Effectiveness of Semaglutide in Weight Reduction in Patients with Obesity: A Systematic Review.

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Abstract.
Purpose: This systematic review aimed to assess the effectiveness of Semaglutide in promoting weight loss among individuals with obesity or overweight, providing an evidence-based reference for clinical treatment.
Methods: We conducted a comprehensive search of PubMed, database for randomized controlled trials (RCTs) evaluating the monotherapy Semaglutide injections up to April 2022.
Results: In this review, we analyze six selected studies focusing on Semaglutide's efficacy in weight reduction among obese individuals. These randomized trials compared different Semaglutide doses with placebos or alternative treatments. The findings consistently demonstrate significant weight loss across all Semaglutide groups, making it a promising intervention for obesity management. These studies provide valuable insights into the potential benefits of Semaglutide in achieving weight loss goals for individuals with obesity.
Conclusion: This systematic review demonstrates that semaglutide are more effective than placebo in promoting weight loss among individuals with obesity or overweight. These findings provide valuable insights into the clinical use of GLP-1RAs for weight management in obese and overweight individuals.
Keywords. Semaglutida, Weight Loss, Obesity.

1. Introduction

The obesity rate has increased significantly over the past five decades, tripling since 1975 (1). Currently, more than a billion people are facing obesity, including approximately 380 million children and adolescents (2). This alarming growth is intrinsically linked to profound social and economic changes that have created a global environment conducive to excessive weight gain, resulting in an energy imbalance (3). However, it is important to note that the growth in obesity rates is not uniform, with significant increases in urban areas in countries considered underdeveloped and developed, while in developed countries, rates are stabilizing or decreasing (1,4).

Obesity is associated with a significant increase in mortality, reducing the average life expectancy of an obese person by 5-10 years (5). Furthermore, obesity is an important risk factor for the development of several comorbidities, including cardiovascular diseases, gastrointestinal disorders, type 2 diabetes mellitus, muscle and joint disorders, respiratory problems, psychological conditions, specific cancers, obstructive sleep apnea, chronic kidney disease, hypertension, dyslipidemia and non-alcoholic fatty liver disease (1,3,5,6).

In the context of the Brazilian Unified Health System (SUS), obesity represents a growing burden for the entire health system. In 2010 alone, the SUS spent approximately 2.1 billion dollars to fund outpatient and hospital treatment for diseases related to obesity and overweight. If obesity rates continue to rise in Brazil, these healthcare costs could double by 2050 (3).

Therefore, several public health policies are being developed to address the problem of obesity, since a target weight loss of 5%-10% in individuals with obesity or overweight already results in significant improvements in associated comorbidities (5). Currently, there are several therapeutic options for patients with obesity, including lifestyle changes, bariatric surgery, fecal microbiota transplantation, and anti-obesity medications (1).

Among the pharmacotherapeutic options for obesity, hypoglycemic agents, such as Semaglutide (Rybelsus and Ozempic), have gained prominence in recent years in the process of reducing body weight. Semaglutide, a glucagon-like peptide 1 (GLP-1), has demonstrated efficacy and good tolerance in both oral (Rybelsus) and subcutaneous (Ozempic) forms

in controlling body weight (7,8). Published clinical studies confirm the ability of the GLP-1 class of analogues to reduce body weight, with Semaglutide standing out as the most effective compound for this purpose. Randomized phase II and III studies demonstrated the safety and efficacy of using Semaglutide in reducing body weight in patients with obesity and related comorbidities (7).

Obesity is now considered a chronic disease that affects a significant portion of the global population. In this context, the use of hypoglycemic drugs, such as Semaglutide, is gaining importance as an effective tool for weight loss. The use of Semaglutide in this patient profile becomes crucial to reduce associated comorbidities and improve quality of life.

2. Reserch Methods

2.1 Study Design

This is a systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis – PRISMA protocol will be used as a guide for the construction of the systematic review.

