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The Effect of Liraglutide on Hypoglycemia in Type 1 Diabetes Mellitus: A Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 June 2024 and was last updated on 13 June 2024.

INTRODUCTION

Review question / Objective Objective
In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have garnered widespread attention for their ability to mimic the action of endogenous incretin hormones, primarily GLP-1, and regulate blood glucose levels. Structurally and functionally similar to GLP-1, GLP-1RAs exhibit significantly extended half-lives, enabling them to enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and reduce food intake, ultimately lowering overall blood glucose levels. Nonetheless, the effects of GLP-1RAs on hypoglycemia in T1DM have been underexplored, with conflicting viewpoints and inconclusive findings that lack statistical substantiation. This study aims to conduct a meta-analysis comparing the use of liraglutide (a commercially available GLP-1RAs) in conjunction with insulin therapy to conventional insulin monotherapy in T1DM patients. The focus of the analysis will be on hypoglycemia-related indicators, with the objective of assessing the impact of GLP-1RAs on hypoglycemia in T1DM patients. The findings of this research endeavor to provide practical guidance and feasibility analysis for preventing and managing hypoglycemia in clinical T1DM treatment.
PICOS framework
(1) Studies of randomized clinical trials (RCTs); (2) Parallel design comparing the combination of liraglutide and insulin therapy with single insulin therapy; (3) Study participants limited to T1DM patients; (4) The included subjects had hypoglycemia-related indexes such as the incidence of hypoglycemia, the duration of hypoglycemia, and the incidence of severe hypoglycemia, etc.; (5) The studies included one of the following indexes: glycated hemoglobin (HbA1c, from baseline to endpoint value), body mass index (BMI), and body weight.

Condition being studied Unlike type 2 diabetes mellitus (T2DM), Patients with type 1 diabetes

mellitus (T1DM) necessitates lifelong insulin therapy to maintain blood glucose control. However, intensified insulin treatment often leads to hypoglycemia, the most common complication in T1DM management, occurring at a frequency of 1–2 times per week. Hypoglycemia can result in symptoms such as dizziness, palpitations, sweating, and neurological impairment, with severe cases leading to cognitive dysfunction and even death, with mortality rates ranging from 4% to 10%. Experimental studies in mice with pancreatic α-cells specific glucagon-like peptide-1 receptor (GLP-1R) gene knockout suggest that glucagon-like peptide-1 (GLP-1) regulates glucagon secretion from pancreatic α-cells in a glucose-dependent manner, inhibiting glucagon release during hyperglycemia and promoting it during hypoglycemia. Therefore, it is theoretically inferred that GLP-1 may have therapeutic potential in diabetes while also mitigating hypoglycemia.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have garnered widespread attention for their ability to mimic the action of endogenous incretin hormones, primarily GLP-1, and regulate blood glucose levels. Structurally and functionally similar to GLP-1, GLP-1RAs exhibit significantly extended half-lives, enabling them to enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and reduce food intake, ultimately lowering overall blood glucose levels. Nonetheless, the effects of GLP-1RAs on hypoglycemia in T1DM have been underexplored, with conflicting viewpoints and inconclusive findings that lack statistical substantiation. This study aims to conduct a meta-analysis comparing the use of liraglutide (a commercially available GLP-1RAs) in conjunction with insulin therapy to conventional insulin monotherapy in T1DM patients. The focus of the analysis will be on hypoglycemia-related indicators, with the objective of assessing the impact of GLP-1RAs on hypoglycemia in T1DM patients. The findings of this research endeavor to provide practical guidance and feasibility analysis for preventing and managing hypoglycemia in clinical T1DM treatment.

METHODS

Search strategy Search Strategy: Computer-based searches were conducted in the following databases: The Cochrane Library, PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang database, and VIP database. The search included literatures published from the inception of these databases up to June 20, 2023, and included the retrieval of references from the selected literatures. Both Chinese and English search terms are provided in Table S1. At the same time, subject headings (Mesh) and free words were used to search. Logic symbols, wildcards and range operators were used to formulate the search formulas, with adjustments made as necessary for each specific database.

Participant or population Study participants limited to T1DM patients.

Intervention liraglutide and insulin therapy.

Comparator Placebo and insulin therapy.

Study designs to be included Studies of randomized clinical trials (RCTs).

Eligibility criteria Exclusion criteria (1) Editorials, review articles, individual case reports, letters to editors; (2) Duplicate RCTs (the most recent published data were selected); (3) Non-randomized controlled studies; (4) Studies not meeting the inclusion criteria mentioned above.

Information sources Electronic databases The Cochrane Library, PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang database, and VIP database.

