XXXIII Congresso de Iniciação Científica da Unicamp

Metabolic Outcomes and Safety of GLP-1 Receptor Agonists in Children and Adolescents with Obesity: A Systematic Review and Meta-Analysis.

Key words: glucagon-like peptide-1 receptor agonist, pediatric obesity, meta-analysis

Luis Gustavo Sedenho-Prado [1], Louise Buonalumi Tacito Yugar [1], Ana Raquel Whitaker [2], Marília Paiva Martins [1], Daniel Campos de Jesus [2], Isadora Maria Castilho da Silva Ferreira [1], Cleide Aparecida Moreira Silva, MSc [3], Wilson Nadruz, MD, PhD [4], Cintia Cercato, MD, PhD [5], **Andrei C Sposito, MD, PhD** [6].

[1] School of Medical Sciences, University of Campinas, Campinas, Brazil.

[2] Center for Life Sciences Courses, Pontifical Catholic University of Campinas, Campinas, Brazil.

[3] Department of Statistics, School of Medical Sciences, University of Campinas, Campinas, Brazil.

[4] Internal Medicine Department, State University of Campinas, Campinas, Brazil.

[5] Obesity Unit, Division of Endocrinology and Metabolism, University of São Paulo Medical School Hospital, São Paulo, Brazil.

[6] Atherosclerosis and Vascular Biology Laboratory (Atherolab), State University of Campinas, Campinas, Brazil.

BOLSISTA: **Luís Gustavo Sedenho Prado** // School of Medical Sciences // l204341@dac.unicamp.br //

MODALIDADE DA BOLSA: **CNPq**

ORIENTADOR: Prof. Dr. Andrei C Sposito / Atherosclerosis and Vascular Biology Laboratory (Aterolab) // sposito@unicamp.br

Complete article – International Journal of Obesity (Nature Portfolio)

https://www.nature.com/articles/s41366-025-01790-w

Introduction

Obesity has become a global issue, affecting all segments of the population, including children. According to the World Obesity Atlas 2022, childhood obesity is projected to reach epidemic proportions by 2030. (1) This concerning trend has been accelerated by the COVID-19 pandemic, during which the rate of increase in body mass index (BMI) doubled compared to pre-pandemic levels. (2) Given that obesity is a precursor to pro-atherogenic conditions such as hypertension, dyslipidemia, diabetes, and systemic inflammation, the early onset of obesity raises significant concern about an increased incidence of premature cardiovascular disease and mortality in the coming years. (3–5)

Comprehensive, multicomponent programs that integrate individual, family, and societal interventions must be swiftly developed and tailored to regional contexts to curb the growing prevalence of childhood obesity. However, data remains limited to guide the framework needed to maximize the efficacy of these programs. It is expected that as excess weight becomes established, compensatory mechanisms for weight loss will emerge, diminishing the long-term efficacy of behavioral and lifestyle interventions. (6,7) In such cases, pharmacological interventions may become essential to prevent obesity-related morbidities. This is particularly relevant for children with severe obesity or life-threatening comorbidities, for whom pharmacotherapy is recommended as an adjunct to behavioral and lifestyle approaches. (3,8)

In adults, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce body weight by approximately 7 kg through inhibition of gastric emptying and regulation of appetite and reward pathways via interactions with the brainstem, hypothalamus, and cerebral nuclei. (9,10) Although GLP-1 RAs have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in children aged 12 and older, robust evidence on their effects on body weight, obesity-related metabolic changes, and safety in this population remains limited. (11–13) This meta-analysis aims to clarify the safety and size effect of GLP-1 RAs therapy on body weight and metabolic parameters in children and adolescents with obesity.

Methods

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: 1) randomized double-blind clinical trials or post-hoc analyses of such trials; 2) comparisons of GLP-1 RA with placebo; 3) pediatric patients with obesity; and 4) participants aged 6 to 18 years. Additionally, studies had to report at least one of the clinical outcomes of interest listed in the sections below. Exclusion criteria included studies with 1) no control group, 2) adult patients (18 years or older), 3) patients with any form of diabetes, or 4) patients with other comorbidities such as hypothalamic obesity or Prader-Willi syndrome.

Search strategy and information sources

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for trials published until half of September/2024. The references from all included studies, previous systematic reviews and meta-analyses were also searched manually for any additional studies. Two authors independently extracted the data following predefined search criteria and quality assessment. Disagreements between authors were resolved by a third author.

Study selection and data collection process

The results obtained from the search across the databases were imported into the Elsevier's reference management software *Mendeley*. After eliminating duplicate entries, records were subjected to a preliminary screening based on their titles and abstracts. Potentially eligible records underwent a full-text analysis with

reasons for exclusion documented. Study selection was carried out independently by two reviewers, and any disparities were resolved through consultation with a third reviewer.

