INPLASY PROTOCOL

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None declared.

Effectiveness of the gut microbiota-bile acid pathway (BAS) in the treatment of Type 2 diabetes: A protocol for systematic review and meta analysis

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Review question / Objective: **To systematically evaluate the efficacy of the intestinal microbiome - bile acid pathway (BAS) in the treatment of T2DM.**
Condition being studied: **Bile acids (BAs), an important component of bile, are also metabolites derived from cholesterol and promote intestinal absorption and transportation of dietary lipids . Studies have shown that bile acid receptor agonists can promote glP-1 secretion and improve glucose metabolism in preclinical mouse models of obesity and insulin resistance , which may become a new therapeutic target for Type 2 diabetes. However, no systematic review and meta-analysis has been found on the treatment of type 2 diabetes by intestinal microbiome - bile acid pathway. Therefore, we conducted a systematic review and meta-analysis to evaluate the safety and effectiveness of intestinal microbiome-bile acid pathway in the treatment of type 2 diabetes.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2022 and was last updated on 28 July 2022 (registration number INPLASY202270117).

INTRODUCTION

Review question / Objective: **To systematically evaluate the efficacy of the intestinal microbiome - bile acid pathway (BAS) in the treatment of T2DM.**

Rationale: **Type 2 diabetes mellitus (T2DM) is a high prevalence metabolic disease. It is characterized by a long disease course, complicated and diverse long-term complications, and is difficult to cure. In recent years, the relationship between intestinal flora, bile acids and the**

occurrence and development of T2DM has become a hot topic in laboratory and clinical research.To systematically review literature evidence to evaluate the efficacy and safety of gut microbial-bile acid pathway (BAS) in the treatment of type 2 diabetes mellitus (T2DM).

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METHODS

Search strategy: Randomized controlled trials (RCTS) on the efficacy and safety of the intestinal microbiota bile acid pathway (BAS) in the treatment of type 2 diabetes were searched from PubMed, Cochrane Library, EMBASE, CNKI, VIP and Wanfang database. Clinical registry trials and gray literature were also searched.and the literature was collected from the establishment of the database to June 2022. The Cochrane bias risk assessment tool RevMan 5.2 was used for quality evaluation and meta-analysis. Publication bias was evaluated by Egger's test.

Participant or population: The patients of type 2 diabetes (using WHO 1999 diagnostic criteria[13]). These types of patients will not be included: patients with acute complications of diabetes; patients with severe heart disease, liver and kidney dysfunction, mental illness, or a relevant drug allergic history and patients during pregnancy or lactation.The literatures of type 2 diabetes patients were included without restriction on gender, age, race, disease course and blood glucose control of the subjects.

Intervention: Both groups were cured with conventional diabetes treatments recommended by the American Diabetes Association (ADA) guidelines, including diet, exercise, and hypoglycemic and lipid-lowering therapies.[14] The experimental group received drugs or diet and exercise that affected bile acid pathway, while the control group applied for placebo or no treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators.

Comparator: While the control group applied for placebo or no treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators.

Study designs to be included: Six databases including PubMed, Cochrane library, EMBASE, the China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), and Wanfang databases were searched from inception to June 2022 for the relevant RCTs of the intestinal microbiome-bile acid pathway (BAS) in the treatment of type 2 diabetes, with “Gastrointestinal Microbiome” and “Type 2 Diabetes Mellitus” as search terms, a subject word plus free words as search form. In order to ensure that eligible relevant between gut microbiota and type 2 diabetes were included as many as possible, the specific name “bile acid pathway (BAS)” was not explicitly searched, and no restriction on language and publication period was set in this review. In addition, we also searched for references that have been included in relevant literature or systematic review.

Eligibility criteria: 1.The literatures of type 2 diabetes patients were included without restriction on gender, age, race, disease course and blood glucose control of the subjects. 2. The relevant literatures included in human intestinal flora do not strictly restrict the test methods and key

indicators of fecal specimens. 3. Relevant literatures with no statistically significant difference in general data between the experimental group and the control group were included. 4.There is no restriction on whether blind method or distributive hiding method is used to include Chinese and English literatures whose research type is correlation study. 5. References that clearly indicated standard deviation (SD), mean value or which could be calculated by formula were included.

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Main outcome(s): The following information was collected from each study: publication year, country, ethnicity, speci-men source, gender and age,case and control numbers, the primary outcomes include 2 hour plasma glucose, fasting plasma glucose, hemoglobin A1c, homeostasis model assessment of insulin resistance, and fasting plasma insulin.

Quality assessment / Risk of bias analysis: The Grading of Recommendations Assessment, Development and Evaluation system will be used to judge the overall quality of evidence supporting outcomes in this work. And the quality of evidence will be defined as high, moderate, low, or very low Cochrane X2 and I2 tests will be used for the evaluation of heterogeneity. It is acknowledged that if P≥.05 and I2≤50%, the assessment of heterogeneity can be neglected; and there is great heterogeneity between included studies if P50%.If more than 10 studies are included in the meta-analysis, a funnel chart will be used to detect reporting deviations.

Strategy of data synthesis: We used the Review Manager(RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark) for statistical analyses. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used to calculate the difference of ADAMTS-5 gene .When some studies reported using the of results of the median of the first and third quartiles (M (P25, P75)), approximation methods were used to calculate the mean and standard deviation (X±S) [16];X=(P25+M+P75)/3 and S =(P75−P25)/1.35. Besides, all standard errors of the correlation coefficient (SE) were calculated as follows [17];SE =√((1-r)/(n-1))2 to combine the r of the random-effect model. Q-statistic (P < 0.05) and I2 statistics (I2>5 0%) were used to evaluate the heterogeneity among studies. In individual studies, we used the Cochrane Collaboration's tool to assess the risk of bias. P <0.05 indicates statistical significant.

Subgroup analysis: If feasible, we will conduct subgroup analysis based on different interventions, controls, treatment duration and outcome indicators.

Sensitivity analysis: A sensitivity analysis will be conducted to investigate the robustness of the research conclusions. Methodological quality, sample size, and the impact of missing data will be included. Therefore, the impact of low-quality research on the overall results will be assessed.

Country(ies) involved: China.

Keywords: Type 2 diabetes; the gut microbiota-bile acid pathway (BAS); systematic review; meta-analysis; protocol.

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