The Rise of GLP-1 Agonists: A Review of Their Role in Weight Management and Obesity Treatment

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Obesity, and overweight, classified by a body mass index of 30 or greater and 25 or greater, respectively, pose a global health crisis with very limited treatment options. While searching for treatments for type-2 diabetes, scientists discovered a hormone which they believed could be synthesized to treat obesity and overweight in addition to type-2 diabetes. Through adjustments made in the chemical composition of the human GLP-1 to increase the half-life and bonding properties of this compound, scientists were able to synthesize medications that replicate the human GLP-1's function to treat overweight and obesity. One of the earliest of these medications was liraglutide, a synthetic GLP-1 agonist that is 97% homologous in its chemical composition to the human GLP-1. While this medication proved effective in treating overweight and obesity, shown in clinical trials to yield a weight loss of 6.1%, it required frequent injections due to its short half-life. As the production of these medications improved, Semaglutide was synthesized yielding a weight loss of -14.9% with less frequent injections. This suggests that semaglutide offers a superior course of treatment than liraglutide, yet the production of GLP-1 agonist medications continues with the creation of tirzepatide, yielding a 20.9% decrease in body weight. While the weight loss benefits of tirzepatide suggest that it is a superior GLP-1 agonist to that of its predecessors, weight loss cannot be the only metric for the efficacy of these GLP-1 agonist medications in treating obesity and overweight. It is important to explore the effects these medications might have on the comorbidities of obesity as well as the potential risks of prolonged usage of GLP-1 medications.

Keywords: "Obesity", "Semaglutide", "Glucagon-Like Peptide 1", "Liraglutide", "Tirzepatide"

Introduction

Since 1990, the frequency of adulthood obesity, a chronic illness with numerous related illnesses, has more than doubled across the world with approximately 43% of adults in the United States being classified as obese [1]. Despite this growing number of individuals experiencing obesity within the United States, treatment options were extremely limited to only lifestyle changes, exercise, or weight loss surgery. These treatment options may not be feasible or accessible for every individual with obesity, leaving a vacuum of treatment options that can be both beneficial and accessible. Overweight and obesity are diagnosed using the individual's body mass index (BMI) which is calculated using their weight in kilograms divided by their height in meters squared. This method of determining qualification for medications and trials is beneficial, as it follows is determined using a ratio of two metrics, making it more universally applicable. For adults, a BMI of 25 or greater is considered overweight while a BMI of 30 or greater is considered obesity [2]. These conditions are also frequently related with numerous other health conditions such as insulin resistance, hypertension, dyslipidemia, type 2 diabetes, heart disease, non-alcoholic fatty liver disease, and worsened outcomes in individuals with HFpEF [3]. Both obesity and these often-coinciding illnesses pose a serious risk to individual and public health worldwide, resulting in lowered life expectancy, drastically increased hospitalizations, and impaired health outcomes when paired with immunocompromisation and viruses such as the coronavirus [4]. Despite the apparent dangers associated with childhood and adult obesity cases, until recently there were very few pharmacological solutions, leaving only lifestyle intervention or highly invasive gastric bypass surgeries to manage obesity [5].

In the past two decades, novel pharmacological methods of intervention have been developed to manage symptoms of type 2 diabetes, a condition in which an individual's body develops an insulin resistance leading to excess glucose in the bloodstream which can then lead to issues in the circulatory, nervous, and immune systems5. In order to stimulate the body to produce more insulin, medications known as Glucagon-like Peptide 1 agonists (GLP-1 Agonists) were synthesized to mimic the naturally produced incretin hormone called Glucagon-like Peptide 1 receptors. These medications were designed to replicate the effects of the natural human glucagon-like peptide-1, which is a hormone expressed in numerous organs such as the pancreas, brain, and stomach. The primary difference between the synthesized GLP-1 medications and the human GLP-1 is an additional

fatty acid side chain that, when attached, enhances the ability of the compound to bind to albumin in plasma, which extends the duration of the effects of the compound [1].

