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Gut microbiota as a key player in triggering obesity, systemic inflammation and insulin resistance

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ABSTRACT

Obesity-related systemic inflammation contributes to develop insulin resistance. The main factors involved in the relationship of obesity with systemic inflammation and insulin resistance have not been completely elucidated. Microbiota includes around 10^{13} to 10^{14} microbes harboring the human gut, which are clustered in approximately a thousand different bacterial species. Several studies suggest that imbalance in the intestinal bacterial population could result in obesity, systemic inflammation and metabolic dysfunction. Here, we review the main bacterial groups observed in obesity as well as their possible role in increasing the intestinal permeability and lipopolysaccharide-related endotoxemia. Furthermore, we point out the role of intestinal dysbiosis in the inflammatory activation of macrophages with the ability to infiltrate in the visceral adipose tissue and induce insulin resistance. Finally, we discuss the apparent beneficial use of prebiotics and probiotics in ameliorating both systemic inflammation and metabolic dysfunction. Present information may be useful in the future design of novel therapies focused on treating obesity and insulin resistance by restoring the gut microbiota balance.

Key words. Gut microbiota. Bacteria. Obesity. Insulin resistance. Inflammation. Macrophages.

La microbiota como agente inductor de la obesidad, la inflamación sistémica y la resistencia a la insulina

RESUMEN

La obesidad se asocia con un estado inflamatorio sistémico que contribuye al desarrollo de resistencia a la insulina. Sin embargo, los factores involucrados en la relación del fenotipo obesogénico con el establecimiento de la respuesta inflamatoria y la pérdida de la sensibilidad a la insulina todavía no han sido identificados completamente. La microbiota está constituida por alrededor de 10^{13} y 10^{14} bacterias que habitan el intestino humano, agrupadas en cerca de 1,000 especies bacterianas distintas. Numerosos estudios sugieren que las alteraciones en las poblaciones bacterianas intestinales podrían conducir a mayor propensión a la obesidad, el desarrollo de un estado de inflamación sistémica y la disfunción metabólica. En esta revisión se exponen los principales filabacterianos asociados con el fenotipo obesogénico, así como su posible papel en el aumento de la permeabilidad intestinal y la generación de la endotoxemia por el lipopolisacárido. Además, discutimos la participación de la disbiosis intestinal en la activación de macrófagos inflamatorios, con capacidad de infiltrar el tejido adiposo visceral induciendo pérdida de la sensibilidad a la insulina. Finalmente, se revisan los aparentes beneficios del uso de prebióticos y probióticos, en el tratamiento de la inflamación sistémica y la disfunción metabólica. En un futuro esta información podría ser útil en el desarrollo de estrategias terapéuticas encaminadas al control de la obesidad y la resistencia a la insulina, a través del restablecimiento del balance poblacional de la microbiota.

Palabras clave. *Microbiota. Bacterias. Obesidad. Resistencia a la insulina. Inflamación. Macrófagos.*

INTRODUCTION

Obesity is a multifactorial disease largely characterized by the excessive accumulation of body fat. Obesity is strongly associated with increased risk of developing metabolic disorders including hyperglycemia and insulin resistance by promoting a systemic inflammatory response.[1] Numerous studies have recently brought to light novel factors involved in the development of obesity and obesity-related systemic inflammation and metabolic dysfunction as is the case of the microbiota. The microbiota has been recently shown to play a key role in inducing obesity, systemic inflammation, and metabolic disease, thus having an enormous impact on both basic and clinical research. Here, we review the most recent basic and clinical evidence concerning the role of microbiota as a possible trigger of obesity, systemic inflammation, and insulin resistance. We also discuss about the use of both prebiotics (non-digestible diet elements working as microbiota's substrate) and probiotics (living microorganisms influencing the microbiota balance) as potential therapeutic agents in ameliorating adiposity and inflammation.

THE HUMAN BEING AND THE MICROBIOTA

The human being has become capable of coexisting in a complex ecosystem as a result of multiple evolutionary mechanisms. A clear scenario exemplifying the intricate relationship between humans and their environment can be seen at the human microbiome. The human intestinal lumen is occupied by 10^{13}-10^{14} microorganisms belonging to more than a thousand different bacterial species that encompass the microbiota.[2-4] The microbiota is involved in numerous important functions as digestion, micronutrient production, restriction of the growth of potentially harmful bacteria, and development of the immune response.[4] However, the microbiota is susceptible to experience changes that may lead to deleterious outcomes in different clinical scenarios including obesity and obesity-related metabolic dysfunction.

