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REVIEW

The human gut microbiota: Metabolism and perspective in obesity

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ABSTRACT

The gut microbiota has been recognized as an important factor in the development of metabolic diseases such as obesity and is considered an endocrine organ involved in the maintenance of energy homeostasis and host immunity. Dysbiosis can change the functioning of the intestinal barrier and the gut-associated lymphoid tissues (GALT) by allowing the passage of structural components of bacteria, such as lipopolysaccharides (LPS), which activate inflammatory pathways that may contribute to the development of insulin resistance. Furthermore, intestinal dysbiosis can alter the production of gastrointestinal peptides related to satiety, resulting in an increased food intake. In obese people, this dysbiosis seems be related to increases of the phylum Firmicutes, the genus *Clostridium*, and the species *Eubacterium rectale, Clostridium coccoides, Lactobacillus reuteri, Akkermansia muciniphila, Clostridium histolyticum*, and *Staphylococcus aureus*.

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Introduction

The gut microbiota has recently been recognized as an important factor for the development of metabolic diseases and is considered an endocrine organ involved in the maintenance of energy homeostasis and host immunity.[1] Changes in the composition of the gut microbiota due to environmental factors may result in a change in the relationship between the bacteria and the host. This change can result in a low-grade chronic inflammatory process and in metabolic disorders such as those present in obesity.[2]

The human gut microbiota consists of up to 100 trillion microbes that exist in a largely symbiotic relationship with their human hosts, carrying at least 150 times more genes (the microbiome) than the human genome.[3] Based on 16S rRNA-targeted molecular analyses, most bacteria detected in fecal samples from healthy human volunteers belong to two phyla, Bacteroidetes and Firmicutes. The gram-negative Bacteroidetes phylum includes the genera *Bacteroides, Prevotella, Parabacteroides*, and *Alistipes*, while the gram-positive *Firmicutes* includes species such as *Faecalibacterium prausnitzii, Eubacterium rectale*, and *Eubacterium hallii*,[4] as well as many other low abundance species.

The metabolism of some bacteria can facilitate the extraction of calories from the diet, increase fat deposition in adipose tissue, exacerbate hepatic inflammatory processes, and provide energy and nutrients for microbial growth and proliferation.[5,6] Several microbial genes involved in human metabolism are enriched or depleted in the guts of obese humans.[7] Obese people tend to have a higher proportion of genes which encode membrane transport functions[8] and are involved in butyrate production,[9] whereas the genes related to cofactor, vitamin, and nucleotide metabolism or transcription are more frequently depleted.[8]

Considering this influence of the gut microbiome on the onset and progression of obesity as well as its consequences, knowledge about the gut microbiota could contribute to the development of adjuvant treatments that can beneficially modulate obesity. Some studies have already evaluated the gut microbiota composition in obese individuals; however, the characterization of this microbiota is still not well established, and some results are discordant. Here, we present a review of the physiology and composition of the human gut microbiota with a focus on obese individuals. We divided our review into two topics: the

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physiology of the gut microbiota and the composition of this microbiota in obese patients.

Methods

In order to discuss gut microbiota composition of obese individuals, we undertook a systematized literature search that included observational studies (cross-sectional, cohort, or case-control) and experimental studies. The following exclusion criteria were used to reduce possible relationships observed due to other comorbidities: diabetes, intestinal diseases, cancer, experimental studies, and studies that supplemented gut microbiota modulators. The literature search was performed in the MEDLINE and Scopus databases, and the references of studies obtained were scanned for other relevant articles that may not have been detected by the primary search. Only studies published in English in the last 10 years were considered for review. The following Medical Subject Headings (MeSH) search strategy was used: (obesity[Title/Abstract] AND full text[sb] AND "last 10 years"[P-Dat]) AND (gut microbiota composition[Title/Abstract]) AND (full text[sb] AND "last 10 years"[P-Dat] AND (Humans[Mesh])).

