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REVIEW ARTICLE

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Major evidence of the GLP-1 analog (liraglutide) in the treatment of obesity: a systematic review

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Abstract

Introduction: Obesity is a chronic disease that affects a significant portion of the population. In Brazil, in the surveillance survey of risk and protective factors for diseases, more than half of the Brazilian population, 55.7% are overweight. **Objective:** A systematic review of the literature was carried out with the primary objective of verifying the effectiveness of weight loss of liraglutide in obesity, the secondary objective is the evaluation and clinical benefits secondary to the medication. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from September to October 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** A total of 84 articles were found, 52 articles were evaluated and 20 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with a high risk of bias and 19 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2 =96.9% >50%. In this context of a serious disease with a high prevalence in the population, a literature review was carried out to verify the effectiveness of weight loss of liraglutide 3.0mg in obesity. A total of 781 works were found, of which all titles and abstracts were individually evaluated and sixteen related to the clinical question and PICOS were selected. Primary studies show the superiority of liraglutide over placebo and orlistat in weight loss and improvements in clinical outcomes. **Conclusion:** Liraglutide 3.0mg proved to be a safe and effective option in the treatment of obesity.

Keywords: Obesity. Liraglutide. GLP-1 analogs. Anti-obesity agents. Weight loss.

Introduction

Obesity is a chronic disease that affects a significant portion of the population. For many years, this disease was underestimated and seen only as a transitory status of weight or aesthetics. Worldwide, overweight and obesity affect more than 2 billion adults and the prevalence has almost tripled in 40 years **[1]**. According to IBGE data between 2003 and 2019, the proportion of obese people in the population aged 20 years or over in the country more than doubled, from 12.2% to 26.8%. In this same period, female obesity increased from 14.5% to 30.2% and remained above male obesity, which rose from 9.6% to 22.8% **[2]**

The problem becomes even greater when we evaluate younger patients in worldwide data where more than 70% of people who have obesity before puberty will also have obesity in adulthood, which highlights the need for effective and durable interventions with adequate safety profiles at the beginning of life **[2,3]**.

In Brazil, in the surveillance survey of risk and protective factors for chronic diseases by telephone survey of 2018 (VIGITEL), the prevalence of obesity in adults in Brazil increased by approximately 67.8% in the last thirteen years, from 11.8% in 2006 to 19.8% in 2018. According to VIGITEL, more than half of the

Brazilian population, 55.7%, is overweight. An increase of 30.8% when compared to a percentage of 42.6% in 2006. The increase in prevalence was greater among the 18 to 24 age groups, with 55.7%. When stratified by sex, obesity among men grew by 21.7%, while among women, this rate was 40% **[3]**.

Being overweight and obese has relevant implications for the health of individuals and society. Body mass index (BMI) values above normal are related to a greater risk for chronic non-communicable diseases (NCDs), such as cardiovascular diseases, diabetes, musculoskeletal diseases, and some types of cancer, in addition to being associated with higher rates of mortality **[3]**.

The treatment of obesity is complex and multidisciplinary. In general terms, pharmacological treatment is an adjunct to targeted therapies focused on changing lifestyle habits related to nutritional guidelines to reduce the consumption of calories in food and exercise to increase caloric expenditure **[4]**. As with any chronic disease, pharmacological treatment begins with secondary prevention to prevent the progression of the disease to a more severe stage and prevent complications and further deterioration and must be maintained to avoid weight regain. There is no long-term pharmacological treatment that does not involve lifestyle changes. Lifestyle changes and cognitive-behavioral techniques are fundamental and pharmacological treatment should not be used as a treatment in the absence of other non-pharmacological measures. The choice of treatment should be based on the severity of the problem and the presence of associated complications **[5]**.

In this scenario, liraglutide, a drug invented a priori for the treatment of diabetes mellitus, is a glucagon-like peptide-1 (GLP-1) agonist that shares 97% homology with native GLP-1, with half- circulation life of GLP-1 increased from 1-2 minutes to 13 hours and at a dose of 3.0 mg, it has a hypothalamic action on neurons involved in energy balance, on centers linked to pleasure and reward, and a smaller action on the speed of gastric emptying. Liraglutide directly stimulates neurons that synthesize proopiomelanocortin and cocaine and amphetamine-regulated transcript and indirectly inhibits neurotransmission in neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), dependent signaling pathways of GABA **[5]**. This molecule is one of the few options approved by the national health surveillance agency (ANVISA) for the drug treatment of obesity available in Brazil.