In terms of microorganisms, the human gastrointestinal tract is sterile before the birth and starts to be progressively inhabited by thousands of bacteria immediately after having contact with the birth canal. Then, the extra-uterine environment involves multiple immune challenges capable of modifying the newborn's microbiota in a few months thus having a decisive influence on the microbiota composition during the adulthood.[5]

The analytical methods for the study of the microbiota have been shown to have numerous limitations that have led to controversial results. Classical culture methods are only able to identify ~30% of the human intestinal bacteria because of a limited knowledge concerning the nutritional requirements of the majority of gut microorganisms. Nevertheless, the accurate characterization of the human microbiota has been achieved with the advent of novel molecular techniques including the 16S ribosomal ribonucleic acid sequence analysis and both metagenomic and metatranscriptomic tools.[6] Such a remarkable molecular techniques have evidenced the three predominant phyla in human and murine microbiota: firmicutes, bacteroidetes, and actinobacteria, which altogether represent ~75% of the total bacterial diversity at the intestine.[7]

Recent studies have pointed out a potential role of obesity in impairing the balance of the intestinal microbiota.[8,9] In obese animals (leptin-deficient mice or exhibiting mutations in the leptin receptor gene), firmicutes significantly predominate over bacteroidetes.[8] In humans, the study of the microbiota in monozygotic twins revealed that bacteroidetes decrease while actinobacteria increase in the obese twin as comparing with the lean twin.[9] It has been also shown that bariatric surgery-related weight loss in morbidly obese patients promotes an increase in the bacteroidetes population accompanied by reduction in firmicutes.[10] In light of this information, obesity in mice and humans seems to be linked to a microbiota profile largely characterized by increasing in firmicutes and actinobacteria as well as decreasing in bacteroidetes. However, which of the multiple factors associated with obesity may be decisively involved in the microbiota imbalance?

THE MICROBIOTA PROFILE IS MODIFIED IN RESPONSE TO OBESITY-RELATED FACTORS

The microbiota diversity can be modified in response to both genetic and environmental factors that may significantly alter the intestinal bacterial composition. In terms of genetic factors, several studies have indicated that monozygotic twins have a more similar microbiota between them with respect to unrelated people.[11,12] Environmental factors include dietary habits and physical activity that have been shown to play a decisive role in defining the intestinal microbiota profile. In this sense, it has been recently demonstrated that the intake of calories, fiber, and monounsaturated and polyunsat-

urated fatty acids is associated with the percentage of *Bacteroides spp* and bifidobacteria, both of them belonging to bacteroidetes and actinobacteria respectively.[13] Moreover, it has been also shown that transplantation of microbial communities from feces of lean individuals to germ free (GF)-mice promotes an intestinal flora similar to that present in healthy adult human beings. Notably, when these GF mice are fed with a high-fat diet a significant change in the microbiota profile is observed, which at the same time correlates with increased adiposity.[14] Furthermore, normal-fat diet-fed mice show decrease in bacteroidetes and increase in both firmicutes and proteobacteria (including *Escherichia spp*, *Salmonella spp*, and *Helicobacter spp*) when feeding a high-fat diet.[15] The abovementioned experimental findings are consistent with clinical evidence showing a clear increase in the bacteroidetes population after restricting consumption of carbohydrates and fats in obese human beings.[16]

In contrast, Duncan, *et al.,* reported conflicting results showing no differences in the firmicutes/bacteroidetes ratio between lean and obese individuals as well as among subjects exposed to different diets aimed to reduce body weight.[17] However, the aforementioned study did not take into consideration the evidence described by Dr. Marie A. Hildebrandt indicating that increased availability of lipids and carbohydrates are *per se* capable of inducing dysbiosis, even independently of the obesity degree.[15] Thus, the exposure to different diets only aimed in reducing body weight without contemplating the origin of the calorie contents does not resemble the experimental conditions proposed by Hildebrandt and coworkers making necessary to reexamine such controversial data.