2.2 Search Strategy

The searches were carried out during the month of March 2023, in the MEDLINE/Pubmed electronic databases through a combination of descriptors, including Medical Subject Headings (MeSH), Health Sciences Descriptors (DECs) and descriptor contractions. The review will include publications written in English and Portuguese. The terms used for the search are related to the population of interest and the outcome to be studied: "Weight Loss" [Mesh Terms] AND "Semaglutide [MeSH Terms] " OR "Rybelsus" OR "Ozempic". References presented in the articles identified by the search strategy were also searched manually in order to add to the work and this systematic literature review.

2.3 Inclusion and Exclusion Criteria

Randomized clinical trials found in the databases, carried out on human beings, over the age of 18, published in the last 5 years, in Portuguese and English, were included.

Studies that evaluated the effect of medication on patients with other comorbidities and patients using medications that reduce weight were excluded.

2.4 Bias Analysis

The risk of bias of the selected studies will be analyzed based on the Cochrane tool for analyzing the risk of bias in randomized clinical trials. Being classified among 5 domains: randomization process, deviations from intended interventions, missing outcome data, outcome mediation, selection of reported outcome. Afterwards, each bias domain is classified as: low risk of bias, high risk of bias or uncertain risk of bias. Studies with the lowest risk of bias will be included.

2.5 Identification and Selection of Studies

The authors will read the titles and abstracts of each pre-selected work from the search of electronic databases, in order to identify only the studies that correctly meet the inclusion and exclusion criteria. To then read the full texts, ensuring the criteria of this systemic review. Divergences will be discussed by both authors, seeking to respect the previously defined inclusion and exclusion criteria.

2.6 Data Extraction

Data were extracted and synthesized in a pre-defined collection form. The characteristics of the studies that will be extracted include: publication date, geographic origin, title, study type, study duration and number of participants.

The clinical variables considered will include: weight loss.

2.7 Assessment of the Methodological quality of studies

To assess the methodological quality of the selected studies and inclusion in the systematic review, the CONSORT tool will be used, which involves the use of a checklist and which evaluates information that should be present in the title, introduction, methods, results and discussion of clinical trials. Studies must necessarily meet a score equal to or greater than 80% of the criteria in their evaluation to be included.

2.8 Ethical Aspects

Approval by the Research Ethics Committee is waived because it is a systematic literature review, in accordance with resolution 466/12 of the Ministry of Health.

