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REVISIÓN

El efecto de los probióticos en el tratamiento y prevención del síndrome metabólico: revisión sistemática

The effect of probiotics in the treatment and prevention of metabolic syndrome: a systematic review

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Abstract

There is consistent clinical evidence, but not yet conclusive, that the consumption of foods or supplements based on probiotics modifies the microbiota and the microenvironment, with beneficial effects that are manifested in the clinical, anthropometric, and biochemical components of metabolic syndrome (MS) in the adult population. The objective of this systematic review was to analyze the effects of probiotic supplementation on the prevention and treatment of MS and its components in the adult population. A systematic review was carried out in the databases: Pubmed-Medline, Scopus, Web of Science, LILACS, Cochrane, SIGN, NICE and Scielo, with articles in Spanish and English from 2010 to 2020, with controlled intervention designs where have compared probiotic supplementation (regardless of dose, strains, route of administration, or duration of use). Sixteen articles were selected (10 randomized clinical trials (RCTs), which included 610 participants). The meta-analysis carried out indicated that no statistically significant differences were found on insulin resistance (HOMA-IR), obesity (body mass index -BMI-), atherogenic dyslipidemia or on blood pressure. These findings conclude the lack of evidence found to recommend the consumption of probiotics as a strategy to reduce the prevalence of MS. The methodological limitations found

among the reviewed studies imply the need for future lines of research on its relevance as a potential nutritional therapy and for the moment it is recommended to integrate variables such as nutritional treatment or diet control.

Key words: Metabolic syndrome; probiotics; microbiota; nutritional therapy.

Resumen Existe evidencia clínica consistente, pero no concluyentes aún, que el consumo de alimentos o suplementos a base de probióticos modifica la microbiota y el microambiente, con efectos benéficos que se manifiestan en los componentes clínicos, antropométricos y bioquímicos del síndrome metabólico (MS) en población adulta. El objetivo de la presente revisión sistemática fue analizar los efectos de la suplementación con probióticos sobre la prevención y tratamiento del MS y sus componentes en población adulta. Se realizó una revisión sistemática en las bases de datos: Pubmed-Medline, Scopus, Web of Science, LILACS, Cochrane, SIGN, NICE y Scielo, con artículos en idioma español e inglés de 2010 a 2020, con diseños de intervención controlados donde se haya comparado la suplementación con probióticos (independientemente de la dosis, las cepas, la vía de administración o la duración del consumo). Fueron seleccionados 16 artículos (10 ensayos clínicos aleatorizados (ECA), que incluyeron 610 participantes). El metaanálisis ejecutado indicó que no se encontraron diferencias estadísticamente significativas sobre la resistencia a la insulina (HOMA-IR), la obesidad (índice de masa corporal -IMC-), la dislipidemia aterogénica o sobre la presión arterial. Estos hallazgos concluyen la falta de evidencia encontrada para recomendar el consumo de probióticos como una estrategia en la disminución de la prevalencia del MS. Las limitantes metodológicas encontradas entre los estudios revisados implican la necesidad de futuras líneas de investigación sobre su relevancia como una potencial terapia nutricional y por el momento se recomienda integrar variables como el tratamiento nutricio o el control de la dieta.

Palabras clave: Síndrome metabólico; probióticos; microbiota; terapia nutricional.

Introduction

Metabolic syndrome (MS) is one of the main public health problems in Mexico, due to its two main complications (ischemic heart disease and type 2 diabetes mellitus (DM2)), which are the leading causes of mortality in the country since 2000 (responsible for 20.1 and 15.2% of the total deaths during 2017, respectively) (Aburto et al., 2018; Soto-Estrada et al., 2013). In addition, in 2013, for three of its components (obesity, DM2 and SAH) it is estimated that almost 90% of the budget of the Ministry of Health was allocated at the federal level and the Mexican Institute of Social Security (IMSS), for the care of chronic non-communicable diseases (Figueroa-Lara et al., 2016).

MS is the set of clinical and metabolic factors that increase the risk of developing DM2 up to 4 times, (an increase of 40%) coronary artery disease (CAD) and cerebrovascular disease (CVD) (Zafar et al., 2018), and is characterized by the presence of prediabetes and another risk component for developing cardiovascular disease (*OPS/OMS | Diabetes*, n.d.). The related risk factors (25-45%) are: central obesity, dyslipidemia, systemic arterial hypertension (SAH), hypercoagulability and insulin resistance (Zafar et al., 2018). By integrating physiological, biochemical, clinical, and metabolic factors, MS together contribute to an increase in cardiometabolic effects, morbidity and mortality (Ford, 2004; Hillier et al., 2005; Lakka et al., 2002). People with MS have a five times greater risk of developing

DM2, and three times of presenting a CVD and myocardial infarction, compared to healthy people (Zafar et al., 2018). Since the 1999 definition of MS was established, the European Group for the Study of Insulin Resistance (EGIR) suggested a definition like that of the WHO but excluded microalbuminuria (AU) and diabetes (Beck-Nielsen, 1999). In 2001, the United States National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) published a more practical definition for MS, however eliminated resistance to insulin as a criterion (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, 2002).

In 2003, the American Association of Clinical Endocrinologists (AACE) provided its criteria for the diagnosis of MS, including oral glucose intolerance (IGT) or the presence of impaired fasting blood glucose (IFG) as part of them, without requiring a specific number of other factors, because the decision is based on the judgment of the clinician. Additional main criteria to be considered include increased serum triglyceride (TG), elevated blood pressure, reduced high-density lipoprotein cholesterol (HDL-C), and obesity (BMI). Other factors that could be used in the trial included: a family history of atherosclerotic vascular disease or DM2, polycystic ovary syndrome (PCOS), and hyperglycemia. This group excluded DM2 as part of their diagnostic criteria (Strazzullo et al., 2008).

In 2005, the International Diabetes Federation (IDF) proposed a new definition for MS and integrated abdominal obesity and classification by ethnic group (Monami et al., 2007), and two years later it integrated the definition of MS for children and adolescents (Alberti et al., 2006). In 2009, to clarify some of the controversy and unify the clinical definitions of MS, a meeting was convened with representatives of the International Diabetes Federation Task Force on Epidemiology and Prevention), the National Heart, Lung, and Blood Institute (NHLBI), the American Heart Association (AHA), the World Heart Federation (World Heart Federation, WHF), the International Atherosclerosis Society (IAS), and the International Association for the Study of Obesity (ASO). These bodies published a 'joint interim statement' where there should be no mandatory component, although there was agreement regarding the importance of central obesity and therefore waist measurement would remain a useful preliminary screening tool, although not an indispensable prerequisite. Three of the five abnormal findings qualify a person with MS. With these criteria, a single set of cut-off points is used for all components except waist circumference, for which further study is required and is currently based on population / country-specific definitions (Alberti et al., 2009). Although each definition has common characteristics, there are several parameters that differ, resulting in a difficulty in terms of applicability, uniformity, and in determining the positive predictive value (PPV). The AACE, WHO and EGIR definitions focus on insulin resistance, which is determined by oral glucose tolerance test, HOMA (Homeostasis Model Assessment) and QUICKI (Quantitative Insulin Check Index) indices or the hyperinsulinemic-euglycemic clamp. However, the latter method, intensive and invasive, is used mainly for clinical research purposes (Ritchie & Connell, 2007).