Physical activity is another factor that could potentially influence the gut microbiota profile. As a matter of fact, the microbiota profile is significantly different in mice with free-access to work out with respect to animals without having physical activity.[18] In addition, mice with free-access to physical activity also show increased fermentation of prebiotic as well as decreased intestinal and systemic inflammatory response, which are presumably associated with high production of n-butyrate.[18] This study has motivated the development of a research protocol aimed to determine the effect of physical activity upon the microbiota profile in obese patients exhibiting different cardiometabolic disorders.[19] However, it is necessary to perform such studies in a population-specific fashion taking into consideration numerous factors including genetic background, diet contents, and lifestyle habits, which can significantly influence the microbiota profile.

All of this evidence suggests that obesity-related factors including diet contents and sedentary lifestyle may have a significant impact on altering the microbiota composition. However, is it possible to induce or restrict the obesity development by switching the intestinal microbiota profile? Such an intriguing question could lead us to a notion in which microbiota appears to play a central role in the development of obesity and obesity-related inflammatory and metabolic disorders.

THE ROLE OF MICROBIOTA IN TRIGGERING OBESITY

GF-mice do not develop obesity despite being exposed to hypercaloric diets, suggesting that gut bacteria could directly promote obesity.[2,20] Besides confirming this observation, further studies have also revealed that bacteria-dependent prebiotic fermentation is largely associated with production of short chain fatty acids (SCFA) and thus restriction of obesity.[21-24] In addition to represent an alternative energy source for humans, numerous SCFA (including n-butyrate, acetate, and propionate) are also capable of acting as intracellular signaling molecules. Acetate and propionate have been shown to act as ligands for the G protein-coupled receptors GPR41 (free fatty acid receptor 3 or FFAR3) and GPR43 (FFAR2). Both GPR41 and GPR43 are located at enteroendocrine cells within the gastrointestinal tract.[21,22]

Peptide YY (PYY) is an anorexigenic hormone capable of promoting delayed gastric emptying thereby inducing nutrient absorption and suitable digestion.[25] Notably, it has been demonstrated that production of PYY can be stimulated when acetate and propionate bind to GPR41 and GPR43, respectively.[26] In addition, GPR41 activation is associated with increased leptin synthesis that in turn favors an anorexigenic effect and thus decreased fat mass gain.[23] Moreover, acetate and/or propionate-dependent GPR43 activation has been shown to promote lipolysis thus decreasing lipid accumulation and improved glucose metabolism in adipocytes.[24]

Interestingly, the bacteroidetes population appears to be closely related to prebiotic fermentation and production of SCFA. As a matter of fact, the intestinal increase in bacteroidetes has been associated with decreased appetite as well as less body fat gain due to stimulation of leptin and PYY secretion.[27] Furthermore, predominance of bacteroidetes

in the intestinal microbiota has been linked to decreased levels of ghrelin, a hormone with well described orexigenic actions.[27] In contrast, elevation in the firmicutes population has been associated with increased production of free fatty acids (FFA) in the intestinal lumen, augmented levels of ghrelin, increased adiposity and intestinal permeability, and insulin resistance (Figure 1).[27] Also, it has been reported that chronic administration of doxycycline and hydroxychloroquine in humans is capable of leading to decreased number of intestinal bacteroidetes and increased amount of firmicutes, which is in turn associated with body weight gain.[28] All of the abovementioned information indicates that alterations in the gut microbiota could decisively contribute to the establishment of obesity.[20-28] Furthermore, recent evidence suggests that intestinal microbiota modifications could not only predispose to obesity but also trigger a systemic state of inflammation and metabolic dysfunction.

