INPLASY PROTOCOL

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

Conflicts of interest:
None.

Dietary supplements for prediabetes: a protocol for a systematic review and meta-analysis

Liu, DY[1]; Wen, Q[2]; Liu, M[3]; Gao, Y[4]; Luo, LH[5]; Zhang, Z[6]; Chen, C;[7].

Review question / Objective: **To comprehensively assess the efficacy and safety of dietary supplements for prediabetes.**
Condition being studied: **According to the International Diabetes Federation, the number of adults with impaired glucose tolerance or diabetes was 318 million and 415 million in 2015, respectively, and it is estimated that the number will rise to 482 million and 642 million in 2040. Compared with normoglycemic individuals, people with prediabetes have an increased risk of coronary heart disease, composite cardiovascular disease, chronic kidney disease, stroke and developing type 2 diabetes mellitus(T2DM), causing severe physical impairment and heavy financial burden. While round 70% of prediabetic individuals eventually reach the irreversible diabetic endpoint, some of them do not convert to the diabetic stage and finally return to normoglycemia.[11] Hence, taking some effective measures at the pre-diabetic phase seems essential. As an important form of complementary and alternative medicine(CAM), dietary supplements(DS) is defined as herbs or other botanicals, minerals, vitamins, enzymes, amino acid, and dietary substances. Using various dietary supplements is increasing steadily recently and relevant trials of different diseases are increasing correspondingly. Its effectiveness has been confirmed in some studies among prediabetic individuals. However, no comprehensive systematic reviews remain so far and we aim to collate the evidence on DS for prediabetes to evaluate its efficacy and safety.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 April 2020 and was last updated on 11 April 2020 (registration number INPLASY202040057).

INTRODUCTION

Review question / Objective: **To comprehensively assess the efficacy and safety of dietary supplements for prediabetes.**

Rationale: **There has been some limited evidence on the efficacy of dietary**

supplements. However, no comprehensive systematic reviews remain so far and we aim to collate the evidence on dietary supplements for prediabetes to evaluate its efficacy and safety. And we are going to perform and report this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis(PRISMA).

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METHODS

Search strategy: Two reviewers will independently search the following electronic databases to identify eligible trials before June 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, the Cochrane Central Register of Controlled Trials(CENTRAL), Allied and Complementary Medicine Database(AMED), Chinese Biomedical Literature database, Wanfang database, Chinese Scientific Journal database (VIP), Chinese National Knowledge Infrastructure database(CNKI), and the ClinicalTrials.gov website. The retrieval strategy will be developed and improved by all the researchers according to the combination of subject words and free words, including the following terms: dietary supplement*, food supplement*, herbal supplement*, nutraceutical*, nutriceutical*, neutraceutical*, supplement*, vitamin*, herb*, protein, mineral, enzymes, amino acid, prediabetes, prediabetic, pre-diabetic, pre-diabetes, impaired fasting glucose, impaired glucose tolerance, impaired glucose regulation, IFG, IGR, IGT, diabetes prevention, hyperglycemia, randomized controlled trial, RCT, controlled clinical trial, randomized, trial, random, placebo, groups.

Participant or population: We intend to incorporate participants with prediabetes diagnosed as IGT, IFG, raised HbA1c or Status of IGT and IFG coexistence irrespective of age, gender and ethnicity.

Intervention: Treatment with dietary supplements.

Comparator: Placebo, conventional treatment(such as LM, medicine or acupuncture) or blank control.

Study designs to be included: Only randomized controlled trials (RCTs) of dietary supplements for prediabetes regardless of language and publication status will be included.

Eligibility criteria: The eligibility criteria includes PICOS listed in this protocol.

Information sources: Two reviewers will independently search the following electronic databases to identify eligible trials before June 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, the Cochrane Central Register of

Controlled Trials (CENTRAL), Allied and Complementary Medicine Database(AMED), Chinese Biomedical Literature database, Wanfang database, Chinese Scientific Journal database (VIP), Chinese National Knowledge Infrastructure database(CNKI), and the ClinicalTrials.gov website. Bibliography lists of involved trials, relevant reviews and meta-analysis will be searched manually to identify additional eligible studies.

Main outcome(s): The primary outcomes reported in this study include the incidence of diabetes and the rate of normoglycaemia.

Additional outcome(s): Secondary outcomes are fasting blood glucose(FBG), postprandial blood glucose(PBG), glycosylated hemoglobin A1c(HbA1c), fasting insulin(FINS), insulin sensitivity, adverse events, plasma lipids, inflammatory markers and body mass index(BMI).

Data management: We plan to import all the retrieved articles to the document management software EndnoteX9 (Thomson Research Soft, Stanford, Connecticut) and initially screen titles and abstracts of records, selecting appropriate RCTs. Then download full texts of the remaining literature for further screening to retain trials meeting the inclusion criteria. Any discrepancy will be resolved by discussing or seeking advice from a third party. A data extraction template predesigned by all the review authors will be used by two independent researchers simultaneously for data extraction. We will extract the following items:1).Publication information: title, author, publication year, source; 2).Study characteristics: design, sample size, duration of follow-up, randomization methodology, allocation concealment, blinding; 3).Participants: gender, age, number of each group, types of prediabetes and its definition criteria; 4).Interventions: types of interventions, types of controls, dosage form, dose, duration of intervention, route of administration; 5).Outcomes: outcome indicators, adverse events, number of withdrawals and participants completing trials, the reason for withdrawing.

Quality assessment / Risk of bias analysis: The quality of the methodology will be assessed independently by two researchers based on the Cochrane collaboration's risk of bias tool in seven dimensions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases.

Strategy of data synthesis: We propose to conduct this meta-analysis using the statistical software, RevMan version 5.3.5 (The Cochrane Collaboration, Oxford, England). To evaluate the treatment efficacy, the dichotomous variables will be merged to risk ratio (RR). For continuous variables, we plan to estimate the overall results with mean difference(MD) or standard mean difference(SMD). $P<0.1$ reveals that heterogeneity exists in the included studies. If I275%, indicating substantial heterogeneity, we will give up pooling the data and perform narrative analysis. For the same outcome measure, where there remain two or more studies with the same type of intervention and clinical heterogeneity is not considered by the reviewers, we intend to conduct a quantitative synthesis. Considering studies with different types of interventions are able to meet this condition, we will analyze by groups which are divided according to outcomes and interventions. Besides, the qualitative description will also be conducted to summarize and explain information and discoveries of the study where no more than one trial with the same intervention exists and meta-analysis is not applicable.

Subgroup analysis: This meta-analysis will be performed based on subgroups of different types of dietary supplements. The analyses of other influence factors (types of prediabetes, duration of treatment, and dose) will be determined on a case-by-case basis.

Sensibility analysis: We are going to omit studies with a high risk of bias or some special studies and repeat the meta-analysis afterward.

Language: No language limits..

Country(ies) involved: China.

Keywords: dietary supplements, prediabetes, diabetes prevention, systematic review.

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

Contributions of each author:
Author 1 - Original draft.
Author 2 - Data curation.
Author 3 - Data curation.
Author 4 - Review & editing.
Author 5 - Review & editing.
Author 6 - Review & editing.
Author 7 - Supervision.