wjpmr, 2022,8(6), 260-264

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

EFFECT OF SUBCUTANEOUS SEMAGLUTIDE VS. DAILY LIRAGLUTIDE ON BODY WEIGHT IN ADULTS WITH OVERWEIGHT OR OBESITY WITHOUT DIABETES: SYSTEMIC REVIEW AND META-ANALYSIS

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Article Received on 20/04/2022 **Article Revised on 10/05/2022** **Article Accepted on 30/05/2022**

ABSTRACT

Objectives: To provide an overview understanding and evaluate the efficacy of semaglutide and liraglutide for weight management and loss in adults without diabetes. **Methods**: Randomized controlled trials studies comparing semaglutide to liraglutide as well as semaglutide to placebo were identified and collected using PubMed. Mean rate differences wereextracted from eligible studies and used to synthesize the results. **Results**: 10 relevant studies with a total sample size of almost 8792 non-diabetic adult patients were included. Both, semaglutide and liraglutide, had a significant effect, however, semagutidehad a higher effect on body weight loss than liraglutide. Also, semagutide had a positive effect on body weight loss in non-diabetic obese adults when compared to the control group that were medicated with a placebo medication. **Conclusions**: Semaglutide 2.4 mg has a higher efficacy in treating obesity in non-diabetic adults.Higher levels semaglutide has higher efficacy than lower levels. Also, semaglutide may be superiorto liraglutide when it comes to managing body weight in non-diabetic adults diagnosed with obesity.

KEYWORDS: Semaglutide, Liraglutide, Obesity, Meta-analysis.

INTRODUCTION

Epidemiologic studies have identified high body-mass index (BMI) as an increasing risk factor for variety of chronic diseases, such as cardiovascular disease, diabetes mellitus, chronic kidney disease, many cancers, and an array of musculoskeletal disorders.[1] As the health community worksto improve and develop new treatments for obesity, more knowledge and information is needed.

It has been proved that obesity is connected to the dysregulation of the appetite in the brain and the counterregulatory hormones which promote regaining weight as a response to reducing calorie intake.[2] One option to correct obesity's maladaptive physiological and hormonal changes is anti-obesity pharmacotherapy.[3] Drugs or medications that are approved for weight control provides a sufficient change in body weight, especially for patients with hypertension, dyslipidemia, sleep apnea and/or cardiovascular disease.[4] These types of medications have high efficacy and safety levels.[3]

The first drug that was approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) is liraglutide, with a dose of once daily 3.0 mg. After that, semaglutide, with a dose of 2.4 mg, was approved by the FDA in 2021, and it is the latest anti-obesity medicationknow to date.[5] Both drugs have good effectiveness, however, semaglutide has higher efficacy levels allowing for once-a-week dose; compared to the once-a-day dose of liraglutide.[6]

Although both drugs have a great efficacy, they as well have substantial variability in weight loss among individuals.[7] This creates a huge challenge when it comes to predicting individual weight reduction. Additionally, nausea, vomiting, delayed gastric emptying are some of the potential side effects of both drugs that can show up shortly after usage.[8,9,10]

However, the coexistence of diabetes in patients who are trying to lose or manage body weight has been consistently correlated with less weight loss using the above-mentioned medication than in patients without diabetes.[4]

The purpose of this systematic review is to provide an overview understanding of the efficacy of medication approved for weight management and loss in adults with and without diabetes. Also, this study aims to address the gap in the knowledge by systematically evaluating the current understanding of the prevalence of the effect of the use of subcutaneous semaglutide or daily liraglutide on body weight in adults with obesity without diabetes.

METHODS

Literature Search

The literature used in this review were obtained using a four-step procedure. First, PubMed research engine was used to collect peer-reviewed articles that fits the research topic using the keyword: "Semaglutide," "Liraglutide," and "Obesity." Then, an overall abstract analysis was performed to identify potential studies to be included and excluded articles that did not satisfy the select criteria mentioned below. After that, the full-text of the chosen articles were further analyzed and excluded those that did not satisfy the selection criteria. The final step was reviewing and summarizing the results of the selected papers/articles.

