Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Effect of Liraglutide on Fat Mass Percentage Among Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review

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Background: Obesity and type 2 diabetes mellitus (T2DM) are two global public health problems. Liraglutide, a glucagon-like peptide 1 analogue (GLP-1), is considered an effective option for weight loss. Hence, it is meaningful to understand the impact of GLP-1 therapy on body composition, particularly fat mass percentage (%), in determining health risks associated with obesity. The current meta-analysis and systematic review aimed to appraise and summarize available studies regarding the efficacy of liraglutide on fat mass (%), anthropometrics and glycemic control.

Methods: Three databases were searched up to March 2022 for randomized clinical trials (RCTs) and studies that evaluated the efficacy of liraglutide on T2DM patients: Cochrane Central Register of Controlled Trials, Web of Science, and PUBMED: Cochrane Central Register of Controlled Trials, Web of Science, and PUBMED. If at least two studies had the same outcome and treatment, a random effect model meta-analysis was used to report pooled mean difference (MD) and 95% confidence interval (CI). The protocol of this review was registered in PROSPERO under registration number CRD42022313002.

Results: From the 4031 articles identified and reviewed, only 5 studies (N = 263 patients) matched the inclusion criteria. Only two out of 3 RCTs have complete data to produce forest plots. No significant changes were observed from the pooled MD for body fat % [−0.56 (−2.63, 1.26)] and weight [−0.68 (−2.63, 1.26)]. A significant change in Hba1c with a pooled MD of −1.25 (−2.13, −0.36) (p = 0.006) was observed. I^2 tests were above the threshold of 50% for weight and Hba1c, indicating heterogeneity among the included studies.

Conclusion: This review suggests that liraglutide is effective in glycemic control with no significant effect on weight and fat mass % among overweight patients with T2DM. It is important to note, however, that the certainty of the available evidence is weak.

Keywords: liraglutide, Saxenda, body composition, fat mass, obesity, type 2 diabetes

Introduction

Obesity is a global public health problem. In fact, between 1975 and 2016, the rate of obesity tripled and continuously escalated in pandemic-like proportions.[1] In 2016 alone, data from the World Health Organization (WHO) revealed that more than 1.9 billion adults aged 18 years and above were overweight, 650 million of whom were obese. The prevalence of overweight and obesity is reported to be higher in women than in men across the globe, in both developed and developing countries.[2] Evidence suggests a sex-specific vulnerability, with women physiologically having greater adipose storage, therefore having higher total percentage of body fat than men.[3]

The WHO defines obesity as an "abnormal or excessive fat accumulation that may impair health", further clarifying that "the fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended". The term "Body Mass Index" (BMI), measured by calculating [(weight in kg)/(height in m^2)], is a simple index intended to classify adults into one of the three categories: "underweight", "overweight", or "obese". The WHO often classifies adult obesity using certain BMI cut-offs; with BMI >25 kg/m^2 considered overweight and >30 kg/m^2 considered obese.[4] Obesity and overweight are considered as precursors to a variety of comorbidities such as cardiovascular and renal disease, type 2 diabetes mellitus (T2DM), some malignancies, musculoskeletal disorders, and other

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chronic illnesses.[5] Most researchers agree that obesity is a complicated health condition that is influenced by a combination of biological, genetic, social, environmental, and behavioral determinants.[2]

Different modalities are available for weight management. The first-line therapy is lifestyle modification which includes caloric restriction and increased physical activity. Moreover, a healthy diet (type and amount) is considered one of the most important lifestyle factors for controlling glycemia and lipid profile, specifically among patients with hypertension and/or type 2 diabetes mellitus (T2DM).[6] For individuals with severe and complicated obesity or who have failed to lose weight by other weight-loss strategies, bariatric surgery is considered the better therapeutic option. Nevertheless, due to the risks associated with surgery, there is a need for less invasive methods to achieve long-term weight loss in people unresponsive to conventional management.[7]

