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Association between Liraglutide (Saxenda®) and weight reduction; a systematic review

Running title: Liraglutide (Saxenda®) and weight reduction

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Abstract

Background: Obesity is one of the most common conditions, especially in developing countries. Many medications have been proposed to have a positive impact on body weight, yet their safety profile was a barrier against their use. Liraglutide is one of the medications that have a weight reduction potential. However, data about its safety and effectiveness in weight reduction is conflicting. Objective: This study aims at examining the medical literature to evaluate the correlation between using Liraglutide and weight reduction. Method: the literature was reviewed through Medline, PubMed, Embase, and Ovid database in the duration between 2009 and 2019. Searching terms included were a combination of ‘Association’ AND ‘Liraglutide’ AND ‘weight reduction’. Following this, results were filtered to include only original research articles investigating weight reduction accompanying the administration of Liraglutide. Selected trials mentioned the target population and any adjunctive intervention or treatment to Liraglutide. Result: A total of 1904 articles were retrieved. Following the exclusion of articles on animals and including only trials on humans, 42 articles appeared. A total of eight articles were identified as eligible, covering a total of 6406 patients with overweight or obesity. All the studies were randomized, blinded studies, except for one study, was observational. Conclusion: Liraglutide showed to be an effective medication in reducing body weight if taken for short term or long term. Hypoglycemia occurring with Liraglutide was minimal.

Key-words: Liraglutide, diabetes mellitus, weight loss, review
**Introduction and Background**

Medications treating type two diabetes usually involve complex regimens and combination therapy that can put patients at risk of hypoglycemia and increased incidence of side effects [1]. A relatively new class of oral ant diabetics is Glucagon-like peptide-1 (GLP-1) inhibitors, which mainly target increasing levels of incretin hormone [2]. Incretin has many physiological actions that can significantly reduce blood glucose levels and modify the pathophysiology of diabetes [3].

Some studies showed that Liraglutide could have some benefits in addition to reducing blood glucose levels, such as cardiovascular protection [4]. Additionally, Liraglutide showed a significant reduction in glycated hemoglobin levels, fasting blood glucose, as well as postprandial blood glucose [5]. All these benefits are added to a good safety profile, with low hypoglycemia risk, in addition to weight reduction [6].

Moreover, monotherapy using Liraglutide or as a part of combination therapy with other agents, revealed a higher level of blood glucose-lowering effect compared to glimepiride, rosiglitazone, and insulin glargine [7].

Previous trials demonstrated that physiological GLP-1 has the potential to reduce appetite, as well as energy intake, either in normal weight or overweight subjects [8]. Liraglutide, mainly, showed a reduction in average body weight about 2 kgs over six to 12 months approximately [9]. This weight reduction reached statistical significance with Liraglutide compared to other therapies [10].
Moreover, Liraglutide has been examined in combination with other ant diabetic agents, in terms of weight loss. The combination with glimepiride showed a reduction of body weight around a half kilogram compared to the control group [11].

In spite of the presence of data evaluating the weight loss potential with Liraglutide, its safety and efficacy are still controversial concerning this indication. Therefore, this systematic review aims to examine the literature for the association between Liraglutide and weight loss.
Methodology

This systematic review of the literature was performed in compliance with the PRISMA checklist recommendations for systematic review and meta-analysis [5]. This systematic review was carried out through searching electronic databases to include eligible trials till October 2019 in four databases, including Medline, Pubmed, Ovid, and Embase.

Search Strategy

Searching terms included ‘‘Association’’ AND ‘‘Liraglutide’’ AND ‘‘weight reduction’’. All the titles, as well as abstracts that appeared from this search, were reviewed thoroughly to prevent missing any eligible articles. The results were then refined to include only original research articles investigating the correlation between weight loss and administration of Liraglutide. Moreover, the selected trials mentioned the type of patient population and any additional therapy or intervention that was done for weight reduction. Additionally, all study designs from different countries were included. Only trials that are published in the English language were classified as related articles, which can be further evaluated in the second step.

