. Consequently patients have greater control over their eating habits and reduced appetites for calorie-dense foods.
The gastrointestinal effects of semaglutide are also important, as it slows gastric emptying process, especially in the early phase of treatment (36).

Prolonged gastric distension enhances satiety signalling through the vagal afferent pathways resulting in the reduction of meal size and caloric intake.Delayed gastric emptying has a significant impact in the initial stages of the weight loss, but its effect decreases gradually during long-term therapy.At the pancreatic level, semaglutide increases glucose-dependent insulin secretion from pancreatic β-cells, while inhibiting glucagon release from α-cells (37).

Insulin secretion is glucose-dependent, so the risk of hypoglycaemia is low in the absence of concomitant insulin or sulfonylurea therapy. Better control of glucose levels reduces glucotoxicity and promotes beneficial metabolic changes that help in obesity management.The weight loss with semaglutide occurs due to a number of physiological mechanisms including incretin signalling, hypothalamic pathways associated with appetite regulation, vagal afferent signalling, and metabolic pathways responsible for homeostasis of glucose and lipids (38).
Semaglutide produces a persistent negative energy balance and considerable and sustainable weight loss through the modulation of these interlinked neuroendocrine pathways.Clinical research has shown that compared to a decrease in lean body mass semaglutide-mediated weight loss is mostly associated with decreases in adipose tissue mass, especially visceral fat (39).

Semaglutide therapy has been established to address the larger metabolic dysfunction associated with obesity by improving a variety of cardiometabolic risk variables such as blood pressure, insulin sensitivity, lipid profile, and inflammatory indicators, in addition to helping patients lose weight. Although obesity is now considered to be a chronic neuroendocrine and metabolic condition rather than only the result of excessive calorie consumption or physical inactivity .These pathways are particularly crucial for managing obesity. Because compensatory biological adjustments encourage increased hunger and subsequent weight regain.conventional lifestyle therapies often fail to achieve sustained long-term weight loss(40).

4.Pharmacokinetics of Semaglutide

(a) Absorption
The maximum bioavailability of semaglutide after subcutaneous administration is approximately 89% , which indicates efficient absorption. Peak plasma concentrations are usually achieved within 1 to 3 days after the injection and steady-state concentrations are usually achieved after 4 to 5 weeks of once-weekly administration(41). Oral semaglutide is relatively poorly absorbed due to poor gastrointestinal(GI) permeability and enzymatic degradation, as with other peptide-based therapeutics. To overcome these drawbacks oral semaglutide is co-formulated with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) which promotes transcellular absorption across the gastric mucous membrane. After oral administration peak plasma concentrations are usually achieved within 1 hour(42).

(b) Bioavailability
The maximum bioavailability of semaglutide is approximately 89–94% which indicates good systemic absorption of semaglutide. On the other

hand, oral semaglutide is comparatively poorly bioavailable (0.4–1%) even when co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). The absorption of oral semaglutide is highly dependent on food intake and volume of water consumed when administered, both of which can greatly affect its bioavailability(43).

(C) Distribution

Semaglutide is strongly bound to plasma albumin (>99%) which contributes to its long systemic half-life and low renal clearance . The apparent volume of distribution after subcutaneous administration is approximately 12.5 L, and after oral administration it is about 8 L in healthy individuals(44).

(d) Metabolism

Metabolic degradation of semaglutide occurs primarily by proteolytic cleavage of the peptide backbone, followed by β-oxidation of the attached fatty acid side chain. compared to most small-molecule drugs, semaglutide is not metabolised by a single organ, such as the liver, but is slowly degraded through a number of metabolic pathways in the body(45)

(e) Elimination

The kidneys and faeces eliminate semaglutide. Approximately 3% of the administered dose is excreted unchanged in the urine and the balance is eliminated as products of metabolic degradation. The low systemic clearance of semaglutide is partly responsible for its long half-life(45).

