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REVIEW ARTICLE

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The role of gut microbiota in the obesity: a literature review

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Abstract

Introduction: Obesity is a multifactorial and polygenic condition that, according to the World Obesity Federation, will affect over 1 billion people by 2030. In this regard, research is being conducted regarding gut microbiota influence on the pathogenesis of this disease, such as inflammation and insulin resistance. Therefore, understanding the gut microbiota and the mechanism by which its modulation through diet and/or the use of probiotics can impact the host and contribute to the treatment of obesity is essential. **Methods:** A systematic review was conducted on the PubMed, Scielo, and ScienceDirect databases, following the PRISMA protocol, from January 2018 to September 2022. **Results and Conclusion:** 415 articles were found. 36 studies were evaluated, and 20 were included in this review. The use of calorierestricting diets, along with the consumption of grains and cereals, was found to be useful in reducing strains that promote inflammation and insulin resistance, factors that are associated with obesity pathogenesis, leading to weight reduction. Other studies examined probiotics use, which led to lipopolysaccharides and insulin resistance reduction, as well as a decrease in the quantity of pro-inflammatory cytokines associated with obesity and type 2 diabetes mellitus. Therefore, combining diets with probiotic therapies may be a strategy for microbiota modulation, aiming to reduce inflammatory markers and insulin resistance.

Keywords: Obesity. Gut microbiota. Nutrological therapy.

Introduction

Obesity is a multifactorial and polygenic condition that, according to the World Obesity Federation, will affect more than 1 billion people by 2030 [1]. There has been evidence since the 1990s that obesity results in chronic inflammation related to Toll-like TNF-γ receptor signaling and the production of pro-inflammatory cytokines and chemokines, promoting

resistance to the action of insulin [2].

The gastrointestinal tract (GIT) is densely populated by microorganisms, approximately 100 trillion microbes, constituting the gut microbiota, which is considered an endocrine organ involved in the maintenance of energy homeostasis, eating behavior, and the central nervous system (CNS) [3,4].

Diets rich in fats, with a positive energy balance, favor GIT inflammation [5], since they lead to an imbalance between the main phyla of bacteria in the body, dysbiosis. This, in turn, can alter the functioning of the intestinal barrier and gut-associated lymphoid tissues (GALT) by allowing the passage of structural components of bacteria, such as lipopolysaccharides (LPS), which activate inflammatory pathways that can contribute to the development of insulin resistance [6].

In this inflammatory context, it is known that certain populations of bacteria produce enzymes that increase the efficiency of nutrient digestion, and therefore, the supply of nutrients to the host, thus contributing to increased energy storage in adipose tissue. In addition, the intestinal microbiome can modulate genes involved in energy storage and expenditure. Such findings indicate that modulation of the gut microbiota may have potential therapeutic implications [7].

Thus, probiotics have been increasingly studied for their modulation of the gut microbiota. It is believed that "probiotic supplementation 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 [8].

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 use of probiotics can act on the host and contribute to the treatment of obesity is essential.

METHODS

A search was conducted in the PubMed, Scielo, and Science Direct databases adhering to the PRISMA protocol. The search for publications used the following descriptors: "obesity" AND "gut microbiota" AND "inflammation" AND "treatment", according to the database algorithm.

The search covered all available texts in English and Portuguese, published between January 2018 and September 2022. The inclusion criteria were: clinical trials, original articles, treatment descriptions, and studies in humans and patients with obesity. The following characteristics were used to eliminate publications: literature reviews, animal studies, letters, articles not available in full, incomplete trials, articles dealing with surgical approaches, the use of vitamins, and physical exercise. Titles and abstracts were analyzed to screen those with positive exclusion criteria. The data were removed from the eligible ones, which include: 1) Probiotic therapy and microbiota change after intervention. 2) Role of these microorganisms in systemic inflammation. 3) Microbiota diversity and its influence on satiety. 4) Influence of microbiota modulation on glucose absorption and insulin resistance. 5) Therapeutic use of intervention with diet and/or live microorganisms such as probiotics in the treatment of obesity.