Eligibility Criteria

After this stage, the inclusion criteria to select the studies that will be considered in the systematic review were determined. Abstracts were examined manually to choose the appropriate abstracts to be considered. The inclusion criteria were mentioning enough data on the patient population and any additional therapy or intervention that was performed to reduce weight. Moreover, only trials recruiting adult participants were included. Furthermore, references of selected trials were evaluated to identify any related articles. Finally, the required data sets were gathered from the final record
of eligible articles and summarized. Articles were excluded in case of in vitro or animal involvement, overlapped or incomplete data, and unavailability of a full-text articles or inappropriate study design. Full details on the search strategy are shown in figure 1.
**Data Review and Analysis**

The first step included a preliminary review, a specially designed excel sheet was used for data extraction. Selected data from eligible studies were then revised through the excel sheet. Any articles that were published by one research group that investigate similar variables were reviewed for any possible duplication. Cochrane, a quality assessment tool, was also used to evaluate the quality of the included clinical studies [6]. Data were then statistically described in terms of frequencies (number of cases) and valid percentages for categorical variables. Mean, standard deviations, Medians, and interquartile ratios were used to describe the numerical variable. All statistical calculations were performed by IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 21 for Microsoft Windows.

Before conducting any study-related procedures, institutional approval was obtained. There was no need to get consent form as the study is not involving any interventions on patients.

**Results**

After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of eight articles were considered as eligible to be included in the present systematic review that was published between 2009 and 2019, covering a total of 6406 patients who were overweight or obese.

Out of the eight studies, seven studies [11-13, 15-18] had a randomized, blinded controlled design, while only one study [14] had an observational design. Additionally, three studies [11, 13, 18] included subjects with type two diabetes; one
study [14] included females with PCOS, and two studies included subjects who are overweight and obese without any other comorbidities [12, 15].

Furthermore, two studies [11, 18] used another anti-diabetic as adjunctive therapy to Liraglutide, while the other remaining studies used lifestyle modifications (physical activity and diet) in conjunction with Liraglutide [12-17].

According to extracted results, all the trials considered the evaluation of the efficacy and safety of Liraglutide, in terms of hypoglycemia, in weight reduction. The included trials are discussed in detail in table 1.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study design</th>
<th>Sample size</th>
<th>Type of patient population</th>
<th>Additional therapy/Interventions</th>
<th>Objective</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albarkah et al. [11]</td>
<td>2019</td>
<td>Randomized Double-blind</td>
<td>38</td>
<td>Type two diabetes (T2DM)</td>
<td>Liraglutide with conventional anti-diabetic agents</td>
<td>To evaluate the alterations in weight, hemoglobin A1c, and hypoglycemia risk after the addition of Liraglutide to different treatment regimens</td>
<td>There were no statistically significant difference concerning the effectiveness of Liraglutide combined with the three treatment regimens on patients’ weight ($P = 0.08, 0.472, 0.08$, respectively). Liraglutide has demonstrated minimal hypoglycemia.</td>
</tr>
<tr>
<td>Sunyer et al. [12]</td>
<td>2015</td>
<td>Randomized Double-blind</td>
<td>3731</td>
<td>Patients without diabetes, with body mass index (BMI) over 27kg/m2</td>
<td>once-daily administration of Liraglutide with 3.0 mg (2487 patients with lifestyle modification)</td>
<td>To investigate the effectiveness and safety profile of 3.0 mg Liraglutide, as a combination with decreased-calorie diet and improved physical activity. It is used for weight loss in overweight or obese adults who did not have diabetes.</td>
<td>After 56 weeks, patients on liraglutide had weight reduction of $8.4 \pm 7.3$ kg, compared to placebo ($P&lt;0.001$). 33.1% patients on liraglutide lost greater than 10% of their weight ($P&lt;0.001$). The most common adverse effect with Liraglutide were mild nausea or vomiting. Serious events occurred in 6.2% of the patients in the liraglutide group and 5.0% of the patients in the placebo group.</td>
</tr>
<tr>
<td>Davies et al. [13]</td>
<td>2015</td>
<td>Randomized Double-blind</td>
<td>846</td>
<td>overweight or obesity and type 2 diabetes</td>
<td>Once-daily liraglutide (3.0mg), liraglutide (1.8mg), with an adjunct to 500 kcal/d dietary</td>
<td>To explore efficacy and safety of liraglutide versus placebo for weight reduction in adults</td>
<td>Weight loss was 6.0% with liraglutide (3.0-mg dose), 4.7% with liraglutide (1.8-mg dose), ($P &lt; .001$). Weight reduction of 5% or greater occurred in 54.3% with liraglutide (3.0mg) and 40.4% with liraglutide (1.8mg) ($P &lt; .001$ for both). Weight reduction more than 10% was shown in 25.2% with liraglutide (3.0mg) and 15.9% with liraglutide (1.8mg), respectively.</td>
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</tbody>
</table>
deficit and increased physical activity (150 min/wk).
More gastrointestinal disorders were reported with liraglutide (3.0mg) versus liraglutide (1.8mg) and placebo. No pancreatitis was reported.

