Review

Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in the Weight Loss Among Obese Individuals: A Systematic Review

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Abstract

Background: Obesity can seriously damage human health and have the potential to raise the likelihood of diabetes mellitus (DM) and other adverse outcomes. Successful therapeutic options and medications have been designed to reduce weight. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended to reduce the weight among obese patients either with or without type 2 DM (T2DM). We intended to perform the systematic review to synthesize the findings from the studies that have explored the efficacy of GLP-1RAs in reducing weight among obese individuals.

Methods: A wide range of electronic bibliographic databases such as PubMed, Embase, and ERIC was searched. Based on the eligibility criteria, both observational and non-observational (experimental) studies that assessed the efficacy of GLP-1RAs in reducing weight loss among obese individuals from January 2010 to July 2021 were incorporated in the review. Following screening and assessing the abstracts, we ended up reviewing 20 full-text articles, and data were extracted on important parameters such as country, sample size, type of non-surgical treatment, time of follow-up, and primary outcomes.

Results: Overall, the findings of the systematic review appear promising for the efficacy of different GLP-1RAs in reducing the weight and related parameters of obesity such as body mass index and lean body mass. More precisely, individuals lost weight of about minimum of 5.1 kg and maximum of 6.16 kg in the intervention group or those who were observed to use any type of GLP-1Ras as opposed to 1.6 - 3.97 kg lost among those individuals who did not use any type of GLP-1Ras. These results with their respective effect sizes were statistically significant with a P-value of < 0.05. A wide variety of GLP-1Ras such as liraglutide, exenatide, semaglutide, and dulaglutide are considered safe to reduce weight loss among individuals aged 18 - 65 years. Out of 13 studies included in this review, 12 showed statistically significant results with a P-value of less than 0.05 in all the included studies.

Conclusion: Given their likely advantages further than glycemic control in reducing the weight, GLP-1 agonists may help to treat the obesity either among diabetic or non-diabetic individuals soon. Though, further research studies mainly large clinical trials are required to broaden and completely explain the favorable effects and potential side effects of GLP-1 agonists.

Keywords: Glucagon-like peptide-1 receptor agonists; Obesity; Weight loss; Systematic review

Introduction

Obesity and overweight can seriously damage human health and have the potential to raise the likelihood of type 2 diabetes mellitus (T2DM) and other adverse outcomes including resistance to insulin at the cellular level, hyperlipidemia, and heart ailments [1, 2]. According to the World Health Organization, around 1.5 billion adults were labeled as overweight in 2011 and around 2.8 million deaths occur among adults annually that are attributed to overweight or obesity [3]. More than 80% of patients with T2DM suffer from obesity or overweight and around three-fourths of patients with DM might experience complications such as diseases of the vessels and other DM-associated complications due to obesity [4, 5]. Many clinicians and also patients strive to lose weight or weight gain while controlling the glucose levels of patients. Both doctors and patients aim to reduce weight and reduce the adverse effects of T2DM or manage their glucose levels [4].

Successful therapeutic options and medications both pharmacological and non-pharmacological interventions have been designed to reduce the weight mainly among patients with DM to reduce the risk of a myriad of impediments [6, 7]. However, it has been found that medications such as sulphphonylureas, insulin, and thioglitazones that are used to manage DM increase weight. On the other hand, metformin, dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide receptor agonists (GLP-1RAs) reduce weight along with appropriate glycemic control.
There is a tendency to choose the options that manage glycemic control with no increments in the weight. One of such options is glucagon-like peptide-1 receptor agonists (GLP-1Ras), which are recommended to reduce the weight among obese patients either with or without T2DM. More specifically, GLP-1Ras is a hormone that is discharged from the gut (intestine) after an individual eats a meal, which in turn triggers the production of insulin and prevents the release of glucagon [8]. This hormone can suppress the appetite and slow down the gastric and stimulate satiation, thereby it plays an essential role to regulate blood glucose and reduce weight among obese individuals [9]. Furthermore, GLP-1Ras could promote satiation by attaching to its receptor on neurons in the hypothalamus and decrease caloric consumption by delaying gastric emptying [10, 11]. There is evidence that by the above mechanisms, GLP-1Ras have the potential to reduce the weight of patients either with or without DM. However, there is a need to review and synthesize the findings of both observational and experimental studies to explore the role of GLP-1Ras in reducing weight and the extent to which these GLP-1Ras can reduce weight. Therefore, we intended to conduct a systematic review to synthesize the findings from the studies that have explored the efficacy of GLP-1Ras on reducing the weight among obese individuals.

Materials and Methods

We performed a review systematically to evaluate, synthesize, and combine the existing evidence on the findings regarding the effect of GLP-1Ras on weight reduction. We used PRISMA guidelines to undertake this systematic review as shown in Table 1 [12].