Current evidence has shown some promising effects of pharmacotherapy in weight management.[8] Analogs of the incretin hormone, glucagon-like peptide 1 (GLP-1), has recently been introduced as a weight loss medication. It was thought that GLP-1-induced weight reduction was a result of several physiological changes including gastric emptying, glycemic control, appetite, and energy metabolism.[7] Liraglutide is a long-acting GLP-1 receptor agonist developed by Novo Nordisk and one of the medications that have been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of T2DM. A number of trials have reported positive results on its efficacy in improving glycemic and cardiovascular risk factors. On December 23, 2014, the FDA approved liraglutide 3.0 mg, a higher-dose version, for the treatment of chronic weight management. This medicine was approved for people with obesity, as well as overweight individuals who have at least one weight-related comorbid condition such as T2DM, hypertension, or hypercholesterolemia.[7] Several years after approval, however, only a few studies have assessed liraglutide's efficacy on body fat-associated weight loss.[9] Thus, the current meta-analysis and systematic review aim to clarify based on available evidence, the efficacy of liraglutide on fat mass percentage, anthropometric measurements and glycated hemoglobin (HbA1c) among overweight patients with T2DM.

Materials and Methods

Search Strategy

An online literature search was done for studies conducted among humans, from inception (no retrospective date limit) to March 2022. Three search databases were included with no language restriction: Cochrane Central Registry of Controlled Trials, Web of Science, and PubMed. The following words and subject terms were used in this search: "Glucagon-like peptide-1 receptor agonists or GLP-1 or liraglutide or Saxenda" and "body composition or fat mass or fat-free mass or obesity" and "type 2 diabetes"; Search strategies for each database have used both keywords and operators. The protocol of this review was registered in Prospero under registration number CRD42022313002.

Eligibility Criteria

Studies were included if they met the following inclusion criteria:

1. Overweight or obese adult males and females from outpatient clinics or from community settings aged ≥18 years and above diagnosed with T2DM or HbA1c >6.5%.
2. Original articles (eg, randomized controlled trials (RCTs) and observational studies).
3. Outcomes of interest include changes in fat mass percentage (%), in addition to other anthropometric measurements, and HbA1c.

Studies were excluded if participants were hospitalized patients, with chronic diseases, prediabetes, Type 1 diabetes and on insulin treatment, pregnant or breastfeeding. Studies conducted among children and adolescents, meta-analysis, review and animal studies and in vitro studies were also excluded.

Study Selection and Data Extraction

The reviewer was assigned for all databases to search using the predefined keywords to initially screen the title and abstract of each generated study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as shown in Figure 1.[10] All studies were extracted from each database into Microsoft Excel for the removal of duplication and to further screen the full text of the final included studies. The data extraction was conducted independently using the Cochrane data collection forms for all included articles found in the Supplementary Materials as data forms 1, 2, 3, 4 and 5. Disagreements between reviewers were resolved by consensus, and if agreement could not be reached, it was planned for a third author to decide.

Assessment of Risk of Bias

Quality assessment of risk of bias of RCT was performed using the Cochrane risk of bias tool (ROB2) using RevMan 5 software. In which, it assesses different domain selection, performance, detection, attrition and reporting bias.[11] However, assessment of observational studies conducted by using the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) assessment tool[12] that evaluates 7 domains; confounding selection, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result bias. The reviewers assessed the risk of bias of included studies followed by a discussion to solve any disagreement.