In the context of severe chronic disease (obesity) with a high prevalence in the population, with few drug options for treatment, a systematic review of the literature was carried out with the primary objective of verifying the effectiveness of weight loss of liraglutide in obesity, a secondary objective of evaluating and clinical benefits secondary to medication.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and meta-analysis: //www.prisma-statement.org/). In clinical drug treatment of obesity, does liraglutide, when compared with placebo and/or other anti-obesity medications, show efficacy in weight loss?

Literary search criteria (Patients; Intervention; Control; Outcomes - PICO)

- Patients: Patients with a BMI greater than 30;
- Intervention: Liraglutide 3.0 mg;
- Control: Placebo or anti-obesity drug;
- Outcome: Weight loss, clinical improvement of chronic diseases, a better quality of life;

Search Strategy

Based on the clinical question and the PICO above, a search strategy was carried out in the primary database of MEDLINE – Pubmed. Search strategy: (Obesity ***AND*** Obesity treatment ***AND*** Anti-obesity agents) ***OR*** **(**Weight loss ***AND*** quality of life ***AND*** clinical improvement).

Results

Summary of Findings

As a corollary of the literary search system, a total of 84 articles were found that were submitted to the eligibility analysis and, then, 20 of the 52 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=96.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with a high risk of bias and 19 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

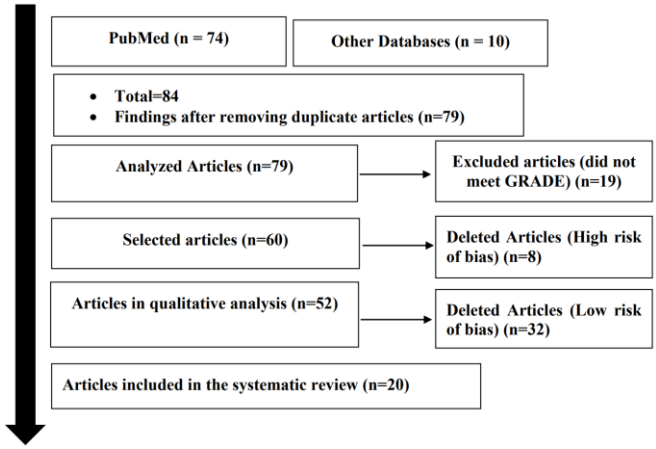
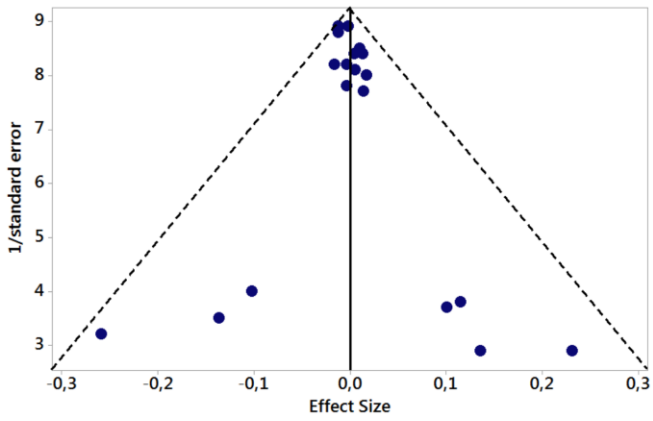


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This chart had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the chart and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=20 studies).



Source: Own authorship.

Main Clinical Findings

The main study to show the efficacy of liraglutide was the study by Xavier PiSunyer et al Scale Obesity and Prediabetes **[6]**, a 56-week double-blind randomized clinical trial involving 3731 patients who did not have type 2 diabetes and who had a BMI of at least 30 or a BMI of at least 27 if they had dyslipidemia or hypertension. Patients received a 2:1 ratio once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients); both groups received lifestyle modification counseling. Outcomes assessed were changes in body weight and proportions of patients who lost at least 5% and more than 10% of baseline body weight. At the end of the study a greater proportion of patients in the liraglutide group than in the placebo group lost at least 5% of body weight (63.2% vs. 27.1%), more than 10% of body weight (33.1% vs. 10.6%), and more than 15% of your body weight (14.4% vs. 3.5%). A sub-analysis of the SCALE study by Careal W Le Roux et. al **[7]**, aimed to assess the proportion of individuals with pre-diabetes who were diagnosed with type 2 diabetes for the study, taking into account the different frequencies of diagnosis between treatment groups. The time to onset of diabetes over 160 weeks among all randomized subjects was 2.7 times longer with liraglutide than with placebo.

