

# INPLASY PROTOCOL

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None declared.

## Efficacy and Safety of the Integration of Traditional Chinese Medicine and Western Medicine in the Treatment of Diabetes-Associated Cognitive Decline: A Systematic Review and Meta-Analysis

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**Review question / Objective:** In the present study, we systematically assessed the efficacy and safety of the integration of Traditional Chinese Medicine and Western Medicine in the treatment of Diabetes-Associated Cognitive Decline (DACD), in order to provide potential clinical treatment evidence of Diabetes-Associated Cognitive Decline.

**Types of Participants.** There is no restriction on age, gender, or race; The included patients had been diagnosed with DACD through a clear definition or internationally recognized diagnostic criteria.

**Types of Interventions.** The intervention measure was TCM plus WM, and the TCM treatment was the only positive intervention in the treatment group compared with the control group. There were no restrictions on the dosage and duration of medication.

**Types of Comparison.** Western Medicine (WM) treatment, such as hypoglycemic agents, insulin, nimodipine, donepezil and so on, can reduce blood glucose level and improve cognitive function. The specifications and dosage of WM used in the control groups were the same as used in the treatment groups.

**Types of Outcomes.** The primary outcome included the total effective rate. The secondary outcomes consisted of FPG, HbA1c, MoCA score, MMSE score, TNF- $\alpha$ , TCM syndrome score, adverse reaction. All included literatures reported at least two results of the above.

**Types of Study Design.** All of the RCTs reporting the application of TCM plus WM for the treatment of DACD were included. No limitations on publication status or language were set.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 February 2023 and was last updated on 16 February 2023 (registration number INPLASY202320072).

### INTRODUCTION

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efficacy and safety of the integration of Traditional Chinese Medicine and Western Medicine in the treatment of Diabetes-

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**Condition being studied:** Diabetes-associated cognitive decline (DACD) is a typical neurological complication of T2DM and mainly manifests as cognitive deficits, involving attention and executive functions. Currently, the treatment for DACD mainly focuses on comprehensively controlling multiple risk factors, including controlling blood glucose, improving blood supply of brain and protecting cognitive function. However, the complexity of multidrug regimens may induce the chance of nonadherence among patients, while long-term use of hypoglycemic agent may increase the incidence of side effects, such as gastrointestinal discomfort, weight gain, and hepatic dysfunction. Hence, clinicians have begun to consider the potential role of Traditional Chinese Medicine (TCM) as an adjuvant or alternative treatment in the

prevention and treatment of DACD due to the unsatisfactory curative effect for using western medicine alone. We conducted a comprehensive search of domestic and foreign literature to objectively evaluate the clinical efficacy and safety of integrated TCM and WM on DACD patients, aiming to shed light on clinical treatment.

## METHODS

**Search strategy:** A comprehensive search was conducted for studies of biological therapeutic interventions for DACD using the following databases: China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, EMBASE, Web of science, and Cochrane Library. The retrieval period was from the inception of databases to December 2022. There was no restriction to language, systemic conditions of the participants, and publication year. The search strategy used a combination of MeSH terms and keywords and was based on the following themes: “diabetic cognitive impairment”, “traditional Chinese medicine and western medicine”, and the names of the various types of intervention measures and disease associated with them, including proprietary Chinese medicine, Chinese medicine herbs, herbal medicine, diabetic cognitive dysfunction, and diabetic encephalopathy etc. In addition, journal literature from the library of the Liaoning University of Traditional Chinese Medicine was also manually searched to supplement the search and find possible omissions.

**Participant or population:** The included patients had been diagnosed with DACD through a clear definition or internationally recognized diagnostic criteria.

**Intervention:** Integration of Traditional Chinese Medicine and Western Medicine.

**Comparator:** Western medicine alone.

**Study designs to be included:** All of the RCTs reporting the application of TCM plus

WM for the treatment of DACD were included.