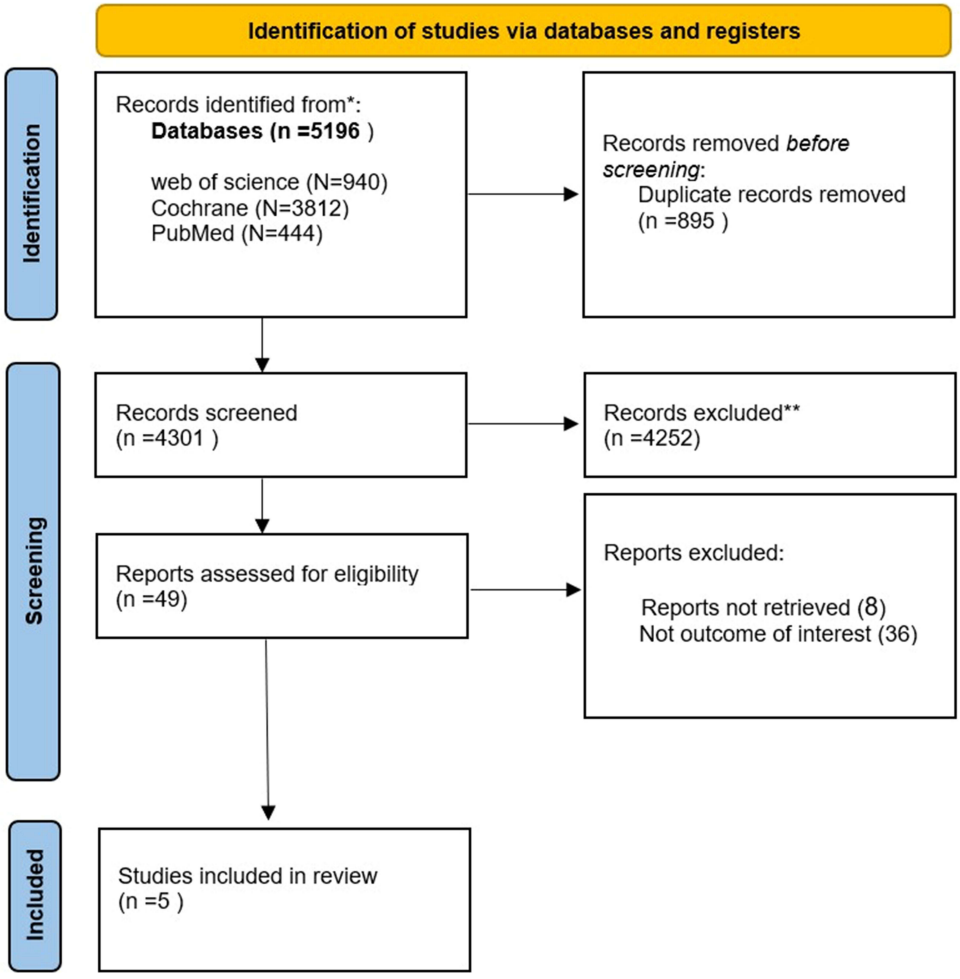

Figure 1 PRISMA 2020 flow diagram of the selection process. *The total number of records identified using the keywords "Glucagon-like peptide-1 receptor agonists or GLP-1 or liraglutide or Saxenda" and "body composition or fat mass or fat-free mass or obesity" and "type 2 diabetes" from all databases (Web of Science, Cochrane, and Pubmed) was 5196. **All excluded records were excluded manually by three independant reviewers.

Data Synthesis

Random effects model was used for the mean difference of change between groups and meta-analysis was done for outcomes (body fat %, weight and/or HbA1c) with at least two studies having mean and standard deviation for each group. I^2 test was used to assess heterogeneity between studies and a value >30.0 denotes high heterogeneity.