However, a major problem with the NCEP ATP III and WHO definitions has been their applicability to different ethnic groups, especially when trying to define the limits of obesity. This is particularly evident for the risk of DM2, the frequency of which increases at much lower cut-points for obesity among Asian individuals compared to Europeans or North Americans (Kaur, 2014). To increase the sensitivity of the definition of MS, it has been suggested that they should integrate family history, habitual physical activity and smoking, together with the specific limits that have been established in each region (Ghosh, 2011) (Table 1).

It is known that patients with MS have between two and five times the risk of developing CVD and DM2, between 5 and 10 years, compared to people without MS (Alberti et al., 2009). An increase in waist circumference of at least 11 cm and weight gain of ≥ 2.25 kg has been associated with an-80% increase in the risk of developing SD in the following five years (Palaniappan et al., 2004)black, and Hispanic participants in the Insulin Resistance Atherosclerosis Study (IRAS.

Metabolic alterations occur simultaneously with greater frequency, which is due cardiovascular risk increases with the number of components of MS present (Andreadis et al., 2007). The importance of studying this syndrome lies in the fact that its alterations appear earlier than its complications, so the timely detection

Table 1. Definition and diagnostic criteria of metabolic syndrome.

Clinical measurement	WHO	EGIR	NCEP ATP III	AACE	FID	IFD/NHLB/AHA/ WHF/IAS/ISO
Dysglycemia	IGT, IFG, or DM2 or decreased insulin sensitivity	Plasma insulin> 75th percentile, plus 2 of the following criteria: IGT or IFG (not DM2)	3 or more of the following: IFG (> 110 mg / dL) or DM2	IGT or IFG (not DM2)	3 or more of the following: IFG (≥ 100 mg / dL) or DM	3 or more of the following: IFG (≥ 100 mg / dL) or DM
Body mass	BMI> 30 kg / m2 or waist-hip ratio> 0.9 in men and> 0.85 in women	Waist ≥ 94 cm in men and ≥ 80 in women	Waist ≥ 102 cm in men and ≥ 88 in women	BMI> 25 kg / m2	Increased waist (specific by ethnicity) (8), necessary condition	Increased waist (ethnic specific) (11)
Serum lipids	TG ≥ 150 mg / dL or HDL-C <35 mg / dL in men and <39 mg / dL in women	TG ≥150 mg / dL or HDL-C <39 mg / dL in both sexes	TG ≥150 mg / dL HDL-C <40 mg / dL in men and <50 mg / dL in women	TG ≥150 mg / dL and HDL-C <40 mg / dL in men and <50 mg / dL in women	TG ≥ 150 mg / dL HDL-C <40 mg / dL in men and <50 mg / dL in women or on treatment	TG ≥150 mg / dL HDL-C <40 mg / dL in men and <50 mg / dL in women or on treatment
Blood pressure	≥ 140/90 mm Hg	≥ 140/90 mm Hg o tratada	≥ 130/85 mm Hg	≥ 130/85 mm Hg	Systolic ≥ 130 mm Hg or diastolic ≥85 mm Hg or under treatment	Systolic ≥ 130 mm Hg or diastolic ≥85 mm Hg or under treatment for SAH
Others	UA: urinary excretion> 20 µg / min or albumin / creatinine ratio> 30 mg / g				Other findings of insulin resistance (sedentary lifestyle, endothelial dysfunction, PCOS, etc.)	

Adapted of Kaur (2014).

of these risk factors allows early interventions that could delay or stop the natural history of diabetes and diabetes. cardiovascular disease, as well as the modification of morbidity and mortality figures. Having an update of the main national and international evidence of its causes, management, treatment, and prognosis can be useful to health personnel to have intervention strategies, prevention, and control of the disease, and therefore its clinical management (Aguilar-Salinas et al., 2004).

Despite, there is no effective therapeutic approach beyond interventions based on the adoption of healthy lifestyles, that there is sufficient evidence of their beneficial effects to achieve an adequate body weight and a decrease in cardiometabolic risk, in addition to beneficial effects on lipids, glucose and blood pressure (Grundy, 2016; Pérez et al., 2019). Diet, physical activity, rest (sleep), psychological and emotional control (stress management), social support, avoiding the consumption of tobacco, alcohol, and other drugs, are key objectives for the prevention and containment of the factors risk factors already mentioned (Aguilar-Salinas & Viveros-Ruiz, 2019).

However, most of the time people fail to maintain these changes and therefore their beneficial effects. It is known that 70 to 80% of people treated with lifestyle modifications regain their previous body composition within 3 to 5 years (Dalle Grave et al., 2010; Montesi et al., 2016). In addition to the difficulty of integrating a multidisciplinary approach (medical professional,

nutritionist, psychologist, physical activator, etc.), due to economic or cultural aspects. The awareness by health personnel of patients to change their eating habits or related behaviors such as environmental or sociodemographic factors, to improve their health, have not achieved the desired effects (Aspry et al., 2018).

In addition to the above, when MS complications occur (eg cardiometabolic, underlying diseases, etc.), drug therapy involves the use of various drugs depending on their present comorbidities, requiring their prolonged use, which implies a challenge for patients due to polypharmacy, costs, low adherence or motivation for compliance, and side effects that may occur (Rask Larsen et al., 2018).

Therefore, it is necessary to continue describing and investigating other strategies that are integrated into current treatments that have already been scientifically validated, such as dietary strategies or the design of food products that modulate MS.

There is growing interest in the study of the effects on the gastrointestinal microbiome, insulin resistance and abdominal obesity (Lee et al., 2019), key elements in the pathophysiology of MS. There is evidence that the gut microbiome, as a pathogenic factor, affects the metabolic balance of the host (Pascale et al., 2018). The intestinal microbiota modulates the host's nutrition and energy harvesting (through the production of vitamins and the fermentation of non-digestible food components by the host), influences intestinal epithelial homeostasis, participates in the development of the immune system of the host, in protection against pathogens, in drug metabolism, etc. (Festi et al., 2014).

Within the microbiota, more than 90% of all phylogenetic types belong to just two of the 70 phyla in the bacterial domain: *Bacteroidetes* and *Firmicutes* (Rinninella et al., 2019). At this point, an alteration in the relationship between both phyla is known to promote a state of subacute systemic inflammation, insulin resistance and an increased risk of CAD; this is due to the expression of various bacterial products and by-products, including bacterial lipopolysaccharide (LPS) (Liang et al., 2013). In this sense, it has been proposed that the intake of probiotics can improve the clinical management of MS (Sáez-Lara et al., 2016).