3. Results

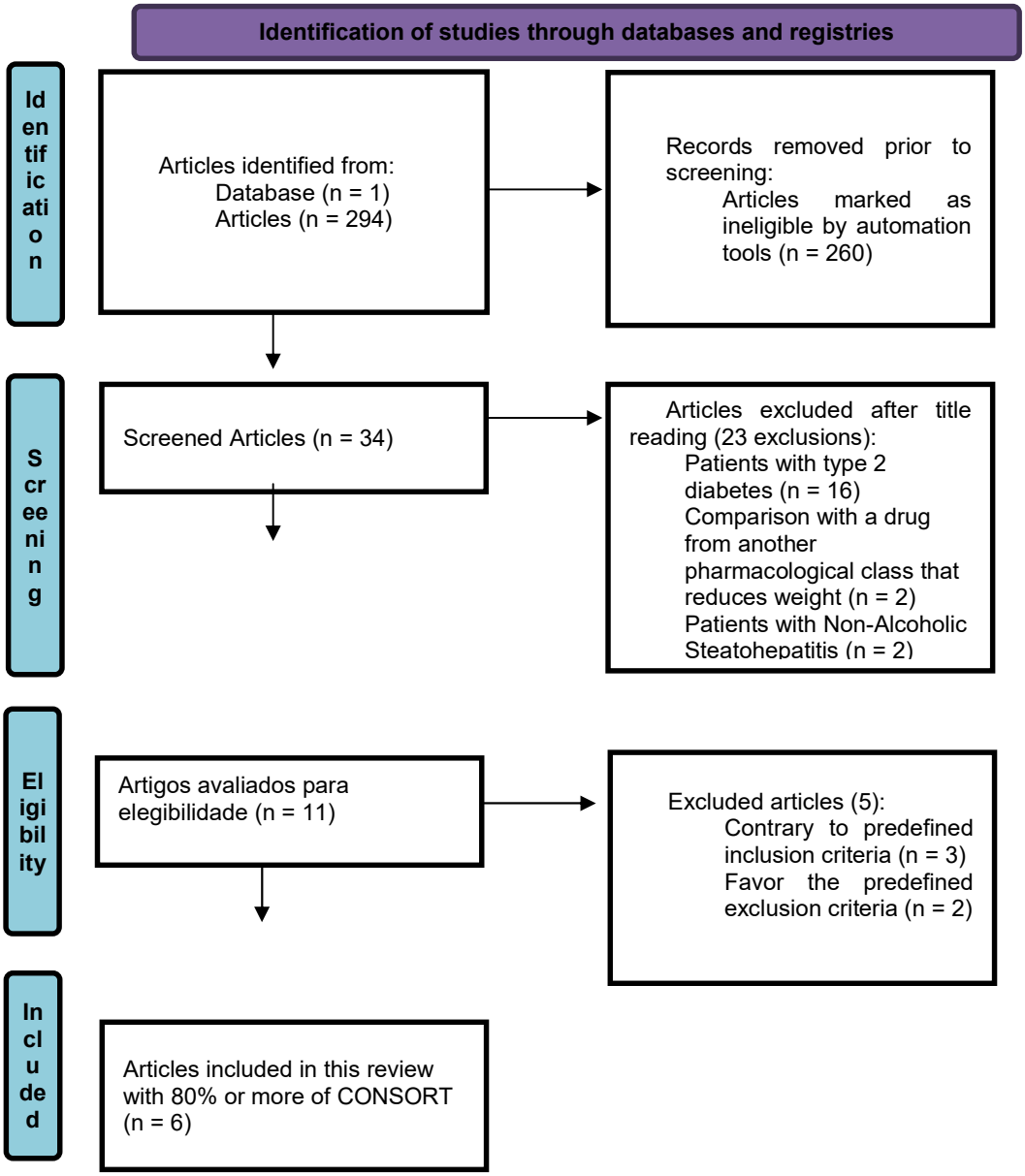
3.1 Identification and Slection of studies

Based on the search strategy outlined in the PubMed database, a total of 294 studies were found using the assistance of all pre-selected descriptors. After conducting a search with filters for randomized clinical trials conducted in the last 5 years, 34 results were found for title reading. Following the review of the titles of these studies, a pre-selection of 11 articles related to the topic was possible. Among these pre-selected studies, 8 evaluated only the use of Semaglutide, while the other 3 compared the use of Semaglutide with Liraglutide, another medication in the same pharmacological class. Ultimately, from the analysis of these studies, only 6 articles met the proposed criteria for full-text reading. Therefore, there are 6 studies remaining to be used in the preparation of this work, with 4 assessing Semaglutide exclusively and the other 2 comparing Semaglutide with Liraglutide (Figure 1).

The selected articles by O'Neil (12), Waddeb (13), Wilding (14), Rubino (15), and Garvey (17)

demonstrated a low risk of bias through the application of the Cochrane tool (Appendix B) for bias risk assessment in randomized clinical trials.

Fig. 1 - Flow chart of study selection process



However, the article by Rubino (16) raised some concerns about bias risk by not using an appropriate analysis to estimate the effect attributed to the intervention in domain 2, which assesses deviations from intended interventions.