Inclusion and exclusion criteria

To answer the study question, the eligibility of a study was contingent for inclusion if a research study evaluated the effectiveness or efficacy of GLP-1Ras to manage obesity, published in English from 2010 to 2020 across different regions of the world. Additionally, only those studies which were quantitative were incorporated. Qualitative studies were excluded and studies without full texts were also excluded. All those studies that consisted of opinions, criticisms of older research studies, and editorials were not included rather studies that compared the efficacy, safety, and effectiveness of GLP-1Ras and their full texts were scrutinized.

Sources of information and strategy for searching the relevant articles

A systematic search of published articles was started and completed in 2021. We searched databases including PubMed, Embase, and ERIC such as Medline, Ovid, and EBSCO. We explored references of pertinent reviews along with the database searches. An independent search was carried out by two authors who also scanned the results for potentially appropriate studies followed by retrieving the full-text articles. The primary endpoint of the review was the efficacy and safety of GLP-1Ras in reducing the weight among obese individuals, which reflected an improvement in the body mass index (BMI) or weight, and lean body mass. We piloted the search strategies without any restrictions by year of publication, geographic area, or other socio-demographic characteristics.

We identified a blend of Medical Subject Heading (MeSH) keywords and text words. We clustered these into four major groups based on the categories of population, intervention, comparison, and outcome as shown in Table 2. The most prevalent search terms found in abstracts and titles comprised “GLP-1Ras”, “glucagon-like peptide-1 receptor agonists (GLP-1Ras)”, “liraglutide”, and “exenatide”. Further, we consulted with a librarian to generate a search in four different parts. The first part was restricted to search terms particular to the primary endpoint such as “efficacy of GLP-1Ras”, and the second part was for the terms limited to obesity including “reduction in the weight”. Besides, we also considered using diverse wordings of main concepts such as obesity management, weight loss, and its management to obtain pertinent research papers. This was followed by combining these major concepts using combinations (AND, OR) relevant to the research question. Moreover, to detect more research articles, we also used truncation (*) with the same root word. We used truncation to make sure to retrieve all potential variants of search terms. We also applied search limits or filters on the language (English), however, and applied restrictions on publication period, age group, and type of studies to include eligible studies in the search.

Data abstraction

We imported all appropriate research studies into the reference manager software (EndNote) file, where each study was reviewed, and we also screened titles for duplicates in this software. We did not consider the abstracts for further review, which did not explicitly explore the study objective. Finally, we obtained and examined the full-text articles of the remaining relevant articles. This was followed by abstracting and summarizing the articles that met the eligibility criteria using a standardized proforma. Thus, after the process of removing duplicates, title, and abstract screening, we removed papers that were beyond the scope of this review as guided by inclusion criteria. Besides, the bibliography of the remaining studies was also verified and examined to evade missing any useful studies. This process of searching the articles was carried out independently by the reviewers, and their judgments and extracted summaries were matched to identify the differences and resolve these accordingly.

Independent reviewers filled a standardized data extraction sheet for the eligible research articles. The reviewers compared the data extraction tables to ensure including the imperative findings of the eligible studies and pilot tested the data extraction sheet before starting the process of data extraction. Besides, prevailing research articles on the chosen topic were reviewed to describe objects of the data extraction proforma.
Table 1. PRISMA Check List That Was Followed for This Review

| Section and topic               | Checklist item                                                                 | Location where item is reported                      |
|--------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------|
| Title                          | Identify the report as a systematic review.                                   | Abstract, Introduction and Methods                   |
| Abstract                       | See the PRISMA 2020 for Abstracts checklist.                                  | Seen and followed this guideline.                    |
| Rationale                      | Describe the rationale for the review in the context of existing knowledge.   | Rationale is described.                              |
| Objectives                     | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Objectives are described.                            |
| Eligibility criteria           | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | All required details are in Methods section.         |
| Information sources            | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Databases are specified in Methods section.         |
| Search strategy                | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | A full table of search strategy is made and details are in Methods section. |
| Selection process              | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | All required details are in Methods section.         |
| Data collection process        | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | All required details are in Methods section.         |
| Data items                     | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | All required details are in Methods section.         |
|                                 | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | These are listed in Methods as well as Tables.      |
| Effect measures                | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. | It is specified in Tables.                           |
| Synthesis methods              | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Flow chart is made with details in Methods.          |
|                                 | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | NA                                                   |
|                                 | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | See the flow chart and Tables.                       |
|                                 | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Since it was not a meta-analysis, we performed qualitative review. |
|                                 | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | NA                                                   |
|                                 | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | NA                                                   |
| Reporting bias assessment      | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | NA                                                   |
| Certainty assessment           | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | NA                                                   |
Any discrepancies between the two reviewers were solved by agreement between the two reviewers. The abstracted data comprised of the author, reference, year of publication, type of study design; total study size and population; average age with range for age, randomization group, duration for follow-up, major study findings, and conclusion of the study.

### Results

#### Findings of the search strategy

We screened the identified articles initially by titles, then by abstracts, and finally, we carried out a full-text articles assessment. Our initial search identified 1,209 citations in different databases; however, 703 articles were duplicates that were removed. Of the remaining 506 unique studies, we reviewed titles and abstracts and found 96 relevant abstracts. Upon reviewing abstracts, 69 articles did not meet the eligibility criteria while reviewing the abstracts and seven did not meet eligibility after reviewing full texts. Hence, we were able to retrieve full texts for 20 articles, which were incorporated in the review as shown in Figure 1.