Selection Criteria

73 literature papers were collected then case reports, systematic review, meta-analyses, and studies that was performed non-adults or diabetic patients. After the exclusion, 10 literature research from 2018-2022 were used in this paper; reviewed and summarized as shown in Table 1.

Data Extraction

The data were extracted from eligible selected studies identified by the investigator.

Statistical Methods

The mean body weight loss expresses the effect-size in each study. The mean body weight loss was used to test the effect of subcutaneous semaglutide and daily liraglutide on body weight in overweight adults without diabetes. If the weight loss is equal to 0, then there is no effect as this means there is no effect of the medication.

Heterogeneity

In order to test the homogeneity between eligible studies used in this systematic analysis, meta- analysis (Cochran's Q) was used. Cochran's Q is computed by summing the squared deviations ofeach study used, using

$$I^2 = 100\,\% \times \frac{Q - df}{Q},$$

Where $df = k - 1$ and k is the number of studies. The value of I^2 lies between 0% and 100%, where a value of 0% indicates no observed heterogeneity and larger values show higher heterogeneity as shown in Table 2.

RESULTS

10 research from 2018-2022 were summarized and analyzed in Table 1. All used studies are randomized clinical trials. A total sample size of almost 8792 non-diabetic adult patients were included. The results were categorized into three groups: high (when drug has > 10% body weight loss), moderate (when drug has 5% − 10% body weight loss), and low (when drugs < 5% body weight loss). In article 1, 5, and 10, both medications had a significant effect, however, semagutidehad a higher effect on body weight loss than liraglutide. Also, in article 2, 3, 4, 6, 8, and 9, semagutide had a positive effect on body weight loss in non-diabetic obese adults when compared to the control group that were medicated with a placebo medication.

Table 1: Summary of characteristics of the studies included in the meta-analysis.

Study	Year	Type	Patients	Results	Limitations
Domenica M. Rubino[11]	2022	STEP 8 randomized clinical trial	338 total non-diabetic adult patients. 126 patients received once-weekly subcutaneous 2.4 mg of semaglutide. 127 patients received once-daily subcutaneous 3.0 mg of liraglutide. 85 pooled patients were in the placebo group	out of the 338 total patients, only 319 of them completed the course of treatment. once-weekly subcutaneous semaglutide resulted in higher weight loss at 68 weeks (-15.8%) in comparison to once-daily subcutaneous liraglutide (-6.4%) and in comparison, with pooled placebo with weight change of -1.9%.	patients discontinued the course of the treatment. Adverse gastrointestinal complications developed during the course of the treatment
Domenica M. Rubino[12]	2021	STEP 4 randomized clinical trial	total of 902 participants received once-weekly subcutaneous of semaglutide including 16 weeks of escalated dose 4 weeks of maintained dose. 803 of patients reached 2.4 mg dose, were randomized into either maintained (535) dose or were switched to placebo (268). patients were subjected to lifestyle changes.	patients who maintained the 2.4 mg once-weekly subcutaneous semaglutide treatment resulted in weight loss over the 48 weeks (-7.9%) in comparison to patients who switched to placebo (-6.9%).	patients discontinued the course of the treatment. Adverse gastrointestinal complications developed during the course of the treatment
John P.H. Wilding[13]	2021	STEP 1 clinical trials	total of 1961 adult patients with body mass index ≥30 and are not diagnosed with diabetes. During a 68-weeks treatment course, patients received either 2.4 mg of once-weekly subcutaneous semaglutide or placebo in addition to being subjected to lifestyle changes.	patients receiving semaglutide treatments lost had -14.9% mean change in body weight compared with patients in the placebo group (-2.4%).	adverse gastrointestinal events with nausea being the most common
Thomas A. Wadden[14]	2021	STEP 3 clinical trial	68-weeks treatment course that included a total of 611 non-diabetic adult patients with a body mass index ≥30. patients were randomized into either semaglutide group or placebo group.	mean body weight change from baseline was −16.0% for patients in the semaglutide group compared with −5.7% for patients in the placebo group.	mild to moderate gastrointestinal events. Patients who developed serious gastrointestinal events discontinued the study.