For data collection, two independent authors extracted study characteristics, participants' demographics and baseline characteristics, and outcome data. Some reported data may not be available in the published papers or supplementary appendices. In these cases, we manually searched the ClinicalTrials.gov register or the European Union Clinical Trials Register of the study. Efficacy outcomes included changes in body weight (BW), BMI, waist circumference (WC), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), heart rate (HR), and systolic (SBP) and diastolic blood pressures (DBP). Outcomes regarding side effects included nausea, diarrhea, vomiting, and upper abdominal pain. We collected data from pooled analyses of the randomized controlled trials and only data regarding double-blind periods. For all outcomes, we extracted data for the intention-to-treat population.

Risk-of-bias assessment

We performed a quality assessment using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials, in which studies are scored as having a high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases. (14) Two independent authors conducted the bias evaluation without the use of automation tools, and disagreements were resolved by a third author. We did not evaluate small-study effect bias with a funnel plot due to the small number of included trials.

Certainty assessment

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was employed to assess the level of certainty of the results. (15) For our analysis, we used GRADEpro software. (16)

Data synthesis and effect measures

This systematic review and meta-analysis was performed following the guidelines of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. (17) To account for variability in data presentation across the included studies, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were employed to evaluate treatment effects for continuous variables. Additionally, mean differences (MDs) were utilized to enhance the clinical relevance and practical applicability of the findings. Odds ratios (ORs) with 95% CIs were used to compare treatment effects for categorical endpoints. The Cochran Q test [$100 \times (Q - df \div Q)$] and I^2 statistics were used to assess heterogeneity; $I^2 > 25\%$ was considered to indicate heterogeneity. We used a DerSimonian and Laird random-effects model for the assessment of outcomes. A statistician (C.A.M.S.) performed the statistical analysis of the efficacy outcomes using R 4.1.0 (R Core Team, 2023), and the *meta* and *metapower* packages. For the summary treatment effect estimate, a p value less than 0.05 was considered statistically significant.

Results

Database characteristics

The initial search yielded 2,016 entries. After deduplication and exclusion of studies not meeting the inclusion criteria, 24 publications were fully reviewed. Of these, 16 were excluded. Ultimately, 8 randomized clinical trials, comprising a total of 715 patients, were deemed eligible (Figure 1) (11,13,18–23).

Studies and participant characteristics

Four trials included liraglutide, three included exenatide, and one included semaglutide. A detailed description of the therapies is presented in Table 1. The trial sample size ranged from 21 to 251. Follow-up durations ranged from 5 to 68 weeks. The mean age of the population analyzed ranged from 9.9 years old to 16

years old, with 56.5% being female. Baseline mean BW averaged from 70 kg to 124 kg; and mean BMI ranged from 31 kg/m^2 to 42.5 kg/m^2. Details of studies and participants' characteristics are presented in Table 2.

Risk of Bias in studies

Using the Cochrane Collaboration's tool for assessing risk of bias, seven studies were classified as low risk, and one as intermediate due to uncertainty regarding the selection of reported outcomes. A risk of bias graph and summary are included in the final analysis (Figure 2). No studies were identified as having a high risk of bias.

Body Weight, BMI, and Waist Circumference

Seven out of eight studies presented data on the effects of GLP-1 RA on BW, with SMD varying from a reduction of -2.02 to an increase of +0.72. The pooled analysis comparing GLP-1 RA to placebo in our meta-analysis demonstrated a significant BW reduction of -0.60 (95% CI -0.80 to -0.41), as shown in Figure 3A. The absolute MD for this outcome was -5.54 kg (95% CI -9.19 to -1.90). The certainty of evidence for this outcome was high and the I^2 was 7%.

Five studies provided data on BMI and the effects of GLP-1 RA on this metabolic measure, whose SMD ranged from a decrease of -2.06 to an increase of +0.23. Our meta-analysis comparing these effects with placebo demonstrated that GLP-1 RA significantly reduced BMI by -0.67 (95% CI -0.89 to -0.44), as presented in Figure 3B. The absolute MD for this outcome was -2.62 kg/m^2 (95% CI -4.30 to -0.93). This was supported by a high certainty of evidence. Also, the I^2 was 33%.

Four studies included data on WC and the effects of GLP-1 RA on this parameter, with SMD ranging from a decrease of -1.16 to an increase of +0.61. The meta-analysis comparing the intervention to placebo indicated that GLP-1 RA led to a significant reduction in WC by -0.40 (95% CI -0.61 to -0.18), as shown in Figure 3C. The absolute MD for this outcome was -4.30 cm (95% CI -8.10 to -0.50). The certainty of evidence for this outcome was high and the I^2 was 12%.

Lipid profile

Three of the eight studies provided data on total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides levels. The studies reported total cholesterol standardized changes ranging from -1.06 to +1.36. In our meta-analysis, we found no significant effect of GLP-1 RA on total cholesterol levels when compared to placebo, with a SMD of 0.06 (95% CI -0.40 to 0.51), as presented in Figure 4A. The absolute MD for this outcome was +1.56 mg/dL (95% CI -7.62 to 10.75). This result was supported by a high certainty of evidence and the I^2 was 37%.