Probiotics are live microorganisms that, when consumed in adequate amounts, confer an effect on the health of the host (Sanders, 2008). The main mechanisms underlying the benefit of probiotics include improved intestinal barrier function, greater competitive adherence to the mucosa and intestinal epithelium, restoration of the balance of the gastrointestinal microbiome, and regulation of the gut-associated lymphoid immune system (decreased inflammation) (Martin & Walker, 2008).

However, there are still inconclusive results on the health benefits of probiotics in metabolic diseases. Some of the studies have reported a beneficial effect on some of the components of MS (blood pressure and lipid profile), while no effects have been found on the modification of obesity (reduction in BMI) in the adult population (Rondanelli et al., 2017).

These differences can be explained by the different study designs and using different strains, doses and forms of administration of probiotics, the type and level of obesity, the age of the study subjects, etc. Therefore, the present study aims to carry out a systematic review of the best evidence on the effects of probiotics in the prevention, treatment and clinical management of MS in the adult population, with the aim of recognizing its clinical utility as a potential therapeutic option and, in this way, identify new strategies that are integrated into clinical management and prevention measures that allow reducing the economic, social and health burden that MS represents in Mexico and in the world.

Methodology

A search was carried out on the subject: "effect of probiotic supplementation in the prevention and treatment of adult patients with metabolic syndrome", according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) (Moher et al., 2009), on indexed scientific articles published in the last 5 years. The search was carried out in the collections of digital biomedical publications: *Pubmed-Medline, Scopus, Web of Science, LILACS, Cochrane, SIGN, NICE* and *Scielo*, on texts published in Spanish or English, limited to studies in adult human beings, defined by *Pubmed* as "those individuals between 19 and 44 years old.

The medical subject headings (MeSH) or descriptors of health sciences (DeCS), of the Pan American Health Organization, named below were used. The construction of the strategy for the Pubmed platform was as follows:

"Probiotics"[Mesh] AND ("Metabolic syndrome"[Mesh] OR "Obesity" [All fields] OR "overweight" [All fields] OR "Obesity, Abdominal"[Mesh] OR "Abdominal obesity metabolic syndrome" [Supplementary Concept] OR "Insulin Resistance"[Mesh] OR "Glycemic control"[tw] OR "Dyslipidemias"[Mesh] OR "Hypertension"[Mesh OR "Diabetes Mellitus, Type 2"[Mesh]) AND "Adult"[Mesh] AND "Human"[Mesh] AND "2010/06/01"[PDAT] : "2020/06/01"[PDAT]) AND (English[Lang] OR Spanish[Lang]).

For Scopus was utilized the next search strategy: TITLE-ABS-KEY (("Obesity" OR "overweight" OR "Metabolic Syndrome" OR "Abdominal Obesity metabolic syndrome" AND "probiotics")) AND ((clinical AND study)) AND (("Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) AND LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English", "Spanish")).

For the rest of the databases, the terms used were «hypertriglyceridemia», «HDL deficiency», «hyperglucemia», «impaired fasting glucose», «fasting blood glucose impairment», «obesity» and «albuminuria», as well as their equivalents in Spanish individually. In addition, a manual reference search was performed using bibliographies of retrieved articles and recent reviews (less than 3 years from publication).

Inclusion criteria

Randomized clinical trials (RCTs), non-randomized (RCTs), with a parallel or crossover design, or comparative observational, cross-sectional or longitudinal, that met the guidelines of the *Strengthening the Reporting of Observational studies in Epidemiology* (STROBE) (Cuschieri, 2019).

Studies that systematically reported the effect (by means of odds ratio [OR] or relative risk [RR]) of probiotic supplementation (indicating the dosage, species and strain used) of adult patients (between 19 and 44 years old), both sexes, with a diagnosis of MS, according to the IDF criteria or some other international consensus.

Studies that broke down the main characteristics of probiotic supplementation (eg duration, route, diet, and treatment control) and analyzed absolute risk, attributable risk, absolute risk reduction, number that need to be treated, and potential adverse ef15fects.

Studies that included the main clinical characteristics (eg duration of DM2, intensity of physical activity, treatment and adherence, presence of comorbidities, complications, etc.) and sociodemographic (eg age, sex, education level), marital status, etc.) of the selected participants.

Non-inclusion criteria

Studies that did not answer the research question.

Studies of reports or series of cases, reviews, expert opinions, personal communications, conference abstracts, thesis, and dissertations.

Interventions that used symbiotics, prebiotics, or without an appropriate control for comparison.

Studies that did not describe the procedures for quantifying blood metabolites (GLT, HDL cholesterol, plasma glucose, plasma insulin, etc.) or anthropometric parameters (abdominal circumference, blood pressure) relevant to metabolic syndrome.

Studies focused on patients with type 2 diabetes mellitus, in pregnancy, puerperium, lactation or in the pediatric or geriatric population.

Statistical analysis

The following information was obtained: name of the first author, year of publication, number of participants, type of study, type of intervention (including dose, species, and frequency of consumption of probiotics) and results related to MS: obesity, atherogenic dyslipidemia, arterial hypertension and dysglycemia. A systematic review of bias in included studies was

performed using Cochrane criteria (Muñoz-Martín & Higgins JPT, Green S, 2012).

The indicators used for the evaluation of each study were the following: study design, randomization, blinding of both investigators and participants and blinding of participants, control of variables, evaluation of results, treatment of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias.

According to the Cochrane Handbook recommendations, a judgment of 'yes' indicated a low risk of bias, while 'no' represented a high risk of bias. Labeling the article as 'unclear' signified imprecise or unknown risk of bias (Muñoz-Martín & Higgins JPT, Green S, 2012).

Since the relevant variables were quantitative, continuous data were used to calculate the difference between means (with 95% confidence intervals [CI]) and, since different variables or identical variables were compared, but with a different scale, the standardized mean difference (SMD) as a measure of effect size.

The weighting of the SMDs was carried out using the inverse variance method. A random effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of the studies in terms of study design, duration of treatment, and characteristics of the studied populations (Higgins & Thompson, 2002).

To integrate the data in the meta-analysis, those studies where data reported medians and interquartile ranges (IQR) were transformed into means and standard deviations (±), as described by Hozo et al., 2005.

Subgroup analysis and meta-regression were incorporated to search for possible sources of heterogeneity if necessary. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or various publications. Publication bias was assessed by reviewing the Begg funnel plots. Formal statistical evaluation of funnel plot skewness has been made using Egger's regression skewness test and Begg's adjusted rank correlation test (Egger et al., 1997).

Heterogeneity between studies was analyzed using the Cochran Q test and the I^2 index. Heterogeneity was considered statistically significant if the p value was <0.10. I^2 values 25%, 50% or 75% were considered to represent low, moderate, or high heterogeneity, respectively (Higgins & Thompson, 2002). To assess the influence of each study on the overall effect size, the sensitivity analysis has been made using the one-out method, that is, iteratively removing one study at a time and repeating the analysis.