RESULTS

The search resulted in 415 articles. The titles and abstracts were evaluated and, based on the exclusion criteria, 288 publications were eliminated. After this initial screening, 127 studies were considered for eligibility, of which 91 were excluded because they met the exclusion criteria. Duplicate publications and those whose content was not within the context of the study were excluded. Thus, 36 studies were considered eligible for analysis. During the full reading of the studies, 16 were disregarded because they met exclusion criteria such as studies in rats, in vitro studies, surgery, use of vitamins, physical exercise as an intervention, and review articles. Consequently, 20 articles were analyzed and included in this review (Table 1), separating those that deal exclusively with probiotics in Table 2.

Table 1. General data of the studies.

References	Microbiota Modulating Therapy	Microbiota After Therapy	Infla
[9]	Whole Grain	No significant changes	Reduct IL6
[10]	Synbiotic supplementation (*Lacticaseibacillus paracasei* strain Shirota; *Bifidobacterium breve*; galactooligosaccharides)	↑Bifidobacterium, ↑Lactobacillus. ↓*Akkermansia muciniphila*	No sig change levels

[11]	Pasteurized Akkermansia muciniphila	No significant changes in the gut microbiota	[15]	Reduces plasma LPS	High-fiber diet	No significant changes	Improved insulin sensitivity; reduced insulinemia and total cholesterol	↑Lachnospira ↑Actinomycetaceae	High concer acetat inhibit produc proinfl cytoki
[12]	Mediterranean diet versus Control	↑*Faecalibacterium prausnitzii*; ↓*Ruminococcus gnavus* (pro-inflammatory)	[16]	Reduction of inflammation by modulation of microbiota	Weight loss through lifestyle changes	No significant changes	No significant changes in glycemia. The reduction in insulin resistance was dependent on increased levels of Bacteroides and reduced levels of *Prevotella sp* and *P. copri*.	No significant changes. Slight increase in families Desulfovibrionaceae, Leptospiraceae, Syntrophomonadacea and , Thermotogaceae and Verrucomicrobiaceae.	Reduc protei to infla
			[17]	Mediterranean diet versus high-protein diet			Mediterranean Diet: Reduction of Ruminococcaceae, Acidaminococcaceae, Coriobacteriaceae.		Criteria evaluat
[13]	Low-Calorie Ketogenic Diet Associated with Synbiotic Supplementation	Diet: Increased microbiota diversity; reduced Proteobacterium; increased Firmicutes. Symbiotic supplementation: no significant changes.		Reduction of inflammation by modulation of the microbiota	Criterion not evaluated	Criterion not evaluated	Increase in Clostridiaceae and Desulfovibrionaceae.		
			[18]	Whole Grains and Fruits+Vegetables			Increased diversity in the Fruits+Vegetables group		Whole and Fruits+V s: Redu Fruits+V s: Redu Whole Reduce
[14]	Probiotic Group: Diet + Bifidobacterium lactis. Symbiotic Group: Diet + Bifidobacterium lactis and fructooligosaccharides Control Group: Diet	Probiotics and Synbiotics: Change in Bacteroidetes, Firmicutes and Verrucomicrobia		All groups showed a reduction in inflammation, so diet alone was sufficient	Criterion not evaluated	The Symbiotic Group obtained an increase in serum glycerol and arginine, which may be related to increased insulin sensitivity and reduced inflammation.			
			[19]	Rye vs Wheat		Rye-based diet increased Agathobacter numbers and reduced Ruminococcus group abundance			Microbi alterati ryebase have re inflamm