THE ROLE OF MICROBIOTA IN TRIGGERING SYSTEMIC INFLAMMATION

In 2008, Cani, *et al.,* reported that high-fat diet-fed mice showed an increase in the intestinal fraction of firmicutes and proteobacteria, fat mass gain, and endotoxemia due to increased blood concentration of lipopolysaccharide (LPS).[29] In these animals, a more severe LPS-induced endotoxemia has been largely associated with augmented intestinal permeability.[29] The intestinal epithelium of obese mice expresses lower levels of occludin and ZO-1 (epithelial cell-binding proteins), thus resulting in increased gut permeability.[30] Both occludin and ZO-1 have been demonstrated to play a key role in initiating an intestinal inflammatory response, which in turn is capable of modifying the epithelial integrity and permeability thus allowing LPS entry into the organism.[30]

Another consequence of the firmicutes/bacteroidetes imbalance is the intestinal accumulation of

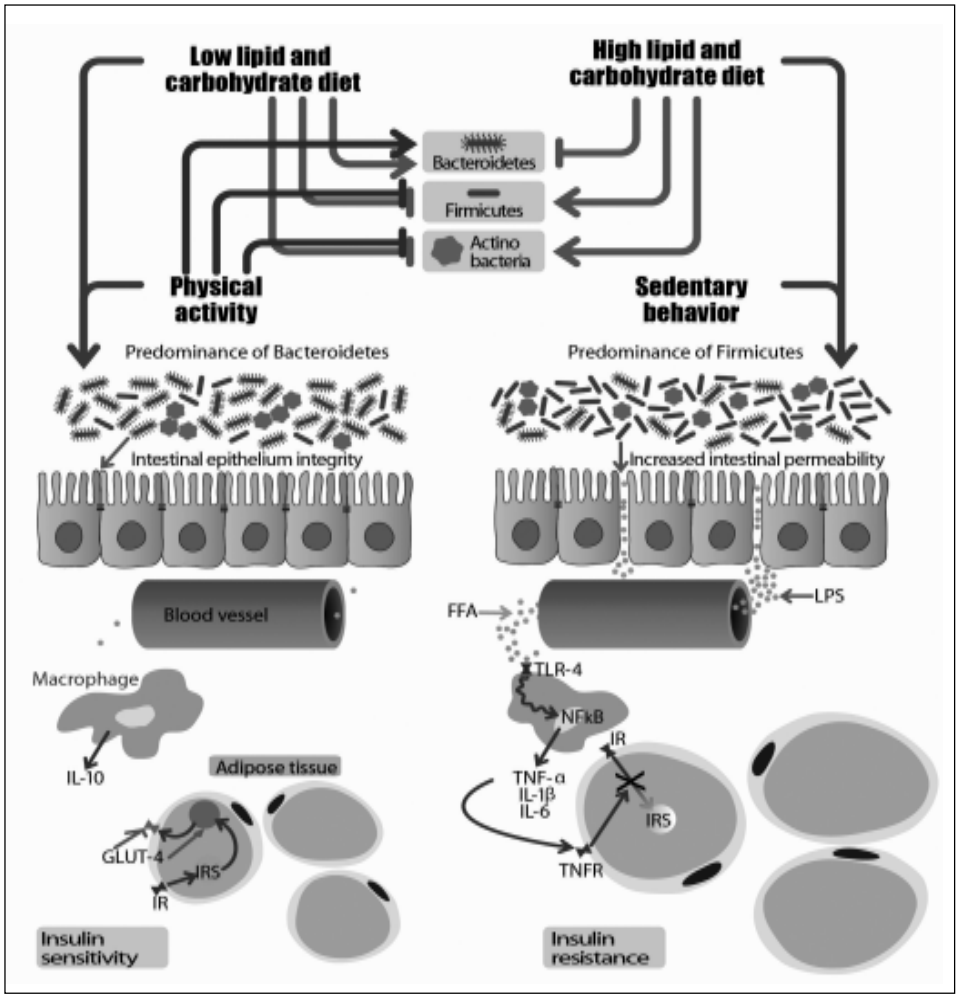

Figure 1. *Possible role of microbiota in the development of insulin resistance. Besides physical activity, a low intake of lipids and carbohydrates favors bacteroidetes, which are associated with decreased levels of LPS and free fatty acids in the intestinal lumen and blood as well as anti-inflammatory activation of macrophages and insulin sensitivity in adipose tissue (left). In contrast, a sedentary behavior accompanied by high intake of lipids and carbohydrates favors firmicutes and actinobacteria thus promoting increased intestinal permeability, LPS-induced endotoxemia, high serum levels of free fatty acids, inflammatory activation of macrophages, and finally insulin resistance (right).*