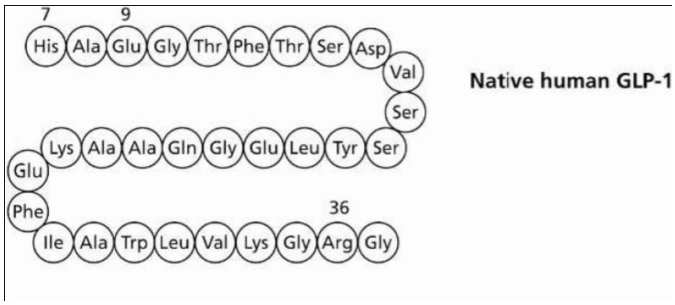

Fig. 1 Depicts the amino acid composition of the endocrine human GLP-1 incretin hormone. During the synthesis of the GLP-1 agonist medication Liraglutide, chemical components such as the c-16 fatty acid would be added to this base chemical structure to enhance the albumin binding efficiency of the synthetic GLP-1 agonist [6].

GLP-1's increase the production of insulin, slow gastric emptying, and suppress hunger cravings in the brain [7]. While this medication has been a monumental aid in managing type 2 diabetes symptoms and illnesses, it also possesses benefits for individuals with overweight, obesity, and many other conditions.

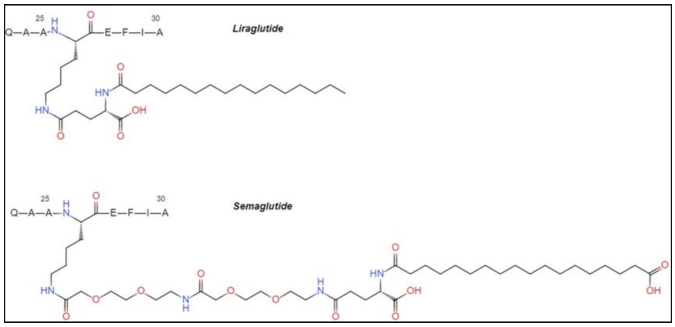

Fig. 2 Displays the chemical structures of the glucagon-like peptide 1 agonist medications Liraglutide and Semaglutide, whose chemical compounds are 97% and 94% homologous to human GLP-1 respectively [8].

In order to assess the efficacy and necessity for GLP-1 medications to be utilized for the treatment of overweight and obesity in adults, in addition to its original purpose for managing glucose in individuals with Type-2 diabetes, studies and experiments have, and continue to be, performed on mice and humans. The New England Journal of Medicine performed a double-blind trial, assessing obese individuals (determined by the participants BMI), who did not possess diabetes which could distort the results of the medication, and randomly assigned them in a 2:1 ratio to receive once-weekly subcutaneous semaglutide injections (2.4 mg a dose) or placebo for 68 weeks [9]. In addition to the medication, all participants were to undergo a particular lifestyle intervention and exercise regimen for both the semaglutide and placebo groups. Throughout the process of the trial, which initially enrolled 1961 adults, 94.3% of individuals completed the trial, 91.2% had body-weight assessments taken at the 68-week mark, and 81.1% adhered to the treatment plan. In the semaglutide group, 7 individuals received rescue interventions, such as bariatric surgery or other anti-obesity medications, and in the placebo group, 13 individuals received rescue interventions. At the end of the trial, the semaglutide group experienced a -14.9% change in body weight while the placebo group experienced a -2.4% change in body weight, showing that the semaglutide and intervention treatment demonstrated an effectiveness that was 12.5% more than that of the placebo and intervention treatment.

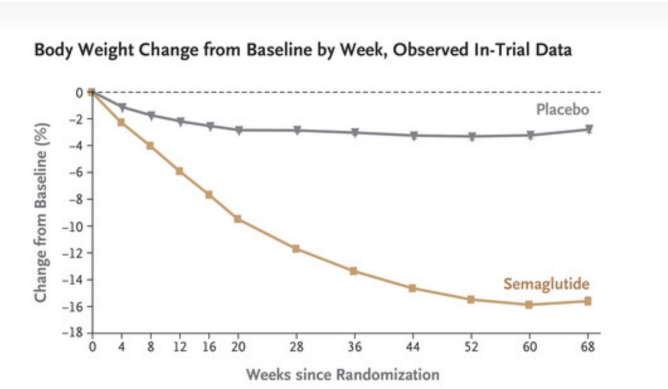

Fig. 3 Displays the percentage change from baseline weight of participants in both the semaglutide and placebo group, demonstrating a considerably higher percent decrease in the semaglutide [10].

