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Review

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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 sulphonylureas, 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.

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Therefore, 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 pre-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

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.
	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.
Study characteristics	Cite each included study and present its characteristics.	Description is given in Tables and results section.
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.

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 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"

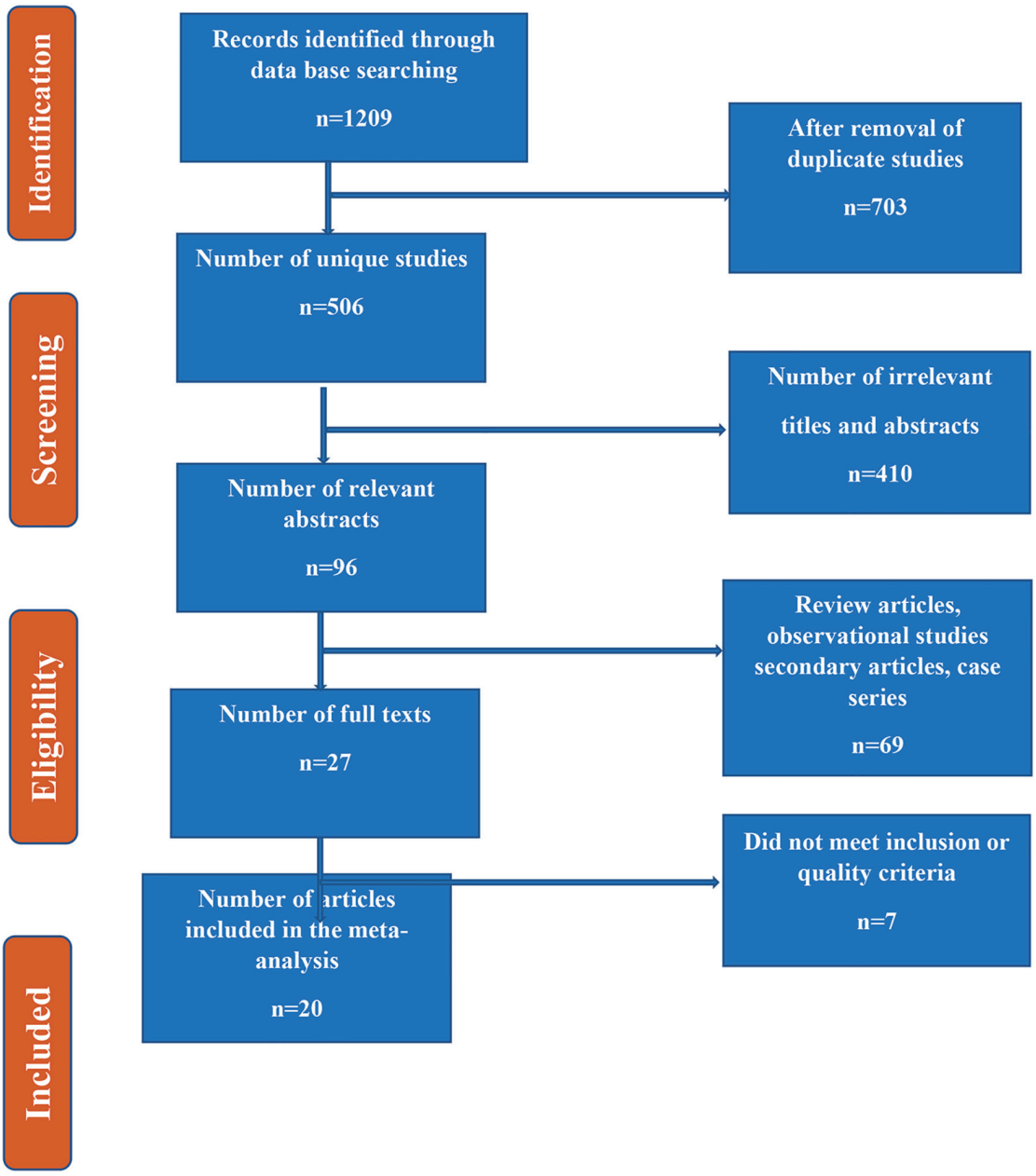

Figure 1. Flow chart summarizing the identification and selection of papers for systematic review.