Patrick M O'Neil[15]	2018	phase-2 clinical trial	957 non-diabetic adult patients with body mass index ≥30. patients were randomized into either placebo or semaglutide doses (0·05 mg, 0·1 mg, 0·2 mg, 0·3 mg, 0·4 mg, and escalating doses initiated with 0.05 mg) or liraglutide (3·0 mg; initiated at 0·6 mg per day and escalated by 0·6 mg per week).	mean weight loss was -2·3% for the placebo group versus -6·0% (0·05 mg), -8·6% (0·1 mg), -11·6% (0·2 mg), -11·2% (0·3 mg), and -13·8% (0·4 mg) for the semaglutide groups. All the semaglutide groups were significantly different compared with placebo. 0·2 mg or more of semaglutide versus liraglutide were all significant (-13·8% to -11·2% vs -7·8%)	adverse gastrointestinal events with nausea being the most common.
Lone B Enebo[16]	2021	phase 1b clinical trial	566 adult patients with body-mass index 27.0-39.9. patients were randomly assigned into once-weekly subcutaneous cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, or 4·5 mg) or matched placebo, in combination with once-weekly subcutaneous semaglutide 2·4 mg, without lifestyle interventions.	No mean percentage body weight reduction was noted in patients receiving either 0·16-0.6 mg. comparing 1.2 mg vs placebo, -6.0% difference, 2.4mg vs placebo had -7.4% difference, and 4.5 mg vs placebo had -7.4% difference.	changes in hormones' levels
Juan P Frías[17]	2021	phase 3b clinical trial	961 adult patients diagnosed with diabetes were screen and randomized into either 1.0 mg or 2.0 mg of once weekly semaglutide.	Mean change at week 40 was -2·2% with semaglutide 2·0 mg and -1·9% with semaglutide 1·0 mg.	adverse gastrointestinal events were reported. Three deaths were reported during the trial.
Melanie Davies[18]	2021	phase 3 clinical trial	1595 adult patients diagnosed with diabetes with body mass index ≥27. over the course of 68-weeks, patients received 1:1:1 ratio of glucose-lowering medication, glycated hemoglobin, and either 1.0 mg or 2.4 mg of semaglutide, or matching placebo.	change in mean body weight was -9·6% with 2.4 mg semaglutide vs -3·4% with placebo.	-
Ofri Mosenzon[19]	2019	phase 3a clinical trial	324 adult patients diagnosed with type 2 diabetes were randomized into groups receiving 1:1 glucose-lowing medication and renal function to oral semaglutide (escalated to 14mg) or matching placebo.	change in mean body weight was -1.0% with oral semaglutide vs -0.2% with placebo.	adverse gastrointestinal events were reported. Three deaths were reported during the course of the trial. Three deaths were also reported, with 2 of them being in the placebo group.
M S Capehorn[20]	2019	phase 3b clinical trial	577 adult patients with diabetes on oral anti-diabetes medications were randomized into groups receiving subcutaneous once-weekly semaglutide 1.0mg or subcutaneous once-daily liraglutide 1.2mg.	Mean body weight (baseline 96.9kg) decreased by 5.8kg with semaglutide and 1.9kg with liraglutide treatment.	patients discontinued the course of the treatment. Adverse gastrointestinal complications developed during the course of the treatment

The results of meta-analysis for the included studies are shown in the following table.

Table 2: Mean body weight loss among studies used in the meta-analysis.

No.	Study	Year	Mean Body Weight Loss %	Effect Type	Heterogeneity Type
1	Domenica M. Rubino [11]	2022	15.8%	High	Q = 642.33
2	Domenica M. Rubino [12]	2021	7.9%	Moderate	P-value
3	John P.H. Wilding [13]	2021	14.9%	High	<0.0001
4	Thomas A. Wadden [14]	2021	16.0%	High	I^2 = 98.6%
5	Patrick M O'Neil [15]	2018	13.8%	High	
6	Lone B Enebo[16]	2021	7.4%	Moderate	
7	Juan P Frías [17]	2021	2.1%	Low	
8	Melanie Davies [18]	2021	9.6%	Moderate	
9	Ofri Mosenzon [19]	2019	1.0%	Low	
10	M S Capehorn [20]	2019	6.0%	Moderate	

