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REVIEW

Clinical Impact of Semaglutide, a Glucagon-Like Peptide-1 Receptor Agonist, on Obesity Management: A Review

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Purpose: Obesity and overweight pose a threat to health and are more common than undernutrition among adults. It is categorized by fat accumulation and a body mass index (BMI) of > 30. A significant increase in worldwide obesity has been ongoing over several decades. Over the past few years, several strategies have been followed for weight management and to counteract the increasing prevalence of the disease; however, room for improvement with pharmacological options still exists. This review aimed to digest selected past clinical and experimental studies and understand the role of semaglutide treatment for obesity.

Methods: Articles related to the clinical uses of semaglutide, mechanism of action, pharmacokinetics, pharmacodynamics, and side effects of the drug were identified. Only studies with human subjects who used Semaglutide for obesity management were included and assessed.

Results: Semaglutide promotes weight loss via appetite and hunger suppression, decreases energy intake, controls eating, and depresses the relative fondness for fatty, energy-dense foods. Moreover, the relationship between obesity and Semaglutide has been widely investigated, and most studies reveal the efficacy of Semaglutide on weight loss. Overall, the pharmacokinetics of semaglutide shows a drop in glycosylated hemoglobin A1c (HbA1c) and total body weight. The usual adverse effects observed in patients treated with Semaglutide include gastrointestinal adverse events, like nausea, vomiting, diarrhea, constipation, and abdominal cramps.

Conclusion: The findings from the review suggest that semaglutide appears to be beneficial, most notably in its contribution to weight reduction.

Keywords: GLP-1, glucagon-like peptide-1, obesity, semaglutide, weight management

Introduction

Obesity and Its Complication

Obesity is a global, chronic, and relapsing disease that considerably influences the health status of individuals, communities, and healthcare systems. The predominance of obesity worldwide has increased dramatically in both children and adults. Recent figures from World Health Organization (WHO) revealed that the incidence of obesity has triplicated since 1975.[1] WHO defined obesity as irregular or disproportionate fat accumulation in the human body fat with a high body mass index (BMI), a degree of the weight relative to the height greater than 30. Fat accumulation beyond healthy limits eventually leads to several cardiovascular complications, including hypertension, heart failure, ischemic heart disease, and stroke.[2–5] Specifically, the metabolic profile is hugely affected by obesity, including hyperinsulinemia, dyslipidemia, impaired fasting glucose, or hypercholesterolemia.[6–8] The severity of obesity increases with continuous weight gain and tends to have higher all-cause mortality and mortality due to a wide range of other serious health complications. The negative impact of obesity also increases in the presence of other diseases, for example, diabetes.[9–11] Oppositely, weight loss results in an improvement in many body functions. For instance, liver histology was improved in people with nonalcoholic fatty liver disease.[12] Also, weight loss can improve cardiovascular health.[13] Moreover, weight loss will cause an improvement in the metabolic health profile in insulin-resistant overweight adults and increase insulin sensitivity.[14,15] Interestingly, a meta-analysis article reported that weight loss

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improves several psychological expressions, including body image, self-esteem, depression, and health-intertwined quality of life.[16] Furthermore, reduced inflammation and improved endothelial function are associated with weight loss.[17]

Weight management is crucial for a healthy lifestyle and for reducing obesity-related complications. Dietary changes and behavior modification with regular exercise may help maintain ideal body weight.[18–20] Specifically, a reduction in caloric intake and a rise in the physical movement are the cornerstones of a bodyweight management program. On the other hand, in some cases, several pharmacological classes of drugs and medical surgery, such as bariatric surgery, along with the change in dietary lifestyle, have been developed over the last decade to counteract obesity and obtain ideal body weight.[21,22] The prescribed medications include liraglutide, naltrexone-bupropion, orlistat, phentermine, and phentermine-topiramate.[19,23–25] The limited available therapeutic options have encouraged researchers, drug manufacturers, and medical teams to think about the available drugs that may help curb the increase in obesity. Several drugs have been used for their anti-obesity activity. Examples of medications include metformin, a biguanide drug, which has been used for diabetes and obesity and has shown a one-unit reduction in BMI for patients treated with it.[26] Also, metformin has been shown to produce a significant drop in body mass index and tends to cause a decline in BMI (kg/m2) and weight (kg).[27] A recent meta-analysis revealed that metformin has unassertive but advantageous effects on human body weight and improves insulin resistance (IR) with a tolerable safety profile among obese patients.[28] However, metformin does not qualify as an anti-obesity drug for different reasons. Recently, Semaglutide received Food and Drug Administration (FDA) approval to treat obesity in 2021. It demonstrated a beneficial outcome in terms of anti-obesity activity. This article will review its role, mechanism of action, pharmacokinetics, pharmacodynamics, adverse drug reactions, and drug-drug interactions, focusing on obesity mechanisms.

