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Effects of sodium-glucose co-transporter 2 inhibitors on liver fibrosis in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: An updated meta-analysis of Randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - This work is supported by the National Natural Science Foundation of China [82073859, 81872637 and 81673658].

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 June 2023 and was last updated on 19 June 2023.

INTRODUCTION

Review question / Objective Sodium-glucose co-transporter 2 inhibitors (SGLT2i) has been verified to improve Non-alcoholic fatty liver disease (NAFLD) in previous clinical practice. Fibrosis is characterized by necrosis and function damage in liver cells, which rise up the risk for the development of NASH. We mainly aim to investigate the effects of SGLT2i on liver fibrosis in NAFLD patients with type 2 diabetes mellitus (T2DM) to evaluate the potential value of SGLT2i in the treatment of NAFLD and NASH. We compare the effect of different types of SGLT2i with placebo or other drugs on the remission of liver fibrosis by comparing the following parameters such as Liver Stiffness Measurement (LSM), Controlled Attenuation Parameter (CAP), Serum ferritin, Serum type 4 collagen 7s, and FIB-4 index.

Rationale This meta-analysis evaluate the effects of SGLT2i on liver fibrosis improvement to determine if SGLT2i medication had a greater impact on preventing advanced NAFLD and the progression to NASH. This is novel information and a systematic study not seen in earlier meta-analyses.

Condition being studied Nonalcoholic fatty liver disease (NAFLD) is currently the most prevalence chronic liver disease in the world, with a prevalence rate of approximately 25%, particularly in highly industrialized countries. It can be histologically categorized into two principle phenotypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), which are differentiated by hepatic steatosis and inflammation with hepatocyte injury (hepatocyte ballooning). NAFLD/NASH is intricately associated with the cause of type 2 diabetes (T2DM). Consequently, T2DM and NAFLD co-occur often. The comorbid condition makes clinical treatment more difficult and has a significant negative impact on patients' quality of life. Consequently, prompt initiation of an effective treatment plan is crucial. However, none of the legal drugs for treating

NAFLD are effective. The sodium-glucose co-transporter 2 (SGLT2) inhibitor (SGLT2i) is a new class of glucose-lowering agents that limit renal glomerular glucose reabsorption. In recent years, there has been an increasing emphasis on SGLT2i for the treatment of NAFLD-related liver damage. Therefore, we conducted this updated meta-analysis to fully analyze the effects of SGLT2i on liver fibrosis improvement and to consolidate the current evidence of the benefits of SGLT2i treatment, which may constitute an attractive strategy for the treatment of NAFLD with T2DM.

METHODS

Search strategy We systematically searched the following four databases: Embase, PubMed, Web of Science and Cochrane Library to get the qualified articles, from inception to 1 October 2022 and with no language restriction.

Participant or population Population were NAFLD patients with T2DM aged 18-75 years and the glycosylated hemoglobin (HbA1c) was of 6-12%. The diagnostic criteria for NAFLD are as follows: fatty liver based on imaging examination (ultrasonography or computed tomography), alcohol intake not exceeding 140 g/week in women and 210 g/week in men, other causes of liver disease were excluded (viral hepatitis, autoimmune hepatitis, hemochromatosis and Wilson's disease, etc) T2DM.

Intervention Therapeutic intervention includes various types of SGLT2i and give sufficient information about baseline and post-treatment.

Comparator Comparator intervention includes placebo or other standard treatment (not SGLT2i).

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

Eligibility criteria The inclusion criteria for this meta-analysis are as follows: (i) must be randomized controlled trial. (ii)population were NAFLD patients with T2DM aged 18-75 years and the glycosylated hemoglobin (HbA1c) was of 6-12%. The diagnostic criteria for NAFLD are as follows: fatty liver based on imaging examination (ultrasonography or computed tomography), alcohol intake not exceeding 140 g/week in women and 210 g/week in men, other causes of liver disease were excluded (viral hepatitis, autoimmune hepatitis, hemochromatosis and Wilson's disease, etc) T2DM. (iii) therapeutic intervention includes various types of SGLT2i and give sufficient information about baseline and post-treatment. (iv) give the data in form of mean and standard deviation (SD), rather interquartile range, etc. The exclusion criteria include the following: (i) animal researches. (ii) commentaries, conference abstracts, editorials, case reports. (iii) incomplete article results, non-randomized controlled trial.

Information sources We conducted a comprehensive literature search utilizing the databases PubMed, Embase, Web of Science, and Cochrane Library, and extracted continuous data in the form of mean and standard deviation of the difference before and after treatment. Commentaries, conference abstracts, editorials, case reports, incomplete article results, non-randomized controlled trial will be excluded.

Main outcome(s) We used the following parameters: Liver Stiffness Measurement (LSM), Controlled Attenuation Parameter (CAP), Serum ferritin, Serum type 4 collagen 7s, and FIB-4 index to measure the ameliorative effect of SGLT2i on liver fibrosis and as our main outcome.

Additional outcome(s) We also focused on the therapeutic effects of SGLT2i on liver fat content, insulin resistance, and body conditions by analyzing relevant parameters.

Data management We use special portable hard drives to keep relevant documents and data.

Quality assessment / Risk of bias analysis Quality assessment of eligible RCTs were performed by Cochrane risk-of-bias tool based on the Cochrane handbook for systematic reviews and meta-analysis in seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases, each project was evaluated as "low risk", "high risk", or "unclear risk" of bias Two reviewers (Yan YUAN and Chen ZHENG) independently assessed the quality of the included RCTs.

Strategy of data synthesis Review Manager 5. 3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for this meta-analysis. The extracted data were continuous variable, standardized mean difference (SMD) with 95% confidence interval (CI) was calculated and used for statistical analysis. A summary of results was pooled in the forest plots. Heterogeneity among the studies was assessed by applying the Chi-square (c2) test and I2 statistic, as well as the calculated Q statistic and p values. Heterogeneity

would be considered as low (I2≤50% or p≥0.1), moderate (50% or p＜0.05). A fixed effect model would be applied if heterogeneity was low. Conversely, a random effect model would be used for moderate or high heterogeneity. Sensitivity analysis was undertaken, since significant heterogeneity related to the pooled effect size was encountered. We used the sequential exclusion to identify which article may lead to the high heterogeneity.

Subgroup analysis We may undertake subgroup analysis based on the different types or dosage of SGLT2i.

Sensitivity analysis Sensitivity analysis was undertaken, since significant heterogeneity related to the pooled effect size was encountered. We used the sequential exclusion to identify which article may lead to the high heterogeneity.

Language restriction We only accept papers published in English.

Country(ies) involved China.

Other relevant information This meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Keywords SGLT2 inhibitors, T2DM, NAFLD, NASH, liver fibrosis.

Contributions of each author

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