3.2 Semaglutide´s efficacy and in weight reduction

The selected articles for a more in-depth analysis included: O'Neil (12), Waddeb (13), Wilding (14), Rubino (15), Rubino (16), and Garvey (17). In terms of their general characteristics, these articles were published between August 2018 and October 2022, with O'Neil (12) being the oldest chronologically, and Garvey (17) being the most recent. Furthermore, the selected articles were randomized, multicenter, double-blind, placebo-controlled clinical trials, primarily aimed at demonstrating the effectiveness of Semaglutide in the weight loss process for individuals with a body mass index (BMI) greater than 30 kg/m^2. Additionally, a varying number of participants were involved in each study, ranging from 304 individuals in Garvey (17) to 1,961 individuals in Wilding (14) (Table 1).

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the weight loss process for individuals with a body mass index (BMI) greater

Tab. 1 – Characteristics of the selected Articles

Author and Year of Publication	Geographic Origin	Study Design	Study Duration	Number of Participants	CONSORT Score (%)
O'Neil (1); August 16, 2018	71 locations in 8 countries	Double-blind, placebo-controlled randomized clinical trial	October 2015 to February 11, 2016	957 participants	100
Waddeb (2); February 24, 2021	41 locations in the United States	Parallel-group double-blind randomized clinical trial	August 2018 to April 2020	611 participants	88
Wilding (3); March 18, 2021	129 locations in 16 countries	Double-blind, placebo-controlled randomized clinical trial	June 2018 to September 2019	1,961 participants	80
Rubino (4); March 23, 2021	73 locations in 10 countries	Double-blind randomized clinical trial	June 2018 to March 2020	902 participants	92
Rubino (5); January 11, 2022	19 locations in the United States	Randomized clinical trial	September 2019 to May 2021	338 participants	92
Garvey (6); October 10, 2022	41 locations in 5 countries	Double-blind, placebo-controlled randomized clinical trial	August 2018 to February 2019	304 participants	88

than 30 kg/m^2. Additionally, a varying number of participants were involved in each study, ranging from 304 individuals in Garvey (17) to 1,961 individuals in Wilding (14) (Table 1).

Finally, in the analysis of the methodological quality of the articles conducted using the CONSORT checklist, all studies achieved a score equal to or higher than 80%. Notably, O'Neil (12) stood out positively by achieving a perfect score of 25 out of a possible 25 points (Table 1).

The selected studies for this review employed different interventions to assess their effectiveness in the weight loss process among obese individuals.

In O'Neil (12), the study compared the efficacy of using Semaglutide (0.05 mg [n=103], 0.1 mg [n=102], 0.2 mg [n=103], 0.3 mg [n=103], or 0.4 mg [n=102]; initiated at 0.05 mg per day and gradually escalated every 4 weeks) and Liraglutide (3.0 mg [n=103]; initiated at 0.6 mg per day and increased by 0.6 mg per week) with their respective placebo groups in the weight loss process. Additionally, two rapid-escalation Semaglutide groups (0.3 mg RE [n=102] and 0.4 mg RE [n=103]) had their doses escalated every 2 weeks. A total of 957 participants were randomized at a 6:1 ratio to each treatment group (Table 1), using a block size of 56. After 52 weeks of intervention, the estimated average weight loss was -2.1% for the placebo group versus -6.0% for Semaglutide 0.05 mg and -13.8% for Semaglutide 0.4 mg (Graph 1).

In Waddeb (13), the intervention involved the use of Semaglutide 2.4 mg (n=407) or placebo (n=204) for weight loss over the course of 68 weeks (Table 1). Both groups also received a hypocaloric diet in the first 8 weeks and intensive behavioral therapy. The 611 participants were randomized at a 2:1 ratio between the Semaglutide and placebo groups. By week 68, the estimated mean change in body weight from baseline was -16.0% for Semaglutide 2.4 mg versus -5.7% for placebo (Graph 1).

In Wilding (14), the 1,961 participants underwent a 68-week study with or without the use of Semaglutide 2.4 mg alongside lifestyle changes (LS) to achieve satisfactory weight loss (Table 1). Participants were randomized at a 2:1 ratio between the intervention group (n=1306) and the control group (n=655). Consequently, the mean change in body weight from baseline to week 68 was -14.9% in the Semaglutide group compared to -2.4% with placebo, resulting in an estimated treatment difference of -12.4 percentage points

(Graph 1).