As a priori liraglutide was produced for the treatment of diabetes, Melanie J. Davies et. Al. (The Scale Diabetes Randomized Clinical Trial) **[8]**, performed a randomized clinical trial with a follow-up of fifty-six weeks, 846 patients with diabetes were randomized. Inclusion criteria were a BMI of 27.0 or greater, and an age equal to or greater than 18 years. Once-daily subcutaneous liraglutide (3.0 mg) (n = 423), liraglutide (1.8 mg) (n = 211), or placebo (n = 212) and all groups with diet and physical activity. Weight loss of 5% or more occurred in 54.3% with liraglutide (3.0 mg) and 40.4% with liraglutide (1.8 mg) vs 21.4% with placebo. Weight loss greater than 10% occurred in 25.2% with liraglutide (3.0 mg) and 15.9% with liraglutide (1.8 mg) vs 6.7% with placebo.

In the evaluation of the articles, 2 studies focused on behavioral therapy were analyzed concerning lifestyle changes Thomas A Wadden et al. **[9]** evaluated intensive behavioral therapy (ICT) associated with liraglutide, 150 adults with obesity were randomized to: ICT alone; TCI combined with liraglutide; or TCI combined with liraglutide plus a low-calorie diet. Respectively, 44.0%, 70.0%, and 74.0% of these participants lost ≥5% of their weight. Liraglutide-treated groups were superior to TCI alone in both outcomes.

In a real-world cohort study conducted in Canada, Sean Wharton et al. **[10]** 311 participants, divided into 2 cohorts of 4 and 6 months of follow-up. The percent change in body weight from baseline was -7.1% in the 6-month follow-up group and 6.3% in the 4month group. Of the participants in the 6-month group, 64.10% and 34.5% lost more than 5% and greater than 10% of body weight, respectively.

In a comparative analysis with other medications,

2 studies were verified comparing liraglutide with orlistat. In a randomized clinical trial carried out with the participation of 19 European countries, Arne Astrup et al. **[11]** compared 564 participants, who were randomized to liraglutide (staggered doses 1.2, 1.8, 2.4, and 3.0) compared to orlistat and placebo, follow-up time of 20 weeks. Mean weight loss with liraglutide 1.2, 1.8, 2.4, and 3 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg respectively compared to 2.8 kg with placebo, and 4 .1 kg with orlistat. Participants in the intervention group with liraglutide 3.0 mg (76%) lost more than 5% more weight than with placebo (30%) or orlistat (44%). On the other Juan J. Gorgojo-Martínez et al. (The Xensor Study) **[12]** performed a retrospective observational cohort study comparing the clinical outcomes of orlistat and liraglutide. Five hundred patients, 400 in the orlistat group and 100 in the liraglutide group were enrolled in the study. Weight loss with liraglutide (−7.7 kg) was significantly greater than that seen with orlistat (−3.3 kg), and more subjects lost at least 5% of their baseline weight on liraglutide (64.7%) than with orlistat (27.4%). In both studies, liraglutide was superior to orlistat in terms of weight loss.

The study by TA Wadden et al. (SCALE Maintenence Study) **[13]** focused on maintaining weight loss, obese and overweight participants who previously lost 5% of baseline weight were randomly assigned to liraglutide 3.0 mg daily or placebo for 56 weeks. From randomization through week 56, weight decreased an additional mean of 6.2% with liraglutide and 0.2% with placebo, more participants receiving liraglutide (81.4%) maintained the 5% baseline weight loss compared to those receiving placebo (48.9%), and 50.5% versus 21.8% of participants lost more than 5% of their weight after randomization.