In a more focused study performed by The New England Journal of Medicine12 centered around semaglutide as a possible method to manage heart failure with preserved ejection fraction (HFpEF), following similar guidelines to the original trial, they observed a -13.3% change in body weight in the semaglutide group compared to a -2.6% change in body weight in the placebo group. In both trials and experiments, there was a considerably greater improvement in weight loss in the group taking once-weekly subcutaneous semaglutide injections, which strongly indicates that the GLP-1 agonist medications offer a strong method of managing and treating overweight and obesity in adults. In an alternative study comparing the high responder groups, defined by a body weight decrease of greater than 10%, for both a bi-weekly subcutaneous exenatide injection group [11], another GLP-1 agonist medication, as well as a placebo group, there was no notable difference in the maximum weight able to be lost between the exenatide group and the placebo group. The study, however, did describe a difference in the frequency of these high responders, with four times as many high responders in the exenatide group as there were in the placebo group. This

suggests that while the threshold for high responsive weight loss is achievable in both the exenatide and the placebo groups, the exenatide medication offers an effective aid in achieving a notable decrease in body weight. This means that subcutaneous semaglutide injections are effective in the treatment of overweight and obesity and could be essential in preventing the development of other weight related illnesses.

Results

In order to assess the comparative effectiveness of the different GLP-1 agonist medications, studies showing the effectiveness of individual medications must be compared against the other for a variety of factors. The first and most important factor is the percentage weight loss yielded under near identical circumstances across the different GLP-1 medications. As noted earlier, in the experiment conducted by the New England Journal of medicine, the subcutaneous semaglutide injection group yielded a -14.9% change in body weight, a weight change that is associated with a reduction in health care costs and a strongly postulated reduction in mortality [12]. In an experiment under near identical parameters, the percentage weight change resulting from subcutaneous 3.0 mg liraglutide daily was -6.1% [13]. Similarly, in a 56-week double blind trial examining the effects of 3.0 mg Liraglutide daily, participants lost an average of 2.8±6.5 kilograms and 96.3% of all participants lost 5-10% of their body weight. The experiment utilized a sample population of 3731 trial participants representing 27 countries across different continents and followed the same exclusion criteria as the semaglutide experiment. Both the vast population of the experiment as well as exclusion criteria based on age and pre-existing conditions that might impact the effectiveness of the medication decreases the probability of these confounding variables distorting the reliability of the trial. The results shown within the liraglutide trials not only demonstrate a drastically smaller weight change as compared to the semaglutide experiment, but also signifies other potential drawbacks of the medication such as the necessity for daily injections (as opposed to weekly with subcutaneous semaglutide injections) due to the short half-life. The frequency required for the injection could pose a potential barrier to patients opting to utilize liraglutide as the medication to treat their overweight or obesity. There were, however, noted reductions in blood pressure and the number of individuals with pre-diabetes observed in those taking 1.8 to 3.0mg daily subcutaneous injections of liraglutide [14]. The longer length of the liraglutide trial combined with the lesser percentage weight change in the participants of the study, daily doses, and injection related symptoms such as nausea which appeared in 48% and 13% if the participants receiving 3.0 mg liraglutide [15], suggest that semaglutide is more effective in terms of weight loss yield and patient comfort as a possible treatment for overweight and obesity. Tirzepatide, on the other hand, offers a potentially more efficient GLP-1 agonist

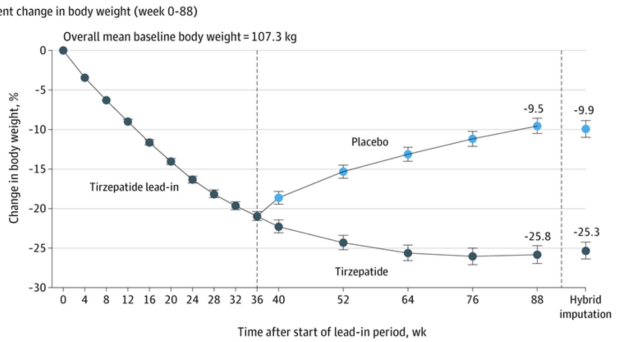

Fig. 4 Displays the results of a Tirzepatide and Placebo trial in which all participants initially underwent medication up to the 36-week mark before part of the participant group was switched to placebo medication while the other part remained on the tirzepatide medication. The final Percentage markers at the end of the 88-week period were a % change in body weight in the tirzepatide group of -25.3% and -9.9% in the tirzepatide/placebo group [17].

than semaglutide. In only a 36-week trial under similar parameters to the aforementioned trials, tirzepatide yielded a -20.9% weight change in its participants [16], and after continuing the trial up to 88 weeks, participants were shown to have experienced a -25.3% change in their body weight.