| Rasmussen et al. [14] | 2014 | Observational | 84 | Overweight and obese females with polycystic ovary syndrome (PCOS) | Liraglutide with metformin and lifestyle modification. | In overweight or obese females with PCOS treated with Liraglutide for a minimum of 4 weeks, a mean weight loss of 9.0 kg (P < 0.0001). A weight loss of more than 5 and 10% of baseline weight was seen in 81.7 and 32.9% of patients, respectively. The mean duration of treatment with Liraglutide was 27.8 weeks. |
| Lean et al. [15] | 2014 | Randomized placebo-controlled, double-blind | 561 | Obese and overweight subjects without any other comorbidity | once-daily subcutaneous Liraglutide (1.2, 1.8, 2.4 or 3.0 mg) and lifestyle modification | In year 1, more participants reported an episode of nausea/vomiting on treatment with Liraglutide 1.2–3.0mg (17–38%) than with placebo or orlistat (both 4%, Pp0.001). Most episodes occurred during dose escalation (weeks 1–6), with 'mild' or 'moderate' symptoms. Among participants on Liraglutide 3.0 mg, 48% reported some nausea, and 13% some vomiting, but only (4%) reported withdrawals. The mean 1-year weight loss on treatment with liraglutide 3.0mg from randomization was 9.2 kg for participants reporting nausea/vomiting episodes, versus 6.3 kg for those with none (P=0.02). Both weight losses were |
significantly higher than the respective weight losses for participants on placebo (P<0.001) or orlistat (P<0.05). Quality-of-life scores at 20 weeks improved similarly with or without nausea/vomiting on treatment with liraglutide 3.0 mg.

Participants lost a mean 6.0% of screening weight during the run-in. From randomization to week 56, weight decreased an additional mean of 6.2% with Liraglutide and 0.2% with placebo (P<0.0001). More participants receiving liraglutide (81.4%) maintained 5% weight loss, compared with those receiving placebo (48.9%) (P<0.0001), and 50.5% versus 21.8% of. Participants lost 5% of weight (P<0.0001). Gastrointestinal (GI) disorders were reported more frequently with Liraglutide than placebo, but most events were transient and mild or moderate in severity.

From randomization to year 1, liraglutide 3.0mg recipients lost 5.8 kg more weight than those on placebo and 3.8 kg (1.6–6.0) more than those on orlistat (P<0.0001). At year 2, participants on liraglutide 2.4/3.0mg for the full two years lost 3.0 kg (1.3–4.7) more weight than those on orlistat (P<0.001). Completers on liraglutide 2.4/3.0mg maintained a 2-year weight loss of 7.8 kg from screening. With liraglutide 3.0 mg, 20-week body fat

<table>
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<tr>
<th>Wadden et al. [16]</th>
<th>2013</th>
<th>Randomized placebo controlled trial</th>
<th>422</th>
<th>Obese and overweight subjects without any other comorbidity</th>
<th>Liraglutide with low-calorie diet (LCD)</th>
<th>the efficacy of Liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD)</th>
</tr>
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<tbody>
<tr>
<td>Astrup et al. [17]</td>
<td>2012</td>
<td>Randomized double-blind</td>
<td>564</td>
<td>Obese and overweight subjects without any other comorbidity</td>
<td>Liraglutide with diet counseling</td>
<td>Evaluate Safety/tolerability (primary outcome) and long-term efficacy for sustaining weight loss (secondary outcome) over two years.</td>
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</tbody>
</table>
The most common drug-related side effects were mild to moderate, transient nausea, and vomiting. With liraglutide 2.4/3.0 mg, the 2-year prevalence of prediabetes and metabolic syndrome decreased by 52 and 59%, with improvements in blood pressure and lipids.

