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Effects of GLP-1 analogs combined with physical exercise on total body mass in Individuals with obesity: a systematic review

Efeitos dos análogos do GLP-1 combinado ao exercício físico na massa corporal em indivíduos com obesidade: uma revisão sistemática

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Abstract – The literature lacks comprehensive evidence integrating results aiming to assess the combined effects of physical exercise and pharmacological therapy on body mass reduction. Therefore, this review aims to analyze the effects of glucagon-like peptide-1 (GLP-1) analogs, specifically liraglutide and semaglutide, combined with physical exercise on changes in body mass among patients with obesity. This systematic literature review is registered in PROSPERO (International Prospective Register of Systematic Reviews) under ID: CRD42023454783. Searches were conducted between September and October 2023, with no restriction on publication year and language, on the following databases: Medline via PubMed; Semantic Scholar, Web of Science, Scopus, and Embase. Nine articles involving 4,236 participants with obesity (with or without diabetes) were included. The participants were aged between 18 and 65 years and had a BMI over 27 kg/m^2, being treated with liraglutide or semaglutide. Liraglutide was increased to 3.0 mg, and semaglutide to 2.4 mg. The combination of liraglutide and exercise led to an average weight loss of 5 kg over 53 weeks. Higher doses of liraglutide and semaglutide effectively reduce total body mass in individuals with obesity. Combining GLP-1 analogs with physical exercise enhances these weight loss outcomes.

Key words: Glucagon like peptide 1; Obesity; Physical activity; Weight loss.

Resumo – *Evidências abrangentes que integrem resultados para avaliar os efeitos combinados do exercício físico e da terapia farmacológica na redução da massa corporal são escassas. O objetivo desta revisão é analisar os efeitos dos análogos do peptídeo semelhante ao glucagon-1 (GLP-1), especificamente liraglutida e semaglutida, em conjunto com exercícios físicos nas mudanças na massa corporal entre pacientes com obesidade. Esta revisão sistemática da literatura está registrada no PROSPERO (Registro Prospectivo Internacional de Revisões Sistemáticas) sob o ID: CRD42023454783. As buscas foram conduzidas entre setembro e outubro de 2023, sem restrição de ano de publicação e idioma, nas seguintes bases de dados: Medline via PubMed, Semantic Scholar, Web of Science, Scopus e Embase. Nove artigos envolvendo 4.236 participantes com obesidade (com ou sem diabetes) foram incluídos. Os participantes, com idade entre 18 e 65 anos e IMC acima de 27 kg/m^2, foram tratados com liraglutida ou semaglutida. A liraglutida foi aumentada para 3,0 mg e a semaglutida para 2,4 mg. A combinação de liraglutida e exercício levou a uma perda média de peso de 5 kg ao longo de 53 semanas. Doses mais altas de liraglutida e semaglutida reduzem efetivamente a massa corporal total em indivíduos com obesidade. A combinação de análogos de GLP-1 com exercícios físicos melhora esses resultados de perda de peso.*

Palavras-chave: *Peptídeo semelhante ao glucagon 1; Obesidade; Atividade física; Perda de peso.*

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INTRODUCTION

Obesity is recognized as a chronic disease and has become a global pandemic, posing a significant challenge to public health[1-3]. This condition affects an increasing number of individuals worldwide, highlighting the urgent need for effective interventions and policies[4]. Characterized by excessive adipose tissue accumulation, obesity poses notable health risks, with its etiology shaped by a complex interplay of genetic, environmental, and socioeconomic factors[2].

Managing obesity requires a multifaceted approach, including behavior change therapy, dietary interventions, physical exercise, pharmacological treatments, and, in some cases, bariatric surgery[4-6]. Regular physical exercise is essential in treating obesity, complementing other therapeutic strategies[5,6]. Regular physical activity is a critical factor in weight reduction, promoting substantial energy expenditure and weight loss, an effect that can be enhanced by pharmacological intervention[7-11].

