

# INPLASY PROTOCOL

To cite: Sun et al. Effects of probiotics on glycemic control and intestinal dominant flora in patients with type 2 diabetes mellitus: a protocol for systematic review and meta-analysis. *Inplasy protocol* 202090104. doi: 10.37766/inplasy2020.9.0104

Received: 29 September 2020

Published: 29 September 2020

**Corresponding author:**  
Yue Sun

1120506394@qq.com

**Author Affiliation:**  
Chengdu University of  
Traditional Chinese Medicine

**Support:** Major new drug  
creation.

**Review Stage at time of this  
submission:** Preliminary  
searches.

**Conflicts of interest:**  
None.

## Effects of probiotics on glycemic control and intestinal dominant flora in patients with type 2 diabetes mellitus: a protocol for systematic review and meta-analysis

Sun, Y<sup>1</sup>; Huang, YC<sup>2</sup>; Ye, FH<sup>3</sup>; Lin, KX<sup>4</sup>; Jin, XH<sup>5</sup>; Wang, JJ<sup>6</sup>; Gao, YX<sup>7</sup>; He, LS<sup>8</sup>.

**Review question / Objective:** The goal of this study is to systematically evaluate the effects of probiotics on blood glucose control and intestinal dominant flora in patients with type 2 diabetes, and then analyze the safety and effectiveness of its efficacy.

**Condition being studied:** More than 90% of diabetic patients have type 2 diabetes mellitus (T2DM). It is currently believed that the onset of T2DM is mainly related to factors such as genetics, insulin resistance, impaired insulin cell function and obesity. The main mechanisms are as follows: 1. It affects the intestinal intake of single-chain fatty acid (SCFAs). The decrease of SCFAs leads to the decrease of the number of islet cells and the decrease of insulin sensitivity, which in turn leads to insulin resistance (IR). 2. Intestinal barrier function is inhibited, which leads to intestinal nonspecific inflammation. Then it leads to changes in the structure and function of intestinal endothelial cells and affects the transport of insulin, which leads to IR. 3. Intestinal flora participates in bile acid metabolism and liver circulation, and affects the metabolism of carbohydrates and lipids. Imbalance of intestinal flora leads to disorders of carbohydrate and lipid metabolism. 4. Intestinal flora can reduce oxidative stress and improve islet cell function and insulin metabolism. Imbalance of intestinal flora can lead to impaired islet cell function and insulin resistance. 5. Normal intestinal flora can increase the content of YY peptide and correct the abnormal nerve conduction in hypothalamic feeding center.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 September 2020 and was last updated on 29 September 2020 (registration number INPLASY202090104).

### INTRODUCTION

**Review question / Objective:** The goal of this study is to systematically evaluate the

effects of probiotics on blood glucose control and intestinal dominant flora in patients with type 2 diabetes, and then

analyze the safety and effectiveness of its efficacy.

**Rationale:** Probiotics can improve T2DM by improving intestinal flora, which have the potential value of intervention in T2DM. Through the supplement of probiotics to the animal model, some researchers found that probiotics effectively improved the blood glucose of T2DM animals. In addition, NF- $\kappa$ B can up-regulate pro-inflammatory cytokines and activate JAK / STAT3 signal pathway. Probiotics reducing pro-inflammatory cytokines by inhibiting NF- $\kappa$ B pathway is also proved to be an effective method for the treatment of diabetes. Inhibition of STAT3 expression can reduce blood glucose level and liver lipid accumulation, and increase liver glycogen. Some studies have shown that supplementation of probiotics can significantly improve the epithelial barrier and reduce the level of inflammatory cytokines, such as IL-8, TNF- $\alpha$  and IL- $\beta$ . Moreover, probiotics can regulate nutrient metabolism at the level of expressed genes, down-regulate the expression of GSK-3 $\beta$ , FAS and SREBP-1, and up-regulate Akt, thus improving T2DM. The regulation of probiotics on intestinal microecology can effectively avoid over harvesting of energy. In addition, oxidative stress plays an important role in the pathogenesis of T2DM. It was found that the supplementation of probiotics could significantly improve the level of FBS, TAS, GSH and MDA, and the improvement of biomarkers of oxidative stress had a positive effect on maintaining glucose homeostasis. Probiotic supplementation has proved to be effective in controlling blood glucose homeostasis in patients with T2DM. At the same time, we speculate that probiotic supplementation can regulate intestinal microecology and actively improve intestinal dominant flora, which is beneficial to T2DM patients as a whole.

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## METHODS

**Search strategy:** The retrieval period of Meta analysis literature is set from January 1, 1990 to September 2020. We will mainly search five English electronic databases, including Cochrane Library, Pubmed, Excerpt Medical Database (EMBASE), Science Direct and Web of Science, and search the following four Chinese databases: China Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science Journal Database (VIP), Wanfang Database and so on. At the same time, (HYC) searched the clinical trial registration and gray literature about probiotic treatment of T2DM in European Drug Administration (EMA) ([www.ema.europa.eu/ema/](http://www.ema.europa.eu/ema/)), World Health Organization (WHO), International Clinical trial Registration platform ([www.wh.int/ICTRP](http://www.wh.int/ICTRP)) and so on. The search strategy for the combination of subject words and free words is decided by all commentators. The key words for this study are: T2DM, probiotic preparation, probiotics, blood glucose, blood glucose

control, fasting blood glucose, two-hour postprandial blood glucose, random blood glucose, *Clostridium perfringens*, *Clostridium globosum*, *Bacillus vulgaris*, *Bifidobacterium*, intestinal dominant flora, intestinal flora.

