

The Effects of Probiotic Supplementation on Glycemic Index, Lipid Profiles and Inflammatory Cytokines in NAFLD Patients: A Protocol for a Systematic Review and Meta-Analysis

Sadegh Mozaffari

Tehran University of Medical Sciences

Pedram Rezaei Amirkiasar

Tehran University of Medical Sciences

Mina Zare

Shiraz Medical School: Shiraz University of Medical Sciences

Solaleh Emamgholipour

Tehran University of Medical Sciences

Hossein Hosseini

Mashhad University of Medical Sciences

Ghodratollah Panahi (✉ pshahriyar@gmail.com)

Tehran University of Medical Sciences <https://orcid.org/0000-0001-8338-4633>

Protocol

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders worldwide. In an aggressive type, non-alcoholic steatohepatitis (NASH) might lead to cirrhosis and hepatocellular carcinoma progression. Currently, there is no certified drug applied to treat NASH. Human studies have demonstrated the beneficial effects of probiotics supplementation in NAFLD. Due to the lack of appropriate studies and the emerging requirements for further illustration over the effects of probiotics on the treatment of NAFLD and NASH-related disorders in humans, in this study, we seek to evaluate this matter often papered over.

Methods: We will search PubMed, EMBASE, Cochrane Library, and Web of Science from inception to February 2021. Search terms are keywords and medical subject headings related to NAFLD, probiotics, glycemic indexes, inflammation, and dyslipidemia. 2 researchers will determine the search strategy after several pre-searches.

The Glycemic outcomes include glycated hemoglobin, fasting blood glucose, fasting insulin, homeostasis model assessment of insulin resistance.

The lipidomic outcomes include differences in High-density lipoprotein, Low-density lipoprotein, Total triglyceride, Total cholesterol.

The Inflammatory outcomes include differences in IL6, IL1 β , TNF α , CRP.

The meta-analysis will be performed using END NOTE and STATA.

Results: Our study will systematically evaluate the effectiveness and safety of probiotics supplementation in NAFLD patients.

Conclusion: This study's results will give the proof for probiotics supplements in NAFLD treatment and provide an evidence for clinical treatment.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide. In an aggressive type, non-alcoholic steatohepatitis (NASH) might lead to cirrhosis and hepatocellular carcinoma progression. Currently, there is no certified drug applied to treat NASH (1).

The pathogenesis path of NASH is yet remained to be known. However, the underlying factors mentioned below could be taken into account: obesity, high-calorie/high-fat diet, diabetes, hypercholesterolemia, and certain drugs either(2). Over this issue, efforts done to alter people's lifestyles have been suggested. Still, they were hardly sustainable, so it necessitates to conduct investigations through some new therapeutic strategies, including weight reduction and diet changes, which are recommended as the first step involved in patients' treatment procedure under such conditions (3).

Once weight loss is obtained and appropriately sustained, it may gradually improve NAFLD(1). Although there is no recognized medication or surgical method approved for the treatment of NAFLD, countless numbers of clinical trials have demonstrated several pharmacological treatments suitable to cure NAFLD/NASH, such as diabetes medications, lipid-lowering drugs, antioxidants, and anti-tumor necrosis factor (TNF)- α agents(4).

The mechanisms related to the development and progression of NAFLD are yet to be fully understood. This process is assumed to be the substantial consequence of the interactions amongst progressive environment-driven epigenetic code changes, genetic background, and molecular alterations. Environmental factors such as unhealthy diet and the appearance of a stagnant sedentary routine, which drive epigenomic reprogramming of the host genome via post-translational modifications of gene expression, could ultimately evolve phenotypic changes in the organism(5). Seamlessly, obesity is thought to be the most vital risk factor affiliated with various NAFLD series in which abdominal fat is correlated with a volume of steatosis observed on liver biopsy(1) with a striking increased risk of insulin resistance and emerging multiple diseases in children as in adults(6).

NAFLD often gives rise to dyslipidemia in which increased serum TG and LDL-C levels and decreased HDL-C levels could be demonstrated (7). Additionally, recent evidence suggested an interaction between the liver and gut called the 'gut-liver axis' might participate in the evolution of phenotypic replacement from NAFL to a much more severe state like NASH NASH-related fibrosis. Indeed, NAFLD is associated with escalating intestinal permeability (IP) and small intestinal bacterial overgrowth (SIBO) in humans, all connected to the severity of hepatic steatosis. Hence, several studies have introduced gut microbiota modulation via probiotics, prebiotics, and synbiotic as an efficacious solution to improve the obesity state and subsequent NAFLD(5).