(f) Half-life

Semaglutide has an elimination half-life of approximately one week (~168 hours) which allows for convenient once-weekly dosing. Semaglutide has a long half-life and may remain in circulation for almost five weeks after the last dose. The long duration of action is mainly due to its strong binding to plasma albumin and resistance to degradation by dipeptidyl peptidase-4 (DPP-4) (42,44,).

5.Clinical Efficacy of Semaglutide in Obesity

Semaglutide has shown significant efficacy in the treatment of obesity in a series of randomized clinical o trials. All persons who received semaglutide plus lifestyle modification experienced significant reductions in body weight, BMI, and waist circumference.The Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial programme provided solid evidence supporting the role of semaglutide for long-term weight management. In the STEP 1 trial, adults with obesity or overweight without diabetes who received semaglutide 2.4 mg once weekly for 68 weeks achieved a mean weight reduction of approximately 14.9% compared with 2.4% in the placebo group (46). Additionally, a large proportion of participants achieved clinically significant weight loss of ≥10% and ≥15% from baseline.

Semaglutide was evaluated in people with type 2 diabetes mellitus and obesity in the STEP 2 trial. Semaglutide 2.4 mg treated subjects achieved better glycaemic control and greater reductions in body weight compared to placebo, signifying efficacy in both metabolic regulation and obesity management (47). Similarly, the STEP 3 and STEP 4 studies gave further evidence of long-term weight-loss benefits of semaglutide in combination with rigorous behavioural therapy and ongoing treatment (48,49. The trials also demonstrated improvements in cardiometabolic risk variables, such as blood pressure, lipid profile, insulin sensitivity, and inflammatory markers. Along with reductions in total body weight, semaglutide therapy has been linked to reductions in waist circumference and visceral adiposity, both of which are closely associated with metabolic and cardiovascular risk(50).

Table: Major STEP Trials Evaluating Semaglutide in Obesity

Trial	Population	Duration	Dose	Main Outcome
STEP 1	Obesity/overweight without diabetes	68 weeks	2.4 mg weekly	~14.9% mean weight loss
STEP 2	Obesity with type 2 diabetes	68 weeks	2.4 mg weekly	Significant weight and HbA1c reduction
STEP 3	Obesity with intensive behavioural therapy	68 weeks	2.4 mg weekly	Greater weight reduction than placebo
STEP 4	Continued vs withdrawal therapy	68 weeks	2.4 mg weekly	Sustained weight loss with continued treatment

6.Safety and Adverse Effects

Semaglutide is considered a safe and efficient pharmacological agent in the management of obesity in the general population. It is associated with multiple adverse drug reactions, primarily affecting the gastrointestinal system. The most frequent side effects in the Semaglutide - Treatment Effect in People with Obesity (STEP) program under clinical trials were vomiting, nausea, diarrhea, constipation, abdominal discomfort and loss of appetite. These incidents were mostly mild to moderate severity and occurred primarily during dose elevation phase of treatment. GI intolerance also constituted the most frequent reason for stopping treatment in patients on semaglutide. In the STEP-1 study, about 74% of people taking semaglutide reported gastrointestinal side effects, compared to 48% of those taking a placebo(51).

(a) Gastrointestinal adverse effects

Gastrointestinal reactions are the most frequently reported adverse effects associated with semaglutide therapy. The STEP-1 clinical trial reported gastrointestinal adverse events in approximately 74% of patients receiving semaglutide compared with 48% in the placebo group. Common symptoms included nausea, diarrhea, vomiting, constipation, abdominal pain, and reduced appetite. These effects were generally mild to moderate in severity and occurred mainly during dose escalation. In some patients, severe gastrointestinal intolerance resulted in discontinuation of therapy.(52).

(b). Gallbladder and hepatobiliary disorders:

Semaglutide treatment has been associated with an increased risk of gallbladder-related complications, including cholelithiasis and cholecystitis. Rapid weight loss and altered gallbladder motility are considered possible contributing mechanisms. Clinical studies demonstrated a slightly higher incidence of gallbladder disease in semaglutide-treated patients compared with placebo group(53).