Methodological quality was assessed using the STROBE recommendations (Strengthening the Reporting of Observational Studies in Epidemiology Statement) with separate checklists for conference case-control studies, cohort studies, and cross-sectional studies, and CONSORT recommendations (Consolidated Standards of Reporting Trials) using a checklist of items for reporting trials of nonpharmacological treatments. The final system was a combination of STROBE and CONSORT.

We also conducted a narrative review about the subject in the following topics: function of the gut microbiota on the development of lymphoid structures, function of the gut microbiota on the immune system, function of the gut microbiota on nutrient and lipid metabolism, function of the gut microbiota on the hormones involved in food intake, and gut microbiota and obesity: future perspectives. There were no restrictions placed on the year of publication in this section.

Physiology of the gut microbiota

The gut microbiota harbors incredibly large microbial and genetic diversity, with distinct species associated with specific parts of the gastrointestinal tract. The stomach contains about 10^1 microbial cells per gram of content. The duodenum contains about 10^3 cells; the jejunum,10^4 cells; the ileum, 10^7 cells; and the colon, 10^{12} microbial cells per gram of contents.[10] Therefore, the quantity of bacteria increases from the proximal to the distal portions of the gastrointestinal tract. Notably, the large intestine contains more than 70% of all microorganisms in the body, which are usually associated with the health/disease of the host.[11] In addition, the diversity of bacteria is higher in the lumen and lower in the mucus layer.[12]

High numbers of bacteria in the gastrointestinal tract result in biochemical diversity and metabolic activity that interacts with host physiology. These microorganisms can facilitate the metabolism of non-digestible polysaccharides, produce essential vitamins, and they also play an important role in the development and differentiation of the intestinal epithelium and the host immune system.[13]

Most species are anaerobic and belong to two phyla: Firmicutes and Bacteroidetes. Bacteria belonging to the phyla Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria are widely spread in human populations, but at much lesser abundance.[14] Although controversial, the ratio of Firmicutes-to-Bacteroidetes has been investigated and associated with the predisposition of diseases.[15] Moreover, the low abundance of phylum Proteobacteria associated with a high amount of the genera *Bacteroides, Prevotella*, and *Ruminococcus* has been associated with a healthy intestinal microbiota.[16] The maintenance of a healthy gut microbiota is important for a symbiosis relationship with the host.

Function of the gut microbiota on the development of lymphoid structures

The lymphatic system consists of a set of lymphatic vessels that interconnect primary to secondary lymphoid organs. Recirculation of the interstitial fluid and the transport of lymphocytes and antigen-presenting cells occur through this system. These immune cells are produced in the primary lymphoid tissues (thymus and bone marrow) and are activated in the secondary lymphoid tissues (spleen, lymph nodes, and mucosa-associated lymphoid tissue (MALT)).[17]

Among the MALT, the gut-associated lymphoid tissues (GALT) are non-encapsulated tissues composed of

Peyer's patches, isolated lymphoid follicles, and crypt plaques[18] that begin to form during embryogenesis, when the environment is sterile. At this stage, the mesenchymal cells are induced by retinoic acid to produce the chemokine (C-X-C motif) ligand 13 (CXCL13) that attracts the human lymphoid tissue inducer (LTi) cells. Mature LTi cells induce differentiation of stromal cells and attract immune cells, which form the GALT.[17]

The maturation of this tissue depends on microbial colonization after birth.[19] The stromal and epithelial cells recognize bacterial peptidoglycan through the signaling pattern recognition receptors (PRR), nucleotide-binding oligomerization domain-containing protein 1 (NOD1), and Toll-like receptors (TLRs). Activation of these receptors by the gut microbiota increases the expression of CC chemokine ligand 20 (CCL20) and β defensin 3 ligand (HBD3), which activate the formation of isolated lymphoid follicles from the binding of chemokine receptor 6 (CCR6) in LTi.[20] Changes in the microbial composition, which happens in obese individuals, can further disrupt the integrity of the intestinal barrier promoted by GALT, leading to pathological bacterial translocation and the initiation of an inflammatory response.[21]

