REVIEW

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Probiotic, prebiotic or symbiotic supplementation impacts on intestinal microbiota in patients with nonalcoholic fatty liver disease: a systematic review

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ABSTRACT – **Background** – Supplementation with probiotics, prebiotics and symbiotics has shown positive effects on clinical markers and risk factors for non-alcoholic fatty liver disease (NAFLD). **Objective** – To evaluate the effect of supplementation with probiotic, prebiotic or symbiotic on intestinal microbiota in NAFLD patients. **Methods** – Two investigators conducted independently search for articles in the Medline databases, via PubMed, Web of Science, Embase, Scopus, Lilacs, Central Cochrane Library, Clinical Trials.gov and on the Ovid platform for the gray literature search. **Results** – A total of 3,423 papers were identified by searching the electronic databases; 1,560 of them were duplicate and they were excluded; 1,825 articles were excluded after reading the title and abstract. A total of 39 articles were select to reading, however only four articles met the eligibility criteria to include in this systematic review. Three of the included studies that used prebiotic or symbiotic supplementation showed that after the intervention there were changes in the intestinal microbiota pattern. Only in one study such changes were not observed. A high risk of bias was observed in most assessments. **Conclusion** – Although there is a possible change in the gut microbiota of individuals with NAFLD after supplementation with symbiotics or prebiotics, a clinical indication as part of NAFLD treatment is not yet possible.

Keywords – Non-alcoholic fatty liver disease; probiotics; prebiotics; symbiotics; intestinal microbiome.

INTRODUCTION

The relationship between the intestine and disease predisposition has been the subject of many studies, especially in experimental animal studies[1]. When there is a dysregulation of intestinal homeostasis, the increase in intestinal permeability, as well as an increase in the amount and/or change in the type of bacteria in the gastrointestinal tract, leads to a bacterial translocation with transport of bacteria and bacterial products from the intestinal lumen to the blood[2].

This bacterial translocation seems to be one of the mechanisms that can predispose to non-alcoholic fatty liver disease (NAFLD)[3], which is characterized by the accumulation of triglycerides in the cytoplasm of hepatocytes in patients with no history of alcohol intake or little intake (less than 20 g/day), presenting a evolutionary potential that can vary from isolated hepatic steatosis, to non-alcoholic steatohepatitis (NASH), progressing to varying degrees of necroinflammation[4].

NAFLD is currently considered the most common cause of chronic liver disease, with an estimated worldwide prevalence of 25% of the general population. The adoption of new diagnostic criteria has been discussed, as well as a new nomenclature called fatty liver disease associated with metabolism[5].

There is still no drug therapy that can control the evolution of NAFLD, and lifestyle interventions, including changes in diet and regular exercise, are the only effective and recommended measures[4].

Studies show that patients with NAFLD appear to present changes in the intestinal microbiota, and an increase in the occurrence of bacterial overgrowth of the small intestine (SIBO). These changes seem to be associated with the severity of NAFLD[6-8]. Thus, in an attempt to intervene in the intestinal microbiota of these patients with NAFLD, the use of probiotic, prebiotic or symbiotic supplements has been the subject of recent studies[9-11].

Recent systematic reviews have evaluated the effect of supplementation of probiotics, prebiotics or symbiotics on clinical markers and risk factors for NAFLD[9-12]. The results of these studies are promising, since the use of these supplements was favorable in reducing fasting blood glucose and insulin[9,11], total cholesterol[11,12], triglycerides[11], alanine aminotransferase (ALT), aspartate aminotransferase (AST)[10-12], as well as in tumor necrosis factor alpha (TNF-α)[11,12]. However, all studies highlight the importance of more evidence that can evaluate the dose-response effect of supplementation, as well as the probiotic strains used.

This systematic review aimed to evaluate the impact of pro-

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biotic, prebiotic or symbiotic supplementation on gut microbiota of NAFLD patients, being conducted according to the guidelines for a systematic review.

METHODS

The study was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) as a systematic review and meta-analysis under registration number CRD42019133407. Preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) were used as a reference for protocol writing[13].