| Jendle et al. [18] | 2009 | Randomized double-blind | 160 | Obese patients with T2DM | Liraglutide with a conventional oral antidiabetic agent (metformin or glimepiride) | The effect of Liraglutide on body weight, a once-daily human glucagon-like peptide-1 analog, as monotherapy or in combination with metformin was considered in patients with type 2 diabetes (T2D). | Fat percentage with liraglutide was 1.2 and 1.8 mg/metformin was significantly reduced versus glimepiride/metformin combination (p < 0.05), not versus placebo. Additionally, visceral and subcutaneous adipose tissue areas were decreased from baseline in all liraglutide/metformin groups. Reductions were significantly different versus alteration in glimepiride (p < 0.05) but not with placebo. The liver-to-spleen attenuation ratio increased with Liraglutide 1.8 mg/metformin, possibly indicating reduced hepatic steatosis. |
Discussion

Obesity and diabetes mellitus are the leading causes of many comorbid conditions globally, especially in developing countries. These two conditions are usually concurrent with each other, which increases the interest in medications that can treat both conditions. Liraglutide is an example of these medications. However, its safety and efficacy for weight reduction are questionable.

The present review investigated the safety and efficacy of Liraglutide in the management of obesity and reducing body weight. Through reviewing the medical literature in the past decade. Liraglutide showed to be safe in terms of hypoglycemia risk. Common reported adverse effects were nausea and vomiting. Concerning efficacy, Liraglutide showed significant weight reduction on both short term and long term basis.

The efficacy of Liraglutide was evaluated in different patient populations. In diabetic patients, three studies evaluated the effectiveness of Liraglutide in reducing body weight [11, 13, 18]. Liraglutide showed a statistically significant reduction in body weight (p <0.001) [11]. Weight loss was also directly correlated to increasing dose, where a higher dosage was accompanied by an increased reduction in body weight [13].

It is worth to mention that lifestyle modifications, such as low-calorie diet and physical activity, should be combined with the administration of Liraglutide [12-17]. Additionally, Liraglutide was used with other anti-diabetics [11,18], which may have a role in weight reduction, including metformin. This should be considered while interpreting the outcomes of these studies.
Another population that was examined is females with the polycystic ovarian syndrome (PCOS) [14]. Females with PCOS are commonly obese with reduced insulin sensitivity. Therefore, medications that can reduce blood glucose levels as well as reducing body weight would be beneficial.

The observational study carried out by Rasmussen et al. [14], which included females with PCOS, showed that the administration of Liraglutide for a minimum duration of one month could lead to an average weight loss of 9 kgs. This rate can reach up to 10% weight reduction with the administration of Liraglutide for approximately six months.

The efficacy of Liraglutide was also examined in subjects who were solely obese or overweight without any comorbidity [12, 15-17]. In combination with lifestyle modification, Liraglutide showed a significant weight reduction compared to placebo (p-value <0.001), when administered for one year [12, 15-17] and two years [17].

Concerning the safety of Liraglutide. Hypoglycemia was extensively examined in all the studies that considered Liraglutide for weight reduction. The incidence of hypoglycemia was deemed to be minimal in different patient populations; however, the most common side effect was nausea and vomiting. These side effects were classified as mild to moderate and can be accompanied by diarrhea [11-18].

However, most of the included studies were performed in one center, which may decrease the validity of outcomes. Also, the sample size is considered small, with a total sample size of 6406 patients. These limitations should be considered in future studies.

Finally, to our knowledge, this is considered the first systematic review to evaluate the correlation between Liraglutide and weight reduction. These results should guide the
prescription of Liraglutide for the indication of weight reduction and minimize the risk of side effects.

**Conclusion**

Liraglutide is considered a useful option for weight reduction, especially in the diabetic patient, due to its effective reduction for HBA1c. Liraglutide has a satisfactory safety profile with minimal hypoglycemia and mild gastrointestinal upsets as common side effects. Future trials should focus on determining the most effective dose that can be used for weight reduction solely without affecting blood glucose levels.
References


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