Glucagon-Like Peptide 1 (GLP-1)

The incretin, glucagon-like peptide 1 (GLP-1), is a well-known incretin peptide discharged into the circulation by scattered gastrointestinal and endocrine cells.[29–31] It is a gut-derived hormone that potentiates glucose-dependent insulin excretion from the pancreatic β-cells when blood glucose is high and contributes to glucose homeostasis.[32–34] Also, GLP-1 can improve metabolic, glycemic control, and weight loss via suppression of glucagon secretion, delay in gastric clearing, gastrointestinal fat absorption, and reduced food intake.[35,36] Moreover, its resulting increase in natriuresis and diuresis leads to an overall improvement in metabolic functions.[37] However, the biology and physiology of GLP-1 remain not fully understood.

Glucagon-Like Peptide 1 (GLP-1) Drugs

GLP-1 receptor agonists approved in the United States for treating type 2 diabetes include exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide.[32] According to reviews, semaglutide is at least as potent and possibly even more so than other GLP-1s.[38]

Method

As this paper focuses on investigating the function of Semaglutide in obesity management. A narrative review of the literature published between 2016 and 2021 was conducted by searching PubMed and Google Scholar with no predetermined research question or specified search strategy, only a topic of interest. Articles relating to the clinical uses of semaglutide, mechanism of action, and pharmacokinetics, and pharmacodynamic side effects of the drug were identified. Only studies with human subjects who used Semaglutide for obesity management were included and assessed.

Pharmacology of Semaglutide

Conducted finished clinical trials with semaglutide resulted in a higher interest in GLP-1-based methods. Semaglutide is a type of GFP-1 with 94% sequence homology to human GLP.[39–42] It serves as a receptor agonist that specifically binds and initiates to the GLP-1 receptor. GLP-1 is known to be a physiological hormone with several functions on glucose, acted and regulated by GLP-1 receptors.[43] The concept of extension consequential in the long half-life of semaglutide is the binding of albumin that eventually leads to lowering renal clearance and defense from metabolic deprivation. Semaglutide, unlike other GLP-1 agonists, resists degradation caused by the dipeptidyl peptidase-IV enzyme.[33] It cuts fasting and postprandial blood glucose levels via a mechanism that arouses insulin and drops glucagon secretions in a glucose-dependent mode.[44] Thus,

insulin release is stimulated under hyperglycemic conditions while inhibiting glucagon secretion. The process of lowering the blood glucose also includes a trivial interruption in gastric draining in the initial postprandial stage. Subcutaneous Semaglutide injection contains human GLP-1 receptor agonist semaglutide. The peptide mainstay is formed by the fermentation of yeast. The central machinery of Semaglutide is binding to albumin, a process simplified by altering the position-26 lysine with hydrophilic spacer and a C-18 fatty di-acid. Lastly, Semaglutide is changed at position-8 to deliver equilibrium in contrast to deprivation by the enzyme dipeptidyl-peptidase IV (DPP-4).[45]