[20]	High-Protein, High-Fat Diet (Low Carbohydrate HighFat/LCHF)	Increase in Alistipes, Odoribacter splanchnicus, Ruminococcus bicirculans, Butyricimonas, and Enterobacteriaceae Reduction in Collinsella and Dorea, often associated with inflammation	[25]	Reduced inflammation due to microbiota change	Western Diet versus Rice-Based Diet Korean Diet	Criterion not evaluated	Western diet: Bacteroides predominant. Rice-based diet: Prevotella predominant. Korean diet: Ruminococcaceae predominant	Participa Korean D lower PC results, indicatin inflamma
			[26]		Multifunctional Diet (potential antiinflammatory) versus Control	Criterion not evaluated	Multifunctiona Diet Group: Increased Prevotella copri	Reductio cardiovas inflamma markers
[21]	Probiotic Group (Bifidobacterium pseudocatenulatum CECT 7765) versus Control Group	Probiotic administration significantly increased the proportion of members of the family Rikenellaceae and the genus Alistipes	[27]	Reduced inflammation with increased groups of bacteria associated with lean phenotype. Increased levels of omentin-1 (antiinflammatory)	Oleoylethanolamide (OEA) versus Placebo		Increase in Akkermansia muciniphila.	Reductio proinflam cytokines
			[28]		Probiotic (*Lactobacillus reuteri* V3401) versus Placebo		Increase in the phylum Verrucomicrobia.	Reductio
[22]	Very Low Calorie Diet (VLCD)	Reduction of the genus Roseburia. Increase of Christensenellaceae;		Criterion not assessed	Pronounced drop in serum leptin levels.		Increased insulin sensitivity	
		—						
[23]	Pomegranate Extract versus Control	Pomegranate Extract Group: Increase in Bacteroides, Faecalibacterium, Butyricicoccus, Odoribacter and Butyricimonas. Reduction in Parvimonas, Methanobrevibacter and Methanosphaera, associated with inflammation.		Pomegranate Extract Group obtained a reduction in PCR.	Criterion not evaluated		Criterion not evaluated	
[24]	Prebiotic (inulin) versus Placebo (maltodextrin)	Inulin Group: increase in Bifidobacterium, at the level of the Bifidobacteriaceae phylum		Inulin Group: reduction of fecal calprotectin, an inflammatory marker, suggesting reduced inflammation	Increase in Short Chain Fatty Acids		Criterion not evaluated	

Table 2. Probiotics.

References	Probiotics	
[8]	Mixed: *Lactobacillus acidophilus and casei; Lactococcus lactis; Bifidobacterium bifidum* and *lactis*	$2x10^{10}$ Col units/day
[10]	*Lacticaseibacillus paracasei strain Shirota* e *Bifidobacterium breve strain Yakult*, e *galactooligosaccharides*	3.0 g pow least 3 ×1 *Lacticaseib* $3×10^8$ Bifi 7.5 g gala per day. P instructed mixture tw powder ar galactooli breakfast and 2.5 g
[11]	*Akkermansia muciniphila*	10^{10} per da

[14]	Probiotic Group: Diet + *Bifidobacterium lactis*. Symbiotic Group: Diet + *Bifidobacterium lactis* and fructooligosaccharides. Control Group: Diet	Probiotic Group: 10^9 colony-forming units of *B. lactis* and one sachet containing 5g of maltodextrin. Symbiotic Group: 10^9 colony-forming units of *B. lactis* and one sachet containing 5g of fructooligosaccharides.	8 weeks
[28]	*L. reuteri* V3401	5 x 10^9 colony-forming units per day	12 weeks

DEVELOPMENT

Influence of Diet on Microbiota Variety

The mechanisms that relate diet, microbiota, and obesity are linked to increased endotoxemia, intestinal permeability [29], and inflammation, mediated by the imbalance of the gut microbiota. Given this, therapies that alter the caloric intake of obese patients, to modulate the intestinal population and reduce the inflammatory status, are the new line of study in the treatment of the disease.

Diets

This study found data that favor the hypothesis that some dietary interventions can modulate the microbiota. Among them, studies that used a diet rich in whole grains did not obtain significant changes in the microbiota, despite proving a reduction in inflammatory cytokines, TNF-alpha (18) and IL-6 [9], restoring intestinal permeability. Given this, the use of a diet rich in grains can be considered a strong ally in the fight against obesity, both in terms of weight loss and in reducing inflammation, despite not significantly modulating the population of intestinal microorganisms.