#### Characteristics of the eligible studies

With respect to the study design, five of the studies were prospective case series, seven were randomized controlled trials (RCTs), and one was a cohort study. The sample size of all included research studies varied between 9 and 564 with an equal distribution between patients who were and were not randomized to different treatment modalities under the umbrella of GLP-1 agonists in the RCTs. The studies were conducted mostly in developed countries such as USA (n = 4), Japan (n = 1), Europe (n = 1), Italy (n = 2), China (n = 2), Korea (n = 1), UK (n = 1), and Denmark (n = 1) (Table 3 [13-32]).

### Table 1. PRISMA Check List That Was Followed for This Review - (continued)

| Section and topic       | Checklist item                                                                 | Location where item is reported                  |
|-------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|
| Quality assessment      | Quality assessment of eligible studies was done                                 | Done using appropriate tools                      |
| Study selection         | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Flow chart and details are in Methods.           |
| Study characteristics   | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Flow chart and details are in Methods.           |
| Results of individual studies | For all outcomes, present, for each study: 1) summary statistics for each group (where appropriate) and 2) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. | Description is given in Tables and results section. |
| Discussion              | Provide a general interpretation of the results in the context of other evidence. | Done                                             |
|                         | Discuss any limitations of the evidence included in the review.                | Done                                             |
|                         | Discuss any limitations of the review processes used.                          | Done                                             |
|                         | Discuss implications of the results for practice, policy, and future research. | Done                                             |

Any discrepancies between the two reviewers were solved by agreement between the two reviewers. The abstracted data comprised of the author, reference, year of publication, type of study design; total study size and population; average age with range for age, randomization group, duration for follow-up, major study findings, and conclusion of the study.

### Table 2. Search Strategy According to PICO Criteria

| Population           | “Adults*” [Mesh] OR “women*adults*” OR obese*men or women OR type-2 diabetes mellitus* OR overweight* OR “diabetic*” OR “adults with type-2 diabetes mellitus” OR “obese adults” OR “diabetic women” “diabetic men” OR “obese women” “obese men” [Mesh] |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intervention         | “GLP-1Ras” OR “Glucagon-like peptide-1 receptor agonists (GLP-1Ras)” OR “Liraglutide” [MeSH Terms] OR “Exenatide” [MeSH Terms] OR Semaglutide [MeSH Terms] OR Dulaglutide [MeSH Terms] OR Exenatide plus changes in the lifestyle [MeSH Terms] OR Dulaglutide plus changes in the lifestyle [MeSH Terms] OR Liraglutide plus changes in the lifestyle [MeSH Terms] OR Semaglutide plus changes in the lifestyle [MeSH Terms] OR Dulaglutide plus changes in life style [MeSH Terms] |
| Comparison           | Adults who were either not randomized to glucagon-like peptide-1 receptor agonists in RCTs or who were not observed to take glucagon-like peptide-1 receptor agonists in observational studies. |
| Outcome              | “Obesity management”, OR “weight loss”, OR “reduction in weight” OR “improving weight” OR “reduction in body mass index” OR “reduction in body fat” OR “weight management” |
Three studies were performed in 2010, two in 2012, one each in 2014, 2018, three in 2016 and 2017, and one was conducted in 2018. In terms of the type of GLP-1 agonists, six studies used exenatide, four reported testing the liraglutide, one each semaglutide and dulaglutide among participants with an age range of 18 - 65 years with differences in the mean age across different studies as illustrated in Table 3. Overall, all eligible studies were of high quality and we checked the quality of studies using the National Institutes of Health (NIH) tool for observational studies and a revised Cochrane risk-of-bias tool for RCTs. Th former consisted of 14 items and almost all of the observational studies met at least 10 out of 14 criteria and the remaining four were either not met or were not reported by authors. On the other hand, the latter tool for RCTs evaluated different biases such as selection bias, attrition bias, reporting bias, performance bias, and detection bias. Almost all of the included RCTs in this systematic review were subject to lower risk of bias.

**Findings regarding the effect of GLP-1 agonists on the weight loss**

Table 4 summarizes the findings regarding the effect of GLP-1
Table 3. Characteristics of the Included Studies With Their Settings and Types of Groups (n = 13)