As shown in the studies above, the most effective dose for weight loss of liraglutide is 3.0 mg, this data was corroborated by the study by J.P.H. Wilding et al. **[14]** where he compiled the results of the studies **[6,8,11]** and found with statistical significance that there was a clear response to exposure to weight loss. Weight loss increased with higher exposure and appeared to stabilize at higher exposures associated with liraglutide 3.0 mg in most subjects, another important aspect assessed in this study was serious adverse effects from the gastrointestinal tract (acute pancreatitis or malignant/breast neoplasms / benign colorectal) did not show increased exposure to liraglutide compared to the general population.

To complement the analysis of primary studies, 2 reviews were analyzed to corroborate and solidify the data above. A 2016 systematic review conducted in the United States by A. Mehta et al. **[15]** evaluated five randomized, placebo-controlled clinical trials of liraglutide for weight management. In addition to the recommended diet and physical activity, liraglutide consistently resulted in a weight loss of 4 to 6 kg, with a greater proportion of patients achieving at least 5 and 10% weight loss compared to placebo. Comparative data suggest that weight loss with liraglutide is greater than that seen with orlistat or lorcaserin, but slightly less than that seen with phentermine/topiramate. This did not have as its main objective the comparison of weight loss medications, however a systematic review with a 2019 meta-analysis by Awadhesh Kumar Singh & Ritu Singh **[16]**, in the process of being published, evaluated pharmacotherapy in obesity, a metaanalysis found a significant reduction on body weight with orlistat (N = 10,435; Δ -3.07 Kg, 95% CI, -3.76 to -2.37), phentermine plus topiramate (N = 2985; Δ -9.77 Kg, 95% CI, -11.73 to -7.81), lorcaserin (N = 16,856; Δ -3.8 kg; 95% CI, - 3.49 to - 2.66), naltrexone plus bupropion (N = 3239; Δ -4.39 kg; 95% CI, -5.05 to -3.72) and liraglutide (N = 4978; Δ -5.25 kg; 95% CI, -6.17 to -4.32), compared to placebo (all p< 0.0001). An observation related to this robust review is that in Brazil we do not have phentermine-topiramate and naltrexone-bupropion combinations approved by ANVISA for weight loss. After these statements, the review shows that liraglutide is a powerful option for weight loss, with only a smaller loss than phentermine-topiramate **[17]**.

Another randomized controlled clinical trial study, with similar analysis and main outcomes, carried out by Thomas A. Wadden (The Scale IBT) **[18]** evaluates the benefit of ICT in primary care associated with liraglutide 3.0 mg, performed a follow-up of 56 weeks, in subjects with obesity who received 3.0 mg liraglutide (n = 142) or placebo (n = 140) as an adjunct to intensive behavioral therapy. Mean weight loss with liraglutide plus TCI was 7.5% and 4.0% with placebo plus TCI. Significantly more subjects on liraglutide than placebo achieved ≥5% weight loss (61.5% vs. 38.8%).

Besides, a medication of the same class as GLP-1 is semaglutide, Patrick M.O`Neil et al. **[19]** performed a multicenter randomized controlled clinical trial in 957 obese patients over 18 years old (BMI greater than 30) and without diabetes. Patients were divided into 7 groups: Semaglutide (0.05 mg; 0.1 mg; 0.2 mg; 0.3 mg and 0.4 mg), liraglutide 3.0 mg, and placebo, follow-up time of 52 weeks. Weight loss was (-2.3%) in the placebo group, (-7.8) liraglutide 3.0 mg, (-6%) semaglutide 0.05 mg, (-8.6%) 0.1 mg, (-11.6%) 0.2 mg, (-11.6%) 0.3 mg and (-13.8%) 0.4 mg of

semaglutide. Semaglutide doses greater than or equal to 0.2 mg demonstrated statistically significant weight loss compared to liraglutide. Another clinical trial that compared medications was the study by Richard Pratley et al. (PIONEER 4) **[20]**, however in different populations, oral semaglutide and with different outcomes, in this multicenter, double-blind, randomized clinical trial, selected patients with type 2 diabetes from 100 sites in 12 countries. The 771 patients were randomized to once-daily oral semaglutide (increased dose to 14 mg), once-daily subcutaneous liraglutide (increased dose to 1.8 mg), or placebo for 52 weeks. The primary outcome was a change from baseline to week 26 in glycated hemoglobin and the confirmatory secondary was a change from baseline in body weight. Oral semaglutide showed non-inferiority concerning liraglutide in the reduction of glycated hemoglobin, however, it showed weight loss concerning liraglutide at the end of 26 weeks (-4.4 kg vs -3.1kg).