Results

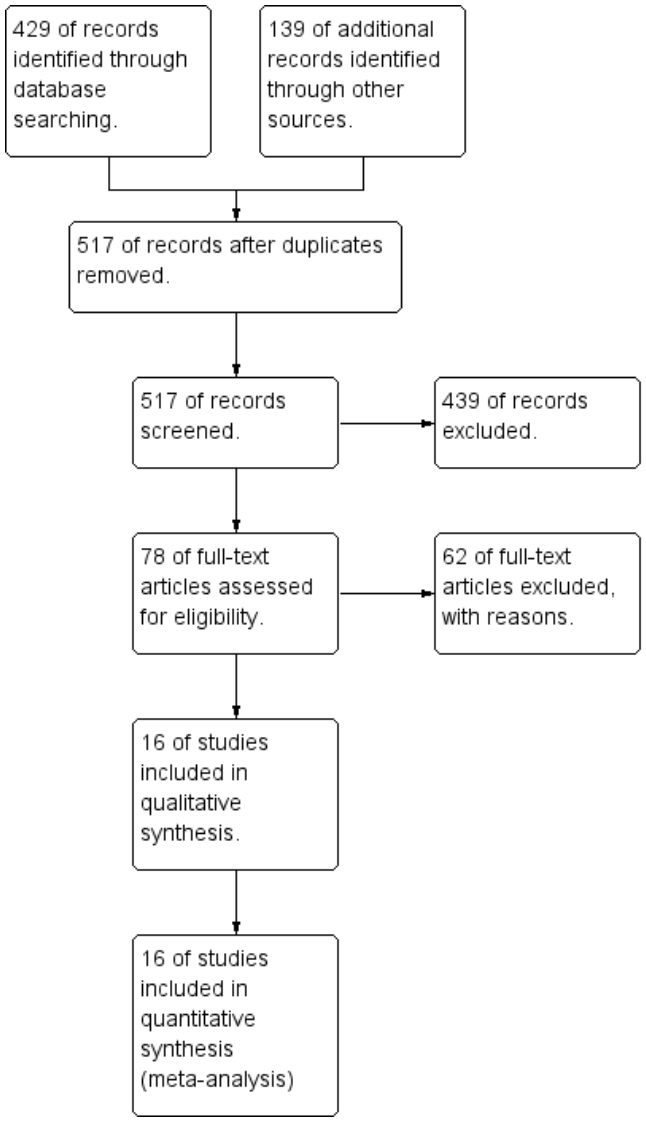
Using the search strategy described above, a total of 429 records (that is, original articles, review articles, personal communications, letters to the editor, errata, etc.) were found in the literature in the *Pubmed-Medline databases, Scopus, Web of Science, LILACS, Cochrane, SIGN, NICE* and *Scielo*. Following manual reference searching, using the bibliographies of retrieved studies, 139 additional records were identified.

A 51 of these were discarded because they were similar. The identification of these was done automatically with the help of the Mendeley bibliographic manager. Of the 517 remaining records, the title, the abstract and, based on the objectives of the study, and 439 were discarded. On the 78 original articles considered, an exhaustive analysis of their content was carried out to define their relevance in this systematic review. At the end of this study, 16 articles were included, because the remaining 62 did not meet the inclusion criteria or did not meet the previously described exclusion or elimination criteria. A summary of the search methodology is shown in Figure 1.

According to various authors patients from the same clinical trial registry were counted, respectively; therefore, nine randomized clinical trials (RCTs) and one non-randomized (RCT) were analyzed. Seven studies were conducted in participants of both sexes and three exclusively in women (2 only with postmenopausal women).

The dose used and the duration of probiotic supplementation ranged from 3.5×10^6 a 1.5×10^{11} UFC/g, between 3 to 24 weeks, respectively. Likewise, they used single or combined species of *Lactobacillus* (L) or *Bifidobacterium* (B) proliferating (in milk, yogurt, or cheese) or lyophilized (in capsules) (Kassaian et al., 2018, 2019, 2020; Stadlbauer et al., 2015; Szulińska, Łoniewski, Skrypnik, et al., 2018; Szulińska, Łoniewski,

Figure 1.
Flow diagram of the literature search process.



van Hemert, et al., 2018; Tripolt et al., 2013, 2013, 2015). The main results for the criteria that define MS, the specific strains used, and the characteristics of the studies are described in Table 2.

The evaluation of the studies showed a low risk of bias in the following categories: selective reporting of results (100%), in data of incomplete results (80%) and in random generation of the sequence (70%). However, the allocation concealment category had a high percentage of unclear risk of bias (70%), and, in the case of blinding of participants and staff, a 40% high risk of bias was found. Blinding of assessors and outcome was 60% unclear and 10% high risk of bias (Figure 2A).

The articles published by Kassaian et al., (2018, 2019 & 2020) and the two articles by Szulińska et al., (2018a & 2018b) had the lowest risk of bias in the reporting of all items. Performance and detection biases were considered unclear or high risk in five of the ten included trials. Figure 2B shows the criteria for each risk of bias element for each clinical study included in the review.

To evaluate the effect of supplementation on body obesity, a meta-analysis was performed in 8 clinical trials that included 387 participants (196 in the probiotics group and 191 in the control group), which showed a trend in the reduction of BMI (*difference mean [MD] - 0.54, 95% CI - 2.14, 1.06*); however, a statistically significant ($p = 0.008$) moderate heterogeneity (I^2 63%) was found (Figure 3A).

In the case of insulin resistance, evaluated using the HOMA-IR, although no heterogeneity was found in the results (I^2 *0%,* $p = 0.72$), probiotic supplementation did not show a statistically significant effect on the main component. of the MS ($p = 0.69$) (Figure 3B).

Along the same lines, in the evaluation of the effect of probiotic supplementation in atherogenic dyslipidemia, which included 8 studies with 409 participants (208 in the probiotics group and 201 as controls), a significant effect on the reduction in HDL-C concentrations ($p = 0.24$), with a trend that did not show heterogeneity (I^2 *0%,* $p = 0.48$) (Figure 4A).

Regarding blood pressure, there was no significant effect ($p = 0.13$) and it showed moderate heterogeneity (I^2 *63%,* $p = 0.02$). As in atherogenic dyslipidemia, where a greater benefit was observed in the group of controls (Figure 4B).

Discussion

The primary mechanisms underlying the antagonistic effects of probiotics include improvement of intestinal barrier function, increased competitive adherence in the mucosa and epithelium, modification of the intestinal microbiota, and regulation of the intestinal lymphoid immune system (Kim et al., 2019).

Table 2. Main characteristics of the selected studies.

