



Relationship between gut microbiota, probiotics, and obesity in the cellular and molecular mechanisms for the activation of regulatory t cells and control of inflammatory processes: a systematic review

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Abstract

Introduction: Obesity represents a pandemic represented as a long-term chronic imbalance between calorie intake and energy expenditure, resulting in more than 30% of the world's population (over two billion people) being overweight or obese. Studies show that Tregs regulate inflammatory cells such as macrophages and T lymphocytes by reducing the production of cytokines IL-6, IL-10, etc., and microRNAs can regulate the gene expression of inflammatory cells. Probiotics have been increasingly studied for modulating the gut microbiota. **Objective:** It was to develop a systematic review to describe the main considerations of the relationship between gut microbiota, probiotics, and obesity, to list the cellular and molecular mechanisms for the activation of regulatory T cells and control of inflammatory processes. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from March to May 2024 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 122 articles were found, and 40 articles were evaluated in full and 24 were included and developed in the present systematic

review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with $X^2=78.7\%>50\%$. It was concluded that probiotic therapy proved to be an important strategy associated with a nutritional change to improve the composition of the gut microbiota. In this context, the probiotics *L. paracasei shirota*, *Akkermansia muciniphila*, and *Lactobacillus reuteri* V3401 stand out, which are responsible for reducing inflammatory markers. Modulation of the gut microbiota through physical exercise, type of nutrients, and use of prebiotics, and/or probiotics have a positive effect on reducing inflammatory markers. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism, with crosstalk with the gut microbiota. Furthermore, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. Expression of miR-15a-5p was found to be associated with *H. parainfluenzae* abundance and insulin levels.

Keywords: Obesity. Probiotics. Gut microbiota. MicroRNAs. Regulatory T cells. Inflammatory processes.

Introduction

Obesity represents a pandemic represented as a long-term chronic imbalance between calorie intake and energy expenditure, which causes serious comorbidities [1-3]. Obesity is the result of complex and incompletely understood pathological processes, resulting from crosstalk between environmental factors, genetic susceptibility, and epigenetic mechanisms, resulting in more than 30% of the world's population (over two billion people) being overweight or obese [1]. By 2030, it is estimated that more than 60% of the world's population will be overweight or obese [1,2]. Most patients with obesity, who have a BMI above 30 kg/m², present an imbalance in inflammatory mediators induced by excess nutrients is the basis of meta-inflammation in obesity, which can be mediated by regulatory T cells (Tregs) and microRNAs. Meta-inflammation in obesity can cause multiple organ dysfunction [3-5].

In this context, studies show that Tregs regulate inflammatory cells such as macrophages and T lymphocytes by reducing the production of cytokines IL-6, IL-10, etc., and microRNAs can regulate the gene expression of inflammatory cells [4-6]. However, it is not yet known how this occurs in obese patients. Therefore, the present study will aim to determine and understand how the behavior and changes that occur in Tregs and microRNAs interfere with the pathophysiological mechanisms of obesity through the action of probiotics on the gut microbiota, to evaluate the possibility of restoring the normal metabolic function ("metabolic regeneration") and, thus, determining the existence of an eventual therapeutic or even preventive potential. The results suggest that probiotics bind to dendritic cells (DC) to stimulate Treg cells, together with microRNAs, to increase the concentration of interleukins (IL-10 and IL-35), TGF- β and upregulate the MHC class II [3-6].

Thus, probiotics have been increasingly studied in terms of modulating the gut microbiota. It is believed that "supplementation with probiotics appears to reduce concentrations of low-density lipoproteins (LDL) and total cholesterol; improve atherogenic indices; improve glycemic control; reduce body weight, waist circumference, BMI and abdominal visceral adipose tissue; to improve body composition, and reduce concentrations of pro-inflammatory markers, such as interleukin 6 (IL-6) and TNF- α [7]. Considering the influence of the microbiota on the genesis and progression of obesity, as well as its consequences, knowledge about the gut microbiota and the mechanism by which its modulation through diet and/or the use of probiotics can act on the host and contribute to the treatment of obesity. obesity is fundamental [3,7].

Added to this, obesity is associated with chronic low-grade inflammation in adipose tissue. The resident immune microenvironment is not only responsible for maintaining homeostasis in adipose tissue but also plays a crucial role in combating obesity and its comorbidities. Increasing evidence suggests that obesity promotes the activation of resident T cells and macrophages. MicroRNAs contribute to the maintenance of the immune response and obesity in adipose tissue. Resident T cells, macrophages, and adipocytes secrete various miRNAs and communicate with other cells to create a potential effect on metabolic organ crosstalk. Resident macrophages and T cell-associated miRNAs have a prominent role in regulating obesity by targeting diverse signaling pathways [8-15].