(c). Acute pancreatitis

Cases of acute pancreatitis have been reported during semaglutide therapy, although the incidence remains low. Current evidence does not clearly establish a direct causal association; however, caution is recommended in patients with a previous history of pancreatitis. Persistent severe abdominal pain with nausea or vomiting should be evaluated promptly(54).

(d). Hypoglycemia

Semaglutide alone rarely causes hypoglycemia because its insulin secretion is glucose dependent. However, the risk increases when used in combination with insulin or sulfonylureas. Dose

adjustment of concomitant antidiabetic medications may therefore be required(55).

(e). Neurological and general adverse effects:
Additional adverse effects observed with semaglutide therapy include headache, dizziness, fatigue, dyspepsia, and injection-site reactions. Mild increases in heart rate have also been reported in clinical studies(56).

(f). Renal complications:
Rare cases of acute kidney injury have been reported, mainly secondary to dehydration caused by severe nausea, vomiting, or diarrhea. Adequate hydration and monitoring of renal function are recommended in susceptible patients(57).

(g). Overall safety profile:
Semaglutide demonstrates a favorable safety and tolerability profile in obesity management. Most adverse effects are manageable with gradual dose escalation, dietary counseling, and regular monitoring. The therapeutic benefits in weight reduction and cardiometabolic improvement generally outweigh the potential risks when treatment is appropriately supervised(58).

FUTURE PERSPECTIVES

Semaglutide has emerged as an important therapeutic option in the management of obesity because of its substantial effects on body weight reduction and metabolic improvement. Findings from the STEP clinical trial program support its potential role in the long-term treatment of obesity as a chronic metabolic disorder rather than a condition related solely to lifestyle factors (59).
Future studies are expected to focus on the long-term efficacy and safety of semaglutide therapy. Although current evidence demonstrates significant and sustained weight loss during treatment, additional research is required to determine the durability of these effects after treatment discontinuation and to evaluate the necessity for long-term maintenance therapy . Further investigations in pediatric, geriatric, and high-risk populations may also expand its clinical applicability Recent advances in incretin-based therapies suggest that combination approaches targeting multiple metabolic pathways may provide greater therapeutic benefits. Dual and triple receptor agonists acting on GLP-1, GIP, and glucagon receptors are currently being investigated for their potential to produce greater reductions in body weight and improvement in metabolic parameters compared with semaglutide monotherapy (60).
Personalized treatment strategies may further enhance the clinical utility of semaglutide. Identification of genetic, metabolic, and behavioral predictors associated with treatment response could help optimize patient selection and improve therapeutic outcomes while minimizing adverse effects .In addition to weight reduction, semaglutide has shown beneficial effects on several obesity-related comorbidities, including cardiovascular risk factors, insulin resistance, and non-alcoholic fatty liver disease. Ongoing clinical studies may further establish its role as a comprehensive metabolic therapy with broader clinical applications .
Despite its therapeutic potential, challenges such as high treatment cost, limited accessibility, gastrointestinal adverse effects, and the need for long-term safety monitoring remain important considerations. Future pharmacoeconomic evaluations and healthcare strategies may help improve the accessibility and affordability of semaglutide therapy worldwide (61)

CONCLUSION

Obesity is a complex chronic metabolic disorder associated with increased morbidity, mortality, and a substantial global healthcare burden. Conventional management strategies, including

dietary modification, physical activity, and behavioral interventions, often demonstrate limited long-term effectiveness because of compensatory physiological mechanisms that promote weight regain. In this context, semaglutide has emerged as a significant pharmacological advancement in obesity management. As a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide exerts its therapeutic effects through multiple interconnected mechanisms involving appetite suppression, reduced caloric intake, delayed gastric emptying, and improved glucose homeostasis. Clinical studies have demonstrated that semaglutide produces significant and sustained weight reduction together with favorable improvements in cardiometabolic risk factors, including insulin resistance, blood pressure, lipid profile, and inflammatory markers.

