INPLASY PROTOCOL

Corresponding author:
Chunguang Xie

1007200125@qq.com

Author Affiliation:
Hospital of Chengdu University of Traditional Chinese Medicine

Review Stage at time of this submission: The review has not yet started.

Conflicts of interest:
None.

The influence of hypoglycemia and hyperglycemia on the adverse outcome of COVID-19 combined with diabetes mellitus: A protocol for systematic review and meta-analysis

Yang, Y[1]; Fan, X[2]; Chen, D[3]; Xie, C[4].

Review question / Objective: In patients with diabetes and SARS-COV-2 infections, does the occurrence of hyperglycemia or hypoglycemia have an impact on the outcomes?

Condition being studied: COVID-19 has become a global epidemic, causing huge loss of life and property. Diabetes will affect the prognosis of COVID-19 patients in many ways. Both hyperglycemia and hypoglycemia can affect oxidative stress and lead to the release of inflammatory mediators. Blood glucose and diabetes are independent risk factors for mortality and morbidity in SARS patients.T2DM patients have comprehensive, systemic and chronic blood hypercoagulability. COVID-19 is coagulopathy, characterised by high D-dimer and fibrinogen concentrations with minor changes in prothrombin time and platelet count. So hyperglycemia and hypoglycemia are important during the progress of diabetes with COVID-19.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 August 2020 and was last updated on 23 August 2020 (registration number INPLASY202080096).

INTRODUCTION

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Rationale: COVID-19 has become a global epidemic, causing huge loss of life and property. Diabetes will affect the prognosis of COVID-19 patients in many ways. Both hyperglycemia and hypoglycemia can affect oxidative stress and lead to the release of inflammatory mediators.Blood glucose and diabetes are independent risk

factors for mortality and morbidity in SARS patients.

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METHODS

Search strategy: We will search electronic databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and Wanfang database using keywords related to COVID-19, diabetes mellitus, hyperglycemia and hypoglycemia.

Participant or population: Diabetes combined weit SARS-COV infections.

Intervention: The happiness of hyperglycemia or hypoglycemia.

Comparator: Diabetic patients with blood sugar control standards.

Study designs to be included: any type of study.

Eligibility criteria: All patients with diagnosed diabetes and COVID-19.

Information sources: We will search electronic databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and Wanfang database using keywords related to COVID-19, diabetes mellitus, hyperglycemia and hypoglycemia.

Main outcome(s): Patients entering the ICU; Dead patients; Course of disease; and Coagulation status.

Additional outcome(s): Dead patients Course of disease Coagulation status.

Data management: Data analysis will be conducted in Review Manager Version 5.3 and stata 14.0 software for Mac. The risk ratio (RR) was used as the analysis statistic and 95% CI was provided. The heterogeneity of the results was analyzed by χ^2 test (the test level was $\alpha = 0.1$), and the degree of heterogeneity was determined byI^2. If there is no statistical heterogeneity between the results of each study, the fixed effect model is used for Meta-analysis; if there is statistical heterogeneity between the results of each study, the source of heterogeneity is further analyzed. After excluding the influence of obvious clinical heterogeneity, the random effect model is used for Meta-analysis. The level of Meta-analysis is set as $\alpha = 0.05$. Significant clinical heterogeneity was treated by subgroup analysis or sensitivity analysis, or only descriptive analysis.

Quality assessment / Risk of bias analysis: The integrity of the studies is an important factor affecting the accuracy of the results and conclusions of meta-analysis. The integrity of the included studies is mainly measured by reporting bias, of which publication bias is the most common. Therefore, this study will identify report bias by publication bias assessment. A funnel plot will be drawn to investigate the publication bias. Funnel plot will be asymmetric when publication bias exists, such as when research with small sample and no statistically significant results are not published. The more obvious the asymmetry of funnel plot is, the more likely

there is publication bias. And then Egger test will be conducted for statistical assessment the publication bias. The publication bias is considered to exist if P <0.05.

Strategy of data synthesis: Based on the pre-determined inclusion criteria, two independent reviewers will evaluate all titles and abstracts to exclude papers that are not considered relevant. The remaining provisions will be included in a further assessment. Reviewers will carefully examine the full text of each potentially relevant article. The process of study identification and exclusion will be described by PRISMA flow chart. Differences in research options will be resolved through consultation. And record in Excel file.

Subgroup analysis: If there is substantial heterogeneity between studies, then we will conduct subgroup analysis to explore the heterogeneity. To avoid post hoc analysis, the subgroup analysis will be conducted according to Diabetes complications. To further improve the reliability of subgroup analysis, we will evaluate the credibility of our subgroup analysis according to the guidance for credible subgroup analysis. If there are enough studies included, then meta-regression will be conducted to further explore the heterogeneity. Those subgroup effects that occur simultaneously in subgroup analysis and regression analysis will be considered credible.

Sensibility analysis: Draw funnel chart for the number of Patients entering the ICU of diabetes combined with COVID-19 patients.To ensure the stability of the results, we will conduct sensitivity analysis of the results by excluding each of the studies included in the analysis one by one, then re-analyzing the results, and comparing the differences between the re-obtained results and the original results. In this way, we will be able to assess the impact of individual studies on overall outcomes and their robustness.

Language: No language restriction.

Country(ies) involved: China.

Other relevant information: None.

Keywords: COVID-19, diabetes mellitus, hyperglycemia, hypoglycemia, protocol, systematic review and meta-analysis.

Dissemination plans: The results will be published at a peer-reviewed journal.

Contributions of each author:
Author 1 - Yan Yang - Yan Yang is responsible for the draft and analysis methods.
Author 2 - Fan Xiumei - the author provides statistical expertise.
Author 3 - Dongqiong Chen - the author provides data curation and form analysis.