Function of the gut microbiota on the immune system

Besides acting on the maturation of GALT, the commensal bacteria also prevent the intestinal colonization by pathogens. The gut microbiota improves the function of the epithelial barrier, while its absence decreases the production of antimicrobial peptides by Paneth cells. This event causes intestinal barrier dysfunction and increases bacterial translocation.[22] Furthermore, bacteria-induced myeloid differentiation factor 88 (MyD88) signaling in the intestine increases epithelial cell IgA secretion. In addition, bacterial flagellin activates Toll-like receptors 5 (TLR5) from dendritic cells, and promotes the differentiation of B lymphocytes into IgA-producing cells[23] IgA binds to the microbial antigens, neutralizes the activity of the pathogens, and prevents infection.[24]

Commensal bacteria modulate the innate immune response of the host by stimulating the production of homeostatic levels of pro-IL-1β by resident macrophages so that the response of these cells to an enteric infection occurs more rapidly.[25] The protective role of IL-1β in intestinal immunity is mediated by the induction of expression of endothelial adhesion molecules, which contribute to neutrophil recruitment and destruction of pathogens in the gut.[26]

Besides that, modulation of natural killer (NK) T cells is also performed by commensal bacteria. NK T cells are a subset of T cells that simultaneously express both T cell receptor (TCR) and NK cell receptors. These cells promote inflammation from the secretion of cytokines IL-2, IL-4, IL-13, IL-17A, IL-21, tumor necrosis factor (TNF), and interferon-γ (IFN- γ).[27] Maintenance of homeostasis of these cells prevents an exaggerated inflammatory reaction.[28]

Also, an increase in inflammation has been associated with an increase in obesity-associated diseases, such as cardiovascular disease[29] and type 2 diabetes.[30] Intestinal dysbiosis (changes in gut microbiota composition) can be related to the trigger of a persistent low-grade inflammatory response in obese individuals. Lipopolysaccharides (LPS) contain lipid A, which can cross the intestinal mucosa through tight junctions or with the aid of chylomicrons.[31,32] Lipoproteins are responsible for the absorption and transport of dietary triglycerides, and could thus initiate an inflammatory process that could result in the insulin resistance often observed in obesity.[31,32] In the systemic circulation, LPS causes an innate immune response in liver and adipose tissue. This occurs from the binding of LPS to the LPS binding protein (LBP), which activates the CD14 receptor.[32] This complex binds to Toll-like 4 receptors (TLR4) on macrophages and adipose tissue, resulting in a signaling pathway that activates the expression of genes encoding pro-inflammatory proteins, such as factor nuclear kappa B (NF-κB) and activator protein 1 (AP-1).[32,33]

LPS concentrations are low in healthy people, but may reach high concentrations in obese individuals and cause metabolic endotoxemia.[31] This metabolic endotoxemia is related to the development of insulin resistance.[34] The molecular mechanisms that relate the activation of TLR4 by LPS with insulin resistance still need to be clarified, but evidence indicates that it involves alteration of insulin receptor signaling by the presence of inflammatory cytokines.[35]

Function of the gut microbiota on nutrient metabolism and lipid metabolism

The gut microbiota derives its nutrients from the fermentation of carbohydrates ingested by the host.

Bacteroides, Roseburia, Bifidobacterium, Fecalibacterium, and *Enterobacteria* are among the bacterial groups that typically ferment undigested carbohydrates and synthesize short chain fatty acids (SCFA)[36] such as acetate, butyrate, and propionate. A significant amount of acetate enters the systemic circulation and reaches the peripheral tissues, while the propionate is mainly used in liver, and the butyrate is used in intestinal epithelium as an energy source.[37] The total and relative concentrations of SCFA depend on the fermentation site, the carbohydrate consumed, and the composition of the gut microbiota.[38]