bacteria-derived metabolic products as is the case of FFA. A recent study showed that bacteria belonging to the phylum firmicutes are able to produce and store a large amount of FFA.[31] Notably, LPS and FFA can be recognized by different Toll-like receptors (TLR) located at the surface of immune cells including T lymphocytes and monocytes-macrophages.[32] Particularly, TLR2 and TLR4 are capable of binding FFA,[33] while LPS recognition is preferentially mediated via TLR4.[34] Both LPS-TLR4 and FFA-TLR2/4 interactions have been shown to elicit an inflammatory signaling cascade characterized by NFκB activation as well as expression of inflammatory cytokines including interleukin (IL) 1β and tumor necrosis factor alpha (TNF-α) in immune cells.[32-34] All of this evidence suggests that obesity-related intestinal dysbiosis could decisively participate in triggering local and systemic inflammatory responses due to endotoxemia that in turn mediates activation of circulating immune cells with capacity of migrating into peripheral tissues including adipose and renal tissue, liver, and muscle.[35]

THE ROLE OF MICROBIOTA IN TRIGGERING SYSTEMIC INFLAMMATION-RELATED INSULIN RESISTANCE

The obesity-related inflammatory process has been largely described as a systemic state of inflammation, characterized by increased circulating levels of inflammatory cytokines and macrophage infiltration in peripheral tissues.[35] In this form, systemic inflammation exhibits major differences with respect to a classically reported local inflammatory response.[35-38] The serum levels of inflammatory cytokines associated with systemic inflammation are below in comparison to those observed during an infectious disease.[36] Furthermore, the tissue-infiltrating macrophages do not induce tissue damage or loss of the normal function on it.[37] Finally, systemic inflammation has been largely associated with developing of metabolic disorders including insulin resistance and hyperglycemia, which has given birth to the term "metainflammation" to refer the systemic inflammatory process related to obesity and metabolic disease.[38]

Interestingly, a growing body of evidence suggests that gut microbiota alterations as well as the risk to become obese and insulin resistant may be linked via metainflammation. As previously mentioned, intestinal dysbiosis may provide the initial step toward establishing metainflammation (Figure 1). Microbiota modification is associated with increased FFA production and LPS-induced endotoxemia.[29-31] Upon TLR-mediated recognition, FFA and LPS are capable of promoting inflammatory activation of monocyte-macrophages, which in turn exert the ability to migrate toward visceral adipose tissue and overproduce IL-1β, IL-6, IL-8, and TNF-α.[32] In parallel, the large amounts of FFA resulting from dysbiosis can be absorbed at the intestinal tissue thus leading to increased FFA storage in visceral adipose cells and consequently fat mass gain.[39] Fat mass gain repeatedly involves accumulation of visceral adipose tissue (also referred to as central obesity) and leads to adipose cells to experience an expansive process affecting both their number and size. The increase in the number of white adipose cells is also called adipose tissue hyperplasia (a frequent histological feature in obese adults who were not obese in childhood), whereas the enlargement in the adipocyte size is known as adipose tissue hypertrophy. Both hyperplasia and hypertrophy have been shown to induce hypoxia, increased lipid peroxidation, oxidative stress, endoplasmic reticular stress, and autophagy in adipose tissue.[40,41] All of these deleterious factors are capable of activating inflammatory signaling cascades thus promoting an accurate microenvironment to attract macrophages and T cells.[42] Macrophages have been demonstrated to surround adipose cells forming crown-like structures (CLS), a distinctive histological feature of metainflammation in hypertrophic fat tissue.[40] Immune cell infiltration is indeed a persistent source of inflammatory cytokines in hypertrophic adipose tissue, which in consequence exhibits high local levels of IL-1β, IL-6, IL-8, and TNF-α, as well as increased chemokine production.[43] Chemokines are cytokines with the ability of recruiting circulating immune cells toward specific tissues. As a matter of fact, the hypertrophic/hyperplasic adipose tissue has been shown to express high levels of macrophage chemoattractant protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF). MCP-1 and MIF have the ability of attracting new monocyte-macrophages toward the hypertrophic fat tissue thus perpetuating the local inflammatory microenvironment. All of the abovementioned immunological events described for visceral adipose tissue are not only restricted to affect in a paracrine fashion but also at the endocrine level. In this sense, obese subjects show increased levels of cytokines, chemokines, and proinflammatory monocytes in circulation.[44-46] Moreover, obesity-induced circulating monocytes seem to be able to differentiate into TNF-α-secreting macrophages at the hypertrophic fat mass thus inducing progressive loss of

the insulin sensitivity in white adipose cells. This tentative physiopathological scenario constitutes one of the latest hypotheses trying to explain the origin of the insulin resistance in the hypertrophic adipose tissue of obese human beings.