The research articles that contained the following search terms in the title or abstract fields were identified in the Medline via PubMed, Web of Science, Embase, Scopus, Lilacs, Central Cochrane Library, ClinicalTials.gov, and the Ovid Gray Literature Platform, between the months of April 2019 to May 2021. Thus, the descriptors were defined based on the Medical Subject Heading (MeSH); health science descriptors (DeCS) and the EMTREE. Boolean operators "AND" and "OR" were used in all combinations. Thus, the search was carried out using the following terms: ("nonalcoholic fatty liver disease" OR "NAFLD" OR "nonalcoholic fatty liver disease" OR "fatty liver, nonalcoholic" OR "fatty livers, nonalcoholic" OR "liver, nonalcoholic fatty" OR "livers, nonalcoholic fatty" OR "nonalcoholic fatty liver" OR "nonalcoholic fatty livers" OR "nonalcoholic steatohepatitis" OR "nonalcoholic steatohepatitides" OR "steatohepatitides, nonalcoholic" OR "steatohepatitis, nonalcoholic") AND ("probiotics" OR "probiotic") AND ("symbiotic") AND ("prebiotics" OR "prebiotic).

The included studies were not limited to the language and year of publication.

Two authors independently decided which studies should be included in this review. Any disagreements were resolved by discussion or mediation by third parties. Only the terms for the components I (intervention) and P (population) were used in the data search.

Were included clinical trials involving adults over 18 years of age and under or equal to 65 years of age, of both sexes and with clinical diagnosis of NAFLD, hepatic statosis by abdominal ultrasound or computed tomography or magnetic resonance imaging or liver biopsy, excluding other liver diseases and alcohol consumption <20 g/day, were included in this study. Animal studies, in vitro, review articles, case reports, conference abstracts and proceedings, observational studies, studies in which individuals used antibiotics or had other clinical conditions such as SIBO or those that did not meet the inclusion criteria, were excluded.

For the intervention group, supplementation with probiotics, prebiotics or symbiotics was considered, being allowed the use of any probiotic strain, without limiting the dose administered and duration of follow-up. For the comparison group, the treatment was not specified. Regarding the evaluation of the intestinal microbiota, there was no restriction on the method used.

The titles and abstracts were initially read to exclude irrelevant articles. The relevant articles were read in full and evaluated according to the eligibility criteria. The reference lists of the articles found and thematic reviews were also searched.

The original articles included in the final list were read in full and the information contained in them was recorded in a specific Excel® spreadsheet, created by a single researcher and standardized for synthesis of evidence.

The risk of bias in the studies included in this review was assessed by two independent reviewers, according to the Cochrane Collaboration criteria for the development of systematic intervention reviews.

This tool consists of two parts, which contain seven domains. Judgment on bias risk for each of the domains analyzed was classified into three categories: bias low risk, bias high risk or bias uncertain risk. Subsequently, the results were entered into the Review Manager 5.3 tool to create figures that could summarize the judgment of risk of bias in the clinical trials included in this review[14].

The results presented by the included articles were not combinable, limiting the meta-analysis execution.

RESULTS

Selection and characteristics of studies

A total of 3,423 references were identified by searching the electronic databases. Of these, 1,560 articles were deleted after duplicate removal and 1,825 articles were deleted after reading the title and abstract. The complete reading was performed in 39 articles of electronic search and manual search in the references of thematic reviews. After reading in full, only four articles met the eligibility criteria and were included in this systematic review. The reasons for the exclusion of the articles were due to the non-assessment of the effect of supplementation on the characteristics of the microbiota (n=9), literature review articles (n=17), studies with animals (n=6), studies with results unpublished (n=2) and full article not available in the database (n=1) (FIGURE 1).