Mean = 9.45%

The average body weight loss rate among studies utilized in the meta-analysis was 9.45% which means that results revealed that use of semaglutide or liraglutide treatment improved body weightloss with an average percent of 9.45%, which is considered to have a moderate to higher effectiveness rate. All 10 studies resulted in positive effect for both medications, with higher body weight loss rate with the use of semaglutide. Cochran's Q test was significant which indicates homogeneity between studies. Also, I^2 index was 98.6% indicates observed heterogeneity betweenstudies.

DISCUSSION

Obesity is known to be a life-threating condition that people are suffering from globally. The results showed high percentages of positive effect of semaglutide in improving overweight adults, especially those not diagnosed with diabetes, when compared to Liraglutide. The average body weight loss rate is around 10%.

The results of weekly subcutaneous semaglutide showed higher weight loss at 68 weeks (-15.8%)in comparison to once-daily subcutaneous liraglutide (-6.4%) and in comparison, with pooled placebo with weight change of -1.9%.[11] Also, the results of patients 48-week trial of

patients who maintained the 2.4 mg once-weekly subcutaneous semaglutide treatment showed weight loss of - 7.9% in comparison to patients who switched to placebo (-6.9%)[12] Some experiment showed that there was no percentage body weight reduction was noted in patients receiving either 0·16-0.6 mg. of semaglutide comparing 1.2 mg vs placebo, on average. Whereas, there was -7.4% difference for patients who were treated with 2.4mg and 4.5 mg of semaglutide.[16] Moreover, another 40- week study showed body weight loss of -2·2% with semaglutide 2·0 mg and -1·9% with semaglutide 1·0 mg. Therefore, it can be concluded that semaglutide 2.4 mg gives the best resultsof body weight reduction for obese adults, especially those with controlled blood sugar showing no signs of diabetes.

Although semaglutide as well as liraglutide provide good results in terms of weight loss and management, there were some side effects observed during the course of the treatment with adverse gastrointestinal complications being the most common side effect. Other reported side effects that were less common were nausea, vomiting, and change of hormone levels.

These possible side effects are dose-related and might be managed by dose reduction. Despise allthe negative side effects of the use of semaglutide and liraglutide, this systematic review determined that the use of both drugs, especially semaglutide, can help with reducing body weightby an average of 10%. Synthesis of the studies on results for overweight adults with controlled blood sugar levels show heterogeneity between studies.

As is the case in most research, all the reviewed studies had limitations. One of the common limitations in a lot of studies is the discontinuing of the treatment by the patients due to the lengthof the trails and required follow-ups or by the medical professional due to health complications developed. Another limitation of the review process includes enclosing to few search motors, searching only in English language. There is still a need for better screening tool for the effect of subcutaneous semaglutide vs. daily liraglutide on body weight in adults with overweight or obesity without diabetes. Thus, other studies are needed to obtain screening tools that are cost effective and simple to use by the general population.

CONCLUSION

Obesity, especially among adults, are one of the biggest problems around the world causing manychronic diseases including cardiovascular disease, diabetes, kidney disease, as well as cancer. With the increasing levels of BMI among adults, health workers including doctors and medical researchers are developing new effect treatments and improving existing ones. Today, semaglutide and liraglutide are two of the most common medications used to treat individuals suffering from obesity to manage body weight loss, especially for adults without diabetes.

The purpose of this systematic review is to provide an overview of the prevalence of obesity and weight loss management and to investigate the effect of semaglutide vs. liraglutide on body weight loss in adults with obesity or overweight, but without diabetes, by evaluating existing studies and research. The reviewed studies and clinical trials showed more positive effects than negative effects on body weight loss in non-diabetic overweight adults. Hence, after reviewing 10 well- performed studies and obtaining an overage of 9.45% body weight loss using semaglutide 2.4 mg. Therefore, it is our recommendation to use semaglutide as a treatment for non-diabetic adult patients who are diagnosed obesity.

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