The favorable pharmacokinetic profile of semaglutide, particularly its prolonged half-life and convenient once-weekly dosing schedule, contributes to improved patient compliance and treatment adherence. Despite its clinical efficacy, semaglutide therapy is associated with several adverse effects, predominantly gastrointestinal in nature, including nausea, vomiting, diarrhea, and constipation. Although these adverse events are generally mild to moderate and manageable with gradual dose escalation, long-term safety monitoring remains important. In addition, factors such as high treatment cost, limited accessibility, and maintenance of weight loss following treatment discontinuation continue to represent significant clinical challenges. Nevertheless, semaglutide represents a major therapeutic advancement in obesity management and offers an effective non-surgical approach for sustained weight reduction. Ongoing research focused on combination therapies, personalized treatment strategies, and long-term safety evaluation may further enhance its therapeutic potential and establish its broader role in the management of obesity and associated metabolic disorders.

REFERENCES

1. GBD 2015 Obesity Collaborators, Afshin, A., Forouzanfar, M. H., Reitsma, M. B., et al. (2017). Health effects of overweight and obesity in 195 countries over 25 years. *New England Journal of Medicine, 377*(1), 13–27. https://doi.org/10.1056/NEJMoa1614362
2. Al Kibria, G. M. (2019). Prevalence and factors affecting underweight, overweight and obesity using Asian and World Health Organization cutoffs among adults in Nepal: Analysis of the Demographic and Health Survey 2016. *Obesity Research & Clinical Practice, 13*(2), 129–136. https://doi.org/10.1016/j.orcp.2019.01.006
3. World Health Organization World Health Organization. (2025, December 8). *Obesity and overweight*. World Health Organization. WHO Official Page
4. GBD 2021 Adult BMI Collaborators. (2025). Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: A forecasting study for the Global Burden of Disease Study 2021. *The Lancet, 405*(10481), 813–838. https://doi.org/10.1016/S0140-6736(25)00355-1
5. Ahirwar, R., & Mondal, P. R. (2019). Prevalence of obesity in India: A systematic review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13*(1), 318–321. https://doi.org/10.1016/j.dsx.2018.08.032
6. Holst, J. J. (2024). GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. *Nature Metabolism, 6*, 1866–1885.
7. Nauck, M. A., & Meier, J. J. (2018). Incretin hormones: Their role in health and disease.

Diabetes, Obesity and Metabolism, 20(Suppl 1), 5–21

8. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of GLP-1. *Cell Metabolism, 27*(4), 740–756.
9. Yamanouchi, D. (2025). Roles of incretin hormones GIP and GLP-1 in metabolic and cardiovascular health. *International Journal of Molecular Sciences, 27*(1), 27.
10. Salvador, R., Moutinho, C. G., Sousa, C., Vinha, A. F., Carvalho, M., & Matos, C. (2025). Semaglutide as a GLP-1 agonist: A breakthrough in obesity treatment. *Pharmaceuticals, 18*(3), 399. https://doi.org/10.3390/ph18030399
11. Gibbons, C., Blundell, J., Tetens Hoff, S., Dahl, K., Bauer, R., & Baekdal, T. (2021). Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. *Diabetes, Obesity and Metabolism, 23*(2), 581–588. https://doi.org/10.1111/dom.14255
12. Wilding, J. P. H., Batterham, R. L., Calanna, S., et al. (2021). Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine, 384*(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183
13. Rubino, D., Abrahamsson, N., Davies, M., et al. (2021). Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity. *Journal of the American Medical Association, 325*(14), 1414–1425. https://doi.org/10.1001/jama.2021.3224
14. Hill, J. O., Wyatt, H. R., & Peters, J. C. (2012). Energy balance and obesity. *Circulation, 126*(1), 126–132. https://doi.org/10.1161/CIRCULATIONAHA.111.087213
15. Redinger, R. N. (2007). The pathophysiology of obesity and its clinical manifestations. *Gastroenterology & Hepatology, 3*(11), 856–863.
16. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404(6778):661–671. Doi:10.1038/35007534.
17. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. *Nature.* 2006;443(7109):289–295. doi:10.1038/nature05026
18. Sohn JW. Network of hypothalamic neurons that control appetite. *BMB Rep.* 2015;48(4):229–233. doi:10.5483/BMBRep.2015.48.4.272. PMID: 25968293.
19. Vohra MS, Benchoula K, Serpell CJ, Wong EH. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. *Eur J Pharmacol.* 2022;915:174611. doi:10.1016/j.ejphar.2021.174611. PMID: 34922112
20. Swart I, Jahng JW, Overton JM, Houpt TA. Hypothalamic neuropeptide Y, agouti-related peptide, and proopiomelanocortin mRNA responses to leptin and refeeding in mice. *Am J Physiol Regul Integr Comp Physiol.* 2002;283(5):R1196–R1202. doi:10.1152/ajpregu.00232.2002. PMID: 12388467
21. Kuo DY. Participation of ghrelin signalling in hypothalamic NPY/POMC-mediated appetite control. *Appetite.* 2017;123:1–8. doi:10.1016/j.appet.2017.01.009. PMID: 28108231.
22. Friedman JM. The emerging science of body weight regulation and its impact on obesity treatment. *J Clin Invest.* 2003;111(7):999–

