INPLASY PROTOCOL

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Support: **Yes**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

Vitamin D supplementation for nonalcoholic fatty liver disease in type 2 diabetes mellitus: a protocol for a systematic review and meta-analysis

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ABSTRACT

Objective: **Is the vitamin D supplementation certainly beneficial for diabetic patients with NAFLD?**

Methods: **We will retrieve each database from the built-in until July 2020.The English literature mainly searches Cochrane Library, Pubmed, EMBASE, and Web of Science. While the Chinese literature comes from CNKI, CBM, VIP and Wangfang database. We adopt the combination of heading terms and free words as search strategy which decided by all the reviewers. Search terms: vitamin D supplementation, vitamin D deficiency, 25-hydroxy vitamin D [25(OH)D], ergocalciferol(s), nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, fatty liver, nonalcoholic fatty liver, liver fibrosis, liver cirrhosis, type 2 diabetes mellitus, type 2 diabetes, diabetes, diabetes mellitus. At the same time, we will retrieve other resources to complete the deficiencies of the electronic databases, mainly searching for the clinical trial registries and grey literature about vitamin D for T2DM combined with NAFLD on the corresponding website.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 March 2020 and was last updated on 29 March 2020 (registration number INPLASY202030012.

INTRODUCTION

Objectives / Review question: **Is the vitamin D supplementation certainly beneficial for diabetic patients with NAFLD?**

Condition being studied: **Nonalcoholic fatty liver disease (NAFLD) is a spectrum of fat-associated liver conditions, may progress to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. The insulin resistance (IR), oxidative stress, and**

inflammation are major contributions the development of NAFLD. It has become the major cause of chronic liver disease worldwide. NAFLD is strongly associated with type 2 diabetes mellitus (T2DM), The disease is extremely concealed and has a great impact on the treat efficiency of diabetic patients.

METHODS

Participant or population: Patients with clinically diagnosed T2DM combined with NAFLD.

Intervention: Vitamin D supplementation for diabetic patients combined with NAFLD.

Comparator: No current/recent vitamin D supplementation.

Study designs to be included: Clinical randomized controlled trials(RCTs).

Eligibility criteria: The study only selects clinical randomized controlled trials of vitamin D supplementation for T2DM combined with NAFLD published in both Chinese and English. However, animal experiments, reviews, case reports and non-randomized controlled trials are excluded.

Information sources: We will retrieve each database from the built-in until July 2020.The English literature mainly searches Cochrane Library, Pubmed, EMBASE, and Web of Science. While the Chinese literature comes from CNKI, CBM, VIP and Wangfang database. We adopt the combination of heading terms and free words as search strategy which decided by all the reviewers. Search terms: vitamin D supplementation, vitamin D deficiency, 25-hydroxy vitamin D [25(OH)D], ergocalciferol(s), nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, fatty liver, nonalcoholic fatty liver, liver fibrosis, liver cirrhosis, type 2 diabetes mellitus, type 2 diabetes, diabetes, diabetes mellitus. At the same time, we will retrieve other resources to complete the deficiencies of the electronic databases, mainly searching for the clinical trial registries and grey literature about vitamin D for T2DM combined with NAFLD on the corresponding website.

Main outcome(s): The primary outcomes include the improvement in clinical efficacy and imaging markers, biomarkers of hepatic steatosis, serological indexes of hepatic fibrosis, serum NAFLD liver fat score.

Additional outcome(s): Secondary outcomes are mainly composed of fasting blood glucose, 2 hours postprandial blood glucose, HbA1c, serum insulin levels, BMI, body weight, serological markers (LDL-cholesterol, triglyceride, HDL-cholesterol, AST, ALT, GGT, albumin, etc.), HOMA-IR and adverse events.

Quality assessment / Risk of bias analysis: The quality assessment of RCTs adopts the risk of bias (ROB) assessment tool provided by the Cochrane Handbook. The following seven items, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias, are evaluated by three grades of “low bias”, “high bias” and “unclear bias”. The discrepancies will get a consistent conclusion by discussing between both reviewers or seeking the third-party consultation.

Strategy of data synthesis: Review Manager software version 5.3 provided by the Cochrane Collaboration will be performed for data synthesis and analysis. The dichotomous data is represented by RR, continuous data is expressed by MD or SMD. If there is no heterogeneity (I20.1), the data is synthesized using a fixed effect model. Otherwise (I2≥50%, $P<0.1$), a random effect model is used to analyze. Then subgroup analysis will be conducted basing on the different causes of heterogeneity. If a meta- analysis cannot be performed, it will be replaced by a general descriptive analysis.

Subgroup analysis: If the results of the study are heterogeneous, we will conduct a subgroup analysis for different reasons. Heterogeneity is manifested in the following several aspects, such as race, age, gender, different intervention forms, pharmaceutical dosage, treatment course.

Sensibility analysis: Sensitivity analysis is mainly used to evaluate the robustness of the primary outcome measures. The method is that removing the low-level quality study one by one and then merge the data to assess the impact of sample size, study quality, statistical method, and missing data on results of meta-analysis.

Language: English.

Countries involved: China.

Keywords: nonalcoholic fatty liver disease; type 2 diabetes mellitus; vitamin D supplementation; meta-analysis; protocol.