Results

Characteristics of Eligible Studies

With respect to the study design, three of the studies were RCTs and two were observational studies (prospective case series, cohort). The characteristics of each study are summarized in Table 1 and 2. The sample size of these studies was relatively small, ranging from 9 to 160 participants. All studies included both genders with uneven distribution. The studies were conducted mostly in developed countries such as USA and Mexico (k = 1), Denmark (k = 2), and Italy (k = 2). The year of publication ranged from 2004 to 2016. As for RCTs, participants were randomized to liraglutide treatment versus placebo. In terms of the intervention group, one study included patients treated with liraglutide along with metformin, the other study participants were on liraglutide plus exercise and the third study participants were on liraglutide only. Fat mass %, anthropometric measurements, and HbA1c were all reported. Outcome measures were evaluated at the end of the intervention, which varied from 8 to 28 weeks. Three RCT studies met the inclusion criteria, involving 226 participants, comparing the effect of liraglutide versus placebo, were chosen and systematically reviewed. The baseline characteristics of participants in the three RCT studies[13–15] were balanced with a mean age of 57.6 years, bodyweight of 96.8 kg, HbA1c of 7.9%. In general, the results of the RCTs revealed non-significant effects of liraglutide on fat mass % and anthropometric measurements compared to placebo. However, significant effects were observed with respect to HbA1c. On the other hand, the two observational studies included in this review involved 37 participants with a mean age of 63.4 years, a bodyweight of 90.2 kg, and HbA1c of 8.08%. The result of the two included observational showed a significant result in all variables (fat mass percentage, anthropometric, and HbA1c). The detailed description of the RCTs was described in detail in the Supplementary Materials in Tables S1a–S1g and S1i, Tables S2a–S2g and Figures S1 and S2, Tables S5a–S5i, whereas the detailed description of the observational studies was described in detail in the Supplementary Materials in Tables S3a–S3h and Tables S4a–S4h.

Study Selection

The initial database searches produced 5196 articles. Of these, 444 articles were from PubMed, 940 from Web of Science, and 3812 from Cochrane (Figure 1). A total of 895 duplicate articles were removed. Titles and abstracts of 4301 articles were reviewed, and 4252 articles were excluded as they did not meet the inclusion criteria. During the full-text screening, 49 articles were assessed for eligibility. Articles were excluded for the following reasons: 8 articles were not retrieved and 36 articles had different outcomes of interest. The final systemic search produced 5 studies.

Quality Assessments

Risk of bias was assessed as a judgment (high, low, or unclear) as showed in Figure 2. The bias of the randomization process was low in all studies except for Harder et al unclear judgments due to inadequate information available. The bias of allocation concealment was unclear, whereas performance and attrition bias were low in all studies included. However, the judgment of sponsorship bias was high among all studies.[13–15] The selection of the reported results was evaluated and considered low risk for all studies except for one study that outcome was reported incompletely.[15] Two studies were displayed unclear risk of the blinding of outcome assessment mainly for the reasons of insufficient information. On the other hand, one RCT presented low risk of bias.[14] Generally, the overall judgment of all RCTs included showed a high risk of bias (Tables S1h and S2h–S5h). The overall risk of bias judgment of the observational studies (non-randomized trials); cohort and case series studies were moderate and serious bias (Tables S3i and S4i).

Table 1 Summary of RCT Studies

Study	Setting	Sample Size	Duration of Intervention	Study Population-Baseline	Intervention Group	Control	Outcome
Harder et al, 2004[16]	Denmark	33	8 weeks	Mean age:60.0 ± 9.5 years Sex (M/F): 21/12 Mean body weight: 101 kg Mean BMI: 36.6 ± 4.1 kg/m2 Mean HbA1c: 7.5 ± 1.2%	Liraglutide (0.6 mg)	Placebo	**% fat mass**: (Liraglutide, −0.98%, and placebo, −0.12%; *P* = 0.088) **Anthropometric measurements**: • Body weight: (Liraglutide, −0.7 kg, and placebo, −0.9 kg; *P* = 0.756) • Waist circumference: (Liraglutide, −0.5 cm, and placebo, −1.1 cm; *P* = 0.505) **HbA1c**: (Liraglutide, −0.33%, and placebo, 0.47%; *P* = 0.028)
Jendle et al, 2009[17] (LEAD-2)	Mexico & US	160	26 weeks	Mean age: 57 years Sex (M/F): 104/56 Mean body weight: 90.5 kg BMI: ≤40 kg/m2 HbA1c: 8.3 ± 1.0%	Liraglutide (0.6, 1.2, 1.8 mg) + metformin (1.5–2 g)	Placebo + metformin (1.5–2 g)	**% fat mass**: Reduction (Liraglutide treatment added to metformin; *P* = 0.9694 for Liraglutide 0.6 mg, *P* = 0.4889 for Liraglutide 1.2 mg, *P* = 0.3871 for Liraglutide 1.8 mg). **Anthropometric measurements**: • Body weight: Mean body weight reduction (Liraglutide 0.6 mg, −0.7 kg, Liraglutide 1.2 mg, −2.0, Liraglutide 1.8 mg, −3.2 and placebo, −1.3 kg) **HbA1c**: in a dose-dependent manner (Liraglutide 0.6 mg, −0.6%, Liraglutide 1.2 mg, −0.9%, Liraglutide 1.8 mg, −1.0%; *P* < 0.0001 and placebo, +0.4%)
Mensberg et al 2016[18]	Denmark	33	16 weeks	Mean age: 56 ± 11 years Sex (M/F): 23/10 Mean body weight: 98.9 ± 15.9 kg Mean BMI: 32.4 ± 4.4 kg/m2 Mean HbA1c: 8.1 ± 1.3%	Liraglutide (1.8 mg) + exercise	Placebo + exercise	**% fat mass**: (Liraglutide added to exercise, −2.5 ± 1.4%, and placebo added to exercise, −2.2 ± 1.9%; *P* = 0.77) **Anthropometric measurements**: • Body weight: (Liraglutide added to exercise−3.4 ± 2.9kg, and placebo added to exercise, −1.6 ± 3.2 kg; *P* = 0.10) • BMI: (Liraglutide added to exercise, −1.1 ± 1.1 kg/m^2, and placebo added to exercise, −0.5 ± 1.0; *P* = 0.11) **HbA1c**: (Liraglutide added to exercise, −2.0 ± 1.2%, and placebo, −0.3 ± 0.9%; *P* <0.001)