Study	Study design	Participants	Intervention	Main results (control *vs* intervention)
Kassaian *et al*. 2018, 2019, 2020	Controlled, double-blind, parallel-group RCT.	120 participants between 35 and 70 years old, both sexes, with prediabetes according to the ADA (53). An 85 participants completed the study.	Control: placebo (maltodextrin) for 24 weeks. Intervention: supplementation with 6 g/day of lyophilized probiotics consisting of: *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *B. lactis* y *B. longum* (1.5 x 10^9 CFU each one) with maltodextrin as an excipient for 24 weeks.	ATP criteria III (table 1). Dysglycemia: 60.7 % *vs* 57.7 % presente (p = 0.95). Central obesity: 71.4 % *vs* 61.5 % present (p = 0.36). High blood pression: 35.7 % *vs* 19.2 % present (p = 0.39) hypertriglyceridaemia: 62.9 % *vs* 34.6 % (p = 0.02). HDL – C low: 75 % *vs* 48 % (p = 0.07). BMI: 30.6 ± 3.4 *vs* 29.5 ± 3.6 kg/m^2. HbA1c: 5.77 ± 0.5 *vs* 5.56 ± 0.3 %. Plasmatic glucose: 103.68 ± 8.9 *vs* 100.7 ± 7.7 mg/dL. Insulin: 14.42 ± 6.5 *vs* 13.11 ± 6.2 µU/L. HOMA-RI: 3.71 ± 1.8 *vs* 3.28 ± 1.6.
Tenorio – Jiménez *et al*. 2019	Controlled, quadruple blind, crossover RCT.	A 53 participants, between 18 and 65 years old, both sexes, with a diagnosis of MS according to the IFD (Table 1). 34 participants completed the study.	Control: maltodextrin capsules daily for 12 weeks. Intervention: supplement, in capsule, of probiotic made up of *Lactobacillus reuteri* V3401 (5 x 10^9 FCU) each 12 weeks.	Plasmatic glucose: 108.08 ± 11.5 *vs* 105.53 ± 10.5 mg/dL. Insulin: 16.18 ± 11.3 *vs* 21.74 ± 11.7 µU/L. HOMA – IR: 4.41 ± 3.3 *vs* 5.66 ± 3.5. BMI: 37.57 ± 7.1 *vs* 36.56 ± 6.6 kg/m^2. SBP: 133.28 ± 15.4 *vs* 132.21 ± 14.6 mm Hg. DAP: 81.96 ± 7.7 *vs* 82.11 ± 10.5 mm Hg. hypertriglyceridaemia: 122.46 ± 59.9 *vs* 118.89 ± 52.2 mg/dL. HDL – C: 50.46 ± 12.2 *vs* 54.11 ± 10.2 mg/dL.
Rezazadeh *et al*. 2019	Controlled, double-blind, parallel-group RCT.	44 participants, both sexes, aged 20 to 65 years, with a diagnosis of MS (criteria not specified). All of these completed the study.	Control: 300 g commercial yogurt for 8 weeks. Intervention: 300 g of yogurt supplemented directly with *L. acidophilus* La5 y *B. lactis* Bb12 (~4.41 x 10^6 y 3.55 x 10^6 FCU/g, each one).	Plasmatic glucose: 97±7.72 *vs* 95.64 ± 10.58 mg/dL. Insulin: 11.52 ± 3.6 *vs* 11.62 ± 4.42 µU/L. HOMA – IR: 2.72 ± 0.93 *vs* 2.76 ± 1.14.
Bernini *et al*. 2016	Parallel group RCT.	A 51 participants, both sexes, between 18 and 60 years old, diagnosed with MS according to the NCEP / ATP III criteria (Table 1).	Control: not treated. Intervention: 80 mL daily of pasteurized milk supplemented with *Bifidobacterium lactis* HN019 (3.4 x 10^8 FCU/mL) during 45 days.	Plasmatic glucose: 99 (IQR 91 – 113) *vs* 97 (IQR 88.3 – 124.3) mg/dL. Insulin: 13.65 (RIC 9.46 – 21.78) *vs* 15.3 (RIC 10.2 – 17.4) µU/L. HOMA – IR: 3.23 (RIC 2.33 – 5.55) *vs* 4.09 (IQR 3.37 – 5.87). BIM: 35.5 (IQR 32.2 – 40.7) *vs* 29.5 (IQR 25.9 – 33.3) kg/m^2. waist: 109 (IQR 99.5 – 124.5) *vs* 107 (IQR 98.5 – 115) cm. SAP: 121 (IQR 110 – 131) *vs* 140 (IQR 127.5 – 150) mm Hg. DAP: 72.5 (RIC 63.5 – 82.3) *vs* 90 (80 – 100) mm Hg. TG: 168.5 (IQR 113.5 – 221.3) *vs* 174 (RIC 124 – 296) mg/dL. HDL: 39 (IQR 35.5 – 47) *vs* 38.5 (IQR 31.3 – 46) mg/dL.

Table 2. Continued.