| Study name                  | Year | Country                  | Study design | Sample size | Group 1               | Group 2       | Group 3       | Age (years) | BMI (kg/m²) |
|-----------------------------|------|--------------------------|--------------|-------------|-----------------------|---------------|---------------|-------------|-------------|
| Rosenstock et al [13]       | 2010 | USA                      | RCT          | 152         | Exenatide             | Placebo      | NA            | 46 ± 12     | 39.6 ± 7.0  |
| Apovian et al [14]          | 2010 | USA                      | RCT          | 194         | Exenatide plus changes in the lifestyle | Placebo plus changes in the lifestyle | NA            | 54.8 ± 9.5  | 25 - 39.9   |
| Bergenstal et al [15]       | 2010 | USA, India, and Mexico   | RCT          | 491, 170 each in three groups | Exenatide               | Sitagliptin   | Pioglitazone  | ≥ 18        | 25 - 45     |
| Astrup et al [16]           | 2012 | Europe                   | RCT          | 564         | Liraglutide           | Placebo      | Orlistat      | 18 - 65     | 30 - 40     |
| Chun-Jun Li et al [17]      | 2014 | China                    | Prospective case series | 31         | Liraglutide           | NA           | NA            | 48.5 ±11.4  | 31.7 ±3.6   |
| Perna et al [18]            | 2016 | Italy                    | Retrospective case series | 9          | Liraglutide           | NA           | NA            | 68.22 ± 3.86 | 32.34 ± 4.89 |
| Rondanelli et al [19]       | 2016 | Italy                    | Cohort study | 28         | Liraglutide           | NA           | NA            | 58.75 ± 9.33 | 34.13 ± 5.46 |
| Bradley et al [20]          | 2012 | USA                      | Prospective case series | 18         | Exenatide             | NA           | NA            | 39 ± 11     | 30 - 40     |
| Ishoy et al [21]            | 2017 | Denmark                  | RCT          | 40          | Exenatide             | Placebo      | NA            | 19 - 65     | 39.5 ± 3.5  |
| Yin et al [22]              | 2018 | China                    | RCT          | 37          | Exenatide             | Glargine     | NA            | 48.3 ± 2.3  | 28.1 ± 0.5  |
| Hong et al [23]             | 2016 | Korea                    | Prospective case series | 32         | Exenatide             | NA           | NA            | 49.0 ± 11.2 | 32.9 ± 4.7  |
| Semaglutide Blundell et al [24] | 2017 | UK                       | RCT          | 30          | Semaglutide           | Placebo      | NA            | 42          | 30 - 45     |
| Seko et al [25]             | 2017 | Japan                    | Retrospective case series | 5          | Dulaglutide           | NA           | NA            | 66.8 ±2.7   | 28.2 ±1.2   |
| Di Prospero et al [26]      | 2021 | USA                      | RCT          | 195         | NJ-64565111, a dual agonist of glucagon-like peptide-1 and glucagon receptors. Three groups were given different doses of NJ-64565111 | Placebo      | NA            | 18 - 70     | 35 - 50     |
| Kim et al [27]              | 2021 | USA                      | RCT          | 35          | Liraglutide (1.8 mg/day) | Placebo      | NA            | 40 - 70     | 27 - 40     |
| Frieling et al [28]         | 2021 | USA                      | Retrospective cohort study | 73         | SGLT-2 inhibitors     | GLP-1 receptor agonists | NA            | 60 - 75     | 30 - 40     |
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agonists on weight loss.

Overall, most of the studies found favorable results regarding the effect of GLP-1 agonists on the loss of weight as there was a decrease in weight from baseline till follow-up in almost all of the RCTs. For example, one of the studies conducted by Rosenstock et al in 2010 on obese individuals followed study participants for 24 weeks after randomizing one group to GLP-1 agonist [13]. The authors found that study participants in the intervention group reduced 5.1 ± 0.5 kg when compared to baseline as opposed to 1.6 ± 0.5 kg in the control arm (P < 0.001). They concluded that exenatide along with the lifestyle changes resulted in a decrease in caloric intake, thereby leading to weight loss among obese individuals and also resulted in improved tolerance to glucose [13]. Likewise, another study conducted by Apovian et al in the same year randomized obese and diabetic individuals to exenatide along with the changes in lifestyle or placebo and followed them for 24 weeks [14]. The study findings revealed that exenatide along with the changes in lifestyle revealed a bigger difference in weight (-6.16 ± 0.54 kg as opposed to the placebo group 3.97 ± 0.52 kg, P = 0.003). The authors concluded that exenatide along with the changes in lifestyle resulted in substantial loss of weight, helped to regulate glucose, and resulted in reduced blood pressure as opposed to placebo plus changes in lifestyle [14].

Similarly, Bergenstal et al conducted a study on diabetic individuals in 2010 and followed them for 26 weeks after randomizing them to either exenatide or sitagliptin or pioglitazone [15]. The authors found more weight reduction among study subjects who received exenatide (-2.3 kg, 95% confidence interval (CI): -2.9 to -1.7) vs. sitagliptin (-1.5 kg, 95% CI: -2.4 to -0.7, P = 0.0002) or pioglitazone (-5.1 kg, 95% CI: -5.9 to -4.3, P < 0.0001). Exenatide resulted in more weight reduction than other medications without causing hypoglycemia [15].