Semaglutide for Weight Management

Semaglutide is the first FDA-approved GLP-1 receptor agonist for chronically obese adults who have at slightest one weight-related illness like type 2 diabetes, hypertension, and abnormal changes in lipid profile for use in concurrence with condensed calorie intake and improved physical activity.[46] Accumulating evidence supports the evaluation of Semaglutide for obesity treatment as it leads to robust improvements in weight loss efficacy of once-daily subcutaneous injection. The anti-obesity activity of semaglutide, a GLP-1 agonist, occurs because of deferred gastric clearing and intensified gastric volume.[47] Among obese adults, subcutaneous Semaglutide (2.4 mg) given once weekly promotes weight loss via appetite and hunger suppression, decreases energy intake, controls eating, and depresses the relative fondness for fatty, energy-dense foods.[39,48,49] This drug has been recently used in several double-blind, randomized placebo-controlled clinical trials, leading to improved weight drop in obese children and adults.[35,48,50,51] The route of drug administration is a vital factor for the duration of action since its subcutaneous delivery allows continuous delivery at a low dose rate.[52] It's the only GLP-1 receptor agonist currently accessible in subcutaneous and oral formulations.[51] Several studies have also discussed the efficacy of using semaglutide for weight management. A recent study in 2021 found that Semaglutide yielded surprising results for continued, clinically pertinent declines in body weight. A 2.4 mg dose was administered to 1306 patients and caused continued, clinically relevant reductions in body weight. The average transformation in body weight from the reference line to week 68 was 14.9% for samples using Semaglutide compared to 2.4% among those taking a placebo.[53] The study revealed that in overweight or obese adults, once a week, subcutaneous injections of Semaglutide in aggregation with lifestyle intervention were related to a substantially constant, clinically substantial mean weight reduction of 14.9%, with 86% of partakers getting at least 5% drop of weight. Another clinical investigation revealed a similar outcome; in overweight or obese partakers, 2.4 mg of Semaglutide per week together with régime interposition was linked with a persistent, clinically noteworthy drop in body weight.[51] Furthermore, subcutaneous injections of 2.4 mg of Semaglutide in 72 obese adults randomized to once weekly injections or placebo for 20 weeks showed suppression in appetite with a concurrent lessening in food ingestion, energy intake, and body weight versus the placebo group.[48] Another recent study involving 1051 participants over 68 weeks, randomized, double-blind, placebo-controlled withdrawal investigation analyzed data from 73 sites in 10 countries and demonstrated a significant mean bodyweight reduction by 10.6% plus a decrease in waist circumference, body mass index, blood pressure, hemoglobin A1c, fasting plasma glucose and progress in lipid profiles after 20 weeks of treatment.[54] Trials investigating the reduction of weight outcomes associated with Semaglutide usage have increased after FDA approval was obtained. Much of the current literature on Semaglutide pays particular attention to other comorbidities, such as cardiovascular risk factors associated with obesity. A comparative study concluded that Semaglutide led to a reduced risk of adverse cardiovascular results likened to placebo when the Semaglutide was added to the standard-of-care regimen.[50] The connection between obesity and Semaglutide has been widely studied, and most studies reveal the efficacy of Semaglutide on weight loss. However, the rigorous mechanism of the action of Semaglutide is not fully comprehended. Table 1 provides an overview of the clinical trials key study characteristics included in this systematic review. Four of the studies were conducted in multicenter setting[48,53,54] and two in single center site.[39,44] The trial phase was specified as Phase I in four of the six studies[39,44,48,53] and two were specific to a Phase III trial.[53,55] In addition to exploring the clinical impact of Semaglutide on weight reduction, some of the studies investigated pharmacokinetics, pharmacodynamics, safety and tolerability.[39,55]

Table 1 A Summary of the Clinical Trials Dedicated in Clinical Impact of Semaglutide on Obesity Management

