INPLASY PROTOCOL

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Chinese Herbal Medicine in the Treatment of Prediabetes: A Systematic Review and Meta-Analysis

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Review question / Objective: **The effectiveness of Chinese herbal medicine for the treatment of prediabetes.**
Condition being studied: **There is a period in the process of gradually developing from a healthy group with normal blood sugar to a diabetes group-pre-diabetes, which includes two cases of impaired fasting blood glucose and impaired glucose tolerance. Almost all diabetics have to go through this period, but it is precisely ignored this stage, missed the period of diabetes reversal, and eventually developed into diabetes. Prediabetes is characterized by mild impaired fasting glucose (IFG) and / or impaired glucose tolerance (IGT).According to the World Health Organization (WHO), high risk for developing diabetes relates to two distinct states, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1–6.9 mmol/L (in the absence of impaired glucose tolerance – IGT) and IGT defined as postload plasma glucose of 7.8–11.0 mmol/L based on 2-h oral glucose tolerance test (OGTT) or a combination of both. The risk of diabetes is greatly increased in subjects with prediabetes. Furthermore, the recent research suggesting that 93% of subjects with prediabetes may develop diabetes within 20 years.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 May 2020 and was last updated on 04 May 2020 (registration number INPLASY202050015).

INTRODUCTION

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METHODS

Search strategy: The databases were searched using the following strategy (take Pubmed as example).

Participant or population: We included participants of any age or sex with prediabetes cleally diagnosed by internationally recognized criteria.

Intervention: The Chinese herbal medicine (CHM) interventions included single herbs (including extracts from a single herb), a Chinese proprietary medicine, or a compound of several herbs irrespective of preparation (for example decoction, oral liquid, tablet, capsule,pill, powder, or injection). We only include the oral delivery (intramuscular or intravenous was excluded). The dosage, and regimen of herbs were not restricted. We included trials if the treatment was given for a minimum of four weeks.

Comparator: The control interventions were: 1. placebo; 2. no treatment; 3.pharmacological compounds (biguanides such as metformin, sulphonylureas);4.non-pharmacological interventions (for example diet, exercise). Co-interventions were allowed as long as all arms of the randomised trial received the same co-intervention. Only interventions performed for a minimum duration of four weeks were included.

Study designs to be included: Randomised controlled trials (RCTs) with a correct description of randomisation procedure were included irrespective of blinding or language.

Eligibility criteria: All included trials met the following selection criteria: (1) the study was a randomized controlled trial (RCT); (2) the study examined prediabetic participants who received Chinese herbal medicine as intervention; (3) the study included participants irrespective of gender, age, or ethnicity, and prediabetes was diagnosed by clearly defined or internationally recognized criteria.

Information sources: The following seven electronic databases were searched to identify eligible trials published from inception to May 2, 2020. The English electronic databases included Pubmed, Embase, and the Cochrane Central Register of Controlled Trials. The Chinese electronic databases were CNKI, CBM Wangfan and VIP. The databases were searched using the following strategy (take Pubmed as example): #1 "Prediabetic State"[Mesh] #2 ((((((((((((((Prediabetic State*[Title/Abstract]) OR (State, Prediabetic[Title/Abstract])) OR (States, Prediabete*[Title/Abstract])) OR (Prediabete*[Title/Abstract])) OR (pre-diabete*[Title/Abstract])) OR (impaired glucose regulation[Title/Abstract])) OR (impaired glucose tolerance[Title/Abstract])) OR (impaired fasting glucose[Title/Abstract])) OR (reduced glucose regulation[Title/Abstract])) OR (reduced glucose tolerance[Title/Abstract])) OR (reduced fasting glucose[Title/Abstract])) OR (insulin resistance[Title/Abstract])) OR (impaired insulin[Title/Abstract])) OR (reduced insulin[Title/Abstract])) OR (Diabete* prevention[Title/Abstract]) #3 #1 OR #2 #4 ((("Medicine, Chinese Traditional"[Mesh]) OR "Drugs, Chinese Herbal"[Mesh]) OR "Medicine, East Asian Traditional"[Mesh]) OR "Materia Medica"[Mesh] #5((((((((((((((((((((((((Traditional Chinese Medicine[Title/Abstract]) OR