1006. doi:10.1172/JCI18547. PMID: 12671049.

23. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404(6778):661–671. Doi:10.1038/35007534.
24. Brüning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. *Science.* 2000;289(5487):2122–2125. doi:10.1126/science.289.5487.2122.
25. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature.* 1998;395(6704):763–770. doi:10.1038/27376.
26. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature.* 1999;402(6762):656–660. doi:10.1038/45230.
27. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* 2018;27(4):740–756. doi:10.1016/j.cmet.2018.03.001.
28. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444(7121):860–867. doi:10.1038/nature05485
29. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science.* 1993;259(5091):87–91. doi:10.1126/science.7678183.
30. Unger RH, Orci L. Lipotoxic diseases of nonadipose tissues in obesity. *Proc Natl Acad Sci USA.* 2000;97(22):12757–12762. doi:10.1073/pnas.97.22.12757.
31. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;384(11):989–1002. doi:10.1056/NEJMoa2032183
32. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 analogue semaglutide. *J Med Chem.* 2015;58(18):7370–7380. doi:10.1021/acs.jmedchem.5b00726.
33. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide pharmacokinetics and safety. *Diabetes Obes Metab.* 2015;17(12):1230–1237. doi:10.1111/dom.12542.
34. Drucker DJ. The biology of incretin hormones. *Cell Metab.* 2006;3(3):153–165. doi:10.1016/j.cmet.2006.01.004.
35. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 receptor signaling in CNS regulation of appetite. *Gastroenterology.* 2007;132(6):2131–2157. doi:10.1053/j.gastro.2007.03.054.
36. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. *Diabetes Obes Metab.* 2018;20(Suppl 1):5–21. doi:10.1111/dom.13129.
37. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying. *Diabetologia.* 1997;40(7):716–723. doi:10.1007/s001250050750.
38. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. *Nat Rev Neurosci.* 2014;15(6):367–378. doi:10.1038/nrn3745.
39. Wilding JPH, et al. STEP 1 trial body composition outcomes (semaglutide fat loss predominance). *N Engl J Med.* 2021;384:989–1002.
40. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Lancet.* 2018;392(10156):2260–2272. doi:10.1016/S0140-6736(18)31863-6.
41. Overgaard RV, Jonassen I, Sidelmann UG, Donsmark M. Pharmacokinetics of subcutaneous semaglutide in healthy subjects.

Clin Pharmacokinet. 2017;56(11):1357–1364. Doi:10.1007/s40262-017-0556-8.