In addition to synthesizing vitamin K and vitamin B components, several species belonging to the Firmicutes and Actinobacteria phyla are conjugated linoleic acid (CLA) producers.[39] CLA is a mixture of positional and geometric isomers of linoleic acid shown by some studies to have anti-obesity properties such as: increase in energy metabolism and expenditure, decrease in adipogenesis, decrease in lipogenesis, and increase in lipolysis and adipocyte apoptosis.[39] The biological effects of CLA have been attributed to two possible mechanisms of action: 1) CLA displaces the arachidonic acid from cell membrane phospholipids, which decreases the synthesis of arachidonic acid-derived eicosanoids such as prostaglandins and leukotrienes involved in inflammation,[40] and 2) CLA mediates activation of transcription factors such as peroxisome proliferator-activated receptors (PPARs), which impact cell processes such as lipid metabolism, apoptosis, and immune function.[40]

Short chain fatty acids

The gut microbiota of obese mice had a higher amount of genes that encode enzymes involved in carbohydrate metabolism and greater capacity to extract energy from the diet and to produce SCFA when compared to non-obese mice.[41] In addition, germ-free mice were resistant to diet-induced obesity.[42]

SCFAs bind to G protein-coupled receptors (GPCR41 and GPCR43).[36] Acetate binds primarily to GPCR43, the propionate binds to both GPCR41 and GPCR43, and the butyrate binds to GPCR41. GPCR41 and GPCR43 receptors are expressed in the intestinal epithelium[37] and in adipose tissue.[36] The presence of GPCRs in adipose tissue suggests that this tissue is an important target for the metabolites produced by the gut microbiota. One study identified that rats fed a high fat diet had higher GPCR43 expression in adipose tissue and in vitro. SCFA increased the expression of PPARs, an important mediator of adipogenesis.[43] SCFAs that are bound to GPCR41 stimulate the expression of leptin in adipocytes and those that bind to GPCR43 appear to stimulate adipogenesis.[44] Thus, the profile of fatty acids produced may be related to the development of obesity. However, further investigations should be performed to confirm these results in humans.

Lipid metabolism

The endocannabinoid system is expressed in tissues that control energy balance (pancreas, muscle, gut, fat, liver, and hypothalamus) and regulates feeding behavior and metabolism.[45] This system is composed of bioactive lipids that bind to cannabinoid receptors, which results in cell signaling. The best characterized of these lipids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG),[46] which activate receptors coupled to G, CB1, and CB2 proteins, thus activating the PPARα, GPR55, and GPR119 receptors.[47] The modulation of the gut microbiota or the reduction of CB1 activation improves the integrity of the intestinal barrier and reduces metabolic endotoxemia and low-grade inflammation.[47] Metabolic endotoxemia increased adipocyte hyperplasia and recruitment of macrophages into adipose tissue in a CD14 dependent pathway and increases the production of activin A, which activated the proliferation of adipocyte precursor cells. In addition, the consumption of a high fat diet caused endotoxemia and favored the development of metabolic diseases, suggesting that components of gut bacteria can remodel adipose tissue.[48] The control of this mechanism can prevent the development of obesity and its comorbidities.[48]

In addition to altering the adiposity process, the microbiota acts at many levels, from lipid processing and absorption to systemic lipid metabolism.[49,50] This change can be explained by the assimilation of cholesterol by bacterial cells, binding of cholesterol to bacterial cell walls, inhibition of hepatic cholesterol synthesis, redistribution of cholesterol from the plasma to the liver through the action of SCFA and/or deconjugation of bile acids by hydrolysis.[51]

Evidence also suggests a link between dysbiosis and pathological changes in the metabolism of deconjugated bile acids in obese patients.[52] Bacterial bile salt hydrolase (BSH) enzymes in the gut cleave the amino acid side chain of glyco- or tauro-conjugated bile acids

to generate unconjugated bile acids (cholic and chenodeoxycholic acids), which are then amenable to further bacterial modification to yield secondary bile acids (deoxycholic and lithocholic acid).[53] Secondary bile acids binded to cellular receptors, such as G protein-coupled receptor TGR5,[54] and reduced macrophage inflammation and lipoprotein uptake resulting in less atherosclerotic plaque formation, which decreased the development of atherosclerosis.[55]