Study	Study design	Participants	Intervention	Main results (control *vs* intervention)
Stadlbauer *et al*. 2015, and Tripolt *et al*. 2013, 2015	RCT, double blind, of parallel groups and permuted blocks	28 adult participants, both sexes, diagnosed with MS according to the NCEP / ATP III criteria (Table 1).	Control: not treated. Intervention: 3 bottles per day of 65 mL containing *Lactobacillus casei Shirota* at a concentration of 1 x 10^8 CFU / mL (Yakult light ®, Yakult Austria, Vienna, Austria).	Plasmatic glucose: 5.8 ± 0.5 *vs* 5.9 ± 0.9 mmol/L. Insulin: 10.5 ± 8.8 *vs* 11.9 ± 7.6 µU/L. HOMA-IR: 2.7 ± 2.2 *vs* 3.2 ± 2.1. BMI: 31.3 ± 4.1 *vs* 34.08 *vs* 5.7 kg/m^2. Waist: 106 ± 9 *vs* 112 ± 12 cm. SAP: 139 ± 11 *vs* 142 ± 16 mm Hg. DAP: 88 ± 9 *vs* 92 ± 12 mm Hg. Tg: 159 ± 66 *vs* 202 ± 123 mg/dL. HDL-C: 42 ± 12 *vs* 40 ± 16 mg/dL.
Madjd *et al*. 2016	Controlled, blinded, parallel group RCT.	89 women, aged 18 to 50, with a BMI between 27 to 40 kg/m^2 and waist circumference> 88 cm. 81 patients completed the study.	Control: consumption of 200 grams of low-fat yogurt, twice a day, for 12 weeks. Intervention: 200 grams of low-fat yogurt, supplemented with a minimum of 1 x 10^7 CFU of *Lactobacillus acidophilus LA5 and Bifidobacterium lactis BB*, twice a day, for 12 weeks.	Plasmatic glucose: 4.80 ± 0.41 *vs* 4.78 ± 0.44 mmol/L. Insulin: 11.36 ± 3.26 *vs* 11.09 ± 3.31 µU/L. HOMA-IR: 2.43 ± 0.77 *vs* 2.38 ± 0.8. BMI: 30.08 ± 3.86 *vs* 30.08 ± 3.15 kg/m^2. Waist: 96.54 ± 10.01 *vs* 96.08 ± 6.98 cm. TG: 1.31 ± 0.27 *vs* 1.31 ± 0.31 mmol/L. HDL-C: 1.25 ± 0.17 *vs* 1.27 ± 0.19 mmol/L.
Ivey *et al*. 2015	Controlled, double-blind, factored and parallel-group RCT.	An 156 participants, both sexes, older than 55 years, BMI ≥ 25 kg / m^2, waist circumference ≥ 94 cm in men and ≥ 80 cm in women, BP ≥ 120/80 mm Hg and a minimum consumption of probiotics (<400 g yogurt / week, without supplementation).	Control: milk and control capsules, once a day, for 6 weeks. Intervention: yogurt and capsules containing: *L. acidophilus LA5 and B. animalis subsp. lactis BB12*, at a minimum concentration of 3.0x10^9 CFU, once a day for 6 weeks.	SAP: 129 ± 1 *vs* 130 ± 1 mm Hg. DAP: 74 ± 1 *vs* 75 ± 1 mm Hg. HDL-C: 1.41 ± 0.09 *vs* 1.39 ± 0.02 mmol/L. TG: 1.57 ± 0.06 *vs* 1.64 ± 0.05 mmol/L.
Szulińska *et al*. (2018a, b)	Controlled, double-blind and parallel-group RCT.	An 81 women, aged 45 to 70 years, in their postmenopause (≥ 1 year of the last menstruation), BMI 30 - 45 kg/m^2, waist circumference> 80 cm, fat mass ≥ 33% and stable body weight during the previous month to the study (±1 kg). 71 patients completed the study.	Control: placebo (2 g of cornstarch, including maltodextrin), twice a day, for 12 weeks. Intervention: 2 g of lyophilized powder containing 1 x 1010 CFU of: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 y *Lactococcus lactis* W58, were divided into two doses, for 12 weeks.	BMI: 36.04 ± 4.32 *vs* 35.51 ± 5.16 kg/m^2. Waist circumference: 107.27 ± 7.16 *vs* 107.97 ± 10.11 cm. Plasmatic glucose: 94.92 ± 8.24 *vs* 90.79 ± 8.82 mg/dL. Insulin: 29.8 ± 8.39 *vs* 27.73 ± 9.23 µU/L. HOMA-IR: 6.94 ± 2.15 *vs* 6.32 ± 2.47. HDL-C: 55.48 ± 10.76 *vs* 54.68 ± 8.63 mg/dL. TG: 135.72 ± 69.0 *vs* 153.4 ± 55.63 mg/dL. SAP: 131.52 ± 12.31 *vs* 131.4 ± 9.41 mm Hg. DAP: 81.88 ± 7.2 *vs* 79.36 ± 7.42 mm Hg.

Table 2. Continued.

Study	Study design	Participants	Intervention	Main results (control *vs* intervention)
Barreto *et al*. (2014)	NECNA of paired groups, in parallel.	27 postmenopausal women who met the ATP III criteria for MS (Table 1). 24 participants completed the study.	Control: 80 mL of non-fermented sweetened milk, per day, for 90 days. Intervention: 80 mL of sweetened milk fermented with L. plantarum LP115, at a final concentration of 1.25 x 10^7 CFU / g, per day, for 90 days	BMI: 28.5 (IQR 24 – 30) *vs* 29 (IQR 26.3 – 34.8) kg/m^2. Waist circumference: 103 (IQR 97.3 – 109.6) *vs* 99.8 (IQR 92.9 *vs* 108) cm. Plasmatic glucose: 95.5 (IQR 84 – 130.8) *vs* 98.5 (IQR 87.5 – 124.8) mg/dL. Insulin: 9.1 (IQR 7.5 – 12.8) *vs* 10.6 (IQR 6.3 – 16.4) µU/L. HOMA-IR: 2.69 (IQR 1.73 – 3.16) *vs* 2.71 (IQR 1.48 – 4.68). DAP: 80 (IQR 70 – 80) *vs* 80 (IQR 80 – 80) mm Hg. TG: 150 (RIC 102.8 – 180.5) *vs* 170 (RIC 119.3 – 220) mg/dL. HDL-C: 49.5 (IQR 43.3 – 53.3) *vs* 45 (IQR 38.5 – 61.5) mg/dL.
Sharafedtinov *et al*. (2013)	Controlled, double-blind, parallel-group RCT.	40 participants, both sexes, between 30 and 69 years old, with MS, defined as the presence of obesity and «arterial hypertonia» (> 130/85 mmHg). 36 participants completed the study.	Control: hypocaloric diet (1,512 kcal) supplemented with 50 g of Edam type cheese, for 3 weeks. Intervention: hypocaloric diet (1,512 kcal) supplemented with 50 gr of Edam type cheese, made from milk enriched with 1.5 x 10^{11} CFU/g de *L. plantarum* TENSIA, per day, for 3 weeks.	BMI: 34.7 ± 4.2 *vs* 35.7 ± 3.8 kg/m^2. Index waist hip: 0.978 ± 0.005 *vs* 0.984 ± 0.005. Serum glucose: 5.64 ± 1.6 *vs* 5.87 ± 3.8 mmol/L. HDL-C: 1.05 ± 0.22 *vs* 0.94 ± 0.17 mmol/L. TG: 1.43 ± 0.56 *vs* 2.09 ± 1.62 mmol/L. SAP: 120 ± 1.8 *vs* 121.8 mm Hg. DAP: 78.6 ± 1 *vs* 78.4 ± 0.9 mm Hg.