Main outcome(s) Eight studies allowed for the extraction or calculation of the total number of hypoglycemia events during the intervention period for both the treatment and control groups. All data were converted to events per person-day, representing the hypoglycemia incidence, to standardize the units for the meta-analysis. The results demonstrated that there was no statistically significant difference in hypoglycemia incidence between the liraglutide group and the control group [OR=1.01, 95% CI (0.82, 1.23), P=0.94] (Figure 3A). Considering substantial heterogeneity among the included studies (P<0.01, I2=98%), a subgroup analysis was performed based on liraglutide dosage. The results showed that both the 1.2 mg subgroup (once daily) and the 1.8 mg subgroup (once daily) had statistically significant differences. Specifically, in the 1.2 mg subgroup, the liraglutide group had a significantly lower hypoglycemia incidence compared to the control group [OR=0.81, 95% CI (0.74, 0.88), P<0.01], while in the 1.8 mg subgroup, the liraglutide group had a significantly higher hypoglycemia incidence compared to the control group [OR=1.33, 95% CI (1.23, 1.44), P<0.01]. Other subgroup variables such as liraglutide intervention duration, BMI, and

single/multi-center studies had no statistically significant impact on hypoglycemia incidence.
Data on the duration of hypoglycemia were extracted from six studies. Meta-analysis results indicated that there was no statistically significant difference in the duration of hypoglycemia between the liraglutide group and the control group [MD=−0.29, 95% CI (−1.21, 0.63), P=0.53]. Subgroup analyses based on liraglutide dosage and intervention duration also showed no statistically significant differences.
Five studies, which included the assessment of severe hypoglycemia incidence, were subjected to meta-analysis. The results showed that there was no statistically significant difference in the incidence of severe hypoglycemia between the experimental group and the control group [OR=0.87, 95% CI (0.57, 1.33), P=0.53]. Furthermore, there was low heterogeneity observed (P=0.55, I2=0%).

Quality assessment / Risk of bias analysis To further reflect the reliability of the results of this meta-analysis, Egger's test was used to assess publication bias for the various measurement indicators in the meta-analysis. The results of Egger's test indicated that there was no publication bias in the meta-analysis for each measurement indicator, including hypoglycemia incidence and its subgroups, duration of hypoglycemia and its subgroups, severe hypoglycemia, HbA1c, weight, and BMI. Therefore, The possibility of systematic error in this meta-analysis is relatively low, and the statistical results after combining the effect sizes are highly reliable.

Strategy of data synthesis When continuous data were reported as median (interquartile) or mean (minimum to maximum), mean values were estimated using the statistical methods described by Luo et al. and standard deviations were estimated using the statistical methods described by Wan et al. Additionally, according to the Cochrane guidelines, changes were calculated using baseline and endpoint data. Any discrepancies were resolved through discussion to reach a consensus.
In EndNote 20, we recorded and managed the literature, and conducted meta-analysis using Review Manager 5.3 and Stata 16. After converting the outcome variables to a unified unit, we compared continuous variables using the mean differences (MD) and binary variables using the odds ratio (OR). Results for continuous and binary variables were presented with 95% confidence intervals (95% CI) of MD or OR, respectively. The Q test and I2 test were utilized to assess heterogeneity among studies. If P>0.10 and I2<50%, indicating no heterogeneity, the fixed effect model was selected for data merge analysis. Otherwise, the random effect model was utilized.
To evaluate the stability and reliability of the meta-analysis results, we used the modified Cochrane risk of bias tool to assess bias risk and quality of the included studies. Sensitivity analysis was conducted by sequentially excluding individual studies and then recombining effect sizes to assess the stability of the meta-analysis results. Egger's test was applied to detect publication bias for each outcome measure, providing further insights into the validity of the meta-analysis results.

Subgroup analysis Considering substantial heterogeneity among the included studies (P<0.01, I2=98%), a subgroup analysis was performed based on liraglutide dosage. The results showed that both the 1.2 mg subgroup (once daily) and the 1.8 mg subgroup (once daily) had statistically significant differences. Specifically, in the 1.2 mg subgroup, the liraglutide group had a significantly lower hypoglycemia incidence compared to the control group [OR=0.81, 95% CI (0.74, 0.88), P<0.01], while in the 1.8 mg subgroup, the liraglutide group had a significantly higher hypoglycemia incidence compared to the control group [OR=1.33, 95% CI (1.23, 1.44), P<0.01]. Other subgroup variables such as liraglutide intervention duration, BMI, and single/multi-center studies had no statistically significant impact on hypoglycemia incidence.

Sensitivity analysis To assess the reliability of the study results, sensitivity analyses were conducted for each outcome measure in this meta-analysis. Using the method of sequentially excluding individual studies and then recombining the effect sizes, it was found that the meta-analysis results for HbA1c were not stable. After excluding the study by Mathieu C (2017), the combined effect size became statistically insignificant (P=0.14). Apart from this, the combined effect sizes for other indicators did not change significantly, indicating the relative stability of the meta-analysis results mentioned above.

Country(ies) involved China.

Keywords Liraglutide; Type 1 diabetes mellitus; Hypoglycemia; Meta-analysis.

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