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Probiotics, prebiotics, and symbiotics in the treatment of obesity: A new vision

Probióticos, prebióticos y simbióticos en el tratamiento de la obesidad: Una nueva visión

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SUMMARY

Obesity is a chronic non-communicable disease whose prevalence has doubled during the last three decades, becoming, along with its metabolic complications, a worldwide public health problem. Recently, the alteration of the intestinal microbiota balance, known as dysbiosis, has been identified as a possible pathophysiological process that promotes weight gain in individuals who suffer from it. Dietary intervention with prebiotics, probiotics, or symbiotics aimed at correcting intestinal dysbiosis in obese patients can provide health benefits by facilitating weight loss and maintenance, improving constipation, glucose, and lipid levels, as well as immunity and expression of regulatory cytokines, thus contributing to the reduction of the chronic inflammatory process of intestinal cells. The purpose of this review is to establish the relationship between intestinal microbiota and obesity, as well as to emphasize the potential role of prebiotics, probiotics, and symbiotics in the prevention and management of obesity.

Keywords*: Obesity, overweight, intestinal microbiota, intestinal dysbiosis, prebiotics, probiotics, symbiotics.*

RESUMEN

La obesidad es una enfermedad crónica no transmisible cuya prevalencia se ha duplicado durante las últimas tres décadas, constituyéndose junto a sus complicaciones metabólicas, un problema de salud pública a nivel mundial. Recientemente, la alteración del equilibrio en la microbiota intestinal, conocida como disbiosis, se ha identificado como un posible proceso fisiopatológico que promueve en el aumento del peso en los individuos que la padecen. La intervención dietética con prebióticos, probióticos o simbióticos destinada a corregir la disbiosis intestinal en el paciente obeso, puede proporcionar beneficios para la salud al facilitar la pérdida y el mantenimiento de peso, mejorar el estreñimiento, los niveles de glucosa y lípidos, así como en la inmunidad y expresión de citoquinas reguladoras, logrando de esta forma contribuir a la disminución del proceso inflamatorio crónico de las células intestinales. Es por todo lo planteado anteriormente que esta revisión tiene como finalidad establecer la relación existente entre la microbiota intestinal y la obesidad, además de enfatizar el papel potencial de los prebióticos, probióticos y simbióticos en la prevención y manejo de la misma.

Palabras clave: *Obesidad, sobrepeso, microbiota intestinal, disbiosis intestinal, prebióticos, probióticos, simbióticos.*

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INTRODUCTION

Obesity, according to the World Health Organization (WHO), is defined as "an abnormal or excessive accumulation of fat that can be harmful to health", whose prevalence has doubled during the last three decades, constituting, together with its metabolic complications, a worldwide public health problem of utmost importance. According to WHO figures, in 2016, more than 1900 million people over the age of 18 were classified as overweight (BMI between 25 and 30 kg/m^2) and 600 million were obese (BMI greater than 30 kg/m^2) (1). Excess weight and obesity are caused by a positive energy balance, which results from an increase in the number of calories ingested, as well as a decrease in energy expenditure, which, together with certain environmental, genetic, and hormonal factors, contribute to its onset (2).

Over time, human beings have co-evolved with different microorganisms, to the point of establishing commensal and even symbiotic relationships, with positive or beneficial effects on health. Thus, the intestinal microbiota, commensal or symbiotic bacterial flora that colonizes the intestinal mucosa, represents one of the biological relationships that, according to emerging evidence, has an essential role in human health and disease, playing a determining role in physiological processes such as digestion, glucose metabolism, energy production and immunomodulation (3).

Studies during the last decades indicate that the intestinal microbiota seems to play a fundamental role in the pathogenesis of obesity and its associated diseases. In this regard, the dysregulation of this microflora that leads to the interruption of the favorable symbiotic relationship, known as dysbiosis, may contribute to the development of obesity by altering the intestinal absorption of nutrients and through the production of metabolites that generate inflammatory processes in the cells of the intestinal microbiota (4,5).