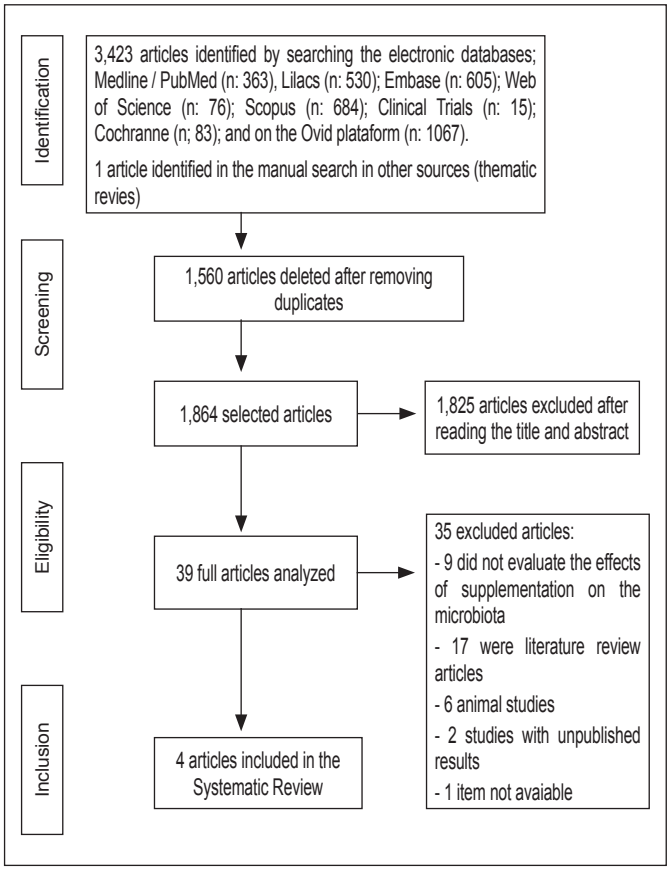

FIGURE 1. Flowchart for selecting articles included in this Systematic Review.

The included studies were carried out in China[15], Ukraine[16], Canada[17], and England[18]. Information was collected between 2009 and 2020 and the intervention time ranged from 1 month to 12 months. Wong et al.[15], Manzhalii et al.[16], and Scorlett et al.[18] used symbiotic supplementation containing a mixture of probiotics with prebiotics and Bomhof et al.[17] used isolated probiotic. The studies involved the only adult population and manuscript published in English.

Population characteristics

The four included studies totaled a sample of 194 patients evaluated, comprising 98 from the intervention group and 96 from the control group, 102 (52.6%) of whom were male. Manzhalii et al.[16] did not include obese individuals (BMI >30 kg/m^2), nor those with any associated comorbidity, such as diabetes and hypertriglyceridemia (TABLE 1).

Methods for characterization of intestinal microbiota

For the characterization of the intestinal microbiota, indirect methods were used, based on the count of bacteria in the fecal sample. Wong et al.[15], Bomhof et al.[17] and Scorlett et al.[18] characterized the fecal microbiota through the analysis of DNA samples for sequences of 16S rRNA by pyose sequencing. Manzhalii et al.[16] did not describe the technique used, only mention that the microbial composition in the feces was quantified.

Intervention characteristics

Three studies used symbiotic preparations[15,16,18], and Bomhof et al.[17] used prebiotic supplementation. All preparations differed in composition, dosage and intervention time. Only in the studies by Wong et al.[15] and Manzhalii et al.[16] the participants were instructed to make specific dietary changes. As for the prebiotic, all used fructooligosaccharide (FOS) and oligofructose (TABLE 2).

Effect of intervention on intestinal microbiota

Wong et al.[15] observed according to the quantification of bacteria in fecal samples, that after the intervention there was no significant change in bacterial biodiversity (P<0.05). Prior to the intervention, all NASH patients had a composition of 67.6% *Bacteroidetes* and 22.3% *Firmicutes*, and after 6 months of dietary

TABLE 1. Characteristics of the population and studies included in this Systematic Review.

Author	Country/ year	Study design	N	Age (years)	Sex (M/F)	NAFLD diagnostic method	BMI (≥25kg/m^2)	Method for evaluation of intestinal microbiota
Wong et al.	China 2013	Randomized controlled trial	I: 7 C: 9	I: 46±6 C: 56±9 P=0.03	I: 5/2 C: 4/5 P=0.36	Liver biopsy	I: 29.8±5.3 C: 28.6±6.1 P=0.69	Microbial composition in fecal sample
Manzhalii et al.	Ukraine 2017	Unblinded prospective randomized controlled trial	I: 38 C: 37	I: 44.3±1.5 C: 43.5±1.3 P=0.62	I: 11/27 C: 16/21 P=0.20	Upper abdominal US and elastography	I: 26.4±0.8 C: 26.6±0.7 P=0.85	Microbial composition in fecal sample
Bomhof et al.	Canada 2019	Pilot clinical trial	I: 8 C: 6	I: 45.3±5.6 C: 53.3±4.8	I: 5/3 C: 3/3	Liver biopsy	I: 33.7±3.0 C: 34.8±2.2	Microbial composition in fecal sample
Scorletti et al.	England 2020	Double-blind, randomised, placebo-controlled trial	I: 45 C: 44	I: 50.2±12.4 C: 51.6±13.1	I: 31/14 C: 27/17	Magnetic resonance spectroscopy	I: 32.9±5.5 C: 33.2±4.9	Microbial composition in fecal sample

N: total population; M: male; F: female; NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: body mass index; I: intervention; C: control; US: ultrasound.