Among the pharmacological options for weight loss, glucagon-like peptide-1 (GLP-1) analogs, such as liraglutide and semaglutide, are widely used in clinical practice[12]. These analogs mimic the endogenous hormone GLP-1, which is secreted in the gastrointestinal tract and amplifies insulin secretion in response to elevated plasma glucose levels[13,14]. During the postprandial period, enteroendocrine L cells in the intestine release GLP-1 in response to nutrient intake, stimulating insulin secretion from β-cells, inhibiting glucagon secretion, and delaying gastric emptying[13-15].

The action of GLP-1 is mediated by its specific receptor (GLP-1R), which is closely coupled to the G protein family and is expressed in several tissues, including the stomach, pancreas, and brain[13-16]. In the central nervous system (CNS), GLP-1 receptors are located in hypothalamic regions that regulate energy homeostasis and food intake, which may explain the effects of GLP-1 on reducing food intake and body weight[13,14].

Despite these insights, there is a lack of comprehensive evidence integrating the results of longitudinal studies to evaluate the combined effects of physical exercise and pharmacological therapy on body mass reduction. Furthermore, the heterogeneity in diet and exercise protocols in primary studies can generate confounding factors that hamper result interpretation.

In this context, this systematic review aims to analyze the available literature regarding the effects of GLP-1 analogs combined with physical exercise on total body mass alteration in patients with obesity.

METHODS

This study consists of a systematic literature review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17]. The original protocol was registered in PROSPERO under ID: CRD42023454783.

Searches were conducted between September and October 2023 on the following databases: MEDLINE via PubMed, Semantic Scholar, Web of Science, Scopus, and Embase, with no restrictions on publication year or language. Google Scholar and reference lists of selected articles were also reviewed. The search was based on Medical Subject Headings (MeSH) terms such as

obesity, liraglutide, semaglutide, GLP-1, and exercise. Keyword combinations used in the search strategy are detailed in the review protocol.

The systematic literature search and study selection were performed independently by two blinded researchers, and any disagreements were resolved by discussion. Full-text analyses assessed eligibility based on trials involving individuals aged 18 or older, with BMI ≥ 27 kg/m^2, using GLP-1 analogs (liraglutide or semaglutide) combined with physical exercise. The primary outcome indicated total body mass reduction. Studies with participants having hypothyroidism, prior bariatric surgery, or those using glucocorticoids were excluded. All studies identified through manual searches followed the same screening process.

Extracted variables included the author's name, year of publication, sample size, study design, exercise protocol, pharmacological intervention protocol, drug administration method, and primary and secondary outcomes. These data were recorded using a standardized form with specific fields for each variable.

Studies meeting the inclusion criteria were assessed according to the PEDro Scale for randomized clinical trials, with scores ranging from 0 to 10 to evaluate bias risk. Methodological quality was classified as 'poor' (< 4), 'fair' (4-5), 'good' (6-8), or 'excellent' (9-10). The ROBINS-I tool assessed bias in the non-randomized cohort and observational studies and only those scoring above 6 were included in this systematic review.

RESULTS

Figure 1 provides a detailed overview of the article selection process.