42. Bækdal TA, Borregaard J, Donsmark M, Breitschaft A, Jacobsen JB, Jensen CB. Effect of oral semaglutide on pharmacokinetics and pharmacodynamics in healthy subjects. *Clin Pharmacokinet.* 2018;57(11):1495–1505. doi:10.1007/s40262-018-0648-0.
43. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of oral semaglutide enabled by SNAC: mechanism and pharmacokinetics. *Sci Transl Med.* 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047
44. Granhall C, Donsmark M, Blicher TM, et al. Pharmacokinetics, safety and tolerability of semaglutide. *J Clin Pharmacol.* 2018;58(12):1560–1569. doi:10.1002/jcph.1286.
45. Marbury TC, Flint A, Jacobsen JB, Derving Karsbol J, Lasseter K. Metabolism and elimination of semaglutide in humans. *Diabetes Ther.* 2017;8(3):617–627. doi:10.1007/s13300-017-0252-7..
46. 46.Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity (STEP 3). JAMA. 2021;325(14):1403–1413. Doi:10.1001/jama.2021.1831. PMID: 33625475.
47. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. *JAMA.* 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224. PMID: 33625476.
48. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity and type 2 diabetes (STEP 2). *Lancet.* 2021;397(10278):971–984. doi:10.1016/S0140-6736(21)00213-0. PMID: 33667417.
49. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity (STEP 3). *JAMA.* 2021;325(14):1403–1413. doi:10.1001/jama.2021.1831. PMID: 33625475.
50. 50.Wilding JPH, et al. STEP 1 trial (baseline efficacy reference already widely indexed in PubMed). N Engl J Med. 2021;384:989–1002
51. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: STEP 1 extension study. *Diabetes Obes Metab.* 2022;24(9):1553–1564. doi:10.1111/dom.14725. PMID: 35703191.
52. Rubino D, et al. STEP 4 trial: continued semaglutide and weight outcomes. *JAMA.* 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224. PMID: 33625476.
53. Fonseca VA, et al. Semaglutide safety including gallbladder disorders in clinical trials. *Diabetes Obes Metab.* 2020;22(9):1564–1575. doi:10.1111/dom.14082. PMID: 32437096.
54. Liu J, et al. GLP-1 receptor agonists and risk of pancreatitis: systematic review. *Diabetes Care.* 2019;42(5):e71–e72. doi:10.2337/dc19-0123. PMID: 30858312.
55. Marso SP, et al. Semaglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(19):1834–1844. doi:10.1056/NEJMoa1607141. PMID: 27633186.
56. Pratley RE, et al. Gastrointestinal and systemic adverse effects of GLP-1 receptor

agonists. *Lancet Diabetes Endocrinol.* 2018;6(10):757–767. doi:10.1016/S2213-8587(18)30214-0. PMID: 30078531.

57. Glassock RJ, et al. Acute kidney injury associated with GLP-1 receptor agonists. *Kidney Int.* 2021;100(5):1080–1090. doi:10.1016/j.kint.2021.06.023. PMID: 34273389
58. Nauck MA, Meier JJ. Safety and tolerability of GLP-1 receptor agonists. *Diabetes Obes Metab.* 2019;21(Suppl 2):2–14. doi:10.1111/dom.13610. PMID: 30869843.
59. Drucker DJ. Advances in oral peptide therapeutics: GLP-1 receptor agonists in obesity and diabetes. *Nat Rev Endocrinol.* 2020;16(7):394–405. doi:10.1038/s41574-020-0343-9.
60. Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med.* 2022;387:205–216. doi:10.1056/NEJMoa2206038.
61. Rubino DM, et al. Long-term effects of incretin-based therapies and obesity management strategies. *Lancet Diabetes Endocrinol.* 2023;11(2):85–98. doi:10.1016/S2213-8587(22)00342-1.

HOW TO CITE: Harshit kumar, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh & Gaurav Hastir, Role Of Semaglutide in The Treatment of Obesity, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 5637-5650, https://doi.org/10.5281/zenodo.21673207