TABLE 2. Main results of studies included in this Systematic Review after intervention with probiotic, prebiotic or symbiotic supplementation.

Author	Intervention	Dose/duration of intervention	Treatment for the control group	Diet composition	Characteristics of the intestinal microbiota
Wong et al.	Symbiotic 10^8 CFU L. plantarum + L. *Bulgaricus* + *L. acidophilus* + *L. rhamnosus* + *B.bifidum* + FOS	13 g (02 times a day) 6 months	Diet + exercise	Low in carbohydrates and fats	There was no significant change in bacterial biodiversity after treatment
Manzhalii et al.	Symbiotic 10^8 CFU *L. casei* + *L. rhamnosis* + *L. bulgaris* + *B. longum* + *S. thermophiles* + FOS	1 capsule 3 months	Diet + exercise	Low fat: 30 to 90 g/day low calories: 1800 kcal/day	Increased bacterial abundance toward normal range compared to healthy individuals (P<0.05)
Bomhof et al.	Oligofructose	8 g/d/ 12 sem. 16 g/d/24 sem	Maltodextrin 8 g/d / 12 week 16 g/d / 24 week	Usual diet	Increased *Bifidocaterium sp.* (P=0.017) and reduction of *Clostridium cluster* (P=0.03)
Scorletti et al.	Symbiotic 10^8 CFU *B. animalis* subsp. *lactis* BB-12 + FOS	1 capsule + 4 g (02 times a day) 12 months	Maltodextrin 4 g (2 times a day)	Usual diet	Significant increase in the abundance of *Bifidobacterium* (P<0.001)

CFU: colony forming units; FOS: fructooligosaccharide.

intervention, patients in the control group had a reduction in *Bacteroidetes* to 63.8% and an increase in the number of *Firmicutes* to 24.3%. The presence of adverse effects due to supplementation has not been investigated.

In the study by Manzhalii et al.[16] an increase in bacteria toward the normal range was observed ($P<0.05$) after symbiotic intervention when compared to standard distribution in healthy subjects. No adverse effects have been reported.

Bomhof et al.[17] observed after supplementation during the 36 weeks of intervention, there was an increase in the abundance of *Bifidobacterium spp*. ($P=0.017$) and reduction of *Clostridium cluster* ($P=0.03$) compared to placebo. Both prebiotic and placebo supplementation were associated with increased *L. leptum*, *Faecali bacterium prausnitzii* ($P=0.017$). The presence of adverse effects due to supplementation has not been investigated.

Scorlett et al.[18] found an increase in *Bifidobacterium* abundance ($P<0.001$) in the symbiotic group but not in the placebo group, considering that at the beginning of the study, both groups had no difference in the abundance of *Bifidobacterium* ($P=0.5$). The presence of adverse effects due to supplementation has not been investigated.

Other effects of the intervention

The Manzhalii et al. study[16] showed improvement after treatment in other parameters, reducing total cholesterol, triglycerides, body mass index (BMI), liver enzymes (ALT and AST) and degree of steatosis ($P<0.05$). However, Wong et al.[15] and Bomhof et al.[17] found no changes in serum liver enzyme values and body composition ($P<0.05$), and Scorlett et al.[18] also found no difference in the reduction of liver fat ($P=0.08$), in circulating levels of lipopolysaccharide ($P=0.08$), in the concentrations of short-chain fatty acids (SCFA) ($P=0.21$), nor in bacteria classically linked to inflammation, obesity and NAFLD.

Bias risk assessment

The study by Scorlett et al.[18] was the only one classified as having a low risk of bias in almost all items evaluated. The other studies[15-17] obtained a high risk of bias at the end of the judgment, as they presented answers that led to doubts about the impact of their results or insufficient and/or absent information, preventing proper judgment. The information was considered insufficient or was not present for the following items: generation of the random sequence[16,17], concealment of allocation[16,17], blinding of participants and personnel[15,16], blinding of outcome evaluators[15-17], incomplete results[18], report of selective outcome[14-16], and other sources of bias[15-18]. In relation to other risks of bias, the four studies[15-18] showed a high risk of bias due to the lack of data on the lifestyle of the patients included, no quantitative specification of the dietary intervention and lack of clarity regarding the classification of hepatic steatosis (FIGURE 2).