The levels of HDL cholesterol presented standardized variations between -0.98 and +1.40. The meta-analysis demonstrated no significant impact of GLP-1 RA on HDL cholesterol levels, with a SMD of 0.07 (95% CI -0.32 to 0.46), as shown in Figure 4B. The absolute MD for this outcome was +2.01 mg/dL (95% CI -1.59 to 5.61). The certainty of evidence for this outcome was high and the I^2 was 26%.

Regarding LDL cholesterol levels, standardized changes ranged from a reduction of -0.99 to an increase of +1.27. The meta-analysis comparing GLP-1 RA with placebo revealed no significant effect on this parameter, with a SMD of 0.15 (95% CI -0.33 to 0.62), as shown in Figure 4C. The absolute MD for this outcome was +2.47 mg/dL (95% CI -5.76 to 10.69). This result was supported by a high certainty of evidence and the I^2 was 39%.

Triglyceride standardized levels ranged from a reduction of -0.86 to an increase of +0.93. When comparing GLP-1 RA to placebo through meta-analysis, the use of GLP-1 RA was associated with a non-significant SMD in triglycerides of -0.07 (95% CI -0.47 to 0.34), as shown in Figure 4D. The absolute MD for this outcome was -2.22 mg/dL (95% CI -19.97 to 15.52). The certainty of evidence for this outcome was high and the I^2 was 7%.

Blood Pressure

Six included studies provided information on the impact of GLP-1 RA on blood pressure. The analysis showed a statistically significant reduction in SBP in the intervention group compared to placebo (SMD -0.20, 95% CI -0.35 to -0.04), while the difference in DBP was not significant (SMD -0.04, 95% CI -0.21 to 0.14) (Figure 5). The absolute MDs for both outcomes were -2.43 mmHg (95% CI -4.26 to -0.59) and -0.47 mmHg (95% CI -2.40 to 1.46), respectively. Both SBP and DBP demonstrated low statistical heterogeneity (I^2 = 0%) and were supported by high certainty of evidence.

Heart Rate

Only four of the included studies contained data regarding the HR effects of GLP-1 RA, which ranged from a standardized reduction of -0.80 to an increase of 1.06. The meta-analysis demonstrated a SMD of 0.26 (95% CI 0.07 to 0.46) in the intervention group compared to placebo (Figure 6). The absolute MD for this outcome was +2.95 bpm (95% CI 0.61 to 5.29). The certainty of evidence for this outcome was high and the I^2 was 0%.

HbA1c and Fasting Blood Glucose

Five out of eight studies provided data on the effects of GLP-1 RA on HbA1c levels, with reported standardized changes ranging from a reduction of -1.57 to an increase of +0.96. The intervention group demonstrated a non-significant SMD in HbA1c of -0.33 (95% CI -0.79 to +0.12), as shown in Figure 7A. The absolute MD for this outcome was -0.09% (95% CI -0.20 to 0.03). The certainty of evidence for this outcome was low and data had high heterogeneity (I^2 = 85%).

Three studies reported the effects of GLP-1 RA on FBG as well, with standardized variations from -2.17 to +0.49. In children with obesity, GLP-1 RA use was associated with a non-significant SMD in FBG of -0.20 (95% CI -0.41 to +0.01) compared to placebo (Figure 7B). The absolute MD for this outcome was -1.93 mg/dL (95% CI -3.88 to 0.02). This outcome was assessed with a high certainty of evidence and the I^2 was 26%.

Side Effects (Diarrhea, Nausea, Vomiting, and Upper Abdominal Pain)

The gastrointestinal adverse effects reported across the trials varied. Seven studies provided data on the incidence of diarrhea, nausea, vomiting, and five reported the number of upper abdominal pain events. Nausea (42.1%) and vomiting (37.9%) were significantly more frequent in the intervention group compared to placebo (16.4% and 6.8%, respectively), which generated an OR for nausea of 3.67 (95% CI 2.51 to 5.38) and of 7.43 for vomiting (95% CI 4.47 to 12.33). While there was a trend towards increased diarrhea in patients receiving GLP-1 RA (23,6% vs. 17,1%; OR 1.46, 95% CI 0.98 to 2.18), this was not statistically significant. The incidence of upper abdominal pain did not differ significantly between the GLP-1 RA and placebo groups (11% vs. 12,8%; OR 0.86, 95% CI 0.51 to 1.43). All gastrointestinal side effects were assessed with a high certainty of evidence, and all presented a I^2 of 0%. The forest plots of these results are presented in Figure 8.

References→https://docs.google.com/document/d/1BK9MdxBNDDOk6ShwW9GnpEk7iDg_0qXUKiDtiFqlcuU/edit?usp=sharing

Figures→ https://docs.google.com/document/d/12Q3tHv9lTetJxHxAXckL8zbP8mmHt8wJw5y-GyaXWr0/edit?usp=sharing

Complete article – International Journal of Obesity (Nature Portfolio)

https://www.nature.com/articles/s41366-025-01790-w