

INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Acupuncture for Type 2 Diabetes Mellitus with Nonalcoholic Fatty Liver Disease: A protocol for systematic review and meta-analysis

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Review question / Objective: 1. This review will provide a comprehensive assessment of the effectiveness and safety of acupuncture in the treatment of T2DM with NAFLD. 2. Most randomized controlled trials of acupuncture for the treatment of T2DM with NAFLD have inadequate sample sizes, and this study will provide more reliable clinical evidence for the treatment of this disease with acupuncture.

Information sources: We will search the Cochrane Central Register of controlled trials, PubMed, MEDLINE, EMBASE, Web of Science. Five Chinese databases, including China National Knowledge Infrastructure (CNKI), WanFang database, VIP, Chinese Biomedical Literature Database (CBM) and the Chinese clinical trial registry.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 April 2021 and was last updated on 29 April 2021 (registration number INPLASY202140140).

INTRODUCTION

Review question / Objective: 1. This review will provide a comprehensive assessment of the effectiveness and safety of acupuncture in the treatment of T2DM with NAFLD. 2. Most randomized controlled trials of acupuncture for the treatment of

T2DM with NAFLD have inadequate sample sizes, and this study will provide more reliable clinical evidence for the treatment of this disease with acupuncture.

Condition being studied: Diabetes Mellitus (DM) is one of the most common chronic metabolic diseases and the increasing

global prevalence and mortality of DM makes it an important topic of medical research. Type 2 diabetes mellitus (T2DM) is far more usual than type 1 diabetes or gestational diabetes, approximately 90% of DM. Nonalcoholic fatty liver disease (NAFLD) has been indicated to be closely linked to T2DM as one of the most common liver disorders worldwide. Growing evidence suggests that the prevalence of NAFLD in T2DM has substantially increased. The combination of T2DM and NAFLD often causes adverse consequences, which not only increases the risk of diabetic complications, but also is a vital factor for liver cirrhosis and liver cancer. Studies have shown that the relationship between T2DM and NAFLD is mutual and bidirectional. NAFLD can accelerate the development of T2DM, but the improvement of NAFLD can also reduce the risk of T2DM. Therefore, the prevention and treatment of T2DM with NAFLD have become the key issues to be solved in modern medicine.

METHODS

Participant or population: Adults only, patients with a confirmed diagnosis of T2DM with NAFLD, race, gender, history and symptoms not specified.

Intervention: The main intervention methods include manual acupuncture, electroacupuncture, moxibustion, ear acupuncture, scalp acupuncture, regardless of acupuncture techniques and stimulation methods.

Comparator: Primary controls included: drugs, placebo, sham acupuncture, or no treatment.

Study designs to be included: We will only include RCTs that are more likely than other study designs to provide impartial details. RCTs assessing the efficacy of acupuncture in the treatment of T2DM with NAFLD will include, whether blinded or not. The following types of articles will be excluded : case reports, observational studies, retrospective studies, animal experiments, and review articles. No

restrictions on language and publication time.

Eligibility criteria: Type of studies: a randomized controlled trial (RCT) on the use of acupuncture for safety and efficacy in patients with T2DM with NAFLD only. Type of intervention: studies included any type of acupuncture method regardless of duration, frequency, dose, and other relevant parameters; Type of control: therapies other than acupuncture. Type of participants: adults only, patients aged ≥ 18 years with a confirmed diagnosis of T2DM with NAFLD, race, gender, history and symptoms not specified; Type of outcome: Primary outcomes: Imaging indicators, biomarkers of hepatic steatosis, serological indicators of hepatic fibrosis, improvement of serum NAFLD liver fat score and clinical efficacy. The secondary outcomes: Body mass index (BMI) ; Blood glucose indexes; Blood lipid indexes; Insulin level; Safety indicators.

Information sources: We will search the Cochrane Central Register of controlled trials, PubMed, MEDLINE, EMBASE, Web of Science. Five Chinese databases, including China National Knowledge Infrastructure (CNKI), WanFang database, VIP, Chinese Biomedical Literature Database (CBM) and the Chinese clinical trial registry.

Main outcome(s): Imaging indicators, biomarkers of hepatic steatosis, serological indicators of hepatic fibrosis, improvement of serum NAFLD liver fat score and clinical efficacy.

Additional outcome(s): ① Body mass index (BMI) ; ② Blood glucose indexes: fasting blood glucose (FPB), 2 hours blood glucose after breakfast, glycosylated hemoglobin (HbA1c); ③ Blood lipid indexes: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C); ④ Insulin level: fasting and 2 hours postprandial blood glucose; ⑤ Safety indicators: alanine aminotransferase (ALT), creatinine (Cr), aspartate aminotransferase

(AST), urea nitrogen (Urea), hemoglobin (Hb), white blood cell count (WBC), and platelet count (PLT).

Quality assessment / Risk of bias analysis:

Using the Cochrane Review Handbook 5.2 recommended quality evaluation criteria - bias risk assessment tool, It mainly involves seven aspects: 1. random assignment method; 2. allocation protocol concealment; 3. blinding of study subjects and treatment protocol implementers (assessed for each study outcome); 4. blinding of outcome measures (assessed for each study outcome); 5. completeness of outcome data (assessed for each study outcome); 6. selective reporting of study results; and 7. other sources of bias. For each included study, the above seven aspects were judged, including three criteria: "low risk", "high risk" and "unclear".

Strategy of data synthesis: Meta-analysis will be performed using the software RevMan 5.3 (where the publication bias section will be performed using stata software). Heterogeneity tests were performed among studies, using I^2 as an evaluation index, and $I^2 \leq 50\%$ and $P > 0.1$, heterogeneity was considered small and a fixed-effect model should be selected. $I^2 = 50\%$, $P < 0.1$, the heterogeneity is large. The random effect model should be selected, and sensitivity analysis or subgroup analysis should be carried out to explore the source of heterogeneity. Wighted mean difference (WMD) was used for continuous variables; relative risk (RR) was used for categorical variables, and each effect size was expressed with 95% confidence interval (CI), and differences were considered statistically significant at $P \leq 0.05$.

Subgroup analysis: If data are sufficient, we will investigate heterogeneity by grouping analyses according to age, gender, acupuncture intervention (acupuncture, electroacupuncture), different control group types (placebo, sham acupuncture, no treatment or medication), duration of treatment, and duration of symptoms at

baseline, and duration of treatment sessions.

Sensitivity analysis: Sensitivity analysis is an important method used in meta analysis to assess the robustness and reliability of the combined results. The specific methods are as follows: 1. Changing the analysis model: when heterogeneity is high ($I^2 > 50\%$), a random-effects model is recommended, and conversely, a fixed-effects model is used. 2. Excluding literature one by one: exclude each included study one by one before combining effect sizes, change the inclusion exclusion criteria or exclude certain types of literature before combining effect sizes.

Country(ies) involved: China.

Keywords: Acupuncture; T2DM with NAFLD; Meta-analysis.

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