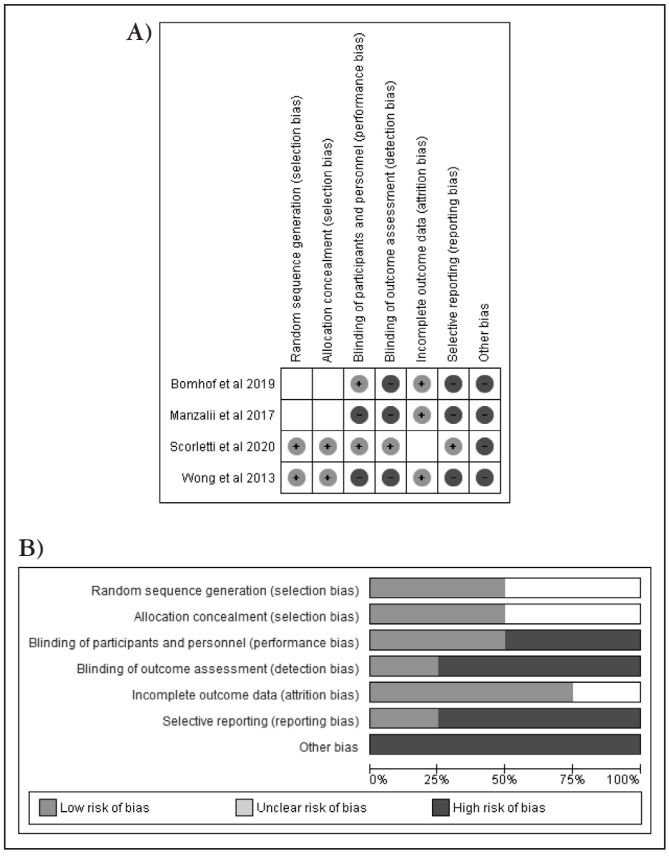

FIGURE 2. Bias risk assessment. **A)** Bias risk summary: review of each bias risk item for each included study. **B)** Bias risk graph: review of each bias risk item (%) for all included studies.

DISCUSSION

This systematic review included studies in which researchers assessed the effect of the symbiotic or prebiotic on the intestinal microbiota in NAFLD patients. Although some studies have shown a change in the abundance of certain strains of bacteria in the intestinal microbiota, the evidence is still not consistent.

For the interpretation of the results on changes in the intestinal microbiota, it is important to highlight that there is no parameter when it comes to a healthy intestinal microbiota, since the most accepted definition is the increase in bacterial diversity and the resilience capacity, that is, the capacity of this microbiota return to a state of equilibrium after a certain disturbance. Thus, it seems very simplistic to define the healthy intestinal microbiota only by specific microorganisms[19].

All studies evaluated here used different techniques for gut microbiota evaluation, as well as differences in the description of results, limiting the conclusion to similar results. This diagnostic limitation is relevant considering the small number of human studies available in the scientific literature and included in this review. Another fact is that patients usually have other associated diseases that may interfere with the composition of the intestinal microbiota[20].

The differences between the techniques of sample evaluation may have contributed to the divergences between the results found, since even being performed the fecal sample analysis the results were described differently between the studies[15-18]. In addition, the small sample size was another factor that may have contributed to the conflicting results between studies.

Participants in the intervention group, in addition to supplementation, were instructed on food intake. For the control group, some received guidance on behavioral changes in relation to regular physical exercise and changes in diet[15,16] and in others the recommendation was to keep the usual diet[17,18]. However, for those who had dietary modifications, it was possible to observe quantitative

variations in the recommendations, which was already expected, as these studies were carried out on different continents, presenting a great cultural diversity. In general, everyone prioritized the food calorie deficit[15,16].

A common feature of most of the included studies was had NASH patients in sample[14-16] which is a more advanced degree of hepatic steatosis in the presence of an inflammatory process. Experimental study[3] show that changes in the intestinal microbiota favor the increase of intestinal permeability and SIBO. There seems to be a relationship between the positive regulation of the toll-like liver receptor (TLR-4) which when bound to lipopolysaccharides, one of the pathogenic bacteria-derived products, activates inflammatory mediators responsible for the development or progression of NASH.