The World Health Organization considers probiotics as live microorganisms that positively impact the intended host as long as administered in sufficient volumes. The prophylactic and therapeutic impacts of these microorganisms, including the equilibration of intestinal microbiota, diminution in cholesterol levels, hypertension enhancement, diabetes, lactose intolerance, gastrointestinal diseases, immune system improvement, and also plummeting the risk of various cancers, have been reported in different trials(7). Administration of *Lactobacillus* and *Bifidobacterium* probiotic strains, prebiotics, synbiotics (blend of probiotics and prebiotics), and their fusion with nutraceuticals have been represented to be advantageous by dwindling the hepatic triglyceride content, the hepatic tissue inflammation, total body and visceral adipose tissue weight, and also by improving the insulin sensitivity in various animal models suffering NAFLD and have a deeply profound effect on NASH either(4). In addition to this, probiotics can make a decline in the activity of Jun N-terminal kinase and nuclear factor kb and also make an increase in the number of natural killer T cells located in the liver. However, other conducted animal studies could not demonstrate an impact on hepatic steatosis and necroinflammation improvement. Probiotics prevented liver fibrosis through the exertion of several alterations over the expression of TGF β . It remains unclear whether probiotics are beneficial in human patients suffering NASH(3).

Due to the lack of appropriate studies and the emerging requirements for further illustration over the effects of probiotics on the treatment of NAFLD and NASH-related disorders in humans, in this study, we seek to evaluate and provide evidence related to the effects of probiotics on the treatment of NAFLD.

Methods

Data sources and selection strategy

We will search the following databases: Medline, EMBASE, Cochrane Library, and Web of Science from inception to February 2021. Search terms are keywords and medical subject headings related to NAFLD, NASH, fatty liver, probiotics, prebiotic, symbiotic, glycemic index, inflammation, and dyslipidemia. 2 researchers will determine the search strategy after several pre-searches.

Inclusion and exclusion criteria

Only randomized controlled trials (RCTs) will be included in this study and related to participants, all adult patients who met the accepted diagnostic criteria for NAFLD will be included in this study without discrimination about sex or ethnic origin

In the case of interventions, only RCTs comparing probiotics and supplementation with placebo will be included in this study. Also, the minimum duration of treatment is eight weeks.

The exclusion criteria will include other causes of hepatic steatosis like hepatitis B, hepatitis C, and genetic liver infection, such as Wilson's illness and hemochromatosis.

Outcomes

The trials should have measured at least one of the following items:

Glycemic outcomes.

- (1) Differences in glycated hemoglobin;
- (2) Differences in fasting blood glucose.
- (3) Differences in fasting insulin;
- (4) Differences in homeostasis model assessment of insulin resistance;

Lipidomic outcomes.

- (1) Differences in High-density lipoprotein;
- (2) Differences in Low-density lipoprotein;
- (3) Differences in Total triglyceride;

(4) Differences in Total cholesterol;

Inflammatory outcomes.

(1) Differences in IL6;

(2) Differences in IL1 β ;

(3) Differences in TNF α ;

(4) Differences in CRP;

Data selection

Two reviewers will freely screen the literature included in the meta-analysis according to the eligibility criteria listed in this study. The title and abstract will be read first in the literature selection process. The full text will be further read to determine the final inclusion after excluding the apparent irrelevant literature. Two other reviewers will independently assess the included studies' reporting quality. The process of literature identification and screening is shown in Fig. 1.

Data extraction and methodological quality

Using a predefined data extraction sheet from all studies that meet the eligibility criteria, data will be extracted by two reviewers independently as follows:

- Basic information, including study design, the author first and last name, country, publication year, sample size, and grouping;
- Characteristics of the participant including age, sex, race, and the number of participants.
- Methodological approach, like randomized method, blinding method, and assessed risk of bias;
- Time and type of interventions and controls;
- Outcomes, including glycemic, lipidomic, and inflammatory outcome indicators, as well as adverse events.

A third reviewer will check the process of data extraction for confirmation. Besides, on the off chance that there's any contradiction in data extraction, it has to be re-examined by the third reviewer.

We will contact the corresponding authors and send a request for additional missing necessary data. The study will be deleted if the lost data is unavailable.

Risk of bias

Two reviewers will assess the study's quality, which will be based on the following items:

- Random allocation method;
- The allocation scheme is hidden;

- Blind methods are used for subjects and treatment planners;
- Blind method for measurement results;
- The integrity of the resulting data;
- Selectively report the results of the study;
- Other sources of bias.

Studies with a low risk of bias were considered high quality. If there were any conflicts while assessing the quality of data, they would be settled through conversation and discussion.

Statistical analysis

We will analyze results qualitatively and quantitatively. The meta-analysis will be performed using the Stata software, and P-value < 0.05 will be statistically significant. The relative risk and the 95% confidence intervals will be used for the outcomes. We will calculate effect size as Standardized Mean Difference (SMD) and 95% CI to evaluate the effects of probiotics on variables. Statistical heterogeneity will be measured using the Q and the Higgins I² statistics. We will perform subgroup analysis according to the type of sample, different dosages of probiotics, and duration treatment to identify potential heterogeneity sources amongst included studies in the meta-analysis. A fixed-effect model or random-effects model will be employed to assess the difference based on statistical homogeneity between the studies (I² < 50% or P > .10) or statistical heterogeneity between the studies (I² ≥ 50% or P < .10). The possibility of publication bias will be assessed with the Begg and the Egger regression test as statistically and also funnel plot as graphically