Author (Year)[Ref.]	Setting	Aim	*n*	Outcomes	Limitations	Study Design
Enebo et al (2021)[39]	Single center of Altasciences Clinical Kansas in Kansas, USA	To study the safety, tolerability, pharmacokinetics, and pharmacodynamics of cagrilintide in combination with semaglutide	96 (18–55 years)	- MBW percentage reductions were greater in case of the combination of cagrilintide and semaglutide 2·4 mg (over 15%) as compared to placebo (about 10%)	- Relatively shorter duration of study (20 weeks) and the treatment time at final target dose was also short (4 weeks) - Primarily worked on safety and tolerability of the combination of drugs, so weight loss outcomes have to be interpreted with caution.	Phase Ib
Blundell et al (2017)[44]	Single center study conducted in UK	To assess the activity of semaglutide in comparison with placebo in relation to body weight and energy intake	30 (18 years or older)	- Reduction in MBW by about 5 kg, but placebo group showed an increase in body weight by about 1 kg	- Lower number of participants in the study - Relatively shorter duration of study (12 weeks)	Phase I
Friedrichsen et al (2021)[45]	Germany	To assess the efficacy of semaglutide 2.4 mg once weekly administration on appetite, gastric emptying, and energy intake	72 (18 to 65 years)	- MBW decreased by about 9.9% with semaglutide administration, while with placebo body weight reduced by about 0.4% - Semaglutide group experienced significantly lower level of hunger and higher level of fullness (all $p < 0.02$)	The use of paracetamol as approach to assessing gastric emptying	Phase I
Wilding et al (2021)[53]	129 sites in 16 countries	To assess the efficacy and safety of semaglutide 2.4mg once weekly administration for 68-weeks	1961 (18 years or older)	- MBW reduction (−14.9%) as compared to placebo (−2.4%, $p < 0.001$)	- Relatively shorter duration of study (12 weeks) and higher number of female participant	Phase III
Rubino et al (2021)[54]	73 sites in 10 countries	To assess the efficacy of semaglutide 2.4mg once weekly administration for 20-weeks on weight maintenance	902 (18 years or older)	- MBW reduction (−7.9%) as compared to placebo (+6.9%, $p < 0.001$) - Waist circumference, physical functioning, and SBP improved significantly with continuous semaglutide administration as compared to placebo (all $p < 0.001$)	- The run-in period was inflexible limiting the outcomes only to patients tolerating the drug outcomes	Phase IIIa
Bækdal et al (2018)[55]	Multicenter	To assess the effect of hepatic impairment on the pharmacokinetics, tolerability, and safety of oral semaglutide	56 (18–85 years)	Once-daily oral administration with 5 mg of drug for first five days and then 10 mg of drug for the next five days did not apparently affected the pharmacokinetics, safety, and tolerability of the drug in patients with hepatic impairment	- Open-label design and short study duration. - Number of participants in the groups was low and was not equal to each other	Phase I

Abbreviation: MBW, Mean Body weight.

Pharmacokinetic, Pharmacodynamic, Side Effect and Drug-Drug Interaction of Semaglutide

Overall, the pharmacokinetics of Semaglutide shows a reduction in glycosylated hemoglobin A1c (HbA1c) and total body weight.[49,55] Across studies and populations, Semaglutide pharmacokinetics were reported with a lengthy eradication half-life and a once-weekly subcutaneous injection of 2.4 mg for its anti-obesity activity.[44,52,56,57] It has shown to be slowly absorbed following subcutaneous injection with a tmax of approximately 1–3 days post-subcutaneous dose. Absolute bioavailability was estimated to be 89%. According to the manufacturer, parallel exposure was attained via subcutaneous dispensation of Semaglutide in the abdomen, thigh, or upper arm and was not affected by other factors except bodyweight.[58] However, Semaglutide exposure was shown to increase in a dose-dependent mode for once-A-week doses of 0.5 mg and 1 mg in diabetic patients treated with Semaglutide. At a dose of 0.5 or 1 mg, Semaglutide has a half-life of 7 days; hence, it would bring off steady-state and present in the circulation for about 4 to 5 weeks.[59] Semaglutide forms a high-affinity non-covalent bond with plasma albumin (> 99%), enhancing drug stability.[49,60,61] Semaglutide distribution does not include crossing the blood-brain barrier.[62] The main elimination routes of semaglutide are thru the urine and feces.[63,64] Roughly 3% of the dose is emitted in an integral form in the urine. The persistent side effects detected in patients taking Semaglutide include gastrointestinal antagonistic episodes, such as nausea, vomiting, diarrhea, constipation, and abdominal cramps.[53,54]

Conclusion

A strong connection between weight loss and reducing obesity complications has been reported in the literature. To date, the most robust finding concerning semaglutide has been the relationship between the GLP-1 and decreased body weight effects with other alteration at the metabolic profile. Given Semaglutide's wide therapeutic window, this relationship's clinical significance is worth investigating. The findings from the review suggest that Semaglutide appears to be beneficial, most notably in its contribution to weight management. This means that Semaglutide provides more patients with a degree of weight reduction that patients feel worthwhile. To conclude, based on semaglutide's beneficial effects on glucose metabolism, blood pressure, body weight, and cardiovascular health, semaglutide has an overall beneficial risk/benefit profile for diabetics and obese patients.

Disclosure

The authors report no conflicts of interest in this work.

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