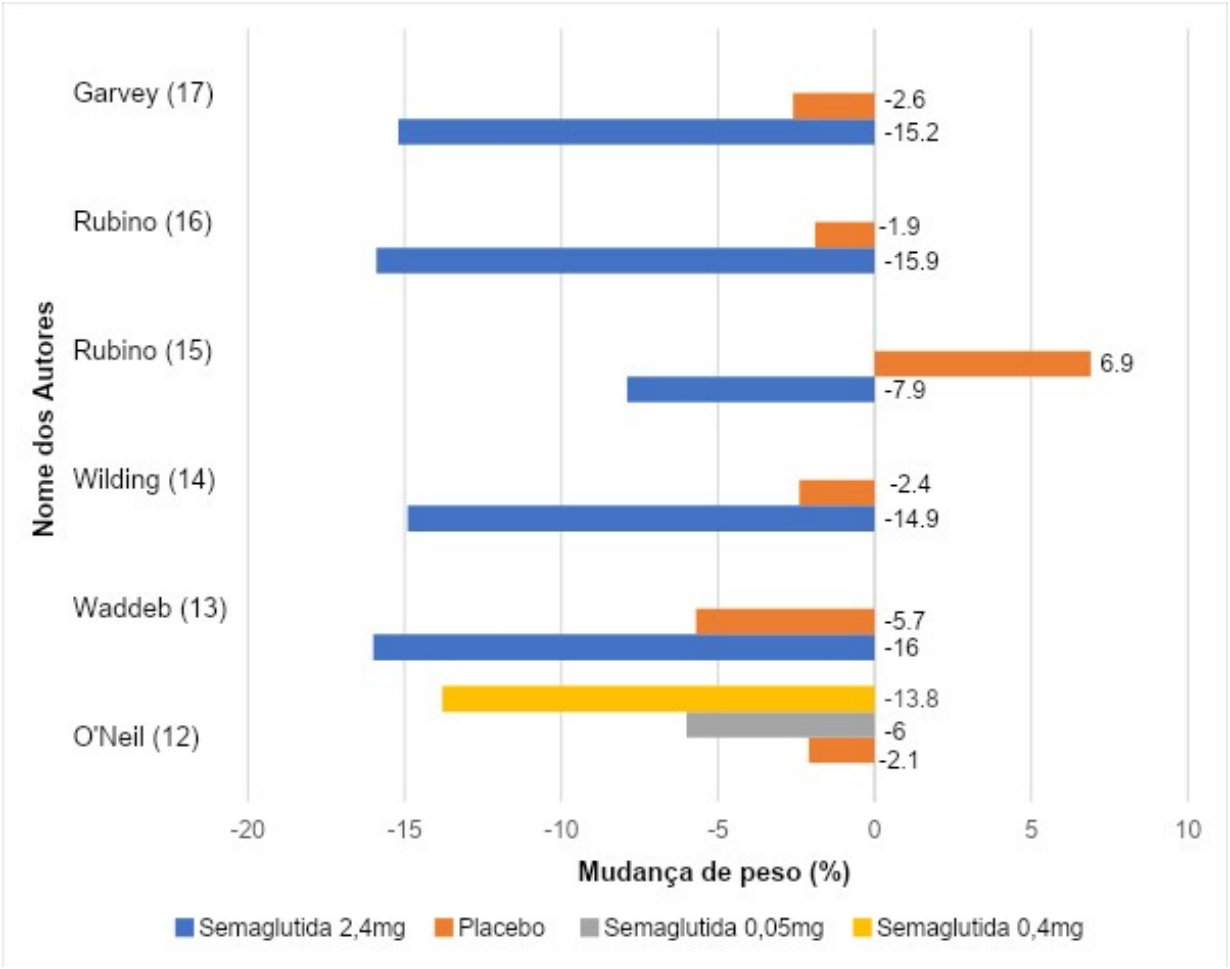

Fig. 2 – Average percentage in body weight at the end of study

In Rubino (15), all 902 study participants initially received once-weekly subcutaneous Semaglutide. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), the 803 participants (89.0%) who reached the maintenance dose of 2.4 mg/week of Semaglutide were randomized at a 2:1 ratio for 48 weeks of continuous subcutaneous Semaglutide (n = 535) or switched to placebo (n = 268), along with lifestyle intervention in both groups (Table 1). Thus, with continued Semaglutide treatment, the mean change in body weight from week 20 to week 68 was -7.9% versus +6.9% with the switch to placebo (Graph 1).

In Rubino (16), 338 participants were randomized at a 3:1:3:1 ratio to receive a once-weekly injection. They were divided into the Semaglutide 2.4 mg group (escalation over 16 weeks; n = 126) or the corresponding placebo group, or the once-daily subcutaneous Liraglutide 3.0 mg group (escalation over 4 weeks; n = 127) or the corresponding placebo group, along with diet and physical activity (Table 1). At week 68, at the end of the study period, the estimated mean change in body weight was -15.8% with Semaglutide, -6.4% with Liraglutide, and -1.9% with the placebo group combined (Graph 1).

Finally, in Garvey (17), the 304 participants were randomly divided at a 1:1 ratio between the Semaglutide 2.4 mg group (n=152) and the placebo group (n=152) to receive subcutaneous injections over 104 weeks, followed by 7 weeks without treatment, along with a standardized behavioral intervention (Table 1). The mean change in body weight from baseline to week 104 was -15.2% in the Semaglutide group (n = 152) versus -2.6% with the placebo group (n = 152) (Graph 1).

4. Discussion

The systematic review encompassed a diverse set of studies that evaluated the effectiveness and safety of Semaglutide in weight reduction among obese patients. The main findings can be summarized based on the variables of interest that were investigated.