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Table 2 Summary of Observational Studies

Study	Setting	Sample Size	Duration of Intervention	Study Population-Baseline	Intervention	Outcome
Rondanelli et al, 2016[19] Cohort	Italy	28	24 weeks	Mean age:58.75 ± 9.33 years Female sex: 12 Mean body weight: 94.58 ±18.32 kg Mean BMI: 34.13 ± 5.64 kg/m2 Mean HbA1c: 8.26 ± 1.51%	Liraglutide (3 mg) + diet modification	**% fat mass:** −**1**.45% (*P*= 0.009) **Anthropometric measurements**: • Body weight: From baseline (*p* = 0.026) • BMI (*P*=0.024) • Waist circumference (*P* < 0.001) **HbA1c**: −1.40% (*P*= 0.001)
Perna et al, 2016[13] Case series	Italy	9	24 weeks	Mean age: 68.22+ 3.86 years Female sex: 3 Mean body weight: 86.01 ±15.01 kg BMI: 32.34 ± 4.89 kg/m2 HbA1c: 7.90 ± 1.79%	Liraglutide (3 mg) +diet modification (1800 to 2500 kcal)	**% fat mass**: (−0.70%). **Anthropometric measurements**: Median from baseline • Body weight: (−2 kg) • BMI = −0.78 Kg/m2 • Waist circumference = −2 cm **HbA1c**: Median from baseline −**0**.80%

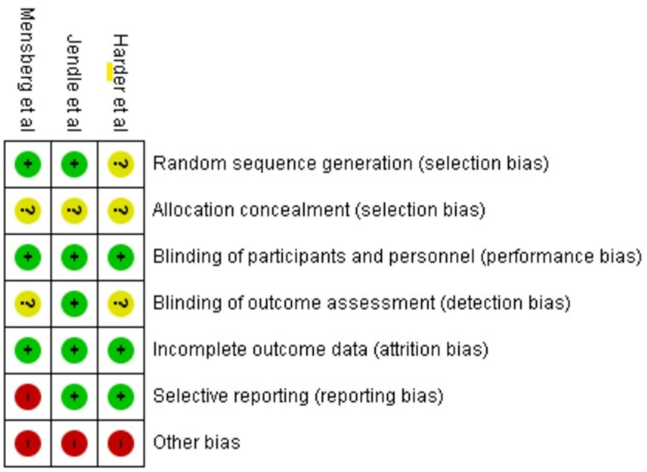

Figure 2 Risk of bias summary for RCTs. Red (-) high risk of bias; yellow (?) unclear risk of bias green (+) low risk of bias.