In normal conditions, insulin binds to its receptor located on the adipose cell surface thus initiating an intracellular signaling pathway mediated by the activation of the insulin receptor substrate 1 (IRS-1). Then, IRS-1 promotes the downstream activation of Akt via phosphoinositide 3 kinase. Activated AKT can then go on to stimulate translocation of glucose transporter proteins (GLUT-4 in the adipose tissue) from the cytosol to the cell membrane and finally mediate glucose entry into adipose cells. Experimental evidence from *in vitro* cultures of adipose cells has recently demonstrated that TNF-α has the ability to inhibit the activation of the insulin signaling pathway by blocking the IRS-1 and AKT phosphorylation via activation of ERK/JNK, PTP1B, and NFκB (Figure 1).[47] Taking these experimental findings into consideration, infiltration of TNF-α-secreting macrophages in the adipose tissue may represent an initial inflammatory step toward promoting a local environment of insulin resistance. Then, insulin resistance in adipose tissue could chronically generate hyperglycemia, compensatory hyperinsulinemia, pancreatic β-cell exhaustion and apoptosis, finally affecting the insulin signaling pathway in liver and skeletal muscle. In brief, gut microbiota alterations may play a key role in triggering systemic inflammation thus leading to macrophage infiltration in the adipose tissue, increased TNF-α production, and progressive loss of the insulin sensitivity. However, these studies have been almost exclusively performed in murine models so it is necessary to incorporate studies in patients in order to clarify whether changes in the intestinal microbiota could be associated with obesity, systemic inflammation, and insulin resistance in human beings.

ROLE OF PREBIOTICS AND PROBIOTICS IN IMPROVING GUT MICROBIOTA, SYSTEMIC INFLAMMATION, AND METABOLIC DYSFUNCTION

Taking into account the possible role of the intestinal dysbiosis in inducing systemic inflammation and insulin resistance, numerous research groups have attempted to study the effect of the microbiota restoration by means of administering prebiotics and probiotics (Table 1). Prebiotics belonging to the inulin family have been shown to increase the amount of bifidobacteria and *Faecalibacterium prausnitzii* thereby decreasing LPS-induced endotoxemia and systemic inflammation in obese subjects.[48] Inulin and oligofructose supply has been also demonstrated to reduce the amount of hepatic triglycerides and thus the liver steatosis development in rats.[27] Taking into consideration that both simple steatosis and steatohepatitis have been shown as endotoxemia-related inflammatory entities,[30,49,50] prebiotic supply could represent a therapeutic complement to treat such liver disorders in obese patients.

Administration of oligofructose has been also associated with increased bacteroidetes population as well as decreased adiposity and glycemia, and improved insulin sensitivity in rodents, even in animals exposed to hypercaloric diets.[51] In humans, administration of fructooligosaccharide has been described to elevate the plasma level of glucagon-like peptide 1, a hormone capable of inhibiting gastric emptying and glucagon release.[52] Prebiotic supply has been also associated with increased SCFA and leptin production and thus decreased appetite sensation in rodents.[27] Notably, n-butyrate is a SCFA capable of modulating the NFκB activity thus being associated with less severity of intestinal inflammatory entities including inflammatory bowel disease and colorectal cancer.[53,54]