Other widely studied cereals are wheat and rye. A recent study [19] compared diets based on these two grains, finding an increase in Agathobacter and a reduction in Ruminococcus in the rye-based diet, suggesting that this change in the microbiota may have reduced systemic inflammation. Among other diets, the Mediterranean diet was studied by Meslier et al. [12], who found a reduction in inflammation resulting from the modulation of the microbiota by changing eating habits, which increased the amount of *Faecalibacterium prausnitzii* and reduced *Ruminococcus gnavus* (pro-inflammatory). The study also found a reduction in insulin resistance, which was dependent on the increase in Bacteroidetes, which is in line with what is found in the current literature.

Still, in the context of the Mediterranean diet, another study [17] compared the effects of this diet with the High Protein Diet. The results favor the Mediterranean diet, as there was a reduction in Ruminococcaceae, Acidaminococcaceae, and Coriobacteriaceae and

an increase in Clostridiaceae and Desulfovibrionaceae. Despite this, the high protein diet was more effective in reducing insulin resistance, thus combating the pathogenesis of obesity. Therefore, further studies comparing the two diets are needed to elucidate the mechanisms of each one in the body and the gut microbiota.

Diets rich in fiber facilitate healthy intestinal flow, so studies have been conducted to evaluate the influence of a fiber-based diet on the microbiota [15]. There was an increase in Lachnospira and a reduction in Actinomycetaceae, contributing to the high concentration of acetate, consequently inhibiting the synthesis of pro-inflammatory cytokines, and combating the systemic inflammation common in obesity. In addition, there was the production of isovalerate, a molecule that contributes to the reduction of insulin resistance.

Low-calorie and low-carbohydrate diets have become famous in the media over the last decade due to their use by influential figures in society. Some studies have been conducted on diets that use the term "low carb", that is, low in carbohydrates. One of them [20] analyzed a diet rich in protein and fat, but low in carbohydrates, finding a reduction in the BMI of volunteers who underwent this intervention. In addition, there was a parallel reduction in the BMI of bacteria commonly associated with inflammatory processes, such as Collinsella and Dorea. Thus, the study found a strong relationship between the reduction in systemic inflammation and the modulation of intestinal microorganisms via dietary changes based on lower carbohydrate intake, which also aids in weight loss by reducing BMI.

In addition to this study, Alemán and colleagues studied the physiological consequences of a low-calorie diet (Very Low-Calorie Diet/VLCD) [22], finding an increase in insulin sensitivity. Other studies have focused on dietary differences between populations. Wu and colleagues compared three different types of diets found in South Korea: a Western diet, a ricebased diet, and the Korean diet [25]. The results found a predominance of different bacteria in each type of diet. In the Korean diet, the predominant group was Ruminococcaceae, which may have contributed to the lower amounts of C-reactive protein, suggesting lower inflammation in those who followed these foods. In this sense, it is essential to conduct studies that delve deeper into the theme of the predominance of different microorganisms

depending on the food culture of different countries and socioeconomic segments of society.

Finally, researchers evaluated some foods with potential anti-inflammatory effects in the diet [26]. Patients who underwent this intervention had an increase in *Prevotella copri* in their gut microbiota with a reduction in cardiovascular inflammatory markers.

Prebiotics, Probiotics and Symbiotics

The findings regarding the use of probiotics are extremely favorable in terms of modulating microorganisms. Symbiotic supplementation with the use of *L. paracasei shirota* [10] increased the number of individuals of the Lactobacillus genus, despite reducing the number of the bacterium *Akkermansia muciniphila*, known for its anti-inflammatory characteristics. Depommier and colleagues [11] 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 type 2 DM.