Clinical Effectiveness

Body Fat %

Experimental Evidence

Two RCTs[13,14] investigated the effect of liraglutide on body composition and fat mass percentage compared to the placebo group. Harder et al studied the effect of 0.6 mg of liraglutide in 8 weeks of intervention and has exhibited a non-significant trend between the groups toward a reduction in total fat mass percentage (- 1.0%, for liraglutide and - 0.1% for placebo, p = 0.09) and toward an increase in lean body mass percentage (+1.0% for liraglutide and +0.2% for the placebo, p = 0.12).[13] Furthermore, a 26 weeks sub-study by Jendle et al also showed a non-significant reduction of total body fat percentage when treated with liraglutide of different doses plus metformin compared to placebo (p = 0.97 for liraglutide 0.6 mg, p = 0.49 for liraglutide 1.2 mg, p = 0.39 for liraglutide 1.8 mg). However, lean body mass has decreased non significantly among all liraglutide groups in a dose-dependent manner (p = 0.15 for liraglutide 0.6 mg, p = 0.75 for liraglutide 1.2 mg, p = 0.98 for liraglutide 1.8 mg).[14]

In contrast, one RCT of 16 weeks of intervention demonstrated a significant reduction in body fat % compared to baseline values (Exercise + 1.8 mg liraglutide; p < 0.001) which was not observed in the placebo group (p = 0.77).[15] With regard to lean body mass, no change detected from baseline in both groups (Exercise + 1.8 mg liraglutide and exercise + placebo; p = 0.42).

Observational Evidence

A cohort study assessed the effect of 3 mg of liraglutide over 24 weeks of intervention. The results showed a significant reduction in fat mass percentage −1.45% (p = 0.009) compared to baseline values. No reduction in fat-free mass was observed (P = 0.40).[19] In a case series study,[9] a relevant reduction of fat mass percentage (−0.70%) with 3 mg of liraglutide treatment once daily over 24 weeks of intervention. In parallel, the fat-free mass has increased with a median of +9 g.

Changes in Anthropometrics

Experimental Evidence

No changes in body weight and waist circumference were detected between liraglutide group and placebo group (p = 0.76, p = 0.50, respectively).[13] Though Jendle et al support the previous findings, a non-significant decrease in body weight with liraglutide group in a dose-dependent manner (mean body weight decreases of −0.9, −2.0, and −3.2 kg with liraglutide 0.6, 1.2 and 1.8 mg respectively) was compared to placebo (−1.3kg). All liraglutide groups and placebo were in combination with metformin. Similar results were shown by Mensberg et al, who showed a meaningless change in body weight and BMI between the groups (p-values 0.10 and 0.11, respectively).[15]

Observational Evidence

A cohort study by Rondanelli et al looked at the effects of 24-week liraglutide treatment on body composition, appetite, and lipid profile in overweight and obese T2DM patients and reported a significant reduction in body weight ($p = 0.03$), BMI ($p = 0.02$) and waist circumference ($p < 0.001$) over time. In addition, a notable reduction in body weight, BMI, and waist circumference with a median of −2000 g, −0.78 kg/m^2 and −2 cm, respectively, were observed from baseline values at doses up to 3.0 mg per day.[9]

Changes in Glycemic Control

Experimental Evidence

The liraglutide group showed a significant reduction in HbA1c (0.6, 0.9, and 1.0% with liraglutide 0.6, 1.2, and 1.8 mg, respectively – all in combination with metformin) compared to the placebo group which showed an increment of 0.4% in HbA1c readings.[14] Similarly, liraglutide has notably reduced HbA1c levels (−0.80%, $p = 0.03$) compared to placebo,[13] as well as a pronounced reduction in HbA1c between groups (exercise plus liraglutide −2 ± 1.2 and exercise plus placebo −0.3 ± 0.9%; $p < 0.001$).[15]

Observational Evidence

Glycemic control improved in the two observational studies (cohort and case series) with a median change of HbA1c (−1.40%, −0.80% respectively).[9,20]