Function of the gut microbiota on the hormones involved in food intake

The gut microbiota has been implicated in the control of food intake and satiety through gut peptide signaling, where bacterial products activate enteroendocrine cells by modulating enterocyte-produced paracrine signaling molecules.[56] Gut microbiota may increase production of certain SCFA, which have been shown to be associated with an increase in peptide YY (PYY),[57] ghrelin, insulin, and glucagon-like peptide-1 (GLP-1) production.[58]

Ghrelin was negatively correlated with *Bifidobacterium, Lactobacillus*, and B. *coccoides/Eubacterium rectale*, and positively correlated with *Bacteroides* and *Prevotella*.[59] Ingestion of oligofructose, a prebiotic that promotes the growth of *Bifidobacterium* and *Lactobacillus*, decreased the secretion of ghrelin in obese human.[60]

GLP-1 also is modulated by the gut microbiota and is responsible for controlling food intake and insulin secretion. The concentration of this hormone was lower in obese individuals compared to eutrophic individuals.[61,62] Butyrate produced by intestinal bacteria was present in smaller amounts in obese individuals[63] and regulated energetic homeostasis by stimulating adipocytes to produce leptin and by inducing GLP-1 secretion by L cells.[64] At least in mice, modulation of the gut microbiota by probiotics increased the production of butyrate by commensal bacteria, inducing the production of GLP-1 by intestinal L cells and thus reducing adiposity.[65]

In addition, the gut microbiota may favor the formation of specific bile acids that activate the TGR5 receptors. Intestinal bacteria dehydrate chenodeoxycholic acid[66] and produce lithocholic acid, which binds to TGR5[67] and increases energy expenditure in brown adipose tissue and GLP-1 secretion by activation in the intestinal L cells,[54] thus preventing obesity and insulin resistance.[68]

The insulin concentrations also appear to be altered in accordance with the gut microbiota.[69] Gut microbiota transplantation from lean subjects to patients with metabolic syndrome increased insulin sensitivity.[70] This effect is probably related to the reduction of chronic low-grade inflammation, resulting from LPS translocation and, consequently, to greater activation of the insulin signaling cascade.[71] Like GLP-1, PYY is also produced by intestinal L cells in the form of PYY1–36 and PYY3–36, the latter being present in higher concentrations in the postprandial period, causing a sensation of satiety.[72] Obese individuals produced less PYY3–36, and no resistance to the hormone was observed. Batterham et al.[73] found a 30% reduction in food intake 90 minutes after the infusion of PYY3–36 in obese individuals, a value similar to eutrophic patients. The modulation of the gut microbiota with prebiotic (oligofructose) of healthy subjects resulted in increased bacterial fermentation, glucose tolerance, and reduced appetite from increased concentrations of GLP-1 and PYY,[74] probably due to a mechanism associated with the production of propionate by intestinal bacteria.[75] Therefore, the gut microbiota is also related to the development of obesity, due to the possible capacity to alter the food intake.

The human gut microbiota composition in obesity

Phyla changes after weight loss

A higher Firmicutes-to-Bacteroidetes ratio related to obesity was observed in obese children when compared to normal weight children,[76,77] in overweight/obese women with metabolic syndrome when compared with overweight/obese women with non-metabolic syndrome,[78] and in Japanese overweight individuals when compared with non-overweight individuals.[79] Furthermore, the Firmicutes phylum has been shown to be negatively correlated with the resting energy expenditure (REE) as well as positively correlated with fat mass percentage.[80] A cross-over clinical trial observed that a 20% increase in the Firmicutes phylum abundance was associated with an increase of 150 kcal in energy harvest.[81] Finally, one study reported a decrease in the Firmicutes-to-Bacteroidetes ratio after weight loss by obese individuals (Table 1).[15]

Obese individuals seem to have fewer Bacteroidetes counts than normal weight individuals.[79,82,83] On the other hand, two studies associated the Bacteroidetes phylum with weight gain in pregnant women.[84,85] A cross-over study with 29 subjects did not find

Table 1. Main results of studies that evaluated the gut microbiota composition in obesity.