**Eligibility criteria:** The PICOS (participant, intervention, comparison, results, and study design) framework was used to establish the inclusion criteria. 2.2.1. Types of Participants. There is no restriction on age, gender, or race; The included patients had been diagnosed with DACD through a clear definition or internationally recognized diagnostic criteria. 2.2.2. Types of Interventions. The intervention measure was TCM plus WM, and the TCM treatment was the only positive intervention in the treatment group compared with the control group. There were no restrictions on the dosage and duration of medication. 2.2.3. Types of Comparison. Western Medicine (WM) treatment, such as hypoglycemic agents, insulin, nimodipine, donepezil and so on, can reduce blood glucose level and improve cognitive function. The specifications and dosage of WM used in the control groups were the same as used in the treatment groups. 2.2.4. Types of Outcomes. The primary outcome included the total effective rate. The secondary outcomes consisted of FPG, HbA1c, MoCA score, MMSE score, TNF- $\alpha$ , TCM syndrome score, adverse reaction. All included literatures reported at least two results of the above. 2.2.5 Types of Study Design. All of the RCTs reporting the application of TCM plus WM for the treatment of DACD were included. No limitations on publication status or language were set.

**Information sources:** A comprehensive search was conducted for studies of biological therapeutic interventions for DACD using the following databases: China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, EMBASE, Web of science, and Cochrane Library. The retrieval period was from the inception of databases to December 2022.

**Main outcome(s):** The primary outcome included the total effective rate. The secondary outcomes consisted of FPG,

HbA1c, MoCA score, MMSE score, TNF- $\alpha$ , TCM syndrome score, adverse reaction.

**Additional outcome(s):** Consisted of FPG, HbA1c, MoCA score, MMSE score, TNF- $\alpha$ , TCM syndrome score, adverse reaction.

**Data management:** The meta-analysis was performed using Review Manager 5.4 and Stata 17.0 software. We used the odds ratio (OR) to assess the binary variables. For continuous variables, the mean difference (MD, when results were in similar units of measure) or standardized mean difference (SMD, when results were in different units of measure) were employed to represent the difference between the groups. The results were represented with a 95% confidence interval (CI). The heterogeneity was evaluated using the chi-square test; if  $P > 0.1$  or  $I^2 < 50\%$ , it was assumed that the heterogeneity was not evident and the fixed-effects model was selected; otherwise, the random effects model was validated. In addition, a sensitivity analysis was performed for each outcome to assess stability. We also completed the Egger test to detect potential publication bias. GRADE pro software was utilized to assess the strength of the evidence to enhance the results' validity.

**Quality assessment / Risk of bias analysis:** Of the studies was performed independently by two reviewers. For this, a spreadsheet in Excel was developed specifically for this study, containing variables such as authors, date of publication, country, study design, sample size, average age, gender, intervention measures, follow-up time, and outcome measures. All data were cross-checked and transferred to Rev Man software (V.5.4). The risk of bias in all included studies was assessed by the Cochrane Handbook for Systematic Reviews which divided them into a low, high, or unclear risk of bias based on the following seven points: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective reporting; and (7) other potential

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risks of bias. Any divergence was resolved by the third reviewer investigator.

**Strategy of data synthesis:** For continuous variables, the mean difference (MD, when results were in similar units of measure) or standardized mean difference (SMD, when results were in different units of measure) were employed to represent the difference between the groups. The results were represented with a 95% confidence interval (CI). The heterogeneity was evaluated using the chi-square test; if  $P > 0.1$  or  $I^2 < 50\%$ , it was assumed that the heterogeneity was not evident and the fixed-effects model was selected; otherwise, the random effects model was validated. We also completed the Egger test to detect potential publication bias. GRADE pro software was utilized to assess the strength of the evidence to enhance the results' validity.

**Subgroup analysis:** In this study, subgroup analysis was conducted to evaluate the effect of treatment course and other factors on efficacy and safety.

**Sensitivity analysis:** In addition, a sensitivity analysis was performed by the metaninf function of STATA 17.0 software for each outcome to assess stability.

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

**Keywords:** Integration of Traditional Chinese Medicine and Western Medicine; Diabetes-Associated Cognitive Decline.

**Contributions of each author:**

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Author 3 - Guiyan Sun.

Author 4 - Yufeng Yang.

Author 5 - Yan Shi.