One of the central findings of this systematic review is the accumulated evidence of Semaglutide's efficacy in promoting weight loss in patients with obesity grade I and II, without other comorbidities (12–17). The combined results of the included studies consistently reveal a significant reduction in body weight associated with Semaglutide treatment (Figure 2). While the exact magnitude of weight loss may vary among studies, the overall trend indicates that Semaglutide offers a promising therapeutic approach for weight reduction in overweight or obese individuals (18). This consistency in results suggests that Semaglutide may be a valuable tool in the treatment arsenal to combat the global obesity epidemic, with the potential to improve the health and quality of life of many patients affected by this condition (19–21).

Despite efforts to conduct a rigorous systematic review, it is important to recognize that this investigation has some inherent limitations.

Furthermore, the limited follow-up time in the studies analyzed is noteworthy. Although the average duration of treatment was approximately 58 weeks, this period may not be sufficient to fully assess the long-term sustainability of the effects of semaglutide. In chronic diseases such as obesity, long-term follow-up is crucial to determine weight loss maintenance as well as any long-term adverse effects that may arise. Therefore, the generalization of results beyond the study follow-up period should be done with caution.

It is important to mention that despite strict study selection criteria and risk of bias assessment, the exclusive inclusion of randomized clinical trials (RCTs) may result in a certain limitation in methodological diversity. While RCTs provide a solid basis for evaluating causal relationships, the exclusion of other types of studies, such as observational studies, may influence the breadth of conclusions and the assessment of broader aspects of semaglutide's efficacy and safety in real-world settings.

In summary, the present investigation faces limitations that may affect the generalization of the results and the comprehensiveness of the conclusions. A cautious approach to interpreting results in broader contexts, combined with consideration of the specific demographic characteristics of the studies analyzed, is crucial for appropriate clinical application of the findings of this systematic review.