**Participant or population:** This review includes patients with T2DM, regardless of race, region, sex, and the phase of Diabetic complications and nosogenesis. Does not include other serious diseases, such as other heart, kidney, blood system diseases, severe hereditary diseases, etc.

**Intervention:** The main intervention is to use probiotics and probiotics to treat T2DM. The intervention group will be treated with probiotics or probiotics alone, or combined with other conventional drugs on the basis of probiotics and their preparations for T2DM treatment. The control group was given other routine treatment, such as routine drug treatment, observation, nursing and so on. The treatment time and period of treatment for the use of probiotics and their preparations are not limited.

**Comparator:** The control group was given other routine treatment, such as routine drug treatment, observation, nursing and so on.

**Study designs to be included:** This study will only include randomized controlled trials (RCTs).

**Eligibility criteria:** This study will only include randomized controlled trials (RCTs), non-RCTs, quasi-RCTs, reviews, case reports and other types of studies will be excluded. And all relevant RCTs published in English and Chinese on probiotic preparation in the treatment of T2DM could be included.

**Information sources:** We will mainly search five English electronic databases, including Cochrane Library, Pubmed, Excerpt Medical Database (EMBASE), Science Direct and Web of Science, and search the following four Chinese databases: China Biomedical Literature Database (CBM),

China National Knowledge Infrastructure (CNKI), China Science Journal Database (VIP), Wanfang Database and so on. At the same time, (HYC) searched the clinical trial registration and gray literature about probiotic treatment of T2DM in European Drug Administration (EMA) ([www.ema.europa.eu/ema/](http://www.ema.europa.eu/ema/)), World Health Organization (WHO), International Clinical trial Registration platform ([www.wh.int/ICTRP](http://www.wh.int/ICTRP)) and so on. The search strategy for the combination of subject words and free words is decided by all commentators. The key words for this study are: T2DM, probiotic preparation, probiotics, blood glucose, blood glucose control, fasting blood glucose, two-hour postprandial blood glucose, random blood glucose, *Clostridium perfringens*, *Clostridium globosum*, *Bacillus vulgaris*, *Bifidobacterium*, intestinal dominant flora, intestinal flora.

**Main outcome(s):** The main outcomes of this study was to observe the blood glucose control (fasting blood glucose, two-hour postprandial blood glucose, random blood glucose) in patients with T2DM under the intervention of probiotics, as well as the intervention of *Clostridium lean*, *Clostridium globosum*, *Bacillus vulgaris*, *Bifidobacterium* and so on.

**Additional outcome(s):** Additional outcomes included improvements in other intestinal floras and complications in patients with T2DM as indicators of secondary evaluation.

**Quality assessment / Risk of bias analysis:** The process of this study will be based on the deviation risk (ROB) assessment tool provided by the Cochrane manual to assess the quality of the included randomized controlled trials. The process will be assessed by two reviewers (HYC and YFH). Evaluation quality items include inclusion criteria, sample size estimates, baselines, randomization, allocation sequence hiding, binding, selective reporting, missing data management, and other deviations. According to the risk judgment criteria, we classify the quality of the above contents into three grades: "low

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deviation risk", "high deviation risk" and "unclear deviation risk". If there are any other differences, we will discuss and reach an agreement with the third-party reviewer (SY).

**Strategy of data synthesis:** We use Revman 5.3 software provided by Cochrane Collaboration for all statistical analysis and data synthesis. In this study, we will use a random effect model for meta-analysis. For binary data, 95% confidence interval (95%CI) and relative risk ratio (RR) is calculated. For continuous results, we will calculate the standard average deviation of 95% confidence interval, and the data results are represented by mean difference (MD) or standardized mean difference (SMD) and 95% confidence interval (95%CI). If there is statistical heterogeneity, the heterogeneity evaluation method is used.

**Subgroup analysis:** In the case of heterogeneity of the data, the subgroup analysis was conducted according to the characteristics of the data (factors that may lead to heterogeneity), that is, the source of heterogeneity was discussed from the aspects of age, sex, regions, races, types of probiotic preparation, types of complications in patients with T2DM and so on.

**Sensibility analysis:** When the effect of subgroup analysis is not satisfactory, we can conduct the sensitivity analysis to explore the impact of deviations in individual studies on the results. The main operation of sensitivity analysis is to eliminate the low-level quality research one by one, then merge the new data with Reven man5.3, and compare the new data with the previous results to judge the difference of sensitivity.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** Probiotics, T2DM, Intestinal dominant flora.

#### **Contributions of each author:**

Author 1 - Yue Sun.

Author 2 - Yucheng Huang.

Author 3 - Fanghang Ye.

Author 4 - Kexin Lin.

Author 5 - Xiaohua Jin.

Author 6 - JingJing Wang.

Author 7 - YongXiang Gao.

Author 8 - LiSha He.