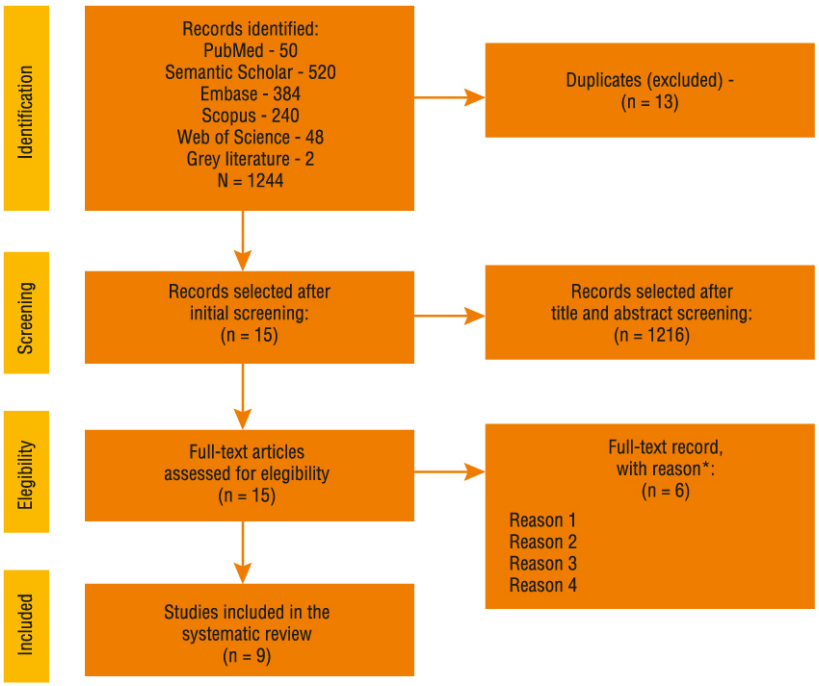

Figure 1. A PRISMA flowchart of the study selection process is included in this systematic review. Note. *Reason 1: Only provided lifestyle change counseling; *Reason 2: No use of physical exercise as an intervention; *Reason 3: Not a clinical trial; *Reason 4: No alteration of body mass as an outcome.

Table 1 summarizes the analysis of 4,236 participants with obesity, including 2,878 women and 1,358 men, aged from 18 to 65 years, and with a BMI over

27 kg/m^2. Some participants had comorbidities such as diabetes, hypertension, and cardiovascular disease, following the inclusion criteria.

Each study employed a randomization method to allocate the participants in the treatment groups. Sandsdal et al.[18], Lundgren et al.[19], and Jensen et al.[20] divided participants into four groups: combination (liraglutide and exercise), liraglutide, exercise, and placebo. Khoo et al.[21] used a strategy that separated groups into diet and exercise (DE group) or liraglutide at 0.6 mg and exercise (LI group). Davies et al.[22] compared different liraglutide dosages (1.8 and 3 mg) to a placebo group, all following physical exercise recommendations. Astrup et al.[23], Mensberg et al.[25], and Tronieri et al.[26] divided participants into exercise and liraglutide or exercise and placebo. Wilding et al.[24] administered semaglutide at 2.4 mg or placebo alongside lifestyle modifications.

In most clinical trials, liraglutide was administered daily, starting at 0.6 mg with weekly increments up to 3 mg, while semaglutide began at 0.25 mg, increasing weekly to 2.4 mg. Physical exercise protocols followed World Health Organization (WHO)[27] guidelines, recommending 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise (AE) weekly. One study also incorporated weekly resistance training. Walking was the most frequently recommended activity, and the average study duration was 53 weeks.

Groups subjected to a combination of GLP-1 analogs and physical exercise exhibited greater reductions in total body mass (TBM) compared to those receiving only liraglutide, performing physical exercise alone, or using a placebo. Participants in the combination groups lost an average of 5 kg over 53 weeks. These results indicate that the combination of GLP-1 analogs and physical exercise is particularly effective in reducing TBM in patients with obesity.

Table 1. Characteristics of the selected studies.