Although there are a variety of therapeutic strategies for the management of excessive weight gain (nutritional, behavioral, pharmacological, and surgical), obesity is still an important problem that requires new medical and/or nutritional approaches, since together with its comorbidities, it represents the main causes of morbidity and mortality worldwide (6). Dietary intervention with prebiotics, probiotics, or symbiotics aimed at correcting the alteration of the intestinal microbiota observed in obesity, can provide health benefits by facilitating weight loss and maintenance, improving constipation, glucose, and lipid levels, as well as immunity and expression of regulatory cytokines, thus contributing to the reduction of the chronic inflammatory process of intestinal cells that occurs in subjects with obesity (4,7). The purpose of this review is to establish the relationship between intestinal microbiota and obesity, as well as to emphasize the potential role of prebiotics, probiotics, and symbiotics in the prevention and management of obesity.

OBESITY AND INTESTINAL MICROBIOTA

Obesity is a chronic non-communicable disease harmful to health, which has been associated with an increased risk of metabolic, cardiovascular, and musculoskeletal diseases, some types of cancers, and mental health diseases, among other disorders (8). Obesity is determined by genetic, environmental, and psychosocial factors, which influence food intake and energy expenditure. Thus, the eating habits that are acquired throughout life, produce alterations in the natural intestinal microbiota acquired from birth, the excessive intake of carbohydrates or fats, which is one of the main causes of the changes in it (9). Likewise, the intestinal microbiome is influenced by genetic, nutritional, hormonal, and other environmental factors that may contribute to the pathogenesis of obesity and related complications (10).

The intestinal microbiota is acquired from birth and develops as more bacteria are consumed throughout life with the diet (11). The intestinal flora is composed of Bacteroidetes (23 %) comprising the genus *Bacteroides*, Firmicutes (64 %) which includes *Bacilli*, Clostridia, and Mollicutes; Proteobacteria (8 %), gram-negative bacteria such as *Escherichia coli* and *Helicobacter pylori*; Fusobacteria, Verrucomicrobia and Actinobacteria (3 %) which include species such as *Bifidobacterium* (12). This intestinal microbiome contains enzymes that metabolize many macronutrients, which is why maintaining its balance is a key point in promoting human health (10). When alterations occur in its structure or diversity, a process known as dysbiosis, metabolic disorders occur due to alteration of metabolic signaling pathways. Among these disorders, we find obesity and the complications it generates in the homeostasis of the organism (13). In studies of overweight or obese animal models, more *Firmicutes* than *Bacteroides* have been found, while in humans there is greater variability in the percentage of these bacteria, which reflects the influence of dietary regimes since certain diets increase or decrease certain types of beneficial bacteria for the microbiota and increase other harmful ones, which trigger obesity (14).

In the pathogenesis of metabolic disorders, the role of dysbiosis is becoming increasingly clear. It has been demonstrated the high risk that a decrease in microbial diversity entails for the development of obesity, likewise, it has been identified that thin subjects have a greater richness of intestinal microbiota compared to obese ones (15). The use of antibiotics has been related to alterations in the intestinal microbiota increasing the risk of developing multiple inflammatory disorders. Antibiotic-induced dysbiosis generates weight gain and increases the proportion of very low-density lipoproteins (16). Bacterial dysbiosis, related to an increase in *Firmicutes* species, has been associated with alterations in gastrointestinal peptides (cholecystokinin, somatostatin, ghrelin, and gastrin), leading to decreased satiety, increased appetite, and food intake (17).

Intestinal microbiota and the metabolism of carbohydrates and lipids are related, which contributes to the collection of energy and the metabolism of nutrients. The intestinal microbiota can alter the signaling of free bile acids; approximately 5 % to 10 % of these are bio-transformed by the anaerobic intestinal microbiota, which demonstrates their relationship with the metabolism of dietary fats (18). It has also been related to the metabolism of essential amino acids, an important source of dietary protein, being the nitrogen obtained from this macronutrient is essential for microbial growth, short-chain amino acid assembly, and carbohydrate assimilation (19).