Only one study investigated adverse effects after the use of symbiotic or probiotic, not observing any adverse effects[16]. A recent review evaluated the adverse effects of probiotic strains in humans, concluding that there is heterogeneity between studies in terms of lifestyle, differences in the intestinal microbiota, relevant genetic differences, sex and age of the participants evaluated, and difference in the treatment period or length of stay treatment. And all these factors can lead to divergent results, and more studies are available to elucidate such effects and mechanisms, as this has been one of the treatments for the safe use of supplementation with probiotic strains[21].

As for the other results found, one study[16] observed at the end of the intervention with symbiotic a reduction in the degree of steatosis. However, it is not possible to know that such intervention is effective as part of the treatment of NAFLD[22].

Most studies showed a high risk of bias[15-17], a small sample size[14,16] and heterogeneity as to the type of probiotic strains used, as well as the dose administered and the intervention time[15,16,18]. Such are in line with the results found regarding the effect of supplementation on the intestinal microbiota.

This systematic review presented as limitation the small number of included studies, given the difficulty to evaluate the established outcome and the heterogeneity regarding the methodology and results presented between the studies.

CONCLUSION

This systematic review has shown that although there is a possible change in the intestinal microbiota of individuals with NAFLD after symbiotic or prebiotic supplementation, a clinical indication as part of NAFLD treatment is not yet possible. The factors that most contributed to this result were the heterogeneity between the techniques used for intestinal microbiota evaluation, as well as the small sample size of these studies. It also observed the lack of standardization regarding the type and quantities of probiotic strains, the different dose administered and the duration of treatment. All these observations suggest that more consistent studies are needed to elucidate the real benefits as well as the long-term consequences of the use of probiotics, prebiotics or symbiotics on the intestinal microbiota in NAFLD.

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Authors' contribution

Souza CA: building the protocol, bibliographic search, analyzing the data and building the manuscript. Rocha R: bibliographic search, data input. Almeida NS: bibliographic search, data input. Farias PRF: study design, critical review of draft. Cotrim HP: study design, critical review of draft.

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Souza CA, Rocha R, Costa PRF, Almeida NS, Cotrim HP. Impacto da suplementação com probióticos, prebióticos e simbióticos na microbiota intestinal em pacientes com doença hepática gordurosa não alcoólica: uma revisão sistemática. Arq Gastroenterol. 2022;59(1):123-8.

RESUMO – **Contexto** – A suplementação com probióticos, prebióticos e simbióticos mostrou efeitos positivos sobre marcadores clínicos e fatores de risco para doença hepática gordurosa não alcoólica (DHGNA). **Objetivo** – Avaliar o efeito da suplementação com probióticos, prebióticos ou simbióticos na microbiota intestinal em pacientes com DHGNA. **Métodos** – Dois pesquisadores realizaram buscas independentes de artigos nas bases de dados Medline, via PubMed, Web of Science, Embase, Scopus, Lilacs, Biblioteca Central Cochrane, Clinical Trials.gov e na plataforma Ovid para busca de literatura cinza. Os títulos e resumos foram lidos para excluir artigos irrelevantes. Em seguida, os artigos selecionados foram lidos na íntegra e avaliados de acordo com os critérios de elegibilidade. O risco de viés foi avaliado de acordo com a Cochrane. **Resultados** – Um total de 3.423 artigos foram identificado por meio de busca nas bases de dados eletrônicas; 1.560 deles eram duplicados e foram excluídos; 1.825 artigos foram excluídos após a leitura do título e do resumo. Um total de 39 artigos foram selecionado para leitura, porém apenas quatro artigos atenderam aos critérios de elegibilidade para inclusão nesta revisão sistemática. Três dos estudos incluídos que utilizaram suplementação de prebióticos ou simbióticos mostraram que após a intervenção ocorreram mudanças no padrão da microbiota intestinal. Apenas em um estudo tais mudanças não foram observadas. Um elevado risco de viés foi observado na maioria das avaliações. **Conclusão** – Embora haja uma possível alteração na microbiota intestinal de indivíduos com DHGNA após a suplementação com simbióticos ou prebióticos, uma indicação clínica como parte do tratamento da DHGNA ainda não é possível.

Palavras-chave – Doença hepática gordurosa não alcoólica, probióticos, prebióticos, simbióticos, microbiota intestinal.

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