A study administered *Lactobacillus reuteri* V3401, managing to alter the microbiota at the phylum level, increasing the amount of Verrucomicrobia. This change was associated with a reduction in IL-6, an inflammatory cytokine [28]. Another way to use synbiotic supplementation was to combine it with already-known diets, such as the Low-Calorie Ketogenic Diet [13]. 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 et al. [14] demonstrated that the use of probiotics and symbiotics is capable of altering the Firmicutes/Bacteroidetes ratio, in addition to altering the quantity of Verrucomicrobia. In the study, the group in which only symbiotics were administered had 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 obtained good results in modulating the microbiota [21]. It significantly increased 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 antiinflammatory cytokine. Another study [24] used prebiotics (inulin) to manipulate the intestinal microbial 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 species of microbiota is also studied, to select the predominant type of microorganism in the intestine and modulate tissue inflammation. In this context, Yahoo et al. studied oleoyl ethanolamide and its effect on the species *Akkermansia muciniphila* [27]. The results were significant regarding the increase in the desired species through the use of the compound, in addition to reducing the production of pro-inflammatory cytokines.

Also in this perspective, another study evaluated the influence of vitamin D supplementation on the microbiota [30], evidencing an increase in the genus Lachnospira and a reduction in the genus Blautia. Despite the 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 regarding the modulation of microbiota and inflammation [23]. The increase in Bacteroides and the reduction in Parvimonas, Methanobrevibacter, and Methanosphaera, bacteria associated with inflammation, contributed positively to the reduction of the systemic inflammatory process.

Does Microbiota Therapy Have Any Influence on Blood Glucose and Insulin Resistance?

Insulin resistance is usually present in patients with Metabolic Syndrome, presenting Type 2 Diabetes Mellitus together with obesity. In this view, the attempt to increase insulin sensitivity in patients is a promising path in the biotherapeutic alternatives for the treatment of obesity.

In this sense, the modulation of Bacteroidetes was positively associated with the reduction of insulin resistance and was dependent on Bacteroides [12]. Another result in this sense was the increase in *Akkermansia muciniphila* causing an increase in insulin sensitivity, reducing insulinemia, and pasteurized *A. muciniphila* markedly and significantly improved the insulin sensitivity index by approximately 30% compared to the Placebo group [11]. Furthermore, probiotics from the Bifidobacterium group were

related to increased insulin sensitivity [14].

Obesity has a complex and multifactorial etiology, and limited progress in the treatment of obesity can largely be attributed to the failure to apply a systems biology-based approach to understand its pathophysiology and develop individualized strategies to achieve sustained weight loss and prevention. It has been identified how the gut microbiota can regulate metabolism, adiposity, homeostasis, and energy balance, as well as central appetite and food reward signaling, which together play crucial roles in obesity. Therefore, it is now another strategy to be added to anti-obesity therapy.

High-fat diets appear to be more relevant in modulating dysbiosis, with most studies showing an increase in the Firmicutes and Bacteroidetes ratio, with several other changes in other taxa, thus leading to inflammatory processes that alter permeability, which can lead to obesity. Further studies are essential to clarify how the various interventional diets can alter the microbiota, preventing inflammatory processes. Furthermore, it is necessary to address the mechanisms of changes in satiety and appetite after modulation of the gut microbiota, to better treat patients with new therapies.

Finally, probiotic therapy may be a strategy in conjunction with dietary changes to improve the composition of the microbiota, among which the following stand out: *L. paracasei Shirota*, *Akkermansia muciniphila*, and *Lactobacillus reuteri* V3401, responsible for the reduction of inflammatory markers. In most of the studies evaluated, it was clear that modulation of the microbiota through physical exercise, diet, use of prebiotics, and/or probiotics have a positive effect in reducing inflammatory markers and stimulating satiety. Regarding the regulation of glucose homeostasis and its relationship with insulin, further studies are needed to evaluate this criterion.

CONCLUSION

It was concluded that the gut microbiota is becoming a target for new anti-obesity therapies. Further research is needed to elucidate the intricate gut-microbiota-host relationship and the potential of gut microbiota-targeted strategies, such as dietary interventions and fecal microbiota transplantation, as promising metabolic therapies that help patients maintain a healthy weight throughout life. This is achieved by combining several mechanisms that have been proven in this regard, including increased insulin sensitivity, reduced systemic inflammation, and control of satiety.

CRediT

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