Therefore, the present study developed a systematic review to describe the main considerations of the relationship between gut microbiota, probiotics, and obesity, to list the cellular and molecular mechanisms for the activation of regulatory T cells and control of inflammatory processes.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: <http://www.prismastatement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: 03/19/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 03/19/2024.

Data Sources and Research Strategy

The literary search process was carried out from March to May 2024 and was developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: "Obesity. Probiotics. Gut microbiota. MicroRNAs. Regulatory T cells. Inflammatory processes", and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case

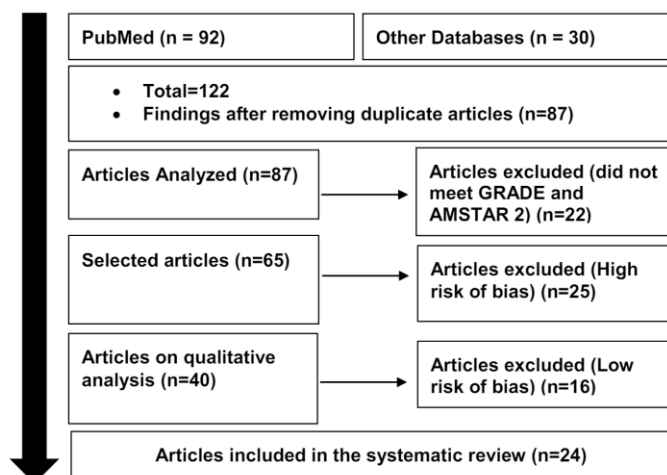
reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 122 articles were found that were subjected to eligibility analysis, with 24 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2=78.7\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Selection of articles.

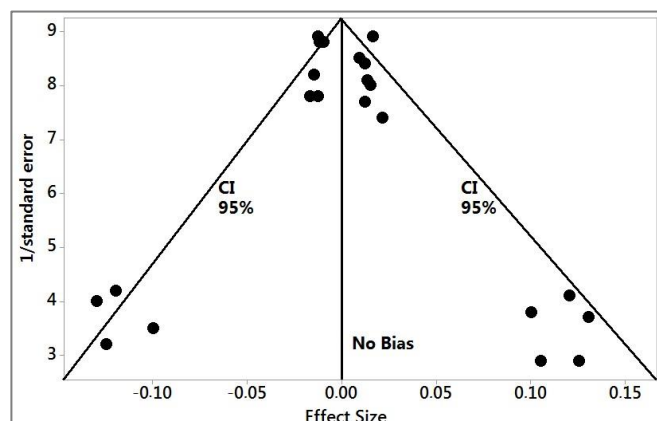


Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of

bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=24 studies).



Source: Own authorship.

Obesity, Probiotics, and Gut Microbiota

The findings regarding the use of probiotics are extremely favorable in terms of modulating microorganisms. Symbiotic supplementation using *L. paracasei shirota* [16] increased the number of individuals of the genus *Lactobacillus*, despite reducing the number of the bacteria *Akkermansia muciniphila*, known for its anti-inflammatory characteristics. Depommier collaborators [17] used pasteurized *Akkermansia muciniphila* supplementation in their study, significantly reducing the concentration of LPS in plasma, a factor that contributed to combating systemic inflammation. Furthermore, the study found good results in improving insulin sensitivity, a factor that contributes immensely to the pathophysiology of obesity associated with T2DM.

One study administered *Lactobacillus reuteri* V3401, managing to alter the microbiota at the phylum level, increasing the amount of Verrucomicrobia. This change is associated with the reduction of IL-6, an inflammatory cytokine [18]. Another way to use symbiotic supplementation was to add it to already-known diets, such as the Low-Calorie Ketogenic Diet [19]. The administration of synbiotics did not affect the diversity of the microbiota but showed an increase in the population of *Odoribacter* and *Lachnospira*, producers of anti-inflammatory mediators.

Crovesy and collaborators [20] demonstrated that the use of probiotics and synbiotics is capable of altering the Firmicutes/Bacteroidetes ratio, in addition to altering the amount of Verrucomicrobia. In the study, the group in which only synbiotics were administered achieved a significant increase in serum glutamine levels, which was associated with increased insulin sensitivity and combating the systemic inflammatory process.