Meta-Analysis

Figures 3–5 represent forest plots showing individual and pooled mean differences (95% CI) of body fat (%), weight (kg) and Hba1c (%), respectively, in liraglutide and placebo subjects. The forest plots provided non-significant pooled mean

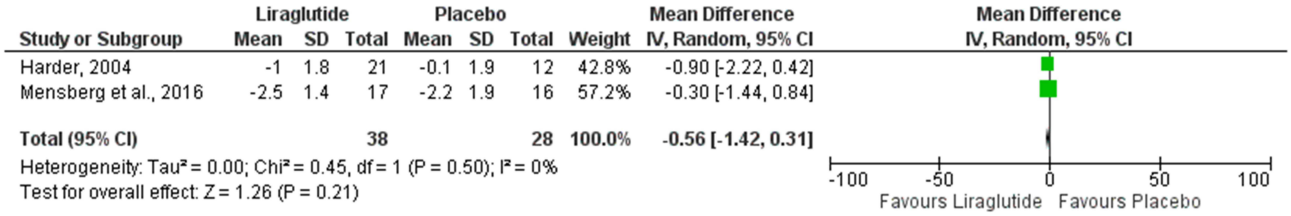

Figure 3 Forest plot of mean change in body fat (%) according to liraglutide and placebo.

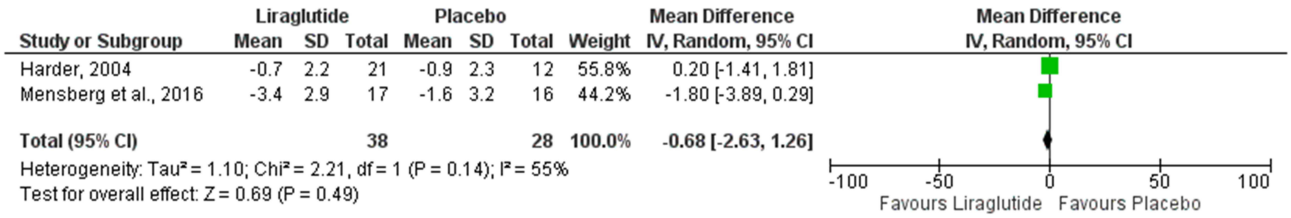

Figure 4 Forest plot of mean change in weight (%) according to liraglutide and placebo.

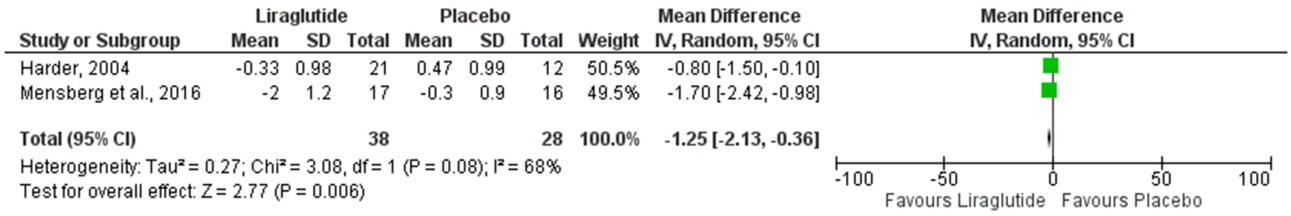

Figure 5 Forest plot of mean change in Hba1c (%) according to liraglutide and placebo.

differences for body fat −0.56 (−2.63, 1.26) and weight −0.68 (−2.63, 1.26). However, there is a significant change in Hba1c with a pooled mean difference of −1.25 (−2.13, −0.36) (p = 0.006). I^2 tests were well above the threshold of 50% for weight and Hba1c, indicating heterogeneity among the included studies. No heterogeneity was observed for body fat (%) with I^2 statistics <0.30.