Author	Sample characteristics	Study design	Exercise protocol	Pharmacological intervention	Results
Sandsdal et al.[18]	50M and 80W; 18-65 years; BMI 32-43 kg/m2.	Randomized clinical trial.	150 minutes/week of moderate AE or 75 minutes/week of vigorous CE.	Liraglutide starting at 0.6 mg/day, increased weekly by 0.6 to 3 mg/day.	After 52 weeks, the L + E group lost weight, while the placebo group showed a significant gain (p<0.001).
Lundgren et al. [19]	71M and 124W; 18-65 years; BMI 32-43 kg/m2.	Randomized clinical trial.	150 minutes/week of moderate AE or 75 minutes/week of vigorous CE.	Liraglutide started at 0.6 mg/day, increasing weekly by 0.6 mg to 3 mg/day or the maximum tolerated dose.	After 52 weeks, the L + E group lost weight, while the placebo group gained (p<0.001).
Jensen et al.[20]	71M and 124W; 18-65 years; BMI 32-43 kg/m2.	Randomized clinical trial.	150 minutes/week of moderate or 75 minutes/week of vigorous AE.	Liraglutide started at 0.6 mg/day, increasing weekly by 0.6 mg to 3 mg/day or the maximum tolerated dose.	After 1 year, the combination group lost weight, while the placebo group gained (p<0.001).
Khoo et al.[21]	28M and 2W; 18-65 years.	Randomized clinical trial.	150 minutes/week of moderate or 75 minutes/week of vigorous AE.	Liraglutide started at 0.6 mg/day, increasing weekly by 0.6 mg to 3 mg/day.	After 52 weeks, group L lost weight, the D+E group had a minimal loss, and the placebo group gained weight (p<0.001).

Note: M: men; W: women; D: diet; E: exercise; L: liraglutide; AE: aerobic exercise; BMI: body mass index; CE: cyclic exercise; HRmax: maximum heart rate.

Table 1. Continued...

Author	Sample characteristics	Study design	Exercise protocol	Pharmacological intervention	Results
Davies et al.[22]	425M and 421W; aged>18 years; BMI ≥ 27 kg/m2.	Randomized clinical trial.	150 minutes/ week of AE (brisk walking).	Liraglutide at 0.6 mg/day, increasing weekly by 0.6 mg for 2 weeks to 1.8 mg and 4 weeks to 3 mg.	The combination groups had weight loss, while the placebo group showed weight gain (p<0.001).
Astrup et al.[23]	135M and 429W; aged 18-65 years; BMI 30-40 kg/m2.	Randomized clinical trial.	Recommendation for maintenance or increase of AE under pedometer monitoring.	Liraglutide with weekly increments or Orlistat three times a day.	The liraglutide group had greater weight loss than the Orlistat and placebo groups.
Wilding et al.[24]	508M and 1453W; aged 18-78 years; BMI ≥ 27 kg/m2.	Randomized clinical trial.	150 minutes/week of AE (walking).	Semaglutide starting at 0.25 mg once a week with weekly increments to 2.4 mg.	The combination group had greater weight loss than the placebo group (p<0.001).
Mensberg et al.[25]	23M and 10W; aged > 18 years; and BMI ≥ 25 kg/m2.	Randomized clinical trial.	Three weekly sessions of 60 minutes at 65-85% HRmax: two sessions of spinning sprints with active recovery and one session of resistance exercise with dumbbells.	Liraglutide administered with increasing dosages weekly.	The combination group showed greater weight loss than the placebo group (p<0.001).
Tronieri et al.[26]	47M and 235W; aged > 18 years; BMI ≥ 30 Kg/m2.	Randomized clinical trial.	100 minutes/week of continuous exercise with incremental increases every 4 weeks to 250 minutes/week.	Liraglutide at 3 mg/day.	The combination group had greater weight loss than the placebo group (p<0.001).

Note: M: men; W: women; D: diet; E: exercise; L: liraglutide; AE: aerobic exercise; BMI: body mass index; CE: cyclic exercise; HRmax: maximum heart rate.

The PEDro Scale was used to assess the quality of evidence and the risk of bias in the studies included in the qualitative synthesis. These studies were classified into different domains, ranging from "good" to "excellent", as presented in Table 2.

Table 2. Classification of the methodological quality of the studies included in this systematic review.