Two years later, Astrup et al conducted another study on diabetic individuals in 2012 and followed them for 26 weeks after randomizing them to placebo and orlistat (P < 0.001). There was 20-week body fat reduced by 15.4% among those who took liraglutide and lean tissue by 2.0% (Table 4). The authors found that liraglutide is tolerated very well and there is sustainable weight loss over the period of 2 years, and there is also improvement in the risk of cardiovascular diseases [16]. Chun-Jun Li et al in 2014 followed obese and diabetic individuals after randomizing them to liraglutide [17]. It was found that subjects treated with liraglutide resulted in a mean weight reduction of 5.03 kg and 61.3% of the patients had a reduction of more than 5% of body weight as opposed to baseline [17]. The authors found that the body weight, waist circumference, total fat, lean mass, and fat percentage were substantially decreased when compared to baseline [17]. Another research done by Perna et al in 2016 assessed the effect of liraglutide on weight loss by following the study participants for 15 weeks [18]. A reduction was observed in the mean BMI (-0.78 kg/m²), weight (-2 kg), fat mass (-1.5 kg) and android fat (-0.9 %) when compared to baseline, which revealed that treatment with liraglutide led to reduction in the mass of fat and android fat [18]. Another study conducted by Rondanelli et al on obese and diabetic individuals where they followed participants for 24 weeks. Af-
Table 4. Summary of Main Findings Regarding Efficacy of GLP-1 Agonists in Reducing Weight Loss (n = 13)

| Study name          | Year | Duration of treatment | Type of population           | Main findings                                                                 | Summary of findings                                                                 |
|---------------------|------|-----------------------|------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Rosenstock et al    | 2010 | 24 weeks              | Obese                       | Study participants in the intervention group lost 5.1 ± 0.5 kg from baseline as opposed to 1.6 ± 0.5 kg in the placebo group (P < 0.001). | Exenatide along with the changes in lifestyle resulted in a decrease in caloric intake, thereby leading to weight reduction and also resulted in improved tolerance to glucose. |
| Apovian et al       | 2010 | 24 weeks              | Obese and diabetic individuals | Exenatide along with the changes in lifestyle revealed a bigger difference in weight (-6.16 ± 0.54 kg as opposed to the placebo group 3.97 ± 0.52 kg (P = 0.003). | Exenatide along with the changes in lifestyle resulted in substantial loss of weight, helped to regulate glucose and resulted in reduced blood pressure as opposed to placebo plus changes in lifestyle. |
| Bergenstal et al    | 2010 | 26 weeks              | Diabetic individuals         | There was more weight reduction among study subjects who received exenatide (-2.3 kg, 95% CI: -2.9 to -1.7) vs. sitagliptin (-1.5 kg, 95% CI: -2.4 to -0.7, P = 0.0002) or pioglitazone (-5.1 kg, 95% CI: -5.9 to -4.3, P < 0.0001). | Exenatide resulted in more weight reduction than other medications without causing hypoglycemia. |
| Astrup et al        | 2012 | 20 weeks              | Obese                       | There was 5.8 kg (95% CI: 3.7 - 8.0) more weight loss in the group 1 as opposed to placebo and there was 3.0 kg more weight loss than orlistat (P < 0.001). There was 20-week body fat reduced by 15.4 among those who took liraglutide and lean tissue by 2.0%. | Liraglutide was tolerated very well and there was sustainable weight loss over the period of 2 years and there was also improvement in the risk of cardiovascular diseases. |
| Chun-Jun Li et al   | 2014 | 12 weeks              | Obese and diabetic individuals | Subjects treated with liraglutide resulted in a mean weight reduction of 5.03 kg and 61.3% of the patients had a reduction of more than 5% of body weight when contrasted to baseline. | The body weight, waist circumference, total fat, lean mass, and fat percentage were substantially decreased when compared to baseline. |
| Perna et al         | 2016 | 15 weeks              | Obese and diabetic individuals | There was a reduction in the mean BMI (-0.78 kg/m²), weight (-2 kg), fat mass (-1.5 kg) and android fat (-0.9%) when compared to baseline. | Treatment with liraglutide led to a reduction in the mass of fat and android fat. |
| Rondanelli et al    | 2016 | 24 weeks              | Obese and diabetic individuals | Significant reductions in BMI (-0.86 kg/m², P = 0.024), fat mass (-2.01 kg, P = 0.015), fat mass index (-0.71 kg/m², P = 0.014), android fat (-1.72%, P = 0.022), trunk fat (-1.52%, P = 0.016), and waist circumference (-6.86 cm, P < 0.001) were observed when compared to baseline. | Treatment with 24-week liraglutide caused decreased fat mass, android fat, trunk fat, and appetite by increasing the lipid profile, glucose control, and insulin sensitivity. |
| Bradley et al       | 2012 | 14 weeks              | Obese individuals           | The reduction in the mean weight due to exenatide was 2.0 ± 2.8 kg (P = 0.01). The average change in BMI was 0.7 ± 1.0 kg/m² (P = 0.01). There was significant reduction in the fat mass by 1.3 ± 1.8 kg (P = 0.01) and fat-free mass was non-significantly reduced by 0.8 ± 2.2 kg (P = 0.14). | The variation in the composition of the body relates to an estimated change in body energy stores of 13 ± 28 kcal/day for fat-free mass lost along with 153 ± 205 kcal/day for fat mass lost. |
| Ishoy et al         | 2017 | 14 weeks              | Obese individuals with schizophrenia | There was weight reduction both in intervention and control arms (P = 0.004), however, similar (P = 0.98) weight losses of 2.24 ± 3.3 and 2.23 ± 4.4 kg. | Treatment with exenatide once per week did not lead to weight reduction in obese, patients with schizophrenia who were on anti-psychotic medications as opposed to placebo. |
Table 4. Summary of Main Findings Regarding Efficacy of GLP-1 Agonisits in Reducing Weight Loss (n = 13) - (continued)

