INPLASY PROTOCOL

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Influence of Dipeptidyl Peptidase-4 Inhibitors on Glucagon in T2DM patients

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Review question / Objective: **An meta-analysis of RCTs was performed to systematically study the effects of dipeptidyl-peptidase 4 (DPP4) inhibitors on changes in glucagon total area under the curve (AUCglucagon) in patients with type 2 diabetes.**
Eligibility criteria: **In the meta-analysis, we excluded studies involving single-dose or single-day DPP4 inhibitors, because we did not intend to assess their acute effects. Furthermore, non-randomized studies, studies involving non-T2DM patients, or those without measurements of AUCglucagon included in MTT or OGTT were excluded from the analysis. In addition, we also excluded studies involving T2DM patients receiving concurrent antidiabetic injections, such as insulin and GLP-1 receptor agonists (GLP-1RAs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 August 2022 and was last updated on 29 August 2022 (registration number INPLASY202280104).

INTRODUCTION

Review question / Objective: **An meta-analysis of RCTs was performed to systematically study the effects of dipeptidyl-peptidase 4 (DPP4) inhibitors on changes in glucagon total area under the curve (AUCglucagon) in patients with type 2 diabetes.**

Rationale: **Hyperglucagonemia, or abnormally high glucagon levels, has been implicated in diabetes pathogenesis. It is also well known that DPP-4 inhibitors lower blood sugar by inhibiting incretin hormone degradation induced by DPP-4. In MTTs or OGTTs, glucagon total area under the curve (AUCglucagon) is typically measured to assess the effects of antidiabetic treatment**

on postprandial glucagon levels. On the other hand, little is known about the comparison of DPP4 inhibitors with placebo in terms of AUCs. of postprandial glucogan.

Condition being studied: By performing a meta-analysis of RCTs, we summarize the influence of DPP4 inhibitors on AUCglucagon, as compared to placebo, or other oral antidiabetic drugs (OADs) in patients with T2DM.

METHODS

Search strategy: Terms: (1) "DPP4" OR "DPP-4" OR "dipeptidyl peptidase-4 inhibitors" OR "sitagliptin" OR "vildagliptin" OR "linagliptin" OR "saxagliptin" OR "alogliptin" OR "dutogliptin" OR "aemigliptin" OR "anagliptin" OR "teneligliptin" OR "trelagliptin" OR "omarigliptin" OR "gemigliptin" OR "evogliptin"; (2) "α cell" OR "α-cell" OR "glucagon" OR "alpha cell" OR "islet" OR "hormone" OR "hormonal" OR "meal" OR "prandial" OR "postprandial" OR "Oral Glucose Tolerance Test" OR "OGTT"; and (3) "random" OR "randomized" OR "randomised" OR "randomly".

Participant or population: T2DM patients.

Intervention: DPP4 inhibitors.

Comparator: Placebo groups, or other OADs.

Study designs to be included: Parallel groups or crossovers RCTs.

Eligibility criteria: In the meta-analysis, we excluded studies involving single-dose or single-day DPP4 inhibitors, because we did not intend to assess their acute effects. Furthermore, non-randomized studies, studies involving non-T2DM patients, or those without measurements of AUCglucagon included in MTT or OGTT were excluded from the analysis. In addition, we also excluded studies involving T2DM patients receiving concurrent antidiabetic injections, such as insulin and GLP-1 receptor agonists (GLP-1RAs).

Information sources: Databases: Medline (PubMed), Embase (Ovid), and CENTER (Cochrane Library).

Main outcome(s): In interventional and control studies, AUCglucagon changed from baseline after treatment utilizing MTT or OGTT was reported.

Additional outcome(s): None.

Data management: Two authors independently searched and collected databases as well as assessed quality of the data.

Quality assessment / Risk of bias analysis: We evaluated the quality of the included RCTs by applying Cochrane Risk of Bias Tool.

Strategy of data synthesis: Statistical pooling was calculated using the random-effects model, since it takes into account heterogeneity and provides more general conclusions.

Subgroup analysis: Analysis of predetermined subgroups was done to see if study factors could have an impact on the outcomes.

Sensitivity analysis: To analyze sensitivity, each study was excluded from the meta-analysis one at a time to see if their results contributed to the pooled results.

Language restriction: English.

Country(ies) involved: China.

Other relevant information: None.

Keywords: dipeptidyl peptidase-4 inhibitor; glucagon; hyperglucagonemia; randomized controlled trials; meta-analysis.

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Conflicts of interest: Shangyu Chai, Ruya Zhang, Ye Zhang and Yiman Zheng are employees of MSD China; Swapnil Rajpathak is employee of Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.