Administration of probiotics (as is the case of *Lactobacillus plantarum)* reduces adipose cell size, adiposity, serum cholesterol, and circulating leptin in animal models.[55] Moreover, supply of probiotics including *Lactobacillus paracasei, L. rhamus,* and *Bifidobacterium animalis* has been also demonstrated to decrease fat mass gain and macrophage infiltration in adipose tissue of mice, even in animals receiving hypercaloric diets.[56] In the same sense, *Lactobacillus gasseri* administration has been shown to reduce body mass index and visceral fat percentage in obese human beings.[57] Furthermore, Lactobacillus acidophilus intake has been observed to promote insulin sensitivity in glucose-intolerant individuals and patients with type 2 diabetes.[58] Probiotic administration has been also associated with decreased serum concentrations of TNF-α and IL-6, NFκB inhibition, reduced liver transaminase levels, and increased insulin sensitivity in obese rodents and humans.[59] In diabetic mice, administration of *Saccharomyces boulardii* has been demonstrated to reduce body weight, adiposity, and lipid contents in the liver. Additionally, supply of *S. boulardii* has been recently associated with decreased macrophage infiltration and IL-1β expression in liver tissue, as

Table 1. Effect of prebiotics and probiotics upon obesity, systemic inflammation, and metabolic dysfunction.

Prebiotic/Probiotic	Study type	Dosage	Duration	Main effect	Reference
Inulin/oligofructose	Randomized, double-blind, placebo-controlled clinical trial	16 g/day, inulin/ oligofructose 1:1	3 months	Increase in bifido bacteria, decrease in adiposity, circulating LPS, and CRP	Dewulf *et al.*[48]
Inulin/oligofructose	Experimental study in JCR:LA-cp rats	Diet containing 10 and 20% of inulin/oligofructose	10 weeks	Decrease in cholesterolemia and liver triglycerides	Parnell *et al.*[25]
Oligofructose	Experimental study in hypercaloric diet-fed ob/ob and C57BL/6 mice	Diet containing 10% of oligofructose	4 weeks	Decrease in firmicutes, adiposity, and systemic levels of TNF-α, IL-1β, and IL-6, as well as increase in bacteroidetes and glucose tolerance	Everard *et al.*[51]
Fructooligo-saccharides (raftilose)	Randomized, double-blind, placebo-controlled clinical trial	20 g/day, raftilose	2 periods of 2 and 7 days	Increase in plasma GLP1 levels	Piche *et al.*[52]
Lactobacillus plantarum	Experimental study in hypercaloric diet-fed C57BL/6 mice	1 x 10^8 CFU/mouse/day	11 weeks	Decrease in adipose tissue hypertrophy, adiposity, serum cholesterol, and leptin levels	Takemura *et al.*[56]
Lactobacillus gasseri	Randomized, double-blind, placebo-controlled clinical trial	200 g/day of fermented milk supplemented with *L. gasseri* SBT2055	12 weeks	Decrease in visceral adiposity, BMI, and waist circumference	Kadooka *et al.*[57]
Lactobacillus acidophilus	Randomized, double-blind, placebo-controlled clinical trial	Lyophilized tablets of *L. acidophilus* NCFM (1 g/day equivalent to 1 x 10^{10} CFU)	4 weeks	Decrease in insulin resistance (HOMA-IR)	Andreasen *et al.*[58]

LPS: lipopolysaccharide. CRP: C-reactive protein. TNF-α: tumor necrosis factor alpha. IL: interleukin. GLP1: glucagon-like peptide 1. CFU: colony forming units. BMI: body mass index. HOMA-IR: homeostasis model assessment of insulin resistance.

well as low serum levels of IL-1β, IL-6, and TNF-α in both obese and diabetic mice.[60]

In summary, administration of prebiotics and probiotics seems to reduce body weight, fat deposition, metainflammation, and metabolic dysfunction in animals and humans.[59] Therefore, restoration of a proper intestinal microbiota by means of supplying prebiotics and/or probiotics could be a promissory therapeutic strategy to treat obesity-related diseases thus preventing systemic inflammation and metabolic complications.

CONCLUDING REMARKS

All of this information indicates that changes in the intestinal microbiota profile might be associated with increased susceptibility to obesity, systemic inflammation establishment, and metabolic dysfunction development. Present knowledge could provide new scientific bases into the development of novel therapeutic strategies to treat obesity and insulin resistance by restoring the balance of the intestinal microbiota. In a near future, a therapy based on administering prebiotics, probiotics, and/or anti-inflammatory drugs (as is the case of recombinant IL-10 or infliximab) could contribute to a better metabolic control of obese patients. However, further clinical research focused on examining the microbiota profile on different ethnic populations is still required to understand the role of microbiota and dysbiosis in the development of chronic noncommunicable diseases in humans.

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