5. Conclusion

This systematic review provided a comprehensive and critical analysis of the effectiveness and safety of semaglutide in weight reduction in patients with obesity. Based on the evaluation of randomized clinical trials of high methodological quality, our results support the efficacy of semaglutide as a promising therapeutic intervention for weight reduction in individuals with grade I and II obesity. The positive association between semaglutide and weight loss is supported by consistent rates of weight reduction observed in several studies.

In summary, this systematic review contributes solid evidence to the field of obesity, highlighting semaglutide as an effective therapeutic option for weight reduction. The conclusions derived from this analysis have important implications for clinical practice, although future investigations are recommended to assess the generalizability of the results in broader populations and in the long term.

6. References

1. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics [Internet]. Vol. 12, Frontiers in Endocrinology. 2021. Available from: www.frontiersin.org
2. Saúde OP-A da. Dia Mundial da Obesidade 2022: acelerar ação para acabar com a obesidade [Internet]. 2022 [cited 2022 Sep 3]. Available from: https://www.paho.org/pt/noticias/4-3-2022-dia-mundial-da-obesidade-2022-acelerar-acao-para-acabar-com-obesidade
3. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. Vol. 33, PharmacoEconomics. 2015. p. 673–89.
4. Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, et al. The Obesity Transition: Stages of the global epidemic Europe PMC Funders Group. Lancet Diabetes Endocrinol. 2019;7(3):231–40.
5. Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. J Am Assoc Nurse Pract [Internet]. 2017;29:S3–14. Available from: https://www.cdc.gov/obesity/data/prevalence-maps.html.
6. Ministério da Saúde. Caderno de Atenção Básica - Obesidade. Primeira. 2006. Brasília - DF;
7. Gallwitz B, Giorgino F. Clinical Perspectives on the Use of Subcutaneous and Oral Formulations of Semaglutide [Internet]. Vol. 12, Frontiers in Endocrinology. 2021. Available from: www.frontiersin.org
8. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide [Internet]. Vol. 10, Frontiers in Endocrinology. 2019. p. 155. Available from: www.frontiersin.org
9. Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. Mol Metab [Internet]. 2021;46(September 2020):101090. Available from: https://doi.org/10.1016/j.molmet.2020.101090
10. Singh G, Krauthamer M, Bjalme-Evans M. Wegovy (semaglutide): a new weight loss drug for chronic weight management [Internet]. Vol. 70, Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2022. p. 5–13. Available from: http://jim.bmj.com/
11. Meier JJ. Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. Front Endocrinol (Lausanne). 2021;12(June):1–11.
12. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active

controlled, dose-ranging, phase 2 trial. Lancet (London, England). 2018 Aug;392(10148):637–49.
13. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021 Apr;325(14):1403–13.
14. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar;384(11):989–1002.
15. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021 Apr;325(14):1414–25.
16. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022 Jan;327(2):138–50.
17. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022 Oct;28(10):2083–91.
18. Smits MM, Van Raalte DH. Safety of Semaglutide. Front Endocrinol (Lausanne). 2021;12(July).
19. Gao X, Hua X, Wang X, Xu W, Zhang Y, Shi C, et al. Efficacy and safety of semaglutide on weight loss in obese or overweight patients without diabetes: A systematic review and meta-analysis of randomized controlled trials. Vol. 13, Frontiers in Pharmacology. 2022. p. 1–14.
20. Xie Z, Yang S, Deng W, Li J, Chen J. Efficacy and Safety of Liraglutide and Semaglutide on Weight Loss in People with Obesity or Overweight: A Systematic Review. Vol. 14, Clinical Epidemiology. 2022. p. 1463–76.
21. Tan HCQ, Dampil OA, Marquez MM. Efficacy and Safety of Semaglutide for Weight Loss in Obesity Without Diabetes: A Systematic Review and Meta-Analysis. Vol. 37, Journal of the ASEAN Federation of Endocrine Societies. 2022. p. 65–72