Ref	Subjects' characteristics	Age	Design	Objective	Methods of detection	Results	Quality
84	Overweight pregnant women (n = 18) Normal weight (n = 36)	**Overweight**: 30.0 years (26.4–34.0) **Normal weight**: 30.5 years (26.6–33.6)	Case-control	To characterize the gut microbiota in women according to their body mass index (BMI) and the effect of weight gain over pregnancy on the composition of microbiota before delivery	FISH and qPCR	**Overweight**: ↑ Bacteroides, *Staphylococcus aureus* and *Clostridium* **Bacteroides**: positive correlation with weight and BMI before pregnancy and weight gain over pregnancy ***Bifidobacterium***: ↑ in women with lower weight gain over pregnancy	**B**
91	Overweight and obese children (n = 25) Normal weight (n = 24)	7 years	Cross-sectional	To establish whether early gut microbiota composition can guide weight development throughout early childhood	FISH and qPCR	**Overweight**: ↑ *Staphylococcus aureus* **Normal weight**: ↑ *Bifidobacterium* numbers	**B**
85	Mothers and their infants. Pre-pregnancy body mass index >25 (n = 16) or normal weight (n = 26)	**Pre-pregnancy overweight**: 28.55 years (26.2–34.12) **Normal weight**: 30.04 years (26.43–33.70) **Infants**: 1–6 months	Cross-sectional	To analyze the fecal microbiota composition of infants with overweight and normal weight mothers and to assess the relationship of weight and excessive weight gain of mothers during pregnancy on the microbiota of infants	FISH and qPCR	**Infants of overweight mothers**: ↓Bacteroides-Prevotella; ↑*Clostridium histolyticum*; ↑*Staphylococcus aureus*; ↑*Akkermansia muciniphila*; ↑*Akkermansia* **Infants of normal weight mothers**: ↑*Bifidobacterium;* ↓*Bifidobacterium adolescentis* **Infants of mothers with excessive weight gains**: ↓Bacteroides-Prevotella; ↑*Clostridium histolyticum*; ↓*Bifidobacterium*; ↑*Staphylococcus aureus*	**B**
88	N = 30 morbidly obese women enrolled in a bariatric surgery program	—	Clinical trial	To examine the impact of Roux-en-Y gastric bypass (RYGB) on modifications of gut microbiota and its potential associations with changes in gene expression in white adipose tissue	Multiplex pyrosequencing	**After RYGB**: ↑richness of gut microbiota; ↓Firmicutes (*Lactobacillus, Dorea*, and *Blautia*); ↓*Bifidobacterium*; ↑Bacteroidetes (Bacteroides and Alistipes); ↑*Escherichia*	**B**
77	Overweight and obese children and adolescents (n = 26) Normal weight (n = 27)	**Overweight and obese**: 11.64 ± 2.43 years **Normal weight**: 10.70 ± 3.12 years	Cross-sectional	To investigate and compare the gut microbiota composition in obese and lean children	qPCR and matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry	**Obese**: ↑Firmicutes-to-Bacteroidetes ratio; ↑*Lactobacillus* spp; ↓*Bacteroides vulgatus* **Lactobacillus spp.**: positively associated with plasma hs-CRP **Staphylococcus spp.**: positively associated with energy intake	**B**
15	N = 12 obese people Fat-restricted low-calorie diet (FAT-R) (n = 6) Carbohydrate-restricted low-calorie diet (CARB-R) (n = 6)	(21–65)	Clinical trial	To investigate the relationship between gut microbial ecology and body fat in humans	qPCR	92.6% of gut microbiota (obese): Bacteroidetes and Firmicutes **Before diet therapy**: ↓Bacteroidetes; ↑Firmicutes **After diet therapy**: ↑Bacteroidetes; ↓Firmicutes ↑**Bacteroidetes**: positively correlated with percentage loss of body weight	**B**