As described in the introduction, obesity has unfortunately been increasing a lot in adolescents, in a clinical trial published in 2020 by Aaron S. Kelly et al. **[4]** evaluated the efficacy and safety of liraglutide in adolescents (older than 12 years and younger than 18) with obesity and a poor response to lifestyle therapy. Participants were randomly assigned to receive liraglutide (3.0 mg) or a placebo in addition to lifestyle therapy. A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group. Liraglutide was superior to placebo for change from baseline in BMI standard deviation score at week 56 (estimated difference, −0.22). A reduction in BMI of at least 5% was seen in 51 of 113 participants in the liraglutide group and 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively (estimated percentage, 26.1% vs. 8.1%).

Also, Blackman's study (The Sleep Apnea Scale) **[17]** investigated whether liraglutide 3.0 mg reduces the severity of obstructive sleep apnea (OSA) compared with placebo, using the primary endpoint of change in apnea index and hypopnea after 32 weeks. Weight loss was assessed as a secondary outcome. After 32 weeks, the mean reduction in AHI was greater with liraglutide than with placebo (-12.2 vs -6.1 events). Liraglutide produced greater mean percent weight loss compared to placebo (-5.7% vs 1.6%). Results with significant data showed an association between the degree of weight loss and improvement in OSA endpoints. Other clinical parameters such as greater reductions in glycated hemoglobin and systolic blood pressure were observed with liraglutide versus placebo.

Discussion

As previously presented, obesity is today a disease with serious secondary health problems directly or indirectly **[1,2]**. Drugs currently available for the treatment of obesity, in addition to a few options, usually have side effects and some contraindications. In this context, GLP-1 analogs hit the market as a therapeutic option for diabetes where, in addition to the benefit concerning glycemia, it would also help with weight loss. The SCALE study group Melanie J. Davies et. al. **[8]** showed the benefit of weight loss in patients with diabetes. The results were also corroborated in the study by Xavier Pi-Sunyer et al **[6]**, where they evaluated weight loss in patients without diabetes or with pre-diabetes. Studies focusing on behavioral lifestyle therapy associated with liraglutide have also shown the benefits of the medication **[8,9]**. Therefore, the association of behavioral changes with diet and physical activity is essential to improve results and maintain weight loss.

Also, two studies compared liraglutide with orlistat and both the GLP-1 analog was superior **[11,12]**. In this context, in which several studies and reviews have shown the benefit of medication in 2020, Aaron S. Kelly et al. **[4]** published a study on adolescents, which showed safety and the same benefit. Therefore, the molecule proved to be effective and safe in different studies in different studied populations, so several lines of research are evaluating the drug class, and Patrick M.O`Neil et al. **[19]** showed that semaglutide was superior in terms of weight loss compared to liraglutide 3.0 mg. However, further studies are needed to corroborate this statement.

In the treatment of obesity, as well as several chronic diseases, we must perform multiple therapies for better therapeutic results, but in the literature, few studies perform associations of medications for weight loss. The review by Kumar Singh & Ritu Singh **[16]** made a comparative assessment of anti-obesity medications alone, as points to be noted, the inclusion of semaglutide in the analysis, topiramate-phentermine which showed better results, is not available in Brazil and also no associations between the drugs were shown.

Another aspect that we must take into account is the fact that obesity as a chronic disease requires treatment with medication for continuous use, a longer follow-up time is needed for long-term evaluation of weight loss and weight maintenance concerning medications. Juxtaposed to this, another aspect that

often limits treatment is the cost of the medication, at this point, liraglutide 3.0 mg still has a high price that can make the continuous use of the medication difficult.

Conclusion

It was concluded that liraglutide 3.0 mg as a medication for the treatment of obesity, in association with lifestyle changes, in patients with and without diabetes, proved to be a good therapeutic option with response to weight loss and maintenance, in addition to benefits secondary to clinical comorbidities associated with obesity.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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