Clinical Pharmacology: Advances and Applications

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

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. 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. The prescribed medications include liraglutide, naltrexone-bupropion, orlistat, phentermine, and phentermine-topiramate. 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. 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). 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. 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. 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. 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. Moreover, its resulting increase in natriuresis and diuresis leads to an overall improvement in metabolic functions. 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. According to reviews, semaglutide is at least as potent and possibly even more so than other GLP-1s.

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. 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. 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. It cuts fasting and postprandial blood glucose levels via a mechanism that arouses insulin and drops glucagon secretions in a glucose-dependent mode. Thus,
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). 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). Semaglutide injection contains human GLP-1 receptor agonist semaglutide. 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| Author (Year)<sup> Ref.</sup> | Setting | Aim | n | Outcomes | Limitations | Study Design |
|-------------------------------|---------|-----|---|----------|-------------|--------------|
| Enebo et al (2021)<sup>39</sup> | 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) | Phase Ib |
| Blundell et al (2017)<sup>44</sup> | 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 | Phase I |
| Friedrichsen et al (2021)<sup>55</sup> | 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% | - Lower number of participants in the study | Phase I |
| Wilding et al (2021)<sup>53</sup> | 129 sites in 16 countries | To assess the efficacy and safety of semaglutide 2.4 mg 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)<sup>54</sup> | 73 sites in 10 countries | To assess the efficacy of semaglutide 2.4 mg 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) | - The run-in period was inflexible limiting the outcomes only to patients tolerating the drug outcomes | Phase IIIa |
| Bakkal et al (2018)<sup>55</sup> | 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. | 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.\textsuperscript{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.\textsuperscript{14,52,56,57} 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.\textsuperscript{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.\textsuperscript{59} Semaglutide forms a high-affinity non-covalent bond with plasma albumin (> 99%), enhancing drug stability.\textsuperscript{49,60,61} Semaglutide distribution does not include crossing the blood-brain barrier.\textsuperscript{62} The main elimination routes of semaglutide are thru the urine and feces.\textsuperscript{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.\textsuperscript{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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