The use of *Bifidobacterium pseudocatenulatum* CECT 7756 as a probiotic achieved good results in modulating the microbiota [21]. Significantly increasing the proportion of members of the Rikenellaceae family and the Alistipes genus, reducing inflammation due to the increase in bacteria commonly associated with the lean phenotype, in addition to increasing the level of omentin-1, an anti-inflammatory cytokine.

Another study [22] used a prebiotic (inulin) to manipulate the gut microbiota population, achieving an increase in Bifidobacterium, in addition to reducing fecal calprotectin, an important intestinal inflammatory marker, a fact that can be associated with changes in the microbiota.

The use of substances that stimulate the growth of specific microbiota species is also studied, to select the predominant type of microorganism in the intestine and modulate tissue inflammation. In this context, Yahoo and collaborators studied oleoyl ethanolamide and its effect on the species *Akkermansia muciniphila* [23]. The results were significant in terms of increasing the desired species through the use of the compound, in addition to reducing the production of pro-inflammatory cytokines.

Still in this light, another study evaluated the influence of vitamin D supplementation on the gut microbiota [24], showing an increase in the genus Lachnospira and a reduction in the genus Blautia. Despite changes in the microbiota, no significant reduction in inflammation or insulin sensitivity was detected. A study that evaluated pomegranate extract as an intervention obtained better results in terms of modulating the microbiota and inflammation [25]. The increase in Bacteroides and the reduction in Parvimonas, Methanobrevibacter, and Methanospaera, bacteria associated with inflammation, contributed positively to the reduction of the systemic inflammatory process.

Furthermore, studies accumulate evidence that circulating miRNAs are associated with obesity [26-29]. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism [30,31]. Thus, miR-21-5p, miR-103a, and miR-221-3p were found downregulated in blood samples from individuals with obesity in a meta-analysis study [32]. Furthermore, miRNAs that were dysregulated in obesity are associated with various metabolic processes such as glucose intolerance, maintenance of pancreatic beta cell mass, adipocyte development and adipose tissue physiology, inflammation pathways, and cardiomyocyte survival [33,34].

Furthermore, an interaction was observed between BMI levels, *B. eggerthii* abundance, and the expression of three miRNAs (miR-130b-3p, miR-185-5p, and miR-

21-5p). *B. eggerthii* is one of the intestinal bacteria that metabolizes phenolic acids, considered beneficial for human health [35]. In a recent study, *B. eggerthii* abundance was significantly higher in children with obesity and correlated positively with body fat percentage but negatively with insoluble fiber intake in Mexican children. On the other hand, this bacteria was found to be underrepresented after sleeve gastrectomy surgery [36].

Still in this reasoning, of the three miRNAs associated with the abundance of *B. eggerthii* and BMI levels, miR-185-5p and miR-21-5p were also correlated with the abundance of *D. longicatena*. Furthermore, miR-185-5p has been described to be involved in oxidative stress, obesity, and diabetes mellitus in many studies [37]. MiR-185-5p has been identified as a regulator of de novo cholesterol biosynthesis and lowdensity lipoprotein uptake [30].

Added to this, an association was found between *B. eggerthii* abundance, miR-183-5p expression, and adiponectin levels. Previous findings demonstrated that miR-183 can contribute to adipocyte differentiation, adipogenesis, and fat cell development [31]. Both gain-of-function and loss-of-function assays showed that miR-183 promoted 3T3-L1 adipocyte differentiation, lipid accumulation, and adipogenesis by increasing the expressions of peroxisome proliferator-activated receptor gamma (PPAR γ), alphabinding protein to the CCAAT enhancer (C/EBP α), adiponectin and fatty acid synthase (FAS) [30].

Expression of miR-15a-5p was found to be associated with *H. parainfluenzae* abundance and insulin levels. miR-15a positively regulates insulin biosynthesis by inhibiting the expression of the endogenous uncoupling protein 2 (UCP2) gene, leading to higher ATP levels in islets and improving glucose-stimulated insulin secretion. Furthermore, circulating levels of miR-15a were found to be downregulated before the onset of T2DM and also in individuals with incident T2DM compared to controls [3,4].

Conclusion

It was concluded that probiotic therapy proved to be an important strategy associated with nutritional change to improve the composition of the gut microbiota. In this context, the probiotics *L. paracasei shirota*, *Akkermansia muciniphila*, and *Lactobacillus reuteri* V3401 stand out, which are responsible for reducing inflammatory markers. Modulation of the gut microbiota through physical exercise, type of nutrients, use of prebiotics, and/or probiotics has a positive effect on reducing inflammatory markers. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid

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Conflict of Interest

The authors declare no conflict of interest.

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