The intense average percentage weight changes across all three medications for the durations of their trials poses an important question for medical professionals as they deliberate on which medication to provide their patients, based on what a safe amount of weight change is over a particular period of time. Additionally, it is relevant to note that certain characteristics within each trial such as the duration, number of trial participants, frequency of injections, characteristics of trial participants, and metric for the results of the trials differ slightly across each medication. This is due to the limitations of published trials for each medication, meaning that the results of each trial are not directly comparable. They do, however, offer results that utilize similar metrics, and the comparisons of each trial can still yield important context regarding each medication.

Discussion

Semaglutide and other GLP-1 agonist medications offer a viable and effective treatment method for overweight and obesity in adults with a BMI of 25 or greater. Semaglutide is shown to be more effective than liraglutide, but less effective than the GLP-1 agonist medication known as Tirzepatide which has uses in the treatment of both type-2 diabetes as well as overweight and obesity [?] . The potential changes in weight through the subcutaneous injections of GLP-1 agonist medications and those of exercise and diet regimens are similar. These findings support the notion that GLP-1 medications can and should be used in the treatment of overweight and obesity, and not solely for

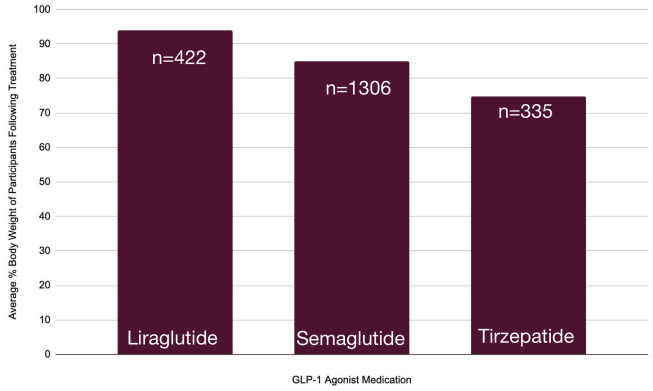

Fig. 5 Using bar charts, displays the average percentage body weight remaining of participants following their trials, with 100% being the original point. The bars are labeled with the respective medication they represent, as well as with the number of trial participants included in each trial[2,18,19].

	1) Duration Of Trial	2) Average % Body Weight Change in Medicated Group	3) Average % Body Weight Change in Placebo Group	4) % Medicated Trial Participants Experiencing Adverse Side Effects	5) Medication Frequency Per Week	6) Medication Dosage in mg	7) Medication Half-Life	8) %Homogeneity to Endogenous Human GLP-1
A) Liraglutide	56 weeks	-6.1%	N/A	N/A	7/week	3.0 mg	13 hours	97%
B) Semaglutide	68 weeks	-14.9%	-2.4%	89.7%	1/week	2.4 mg	7 days	94%
C) Tirzepatide	88 weeks	-25.3%	-9.9%	N/A	1/week	10-15 mg	5 days	N/A

Fig. 6 A)1, 2, 5, 6[20]. A)7, 8[14]. B)1, 2, 3, 4, 5, 6[21]. B)7[22]. B)8[23]. C)1, 2, 3, 5, 6[24]. C)7[25]: displays the collected values for important categories and statistics related to trials of the three GLP-1 medications. Sources can be distinguished using the letter, then number value.