| Study name | Year | Duration of treatment | Type of population | Main findings | Summary of findings |
|------------|------|-----------------------|--------------------|---------------|---------------------|
| Yin et al [22] | 2018 | 16 weeks | Obese and diabetic | Decreases in weight, BMI, body fat mass, and percent fat mass (except for gynoid) were greater with exenatide than with glargine, and percent lean tissue (other than the limbs) increased with exenatide. | Exenatide and glargine attained comparable increases in glycemic control, sensitivity to insulin, and function of β cells. Nevertheless, exenatide created better weight and fat mass decreases, which were beneficial for blood glucose control. |
| Hong et al [23] | 2016 | 12 weeks | Obese and diabetic | Body weight and fat mass declined substantially (P = 0.002 and P = 0.001, respectively), although muscle mass did not decline (P = 0.289). | Impacts of exenatide among obese individuals with comorbid such as cardiometabolic high-risk patients decreased body weight without muscle mass loss, body fat mass, and glycated hemoglobin levels. |
| Semaglutide Blundell et al [24] | 2017 | 12 weeks | Obese | Semaglutide led to a reduction from baseline in mean body weight of 5.0 kg, predominantly from body fat mass. | Libutum energy intake was significantly shorter with semaglutide vs. placebo with a corresponding loss of body weight observed with semaglutide. |
| Seko et al [25] | 2017 | 12 weeks | Diabetic | Not only body weight and hemoglobin A1c but also transaminase activities were significantly decreased after the 12-week therapy with dulaglutide. Total body fat mass and liver stiffness measurement also decreased after the treatment. | Dulaglutide, a new glucagon-like peptidase-1 receptor agonist, could be a novel promising agent for the treatment for NAFLD patients with T2DM due to its efficacy in body weight reduction, the nature of weekly injection, and patient preference. |
| Di Prospero et al [26] | 2021 | 12 weeks | Obese and diabetic individuals | There was a significant recution in body weight in a dose response manner. More precisely, changes in body weight were -4.6% with 5.0 mg of glucagon receptor agonists, -5.9% with 7.4 mg, and -7.2% with 10.0 mg. There was more than 5% weight loss in the treatment arm than placebo. | Overall, glucagon receptor agonists resulted in weight reduction in dose dependent manner when compared with placebo. However, there were more side effects reported with glucagon receptor agonists as compared to placebo. These side effects included nausea and vomiting. |
| Kim et al [27] | 2021 | 14 weeks | Obese and pre-diabetic | Study subjects randomized to intervention arm were found to have a significant reduction in mean weight: -3.6% with 95% CI of -5.2% to -2.1%. | Linsitide resulted in improved weight by the end of 14 weeks among prediabetic individuals. |
| Frieling et al [28] | 2021 | 6 months | Diabetic and obese adult patients | There was a median loss of about -2.8 kg with an IQR of -5.40 to -1.50 among those patients who received SGLT-2 inhibitors, whereas those who received GLP-1 receptor agonists lost about 1.15 kg with an IQR of -3.38 to 0.975 with a P-value of 0.014. | SGLT-2 inhibitors when used in combination with other antidiabetic medications can results in more weight loss than GLP-1 receptor agonists. |
| Wilding et al [29] | 2021 | 68 weeks | Obese adults with at least one attempt of weight unsuccessful weight loss | A mean difference in BMI between intervention (semaglutide) and control arm was -12.4 percentage points (95% CI: -13.4 to -11.5 and P < 0.001). | There was sustained and clinically meaningful reduction in the body weight among those who were randomized to semaglutide than placebo group. |
| Davies et al [30] | 2021 | 68 weeks | Obese and diabetic adults | An estimated mean difference in BMI between intervention (semaglutide 2.4 mg) and placebo was -6.2 percentage points (95% CI: -7.3 to -5.2 and P < 0.001). | Semaglutide 2.4 mg given once a week showed superior findings internms on weight reduction than placebo. |
Efficacy of GLP-1 Receptor Agonists in Weight Loss

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After treating patients with liraglutide, significant reductions in BMI (-0.86 kg/m², \( P = 0.024 \)), fat mass (-2.01 kg, \( P = 0.015 \)), fat mass index (-0.71 kg/m², \( P = 0.014 \)), fat in android area (-1.72%, \( P = 0.022 \)), fat in trunk region (-1.52%, \( P = 0.016 \)), and waist circumference (-6.86 cm, \( P < 0.001 \)) were observed when compared to baseline [19].