The intestinal microbiota, through the production of short-chain fatty acids (SCFA), plays a role in energy metabolism. These fatty acids are produced by the fermentation of fiber and protein at the colonic level and are microbial waste products whose function is to balance intestinal homeostasis (19,20). SCFA, specifically acetate, butyrate, and propionate can affect human metabolism. Their beneficial effects have been observed on insulin sensitivity, glucose balance, and body weight, in addition, can reduce inflammation through the strengthening of the intestinal barrier and have a positive effect on lipid metabolism, as well as reduce appetite and regulate satiety through activity on free fatty acid receptor 2 by stimulating the release of the hormone peptide YY (PYY) and incretin GLP-1 (21,22).

Probiotic supplementation can increase SCFA-producing bacteria, reduce quantitative LPS producers, and reduce tissue loss and organ inflammation, with these modulatory effects on glucose homeostasis and appetite, human immunity, lipid metabolism, and gastrointestinal cell integrity (4). The amounts of SCFA differ in lean versus overweight or obese subjects, the latter having higher amounts of fecal acetate, butyrate, and propionate, produced by anaerobic catabolism of *Bacteroidetes* (15). Increasing butyrate consumption and production can increase the biodiversity of the intestinal microbiota, thereby increasing mitochondrial function and energy expenditure and decreasing insulin resistance. Probiotics also reduce opportunistic pathogens with their metabolites (indole, trimethylamine, and LPS), as well as fat accumulation, inflammation, and insulin resistance, and regulate neuropeptides and gastrointestinal peptides (20).

Intestinal bacteria modulate the secretion of inflammatory cytokines, and elevated levels of inflammatory biomarkers such as C-reactive protein, tumor necrosis factor (TNF), and interleukin-6 (IL-6) appear to be associated with obesity (23,24). Probiotics have been shown to decrease inflammatory factors, increase SCFA levels through fermentation of non-digestible carbohydrates, enhance intestinal cell growth and thereby strengthen the intestinal barrier, mucin production, and immunomodulation of intestinal immune cells (25).

Supplementation with prebiotics promotes changes in both the composition and function of the intestinal microbiota, with inulin, galacto-oligosaccharides (GOS), and fructo-oligosaccharides (FOS) being the most frequently used and studied (26). Inulin works by increasing the density of cells in charge of producing the appetite-suppressing hormone PYY, GOS increases the number of *Bifidobacterium spp*. and decreases the number of *Bacteroides,* and FOS has been associated with an increased presence of *Lactobacillus, in* addition to its bifidogenic function, with a consequent decrease in ghrelin levels and increase in butyrate producers, leading to improvements in metabolic performance and intestinal barrier against pathogens (17,27). In addition, supplementation with prebiotics generates a decrease in leptin resistance that occurs in those subjects with a high-fat diet.

PREBIOTICS, PROBIOTICS, AND SYMBIOTICS IN OBESITY

General

Prebiotics are non-digestible, non-viable, selectively fermented food ingredients that have beneficial effects on the host by promoting the growth or activity of the intestinal microbiota (7,28). They are short-chain carbohydrates whose structure is mainly composed of two chemical groups, inulin-type fructans (ITF) and galactooligosaccharides (GOS), biomolecules capable of stimulating the growth of bifidobacteria and lactobacilli (29). Starchy fruits, cereals, beans, legumes, and soybeans are just some of the natural sources of prebiotics (30). According to studies, the consumption of prebiotics has several benefits among them the production of short-chain fatty acids, cholesterol reduction, stimulation of the local immune system, and improvement of gastrointestinal motility and function, among others (31).

Probiotics are microorganisms beneficial to the health of their host when administered or consumed in adequate amounts, as they have been shown to improve the microbial balance of the intestinal flora by inhibiting colonization by other enteric pathogens (32). Generally, they are marketed as freeze-dried pills for the management of diarrhea of various etiologies, in addition to inflammatory bowel diseases, although they are also used as food supplements, with a variety of foods enriched with probiotics, being *Bifidobacterium* and *Lactobacillus* strains the most commonly used in dietary supplements (33,34). The various genera of bacteria most commonly used in the formulation of probiotics are *Lactobacillus*, *Bifidobacterium*, *Enterococcus,* and *Streptococcus* (35).