(Traditional Medicine, Chinese[Title/Abstract])) OR (Chinese Traditional Medicine[Title/Abstract])) OR (Chinese Medicine, Traditional[Title/Abstract])) OR (Zhong Yi[Title/Abstract])) OR (Chinese Drug*, Plant[Title/Abstract])) OR (Chinese Herbal Drug*[Title/Abstract])) OR (Herbal Drug*, Chinese[Title/Abstract])) OR (Plant Extract*, Chinese[Title/Abstract])) OR (Chinese Plant Extract*[Title/Abstract])) OR (Extract*, Chinese Plant[Title/Abstract])) OR (Oriental Medicine, Traditional[Title/Abstract])) OR (Medicine, Traditional Oriental[Title/Abstract])) OR (Traditional Oriental Medicine[Title/Abstract])) OR (Traditional Far Eastern Medicine[Title/Abstract])) OR (Oriental Traditional Medicine[Title/Abstract])) OR (Oriental Medicine[Title/Abstract])) OR (Far East Medicine[Title/Abstract])) OR (Plants, Medicinal[Title/Abstract])) OR (Medicinal Plant*[Title/Abstract])) OR (Pharmaceutical Plant*[Title/Abstract])) OR (Medicinal Herb*[Title/Abstract])) OR (Herb*, Medicinal[Title/Abstract])) OR (Medica, Materia[Title/Abstract])) OR (Materia Medica[Title/Abstract]) #6 #4 OR #5 #7 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])) #8 #3 AND #6 AND #7.

Main outcome(s): 1) Incidence of type 2 diabetes mellitus: as diagnosed with at the time of the diagnosis prevailing diagnostic criteria (for example, WHO 1985, ADA 1997; ADA 1999); (2) glycaemic control: glycosylated haemoglobin levels A1c (HbA1c), fasting glucose and 2-hour postprandial blood glucose levels. (3) Incidence of adverse outcomes; (4) Incidence of the normalization of blood glucose (the number of participants who returned to a normal blood glucose range by the end of the trial).

Additional outcome(s): (1) insulin sensitivity, fasting and post-load insulin level; (2) reduction in body mass index (BMI).

Data management: Two review authors independently will extract data concerning details of study population, intervention, and outcomes using a predesigned data extraction form. The following data would be extracted: general trial characteristics (title, authors, year); baseline patient and disease data (sample size, age, gender); interventions (component and dose TCPM, details of control interventions); and outcomes (follow-up length, outcome measures, adverse events). We plan to resolve differences in data extraction by consensus or a third party. One author enter data into the Cochrane software Review Manager 5 (RevMan 5) and another check the data to reduce the possibility of data entry errors.

Quality assessment / Risk of bias analysis: Two authors independently will assess the " risk of bias" according to guidance in the Cochrane Handbook for Systematic Reviews of Interventions. This involved the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. We would complete a ' Risk of bias ' table according to Cochrane guidelines. We would make judgement on each of these criteria relating to the risk of bias: low, high or unclear (indicating unclear or unknown risk of bias). Discrepancies in this interpretation would be resolved by consensus or after discussion with a third party.

Strategy of data synthesis: We plan to analyze data by using Review Manager 5.3 software Publication bias was examined using funnel plots. For outcomes, data regarding incidence are dichotomous, and others are continuous. Risk ratios (RRs) would be calculated using the Mantel-Haenszel method for dichotomous outcomes, and weighted mean differences (MDs) would be calculated using the inverse variance method for continuous variables. I2 statistics would be used to assess heterogeneity. A fixed-effects (FE) model would be used if there is no

significant heterogeneity in the data (I250%). Sensitivity analysis would beperformed to assess the stability of conclusions. Where heterogeneity was detected, accepted methods would be used to explore the statistical heterogeneity using clinical parameters such as treatment duration, sample size, publication year, diagnostic criteria, publication language, and TCM syndrome. Publication bias would be assessed using funnel plots.

Subgroup analysis: We plan to perform subgroup analyses if one of the primary outcome parameters demonstrated statistically significant differences between treatment groups. The following subgroup analyses are planned: age (subdivided into groups, based on data);gender; body mass index (BMI) (subdivided into groups, based on data); duration of intervention (subdivided into groups, based on data).

Sensibility analysis: If we had identified a suficient number of RCTs, we plan to undertake sensitivity analyses to explore the influence of risk of bias on effect estimates. The following aspects of quality will be considered for this sensitivity analysis: inadequate blinding, non-comparable groups (because they had different baseline characteristics), and no intention-to-treat analysis.

Language: No language limits.

Country(ies) involved: China.

Keywords: Prediabetes; Chinese herbal medicine; Impaired glucose regulation;impaired fasting glucose; impaired glucose tolerance.

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