Also, Bradley et al found a reduction in the mean weight of 2.0 ± 2.8 kg (\( P = 0.01 \)) due to exenatide. The mean difference in BMI was 0.7 ± 1.0 kg/m² (\( P = 0.01 \)). A substantial decrease was detected in the fat mass by 1.3 ± 1.8 kg (\( P = 0.01 \)) and fat-free mass was non-significantly reduced by 0.8 ± 2.2 kg (\( P = 0.14 \)) [20]. However, these findings were not supported by a study conducted by Ishoy et al in 2017 where authors found a weight reduction both in the intervention and control arms (\( P = 0.004 \)), though comparable (\( P = 0.98 \)), weight losses of 2.24 ± 3.3 and 2.23 ± 4.4 kg were observed in both groups [21]. The authors observed that in contrast to placebo, treatment with exenatide once per week did not stimulate weight reduction among obese individuals, patients with schizophrenia who were on antipsychotic medications. In contrast, Yin et al conducted the study in 2018 by following obese and diabetic individuals for 16 weeks [22]. The authors found decreases in weight, BMI, body fat mass, and percent fat mass (except for gynoid) and such loss in weight was greater with exenatide than with glargine. Finally, Hong et al [23], Semaglutide Blundell et al [24], and Seko et al [25] found a reduction in the weight with exenatide, semaglutide, and dulaglutide, respectively.

Recently an RCT was conducted on 195 individuals who were randomized to either NJ-64565111 with three different doses of 5.0, 7.4, and 10.0 mg and placebo group [26]. These participants were 18 - 70 years old with a BMI of 35 - 50 kg/m² and were followed for 12 weeks after being assessed at baseline for various clinical and demographic factors. The study findings revealed a significant reduction in body weight in a dose response manner [26]. More precisely, changes in body weight were -4.6% with 5.0 mg of glucagon receptor agonists, -5.9% with 7.4 mg, and -7.2% with 10.0 mg [26]. There was more than 5% weight loss in the treatment arm than placebo. Overall, glucagon receptor agonists resulted in weight reduction in dose-dependent manner when compared with placebo. However, there were more side effects reported with glucagon receptor agonists as compared to placebo. These side effects included nausea and vomiting [26]. Likewise, another trial conducted by Kim et al on 35 patients for 14 weeks found the similar results in terms of weight loss [27]. More precisely, authors found that subjects randomized to intervention arm (liraglutide 1.8 mg/day) were found to have a significant reduction in mean weight: -3.6% with 95% CI of -5.2% to -2.1% when compared to the placebo [27].

Further, one retrospective study conducted on 73 patients in 2021 for about 6 months on diabetic and obese individuals found a median loss of about -2.8 kg with an intr quartile range (IQR) of -5.4 to -1.5 among those patients who received SGLT-2 inhibitors, whereas those who received GLP-1Rass lost about 1.15 kg with an IQR of -3.38 to 0.975 with a \( P \)-value of 0.014 [28]. Authors concluded that SGLT-2 inhibitors when used in combination with other antidiabetic medications can result in more weight loss than GLP-1Ras [28].
We also assessed the findings of STEP 1 to STEP 4 trials recently conducted in 2021. A STEP 1 study was a double-blinded RCT of 1,961 participants conducted by Wilding et al. The authors found that a mean change in the BMI was -14.9% in the group that was randomized to semaglutide when compared with -2.4% change in the BMI among those who were randomized to placebo group [29]. Overall, the mean difference in BMI between intervention (semaglutide) and control arm was -12.4 percentage points (95% CI: -13.4 to -11.5 and P < 0.001) [29]. Further, change in the weight of study subjects in the intervention arm was -15.3 from baseline to follow-up (< 0.001) [29].

Further the efficacy of semaglutide 2.4 mg against placebo [31]. At the end of follow-up of 68 weeks, the estimated mean change in body weight was -16.0% from baseline among those who were randomized to semaglutide 2.4 mg and placebo was -6.2 percentage points (95% CI: -7.3 to -5.2 and P < 0.001) [30]. There was a weight reduction of at least 5% among 68.8% of the study participants in the semaglutide 2.4 mg group when compared to 28.5% among placebo arm (P < 0.001) [30].

Likewise, a STEP 2 study group conducted a double-blind RCT to assess the efficacy of semaglutide 2.4 mg versus 1.0 mg and placebo for 68 weeks [30]. Authors found that there was an estimated change in mean body weight, from baseline to 68 weeks, of -9.6% with the intervention arm when compared to -3.4% with the placebo group. An estimated mean difference in BMI between intervention (semaglutide 2.4 mg) and placebo was -6.2 percentage points (95% CI: -7.3 to -5.2 and P < 0.001) [30]. There was a weight reduction of at least 5% among 68.8% of the study participants in the semaglutide 2.4 mg group when compared to 28.5% among placebo arm (P < 0.001) [30].