Thus, to this date, the beneficial effect of probiotics has only been clinically demonstrated in the management of antibiotic- and *Clostridium difficile-* associated diarrhea, as well as in the management of certain respiratory tract infections. (36). However, neither the U.S. Food and Drug Administration nor the European Food Safety Authority has approved any probiotic formulation as a therapeutic agent (36,37) except for *Lactobacillus gasseri* BNR17, which has been approved as a functional component for body fat reduction by the South Korean Food and Drug Administration (38).

Symbiotics are combinations of prebiotics and probiotics, generally used for the management of intestinal dysbiosis (39). Thus, symbiotics are complex mixtures of bacterial strains and different doses of prebiotic fibers that have been shown to be more effective in modulating the intestinal microbiota than prebiotics and probiotics alone (40). The use of symbiotics in humans has been contradictory and remains under ongoing study as no significant change in weight, BMI, or fat mass has been noted, but they have been shown to reduce blood cholesterol levels and lower blood pressure, perhaps due to the concentrations, ratio, and duration of administration of the symbiotics (30).

Preclinical evidence

Preclinical studies have demonstrated the potential benefits of the use of prebiotics, probiotics, and symbiotics in the management of intestinal dysbiosis in obese patients. Some biomolecules present in nature, such as phenols, polyphenols, and non-digestible complex carbohydrates, have been shown to have prebiotic properties in studies conducted in animal models. In this regard, resveratrol, and quercetin, both phenolic compounds, have been associated with adipose tissue browning and thermogenesis, phenomena which, in turn, are related to weight loss. Different authors have found that the use of resveratrol, alone or combined with quercetin, is associated with increases in *Lactobacillus* and *Bifidobacterium* generation in the intestinal microbiota while reducing the *Firmicutes/Bacteroidetes* ratio (41-43). The use of these phenols has also been found to reduce trimethylamine N-oxide (TMAO) levels and the risk atherosclerosis, through the induction of hepatic bile acid synthesis, which results from the remodeling of the intestinal flora (41).

Likewise, camu camu, a polyphenolic fruit extract, also appears to have anti-obesogenic prebiotic properties. In a study conducted in mice fed a high-fat diet, it was found that this extract promoted a remodeling of the intestinal microbiota, which in turn, induced an increase in energy expenditure by increasing the production of UCP-1 in the TAP and white adipose tissue (WAT), which conferred protection against obesity; In addition, camu camu extract also induced an increase in secondary unconjugated bile acid novels (44,45).

Among the non-digestible complex carbohydrates, highly esterified pectin, inulin, guar gum (guaran), and epilactose have been shown to be able to remodel the intestinal microbiota with important effects on obesity. Pectin, one of the main sources of soluble fiber in the diet, is a polysaccharide present in a wide variety of vegetables and fruits since it is one of the most abundant constituents of the cell wall of the plant kingdom; studies attribute its anti-obesogenic prebiotic effects to the thermogenic capacity of this component in adipose tissue (46-48). On the other hand, inulin and guaran have been attributed to slimming effects in animal models of high-fat diets (49) while epilactose has been attributed to protective effects against obesity by improving the SCFA profile in the cecum, increasing acetate and propionate levels, and reducing weight gain (50) through the expression of UCP-1 in TAP and muscle (51).

Now, some of the lactic acid bacteria, such as *Lactobacillus spp*. and *Bifidobacterium spp*. are two of the most widely studied probiotics at the preclinical level, which have provided anti-obesity effects through the remodeling of the intestinal flora (52-55). Other authors have demonstrated in *vitro* and *in vivo*, the anti-inflammatory potential of *Faecalibacterium prausnitzii, a* species with the ability to inhibit the NF-ϰB pathway; likewise, this species can produce SCFA such as butyrate, which confers slimming effects in animal models (56,57). *Akkermansia muciniphila* is another species with potential probiotic effects in animal models with metabolic disorders and obesity. Thus, authors have documented that *A. muciniphila* also has anti-inflammatory properties, reverses atherosclerotic lesions, reverses metabolic alterations in adipose tissue, and decreases translocation at the intestinal barrier (58,59). In relation to symbiotics, a study in mice fed high-fat diets and given a symbiotic supplement of D-allulose and two probiotic species, *Lactobacillus sakei,* and *Leuconostoc kimchi,* found that the use of this mixture significantly decreased the body weight and visceral adipose tissue of the mice, while reducing the leptin/adiponectin ratio (60). Some authors have been able to demonstrate that postnatal symbiotic supplementation of mice induced changes in the gut microbiota that protected them from diet-induced obesity later in life (61-63).

