Hypoglycemic agents for non-alcoholic fatty liver disease with type 2 diabetes mellitus: A protocol for systematic review and network meta-analysis

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**Review question / Objective:** This study is to systematically evaluate the efficacy and safety of hypoglycemic agents for the treatment of non-alcoholic fatty liver disease (NAFLD) with type 2 diabetes mellitus (T2DM). The network meta-analysis will be used to indirectly compare different hypoglycemic agents to find out the optimal treatment plan for NAFLD with T2DM and to provide evidence-based bias for clinical treatments decision-making. Only randomized controlled trial will be included.

**Condition being studied:** NAFLD is the most common cause of chronic liver disease in Western countries, and strongly associated with T2DM. Several studies have shown that hypoglycemic agents are effective for NAFLD combined with T2DM. However, there is still no relevant systematic study on the efficacy and safety of those various hypoglycemic agents in the treatment of NAFLD combined with T2DM. Therefore, there is no strong evidence to support which drug is appropriate for patients, the newer, the better; or the more expensive, the better? In this study, the efficacy and safety of multiple hypoglycemic agents will be compared to provide a bias for patients to selectively take hypoglycemic agents.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 July 2020 and was last updated on 04 July 2020 (registration number INPLASY202070016).
A randomized controlled trial will be included.

**Rationale:** Meta-analysis summarizes the results of multiple independent studies of the same kind to achieve the purpose of increasing the sample size and improving the test efficiency. Ordinary meta-analysis can only achieve pairwise comparison, but network meta-analysis can achieve indirect comparison of a variety of different intervention approaches, so that some treatment methods that are not directly compared can be indirectly compared to choose the best plan.

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**METHODS**

**Search strategy:** The search strategy will include medical subject headings (MeSH) and key words associated with hypoglycemic agents in the treatment of NAFLD with T2DM. The subject headings include “hypoglycemic agents”, “non-alcoholic fatty liver disease”, “diabetes mellitus, type 2”, and “randomized controlled trials”. The retrieval time will be set to the time of database-building to May 31, 2020.

**Participant or population:** Participants were individuals who are clinically diagnosed with NAFLD combined with T2DM and are simultaneously treated with hypoglycemic agents. There are no restrictions on race, gender, or age. Participants with non-alcoholic fatty liver disease caused by other reasons and participants with severe heart disease, liver and kidney dysfunction, mental illness, pregnant or allergies to hypoglycemic agents will be excluded.

**Eligibility criteria:**

1. **Types of Study:** randomized controlled trials (RCTs).
2. **Participants:** participants were individuals who are clinically diagnosed with NAFLD combined with T2DM and are simultaneously treated with hypoglycemic agents. There are no restrictions on race, gender, or age.
3. **Interventions:** both groups of participants were treated with different hypoglycemic agents, or one group received hypoglycemic agents, while the other group received placebo, or no treatment was applied. In addition, neither group took any drugs that interfered with the outcome indicators. Studies that do not meet the inclusion criteria or that are difficult to extract data from will be excluded.

**Information sources:** We will search publications in the following English and Chinese databases: Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Clinical Trials, and Chinese Biomedical Medicine (CBM) to collect studies.

**Main outcome(s):** The main 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):** The additional outcomes are mainly composed of fasting blood glucose, 2 hours postprandial blood glucose, HbA1c, serum insulin levels, aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT), and adverse events.

**Data management:** Firstly, all the retrieved data will be imported into Endnote X7 software. Two researchers will independently screen and remove the literature that clearly does not meet the inclusion criteria by reading the title and abstract, and eliminate the research that does not meet the requirements, and then carefully read the full text and select the research that meet the requirements. Secondly, we will carefully read the full text of the remaining literature to further decide whether to include or not. Finally, the two researchers will independently extract the data and carefully check it by a third researcher. If there are any disagreements during the data collection process, we will reach agreement through discussion or seek advice from a third party.

**Quality assessment / Risk of bias analysis:** We will use the RCT bias risk assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 to perform bias risk assessment and methodological quality assessment of included RCTs. Disagreement will be resolved by a third party.

**Strategy of data synthesis:** 1. Direct meta-analysis; 2. Network meta-analysis; 3. We will combine the data based on the random-effect model. We will use odds ratio (OR) for the dichotomous data, and use the weighted mean difference (WMD) or standard mean difference (SMD) for the continuous outcomes.

**Subgroup analysis:** If necessary, we will conduct subgroup analyses on characteristics such as gender, age, race, nationality, type of hypoglycemic agents, and duration of medication to explore whether treatment effects for our primary outcomes are robust.

**Sensibility analysis:** In the direct comparison, if there is a large heterogeneity and the number of studies included is enough, we will use the method of meta regression for sensitivity analysis, otherwise we will exclude the studies one by one for sensitivity analysis.

**Language:** No language restrictions.

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

**Other relevant information:** None.

**Keywords:** Hypoglycemic agents; non-alcoholic fatty liver disease; type 2 diabetes mellitus; network meta-analysis; systematic review.

**Dissemination plans:** Ethical approval is not required for this study, as all analyses were based on previously literature. The findings will be disseminated through conference presentations, media, and peer-reviewed journals.

**Contributions of each author:**
- **Author 1 - Su-tong Liu** - Drafted the manuscript, responsible for research design and search strategy formulation, and data analysis.
- **Author 2 - Kai-qi Su** - Drafted the manuscript, literature search, data extraction and evaluation of bias.
- **Author 3 - Li-hui Zhang** - Literature search, data extraction and evaluation of bias.
- **Author 4 - Ming-hao Liu** - Provide statistical expertise and guide the extraction of research data and the evaluation of bias.
- **Author 5 - Wen-xia Zhao** - Provide financial support, read and approved the final manuscript.