Similarly a STEP 3 trial was conducted by Wadden et al in 2021 at 41 sites in the USA to compare the efficacy of semaglutide 2.4 mg against placebo [31]. At the end of follow-up of 68 weeks, the estimated mean change in weight was -16.0% from baseline among those who were randomized to semaglutide 2.4 mg when compared to -5.7% for placebo group [31]. The mean difference was -10.3 percentage points (95% CI: -12.0 to 8.6 and P < 0.001). Around 87% of the study participants lost at least 5% of body weight in intervention arm versus 47.6% who lost the same percentage of body weight in placebo group (P < 0.001) [31].

STEP 4 investigators recently published findings of an RCT that compared the efficacy of semaglutide 2.4 mg (once weekly) against placebo [32]. This trial was completed by 803 overweight and obese study participants for 68 weeks. The findings revealed that mean change in body weight was -7.9% from baseline to follow-up in the intervention arm versus 6.9% in the placebo arm. The mean difference in body weight between two groups was -14.8 with 95% CI of -16.0 to -13.50 (P < 0.001) [32].

Discussion

We undertook this systematic review to assess the efficacy of GLP-1 agonists to reduce the weight among obese diabetic or non-diabetic individuals. We reviewed all RCTs and case series that had assessed the efficacy of GLP-1 agonists such as exenatide, liraglutide, semaglutide, and dulaglutide and assessed the effect of these modalities on range of outcomes related to the weight. Overall, we found positive findings regarding these methods with equivalent results using different types of GLP-1 agonists. The findings of this systematic review revealed that in most cases, the weight reduction due to GLP-1RAs was remarkable. GLP-1 receptors are found all over the human body, and therefore are expected to facilitate various physiological outcomes other than the glycemic control such as reduction in weight [33].

Our findings are consistent with the existing literature which previously have endorsed that apart from improving the glycemic levels, GLP-1RAs have been used by clinicians for the obesity as they can show promising results in reducing the weight, BMI and other constructs related to the obesity regardless of T2DM [34, 35]. For example, findings from a meta-analysis revealed that infusion of GLP-1 agonists resulted in an average of % of the libitum intake of energy when compared to the saline [36]. The underlying process by which GLP-1RAs help reduce the weight loss is not yet completely recognized. However, there is an evidence supporting that GLP-1RAs such as liraglutide raised satiety after meals, decreased appetite, reduced the consumption of food, and decreased energy expenditure [37]. Further, there is evidence that GLP-1RAs might postpone gastric emptying by inhibiting the vagal stimulation and in fact, it reduces weight loss by both working through peripheral and central pathways [36-38]. Hence, the existing premise endorses decreased hunger and intake of food, with no raised expenditure in energy, as the process causing weight loss associated with GLP-1RAs such as liraglutide. According to the studies related to the body, a reduction in the weight associated with liraglutide appears to parallel to a decrease in primarily visceral and subcutaneous fat instead of lean tissue mass [16]. There is also evidence of the analogous effects of liraglutide and exenatide as both result in remarkable suppression of food consumption and weight loss both among animals and human beings [38]. However, there is a need for more research about how the weight loss effect of liraglutide contrasts to that of exenatide.

Further the efficacy of GLP-1RAs can be linked to cardiovascular outcome trials (CVOTs) where there is evidence that CVOTs of GLP-1RAs among patients with T2DM have revealed that some of the GLP-1RAs have potential to reduce cardiovascular risk and may help to design and implement CVOTs in obesity in near future. Since obesity is one of the risk factors for cardiovascular morbidity and mortality, GLP-1RAs can be beneficial in reducing the risk of cardiovascular risk indirectly by reducing the weight of obese individuals. There is well-established evidence that weight reduction can lead to reduction in proinflammatory markers, which, in turn, can be helpful to improve the risk factors of coronary heart disease by reducing inflammation, thereby better cardiovascular outcomes.

Strengths and limitations

This review has endorsed the findings regarding the efficacy of GLP-1 agonists to help reduce the weight among obese individuals. The systematic review is strengthened due to robust evidence from both observational studies and RCTs, which is considered as the superior and gold standard in the hierarchy of study designs. We also found diverse studies from across the
globe that gave us confidence that the GLP-1 agonists available to treat obesity can be generalized outside a given setting mainly across the globe. We found a considerable consistency in the primary outcomes for included studies as most of the studies assessed identical outcomes. However, the length of follow-up varied across the studies with lengthier follow-up for about 1 year, which might miss the recurrence that occurs in the longer run. Lastly, we tried to compare all modalities, which allude to understand the differences between different types of GLP-1 agonists to assess whether one is superior to the other.

Conclusion

Given their likely advantages further than glycemic control in reducing the weight, GLP-1 agonists may contribute to the treatment of obesity either among diabetic or non-diabetic individuals soon. Though, further research studies mainly large clinical trials are required to broaden and completely explain the favorable effects and potential side effects of GLP-1 agonists. Although this systematic review found positive effects of GLP-1 agonists in weight reduction, physicians need to write the prescriptions vigilantly to evade possibly side effects of the GLP-1 agonists, while offering opportunity for the overall health of obese individuals with or without diabetes.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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