Clinical evidence

Epidemiological evidence reveals that nutritional regimens rich in prebiotic components are associated with decreased appetite, reduced fat mass, and weight loss in overweight and obese patients (64,65). However, the clinical evidence is not as promising (Table 1), since most studies reveal that the changes induced by prebiotics in obese or overweight patients are null or minor, as well as the improvements in total cholesterol, LDL cholesterol, and serum CRP levels are minor (Table 1) (27,66,67).

In relation to probiotics, evidence in humans shows that the use of these supplements

Table 1. Clinical evidence on the efficacy of prebiotics and probiotics in obesity.

Authors (year)	Journal	Methodology	Results	Conclusion
PREBIOTICS				
Da Silva Borges et al. (2019).	Nutrition Reviews (Q1)	Meta-analysis: 10 RCTs and 3 cross-over trials. (n= 566 participants).	No decrease in ghrelin (WMD = - 71.66; CI9 %: - 148.83 to 5.50; p = 0.069), significant decrease in CRP (SMD= - 0.31; 95%CI: - 0.58 to - 0.04; p = 0.027).	Prebiotics may help regu-late plasma concentrations of C- reactive protein but not ghrelin in overweight or obese individuals.
Beserra BT et al (2015).	Clinical Nutrition (Q1)	Meta-analysis: 13 RCTs (n=513 participants).	Reduction of total cholesterol (SMD= -0.25; 95%CI: -0.48, -0.02) and LDL-cholesterol (SMD= -0.22; 95%CI: -0.44, -0.00). Reduction of triglycerides (SMD= -0.72; 95%CI: -1.20, -0.23) and increase of HDL-cholesterol (SMD= 0.49; 95%CI: 0.01, 0.97).	The improvement in the parameters evaluated supports supplementation with prebiotics as adjuvant therapy in obesity-related comorbidities such as dyslipidemia and insulin resistance.
Kunnackal J et al (2018).	Genes (Q2)	Meta-analysis: 6 RCTs.	DM= 27 (95%IC: - 0.56, 0.2), p = 0.07	Dietary agents for modulation of the intestinal mi-crobiome significantly reduce body weight without changes in fat mass.
PROBIOTICS				
Wang ZB et al (2019).	Evidence-based Complementary and Alternative Medicine (Q2)	Meta-analysis: 12 RCTs (n=821 participants)	Reduction in body weight (WMD=- 0.55 kg; 95 % CI: - 0.91, - 0.19), BMI (WMD= -0.30 kg/m2; 95 % CI: - 0.43, - 0.18), waist circumference (WMD= - 1.20 cm; 95 % CI: -2.21, - 0.19), fat mass (WMD= - 0.91 kg; 95 % CI: -1.19, - 0.63), compared to control groups	Probiotic supplementation could potentially reduce weight gain and improve some of the associated met-abolic parameters
Borgeraas H et al (2018).	Obesity Reviews (Q1)	Meta-analysis: 15 RCTs (n=957)	Body weight reduction (WMD (95%CI)); - 0.60 kg (- 1.19, - 0.01); BMI (- 0.27 kgm-2 (- 0.45, - 0.08); and fat percentage (- 0.60%) - 1.20, - 0.01).	Probiotic supplementation significantly reduces BMI, body weight, and fat mass percentage.
Park S et al (2015).	Nutrition Research (Q3)	Meta-analysis: 4 RCTs (n=449)	No significant effect of probiotics on body weight (WMD= - 1.77; 95 % CI: - 4.84 to 1.29; p = 0.26) and BMI (WMD= 0.77; 95 % CI: - 0.24 to 1.78; p = 0.14).	The RCTs reviewed in this meta-analysis indicated that probiotics have limited efficacy in terms of decreasing body weight and BMI and were not effective for weight loss.