Discussion

Over the past decade, the number of studies evaluating the effect of probiotics on NAFLD patients has increased and provided data related to improving glycemic, lipidomic, and inflammatory conditions (8). This systemic review and meta-analysis aim to precisely estimate the impacts of probiotics supplementation on glycemic, lipidomic, and inflammatory factors in NAFLD patients. To determine and interpret probiotic effect on improving NAFLD condition, we will evaluate and perform further subgroup analysis related to probiotics' efficacy and safety and different duration treatment time. There will be several strengths in our systematic review and meta-analysis. Our search strategy is very detailed and spanned multiple conditions in NAFLD. We will also perform subgroup analysis to explore the possible sources of the heterogeneity, and attempts will be made to select studies from different countries, which will provide more generalizable results. In addition data screening and extraction, the quality assessment will be performed independently by two reviewers. We hope that this systematic review and meta-analysis provide evidence assessing the effectiveness and safety of probiotics supplementation in NAFLD regarding glycemic, lipidomic, and inflammatory factors.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Data sharing not applicable to this article as no datasets were generated or analyzed

Competing interests

The authors declare that there is no conflict of interest

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Authors' contributions

SM, PRM and GP: provided the conception and design of the study. SM and HH provide drafting the article and preliminary search. SE and MZ revised it critically, and final approval of the version to be submitted; GP: writing – review & editing.

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Figures

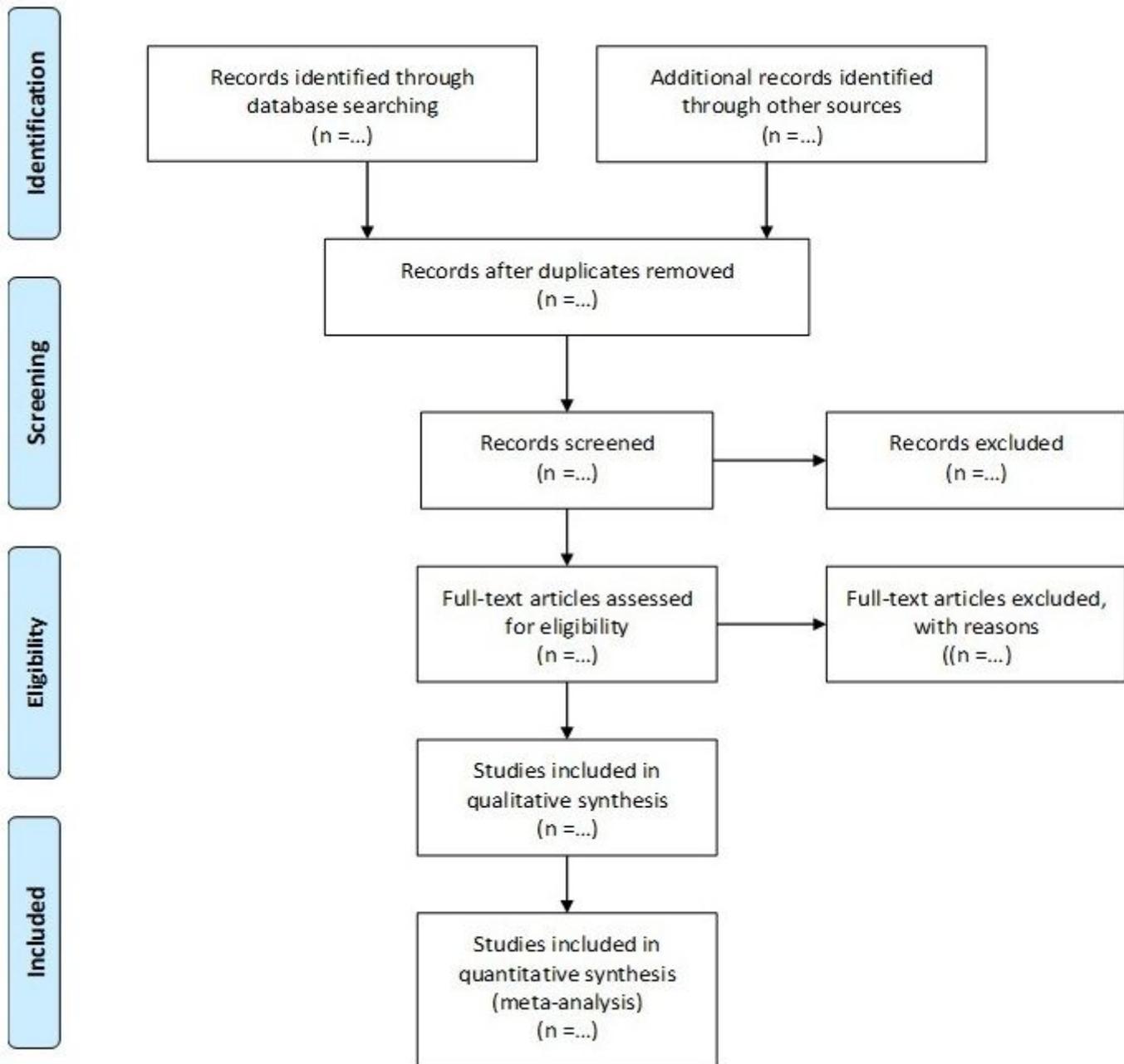


Figure 1

Studies selection strategy