Discussion

To the author's knowledge, this is the first systematic review that compiles and provides evidence about the effect of liraglutide on fat mass percentage among obese patients with T2DM. Based on 5 included studies, the results of both interventional and observational trials revealed patients in liraglutide group had significantly improved HbA1c levels over time. On the other hand, the results for weight loss and fat mass percentage were inconsistent between the studies.

A study on human adipose stem cells (ASCs) obtained from subcutaneous adipose tissue of morbidly obese subjects who underwent bariatric surgery suggested that GLP-1 may affect adipose tissues (AT) directly and independently of weight loss.[16] Two observational studies conducted among Italian overweight and obese patients with T2DM showed that treatment with liraglutide (3 mg) over 24 weeks led to a mean weight loss of (−2.0 kg, −2.45 kg), particularly fat mass (0.70%–1.45%) respectively.[9,20] At the same time, it preserved muscle mass by preventing muscle protein breakdown.[9] The most important result of the previous findings is that weight loss caused by liraglutide mainly originated from a reduction in fat mass rather than lean tissue mass.[9,20] Furthermore, A 16-week RCT study among obese subjects has found that liraglutide (3mg) combined with dietetic and behavioral modification resulted in reducing fat mass % compared to placebo (−2.0% for liraglutide and −0.4% for the placebo, p = 0.03).[17] This favorable effect on fat mass % was not observed in other studies.[13–15]

GLP-1 receptors are found all over the human body and hence are expected to promote many physiological outcomes such as glycemic control and weight reduction.[18] The possible mechanism by which GLP-1 has an effect on weight change includes slowing gastric emptying, increasing postprandial satiety, and reducing the appetite and food consumption by influencing the central nervous system.[1] In contrast, none of the RCT participants included in this review had significantly lost weight.[13–15] This may be explained by the short duration and small doses of liraglutide which are considered low for inducing pronounced effect.[1] The drug is also considered a novel glucose-lowering therapy that is well known in recent guidelines for the management of hyperglycemia in T2DM and is recommended alongside lifestyle management (diet and physical activity).[12] It works by activating GLP-1 receptors in the pancreas, leading to enhanced insulin release and insulin sensitivity, and reducing glucagon release that are both glucose-dependent-with a resultant of low risk for hypoglycemia.[1] Mensberg et al have revealed that treatment with liraglutide (1.8 mg) plus exercise helps patients to obtain better glycemic control. After 16 weeks of liraglutide treatment, a significant decrease of 2.0% in HbA1c levels from baseline was detected. This represents the highest positive effect when compared with other studies where HbA1c reduced by 0.6%, 0.8%, 0.9%, 1.0%, and −1.40%.[9,13,14,20] Moreover, all included studies have also showed an improvement in fasting blood glucose. Findings from a systematic review and meta-analysis of 5 RCT studies (n = 1634) that compared liraglutide with either placebo or active control (exenatide or glimepiride) were consistent with the previous results.[19] Safety data from some of the included trials were generally well tolerated, while the most reported adverse effect was gastrointestinal in nature (nausea and diarrhea) with no reported episodes of hypoglycemia.[13,15]

The authors acknowledge a few limitations and therefore results should be interpreted with caution. First, the limited number of included articles. Second, the small sample size of most of the included evidence besides the relatively short duration of the treatment intervention. Lastly, RCT studies have high risk of bias due to NOVO Nordisk Sponsorship.

Conclusions

To conclude, the present meta-analysis and systematic review elucidated that liraglutide provides better glycemic control by enhancing HbA1c reduction with no pronounced effect on weight and fat mass reduction for overweight and obese patients with T2DM. The present results are based only on a few RCTs and are considered weak. More studies with larger sample size and longer duration, fixed does and higher quality trials are needed to investigate the true efficacy of liraglutide on fat mass % in overweight and obese patients with T2DM.

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Author Contributions

Conceptualization and design, A.A., J.A. and R.B.; study selection, A.A., J.A. and R.B.; data extraction, A.A., J.A. and R.B.; data synthesis, A.A., J.A. and R.B.; writing—original draft preparation, A.A., J.A. and R.B.; writing—review and editing, A.A., J.A. and R.B. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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