BMI, body mass index; BMI, body mass index; Q, quartile; RCT, randomized clinical trial; CI, confidence interval. WMD, weighted mean difference; SMD, standardized mean difference; RCT, randomized clinical trial; SD, standardized mean difference.

decreases the BMI and body weight of patients (Table 1), although other authors point out that the reductions in these measures are not significant (68-70). Probiotics based on strains of bacteria common in the human intestinal microbiota, such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila,* or *Clostridia* strains, represent the next generation of probiotics. Studies have shown that the depletion of these bacteria in the gut microbiota has been associated with an increased risk of obesity, type 2 diabetes mellitus, immunometabolic diseases, and metabolic syndrome (68,71). In this regard, one study reported an inverse and significant correlation between the number of *A. muciniphila* in the intestinal flora and the presence of overweight, obesity, and arterial hypertension in its sample (72). In another study conducted in overweight or obese patients, who were administered live/pasteurized *A. muciniphila* supplements or placebo for 3 months, it was observed that, although the use of this probiotic did not significantly remodel the composition of the intestinal flora, it did promote a decrease in hip circumference, fat mass proportions and a slight reduction in body weight (73).

However, the clinical evidence on the efficacy of symbiotics in the management of obesity is more contrasting than that of the use of prebiotics and probiotics separately. In this regard, some authors reported that the use of symbiotics improved leptin levels, total and LDL cholesterol, and triglyceride levels, while significantly reducing body weight, fat mass, and BMI of patients; however, other authors reported that no significant reductions in any of the last 3 anthropometric parameters were observed (67,74-76). Thus, in one study, symbiotics were found to have a modest but consistent effect on BMI and abdominal circumference, although no significant improvement in the pro-inflammatory profile of adipose tissue or adiponectin levels was demonstrated (77). In addition, a randomized clinical study conducted in children with obesity, who were administered symbiotics orally for 12 weeks, concluded that there was a marked decrease in weight, as well as an improvement in glycemia, total cholesterol, triglycerides, and LDL cholesterol values (78).

Safety profile

The use of probiotics in foods throughout history, together with the information reported by different clinical trials, has allowed the demonstration of the safety profile of this supplementation in humans (39,74,79). However, although probiotics are safe in healthy adults, evidence has shown that their use increases the risk of infection and morbidity in immunocompromised patients, patients in intensive care, postoperative or hospitalized patients, and small infants or newborns with low birth weight (80-82). In this regard, infection, bacteremia, sepsis, endocarditis, and/or cholangitis induced by *L. rhamnosus GG* or *L. casei* or by *Bacillus subtilis* have been reported (83,84).

In general, supplements with prebiotics, probiotics, and symbiotics have a safe profile for use in immunocompetent humans. However, large-scale clinical trials are needed to evaluate the actual efficacy of these supplements in the prevention and treatment of obesity, as well as to determine the most effective ideal dose response, or to assess whether the beneficial effect is maintained after discontinuation of treatment (85).

The use of prebiotics in the context of a symbiotic formulation should be carefully evaluated, since, to observe its beneficial effects, the dose given to the patient should be higher than in cases where it is used as a single agent when an additional load of viable bacteria (probiotics) is administered to the intestinal microbiota, a higher concentration of prebiotics would be required to stimulate the complete flora (85).

CONCLUSIONS

The use of probiotics, prebiotics, and symbiotics is emerging as an alternative therapy in the prevention and treatment of obesity and overweight. Evidence suggests that such formulations may reduce body weight, fat mass percentage, and BMI, as well as improve the inflammatory profile and other cardio-metabolic parameters associated with obesity. The use of these supplements is generally safe in different clinical settings, but more research is still needed in all other fields before final recommendations for their use can be made.

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