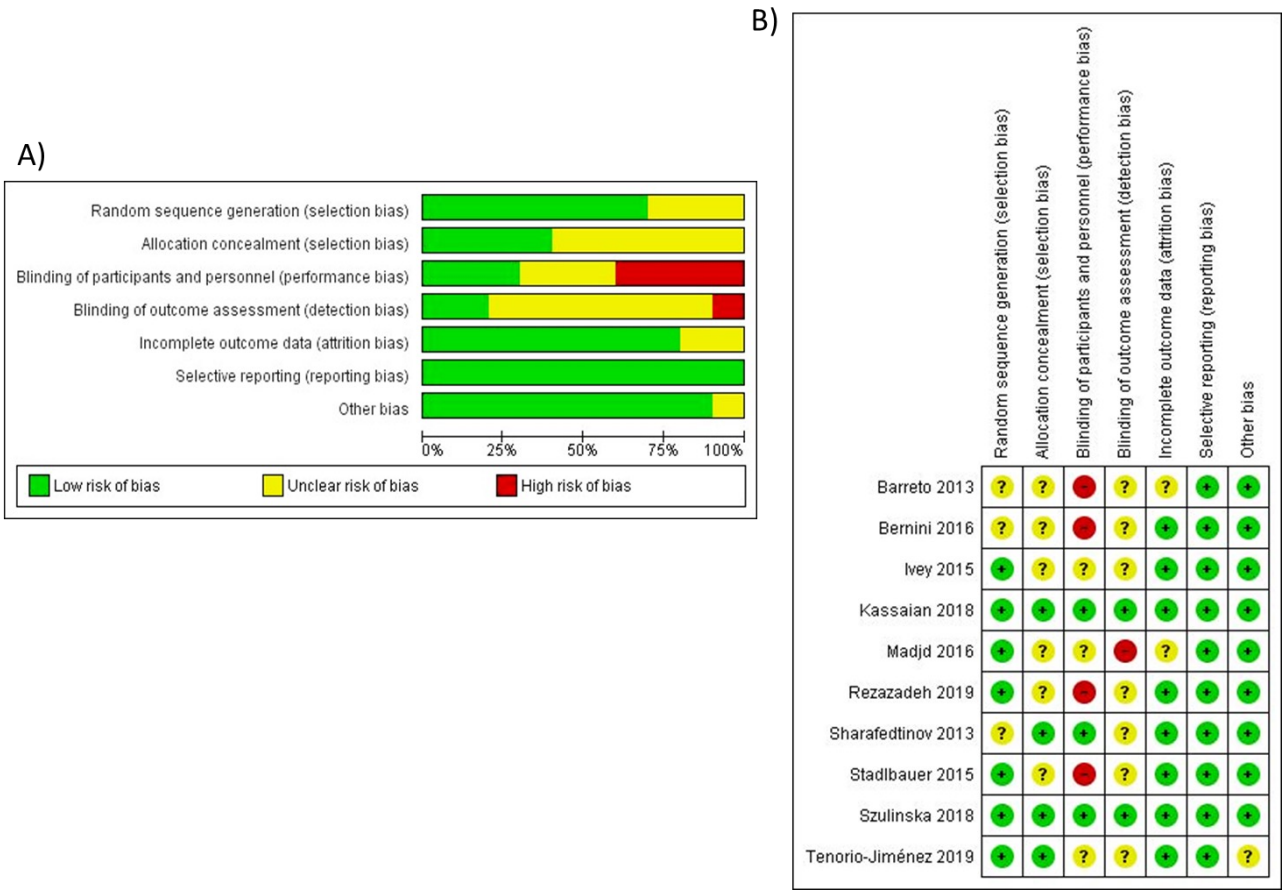
Probiotics communicate with the host through gut cell pattern recognition receptors, such as Toll-like receptors and protein-like receptors that contain nucleotide-binding oligomerization domains, which modulate important key signaling pathways, such as nuclear factor κB, key protein kinase for enhancing or suppressing cell activation and influencing downstream pathways (Llewellyn & Foey, 2017).

In 10 clinical trials of the 16 articles, which used fortified foods or a probiotic supplementation of *Lactobacillus spp.* or *Bifidobacterium spp.* single, multiple or combined, to reduce the clinical, anthropometric, and biochemical components of MS in adult patients, in the absence of other comorbidities.

Although 5 of the 10 studies reported significant benefits among the evaluated parameters, the criteria used as representative for each dimension used (BMI, HOMA-IR, HDL-C and SBP) did not show a significant difference with respect to their corresponding controls. This is like that published by Tenorio-Jiménez et al., 2020. Who, through a systematic review of nine RCTs, identified that, although there are potential beneficial effects of probiotics on the clinical and inflammatory components of MS, these were marginal in comparison with drug therapy and a healthy lifestyle; therefore, they were described as clinically not relevant.

Similarly, Dong et al., conducted a systematic review with the objective of using anthropometric and biochemical parameters as indicators to evaluate the efficacy of the use of probiotics among people with MS, through 18 RCTs with a total of 1544 participants, found no significant differences in: BMI, body fat percentage, waist circumference, hip circumference, waist-hip ratio, SBP, DBP, fasting glucose, fasting insulin, total cholesterol, HDL-C, HbA1c or triglycerides between intervention and control and only found significant standardized mean net differences in body fat mass and LDL-C (Dong et al., 2019).

Figure 2.
Assessment (A) and Summary (B) of risk of bias.



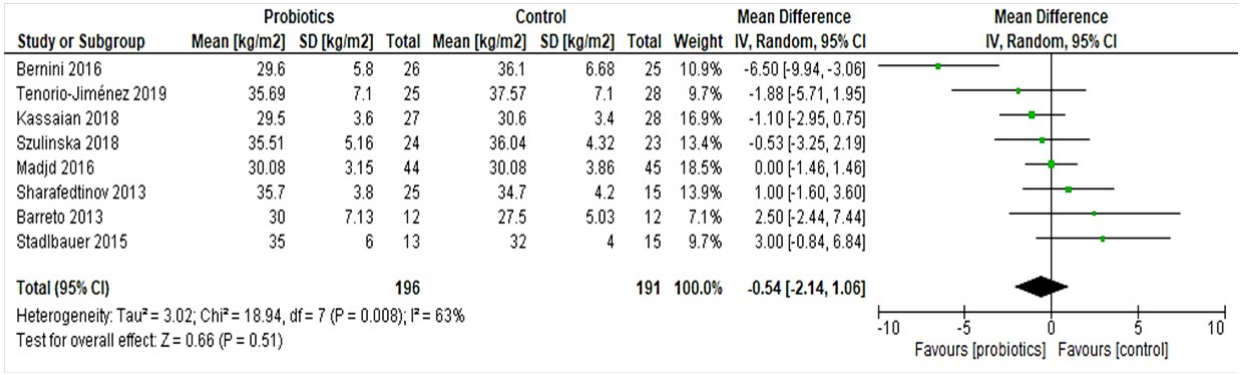
Unfortunately, MS, as a group of anthropometric, clinical, and metabolic anomalies, has different definitions developed under the auspices of various scientific societies and some of the cut-off points of its criteria vary according to ethnic origin, sex, or the availability of tests clinics. Likewise, unlike the meta-analyzes carried out on drugs, those carried out based on nutritional parameters do not allow the extraction of relevant information in a systematic way, due to the heterogeneity in the designs, strategies and participants of the interventions and protocols (Barnard et al., 2017).

Despite the identification as a selection criterion of some clinical consensus of MS, important sources of heterogeneity appeared among the participants of the selected trials: studies with only women (2 of them in postmenopause (Szulińska, Łoniewski, Skrypnik, et al., 2018; Szulińska, Łoniewski, van Hemert, et al., 2018)), variability in the ages (groups of participants with age ranges from under 20 years to over 40 years), inclusion of subjects with type 2 diabetes mellitus or systemic arterial hypertension as well as heterogeneity with different strains, doses and routes of administration of probiotics (Table 2).

