INPLASY PROTOCOL

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Support: Yes.

Review Stage at time of this submission: Preliminary searches.

Conflicts of interest: None.

The effect of vitamin D supplementation on the progression of fibrosis in patients with chronic liver disease: a protocol for a systematic review and meta-analysis

Gao, Y[1]; Chen T;[2].

Review question / Objective: Does vitamin D supplementation delay the progression of fibrosis in patients with chronic liver disease?

Condition being studied: Hepatic fibrosis (HF) is a disease in which extracellular matrix (ECM) is deposited in the liver in large amounts. HF is the common pathological basis of all chronic liver diseases. Many data indicate that serum vitamin D levels in patients with liver fibrosis are significantly lower than those without liver fibrosis, and lower level of serum 1,25 (OH) 2D3 is an independent risk factor for patients with liver fibrosis combined with other chronic diseases, such as hypertension, type 2 diabetes, etc. In vitro experiments show that 1,25 (OH) 2D3 can inhibit the proliferation and collagen secretion of HSC-T6 and HSC-T6 activated by TGF-β1, and lipogenesis and inflammation gene expressions were diminished with vitamin D supplementation. Therefore, serum 1,25 (OH) 2D3 level may be negatively correlated with the progression of liver fibrosis.

INTRODUCTION

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METHODS

Participant or population: Patients with clinically diagnosed chronic liver disease combined with hepatic fibrosis.

Intervention: Vitamin D supplementation.

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 chronic liver disease combined with hepatic fibrosis 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 September 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: erum vitamin D level, 25(OH)D, VD, 1,25（OH）2D3, vitamin D deficiency, vitamin D supplementation, nonalcoholic fatty liver disease, alcoholic fatty liver, steatohepatitis, liver fibrosis, liver cirrhosis, chronic hepatitis B ,chronic hepatitis C, biliary atresia, primary biliary cirrhosis, schistosoma hepatic fibrosis, autoimmune

hepatitis. 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 with chronic liver disease on the corresponding website.

Main outcome(s): The primary outcomes include the improvement in clinical efficacy, serum vitamin D level, hepatic function (ALT,AST), and hepatic indicators associated with fibrosis(HA, PC-III, C-IV, LN), blood test (PLT), Calculate the APRI score and FIB-4 index based on the relevant indicators above.

Additional outcome(s): Secondary outcomes are mainly other indicators of liver function (GGT, TBIL, LDH, ALP, albumin, etc.), coagulation test (APTT, PT, etc.), blood calcium, blood phosphorus, portal vein inner diameter width 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.

Country(ies) involved: China.

Keywords: chronic liver disease; vitamin D supplementation; hepatic fibrosis; meta-analysis; protocol.