the treatment of type-2 diabetes. As the rates of obesity across the world increase, so do health concerns and other potentially life-threatening illnesses. Despite this, there is a large social stigma surrounding the use of GLP-1 agonist medications for the treatment of overweight and obesity, often stemming from the perspective that GLP-1 medications should be exclusively utilized to help manage type-2 diabetes. The de-stigmatization of GLP-1 medications would enable individuals who may currently have, or be at risk of developing, obesity related illnesses and conditions to manage their weight and potentially avoid life-threatening illnesses. An important inquiry for future physicians and scientists to assess would be the issue of longevity with these medications. In the tirzepatide trial, when half of the study participants were switched from receiving the medication to receiving a placebo, their weight changed greatly in an upward trend, while the medicated groups continued in a downward trend. The placebo group ended at an average percentage weight change from the start of the experiment of -9.9%, a value larger than the placebo group in the semaglutide experiment. This is largely explicable due to the fact that they had undergone medication previously, distorting their final average percent weight change. The more compelling question resulting from this data, however, is how long should patients spend on the medication to arrive at, and remain at a healthy weight agreed upon with their physician? All three medications in their respective trials demonstrated compelling evidence to suggest their immense aptitude as treatment options for the treatment of obesity and overweight that are substantially less invasive yet rival the results of highly invasive bariatric surgeries[?]. In spite of their effectiveness at yielding weight loss results in patients with overweight and obesity, GLP-1 medications pose a substantial number of ethical dilemmas that are important to explore if these medications are to become more commonplace. Due to the relative novelty of these medications, there is not a substantial amount of data surrounding the potential long-term side effects of these medications or the potential for the misuse of these medications or the possibility that prolonged usage of the medication could lead to an addictive or reliant relationship with the medication. Additionally, there are potential risks surrounding these medications as a proponent of diet culture and unhealthy body-standards that could pose a risk to those considering the medications. It is important that guidelines to prevent the misuse of these medications as well as to analyze the long-term effects of the medications be put in place as the development of GLP-1 medications continues.

Limitations

Due to the nature of this paper, there are a few inherent limitations surrounding the findings of this study. Evidence utilized within this study is extracted from clinical trials performed by various organizations and publications, leading to variations in

factors such as the selection criteria of the trial participants, the duration of the trials, the number of participants, as well as the metrics used to describe the results of each study. This leads to some inconsistencies that make it impossible to determine direct comparisons across studies. They are, however, similar enough in these factors that the information used in this study maintains some effectiveness in comparing the medications. Additionally, due to the novelty of GLP-1 medications, there are extremely limited longitudinal studies to indicate potential future health risks resulting from prolonged use of the medication. This offers an important area for future research to be conducted in order to collect data regarding the long-term effects of these medications. Many of the studies utilized throughout this review measure the effectiveness of the GLP-1 medications as a percent change in the body weight of the trial participants, however there are numerous other factors that contribute to the health of individuals with overweight and obesity, that are not evaluated here. Factors such as blood glucose levels, blood pressure, cholesterol, as well as comorbidities such as heart disease and diabetes are similarly important metrics for determining the effectiveness of GLP-1 medications. In order to best compare the medications, however, only body-weight percentage changes fell within the scope of this paper, otherwise there would not be enough comparable metrics across the various studies, as they did not all include each of these factors, to draw any conclusions. A more in-depth exploration into these factors for each of the medications would be a beneficial research endeavor for future researchers in order to most accurately and consistently compare the effectiveness of GLP-1 medications as treatment for overweight and obesity.

Methods

The weight loss experiment statistics for the different GLP-1 agonist medications as well as the academic articles used for the literature review were collected using google-scholar with key words such as: Semaglutide, GLP-1 agonist, overweight, Liraglutide, Tirzepatide. In order to be included in the study, papers had to include experiments in which the selection criteria of the participants were near or completely identical, in order to accurately compare the effectiveness of the medications. Some of these selection criteria included an absence of pre-existing health conditions, falling within the same range of BMI, and being over the age of 18. While no study is likely to have exactly the same trial population, it is important that the selection criteria and trial methods are as similar as possible across the different trials for each medication, allowing for more accurate conclusions and comparisons to be drawn. The main contributor of studies was the New England Journal of Medicine as well as trials performed by the National Institute of Health (NIH), which performed similar experiments for many of the GLP-1 agonist medication individually, as well as comparing the medications individually to semaglutide for the experiments. This simplified the data extraction and facilitated easier comparisons across the medications. The included studies used to compare the medications followed rigorous selection criteria for the participants of their experiments, making them viable for use in this paper. To design the figures, comparable values across the different medications were extracted in order to be utilized for comparison, as well as to make apparent some of the important differences across the medications such as trial lengths and dosage sizes of the three medications.

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