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 almot 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 biasm, 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/m^2)
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

Table 3. Characteristics of the Included Studies With Their Settings and Types of Groups (n = 13) - *(continued)*

Study name	Year	Country	Study design	Sample size	Group 1	Group 2	Group 3	Age (years)	BMI (kg/m^2)
Wilding et al [29]	2021	16 countries of Asia, Europe, North America, and South America	RCT	1,961	2.4 mg semaglutide administered subcutaneously	Placebo	NA	18 years of age or older adults	> 27
Davies et al [30]	2021	12 countries of Asia, Europe, North and America, and South America, South Africa, and Middle East	RCT	1,595	2.4 mg semaglutide administered subcutaneously	1.0 mg semaglutide administered	Placebo	18 years of age or older adults	> 27
Wadden et al [31]	2021	41 sites in the USA	RCT	611	2.4 mg semaglutide administered subcutaneously	Placebo	NA	46 ± 13	38.0 ± 6.7
Rubino et al [32]	2021	73 sites in 10 countries	RCT	803	2.4 mg semaglutide administered subcutaneously	Placebo	NA	46 ± 12	38.4 ± 6.9

BMI: body mass index; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter-2; GLP-1: glucagon-like peptide-1.

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 among obese individuals and followed them for 20 weeks [16]. There was 5.8 kg (95% CI: 3.7 - 8.0) more weight lost in group 1 as opposed to placebo and there was 3.0 kg additional weight loss as opposed to 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/m^2), 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 Agonisits in Reducing Weight Loss (n = 13)

Study name	Year	Duration of treatment	Type of population	Main findings	Summary of findings
Rosenstock et al [13]	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 [14]	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 [15]	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 [16]	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 [17]	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 [18]	2016	15 weeks	Obese and diabetic individuals	There was a reduction in the mean BMI (-0.78 kg/m^2), 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 [19]	2016	24 weeks	Obese and diabetic individuals	Significant reductions in BMI (-0.86 kg/m^2, P = 0.024), fat mass (-2.01 kg, P = 0.015), fat mass index (-0.71 kg/m^2, 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 [20]	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/m^2 (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 [21]	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 anit-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.	Libitum 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 agonisits, -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 agonisits resulted in weight reduction in dose dependent manner when compared with placebo. However, there were more side effects reported with glucagon receptor agonisits 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%.	Liraglutide resulted in improved weight by the end of 14 weeks amon 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 agonisits 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 agonisits.
Wilding et al [29]	2021	68 weeks	Obese adults with at least one attempt of weight unsuccesful 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 interms on weight reduction than 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
Wadden et al [31]	2021	68 weeks	Obese and overweight adults	The mean difference was -10.3 percentage points (95% CI: -12.0 to 8.6 and P < 0.001).	Semaglutide 2.4 mg given once a week along with behavioural therapy and low-calorie diet redulted in substantial weight loss than placebo group.
Rubino et al [32]	2021	68 weeks	Obese and overweight adults	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 the body weight between two groups was -14.8 with 95% CI of -16.0 to -13.50 (P < 0.001).	There was substantial weight loss in the group that received Semaglutide 2.4 mg than placebo.

CI: confidence interval; T2DM: type 2 diabetic mellitus; NAFLD: non-alcoholic fatty liver disease; IQR: intraquartile range; SGLT-2: sodium-glucose cotransporter-2; GLP-1: glucagon-like peptide-1.

ter treating patients with liraglutide, significant reductions in BMI (-0.86 kg/m^2, P = 0.024), fat mass (-2.01 kg, P = 0.015), fat mass index (-0.71 kg/m^2, 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/m^2 (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/m^2 and were followed for 12 weeks after being assessed at baseline for various clinical and demographic factors. The study findings revealed a significant recution 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 agonisits, -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 agonisits resulted in weight reduction in dose-dependent manner when compared with placebo. However, there were more side effects reported with glucagon receptor agonisits as compared to placebo. These side effects included nausea and vomiting [26]. Likewsie, 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 intraquartile range (IQR) of -5.40 to -1.50 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]. Auhtors 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 findingds 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 in the intervention arm (semaglutide) compared to -2.6 kg in the control arm with a mean difference of -12.7 kg (95% CI: -13.7 to -11.7).

Likwise, a STEP 2 study group conducted a double-blinded RCT to assess the efficiacy 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 particopants in the semaglutide 2.4 mg group when compared to 28.5% among placebo arm (P < 0.0001) [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 weight change 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 invetigators 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 the 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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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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