Author	Score	Items from the PEDro Scale										
		1	2	3	4	5	6	7	8	9	10	11
Sandsdal et al.[18]	9	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Lundgren et al.[19]	7	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
Jensen et al.[20]	7	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
Khoo et al.[21]	6	Y	Y	Y	Y	N	N	N	N	N	Y	Y
Davies et al.[22]	6	Y	Y	Y	N	N	N	Y	N	Y	Y	N
Astrup et al.[23]	10	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Wilding et al.[24]	7	Y	Y	N	N	N	N	Y	Y	Y	Y	Y
Mensberg et al.[25]	9	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Tronieri et al.[26]	8	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y

Note: Y: Yes, N: No.

DISCUSSION

This systematic review aimed to comprehensively analyze the literature regarding the effects of GLP-1 analogs combined with physical exercise on

the modification of TBM in individuals with obesity. Within this perspective, studies that met the inclusion criteria suggest that liraglutide and semaglutide effectively promote weight loss in individuals with obesity[18-26]. Furthermore, the analogs proved superior when used combined with physical exercise[18-26].

The results indicate that combining GLP-1 analogs and exercise promoted the most significant weight loss. This dynamic is established due to the increase in energy expenditure promoted by physical exercise, inducing changes in adipose tissue and improving the body's metabolic health. Additionally, the satiety effect resulting from the action of analogs, previously discussed herein, complements this process[28,29].

Most articles in this review emphasized the importance of recommending physical exercise for obesity management[18-21,23,25,26], with guidance primarily focusing on cyclical exercises or weight training[18-26]. However, many studies lacked specificity in their aerobic exercise (AE) protocols, which may limit the assessment of the differential impact of various exercise types on the therapeutic response to GLP-1 analogs[18-24,26]. Despite substantial evidence supporting the benefits of physical exercise for weight management and body composition, most of the studies adopted a general approach to physical activity without detailing the specific types or intensities of exercises used[18-24,26].

The study by Mensberg et al.[25] was notable for specifying the use of aerobic exercise (AE), which may have significant implications for understanding the effectiveness of this combination with GLP-1 analogs. While there is clear evidence that physical exercise benefits weight management when combined with GLP-1 analogs, further investigations should explore the specificity of exercise protocols and establish more uniform assessment criteria to enhance understanding of this therapeutic approach[18-26].

Studies comparing different doses of liraglutide indicated that a 3 mg dose resulted in the most significant weight loss, suggesting a dose-response relationship where greater quantities of the substance are positively associated with increased weight loss[22,23,25]. In turn, the administration of semaglutide combined with physical exercise proved to be more effective in reducing TBM compared to the placebo group[24].

Some findings, notably reported in the studies conducted by Sandsdal et al.[18], Lundgren et al.[19], and Jensen et al.[20], indicated weight gain in the groups that received the placebo treatment. In the three mentioned studies[18-20], participants underwent a hypocaloric diet before randomization. Thus, while the overall results suggest that the combination of treatments is more effective in weight reduction, it is worth acknowledging that the participants' initial conditions, such as a hypocaloric diet, can influence outcomes substantially.

Given the limitations of this review, future research should focus on evaluating body composition to better understand how obesity pharmacotherapy affects skeletal muscle mass and body fat distribution. Such studies could provide insights into changes in body composition over time, contributing to a deeper understanding of treatment outcomes.

CONCLUSION

Higher doses of liraglutide and semaglutide are associated with significant reductions in total body mass, confirming their efficacy in weight control. GLP-1 analogs show superior results when combined with physical exercise, emphasizing the importance of a multifaceted approach in obesity management.

Compliance with ethical standards

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Ethical approval

This research follows the standards set by the Declaration of Helsinki.

Conflict of interest statement

The authors have no conflict of interest to declare.

Author Contributions

Contribution to the design and planning: AMSGF, CPCS, LABA, LLTP; Acquisition of data: AMSGF, JML, LAJS; Analyzed and interpretation the data: DSJ, AMSGF, JML, LSL; Writing and drafting of the article: AMSGF, LSL, JML, ESB; Critical intellectual review: CPCS, LABA, LLTP, DSJ; Approval of the final version to be published: CPCS, LAJS, ESB.

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