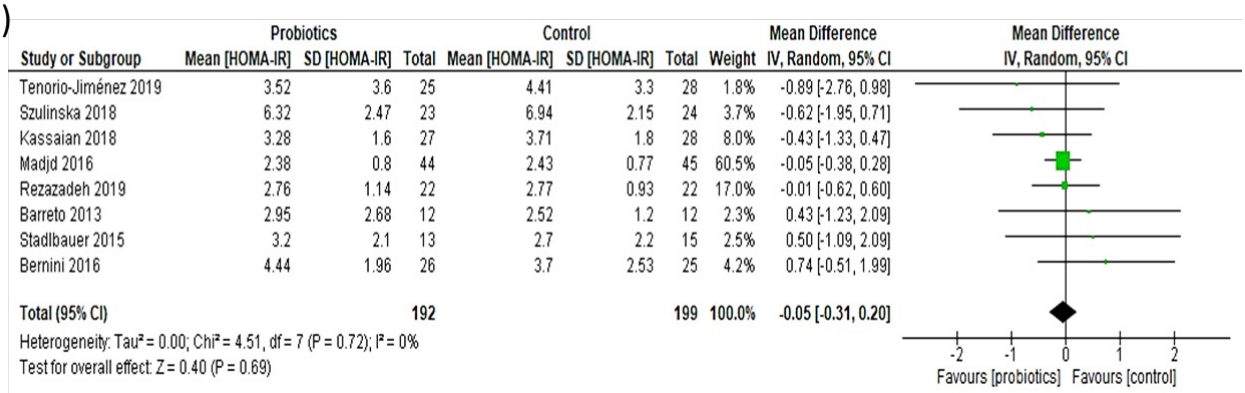
Furthermore, in three of the included studies, the intervention time (3 to 6 weeks) may not have been long enough to demonstrate changes in some of the parameters related to glucose metabolism and insulin resistance, such as hemoglobin. glycated (HbA1c), the main marker of diabetes control in clinical practice (American Diabetes Association, 2020; Davis & Edelman, 2004; Durán-Varela et al., 2001)general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc20-SPPC.

Figure 3.
Effect of probiotic supplementation in adult subjects with MS. A) Effect of probiotic supplementation on BMI. B) Effect of probiotic supplementation on insulin resistance

A)



B)



These characteristics could mean important limitations of the scope of the study. However, this review provides a broad overview of a nutritional strategy with potential applications yet to be identified within the field of clinical nutrition.

Conclusion

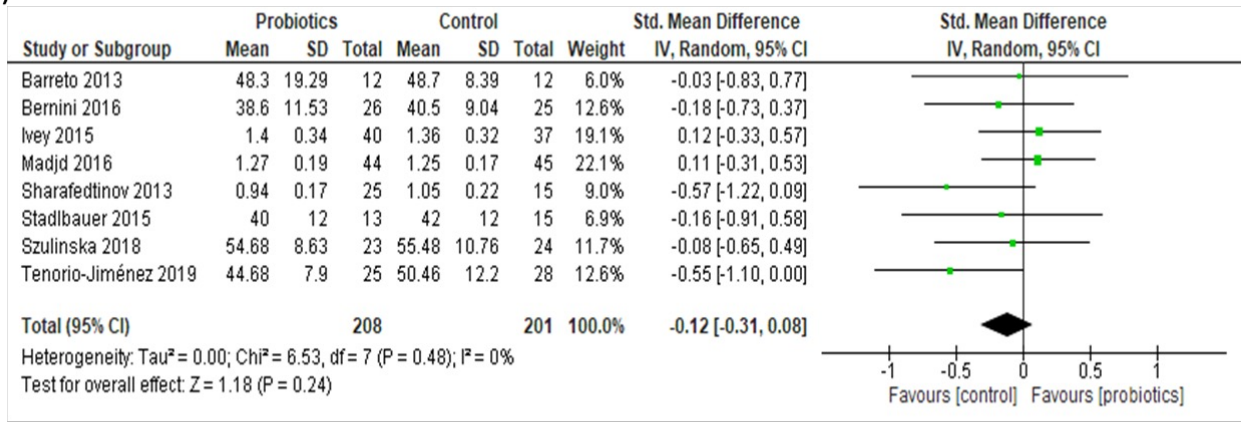
According to the clinical information available for this review, most of the articles analyzed describe that probiotic supplementation, as part of the nutritional management of adult patients with MS, could offer a slight advantage over current conventional medical treatment, in terms of improvement. of some, but not all, of the clinical, anthropometric, and biomedical components of MS.

However, although, based on the results of the meta-analyzes, we cannot conclude that probiotics exert a beneficial effect on MS and their consumption could mean some positive effects that, although they are marginal compared to drug therapy, bariatric surgery or with the implementation of healthy lifestyles, these could be mainly related to the dose, the strain, the period of its consumption, the route of administration and the personal lifestyle itself.

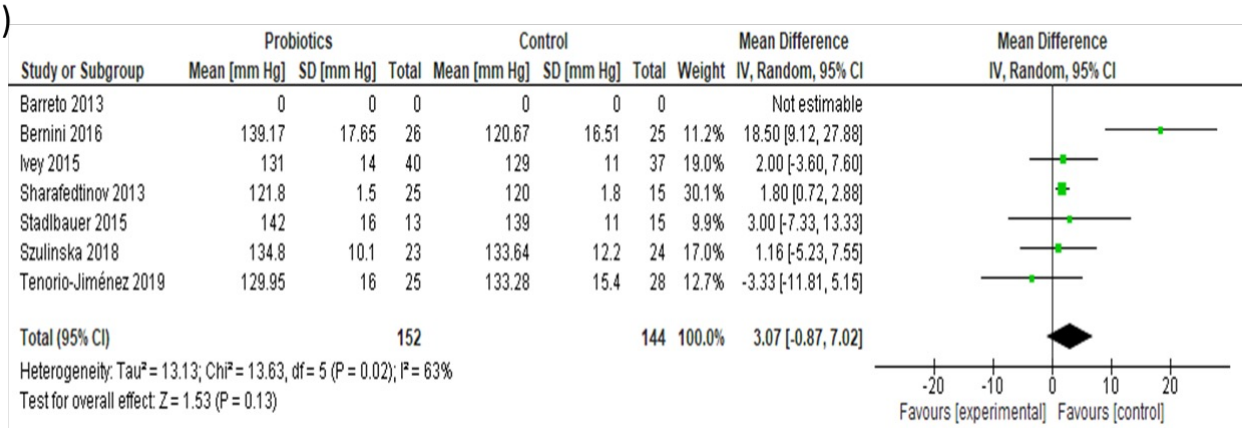
For this reason, as future lines of research, it is necessary to have RCTs to fully identify whether probiotics can be used regularly as adjunctive therapy for this condition.

Figure 4.
Effect of probiotic supplementation in adult subjects with metabolic syndrome.
A) Effect of probiotic supplementation on atherogenic dyslipidemia.
B) Effect of probiotic supplementation in atherogenic dyslipidemia.

A)



B)



In this sense, it is suggested that: crossover designs provide a more appropriate approach to determine the health benefits of clinical interventions than a parallel design; a more precise segmentation of the different clinical contexts that are related to MS in the adult patient needs to be achieved, RCTs should be designed considering the duration, type of strain, dose and mode of administration and, finally, it is recommended consider not only the statistical significance but also the clinical or the magnitude of the effect so that they lead towards new hypotheses.

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