80	Obese (n = 50) Normal weight (n = 30)	**Obese**: 51.9 years (48.1–55.7) **Normal weight**: 42.6 years (38.1–47.1)	Cross-sectional	To assess the composition of gut microbiota and its association with resting energy expenditure (REE) in obese and normal weight subjects	Semi-quantitative analysis of gut microbiota composition in aerobic and anaerobic conditions	Bacteroides-to-Firmicutes rate was similar in both study groups **Positive correlation between**: REE (kcal/day) and total bacterial count REE (kcal/m^2/h) and total bacterial count Firmicutes count and percentage of fat mass **Negative correlation between**: REE (kcal/day) and percentage of Firmicutes REE (kcal/m^2/h) and percentage of Firmicutes	**B**
89	Obese women who underwent laparoscopic sleeve gastrectomy (LSG) (n = 5) or dietary weight loss regimen (n = 5)	48 ± 3 years	Longitudinal pilot clinical trial	To investigate functional weight loss mechanisms with regard to gut microbial changes and energy harvest induced by LSG and a very lowcalorie diet	SOLiD long-mate-paired shotgun sequencing	**LSG**: ↑Bacteroidetes and ↓Firmicutes (*Clostridium, Eubacterium, Faecalibacterium, Dorea*, and *Coprococcus*); ↑*Butyrivibrio fibrisolvens*; ↑*Clostridium saccharolyticum*; ↑*Eubacterium*; ↑*Blautia hydrogenotrophica*; Bacteroidetes showed a negative correlation with body weight; Firmicutes were positively correlated with body weight **Dietary intervention**: ↓Bacteroidetes; body weight correlated significantly positively with Bacteroidetes and negatively with Firmicutes	**B**
103	African Americans (n = 42) Caucasian Americans (n = 40)	**African Americans**: 51.2 years **Caucasian Americans**: 52.3 years	Cross-sectional	To investigate if differences in dietary habits between the two groups are associated with cytotoxicity/ genotoxicity of fecal water and with fecal microbiota composition To evaluate associations between obesity and microbiota composition, 14 lean (BMI <25) and 14 randomly chosen obese subjects (BMI >30) were selected	FISH and qPCR	↑ **Calories from fat**: ↓*Clostridium*; ↑ **Dietary fiber**: ↑lactic acid bacteria; BMI was not associated with proportions of Bacteroides or Firmicutes	**B**
83	Obese (n = 68) Control (n = 47)	**Obese**: 50.5 ± 14.4 years **Control**: 42.6 ± 17.5 years	Cross-sectional	To test whether *Lactobacillus* or *Bifidobacterium* species found in the human gut are associated with obesity or lean status	qPCR	**Obese**: ↑*Lactobacillus reuteri*; ↑*Lactobacillus*; *E. coli* **Control**: ↑*Lactobacillus paracasei*; *Lactobacillus plantarum*; ***B. animalis***: was associated with normal weight *Methanobrevibacter smithii, Bifidobacterium animalis* ***L. reuteri***: was associated with obesity	**A**
78	Overweight/obese women in metabolic disorder group (MDG, n = 27) or in non-metabolic disorder group (NMDG, n = 47) or normal weight women group (NWG, n = 11)	**MDG**: 42 ± 8 years **NMDG**: 39 ± 9 years **NWG**: 31 ± 14 years	Cross-sectional	To investigate whether overweight/obese women in MDG differ in their gut microbiota composition from overweight/obese women in NMDG and NWG	FISH	**MDG**: ↑E.rectale-C.coccoides, ↑gram-negative, ↑Erec-to-Bacto ratio, ↑Firmicutes/Bacteroidetes ratio **E. rectale-C. coccoides group**: positive correlation with ↑body weight, BMI, FM, FM%, visceral fat area, and serum triglycerides; negative correlation with HDL concentrations **Bacteroides**: inverse correlation with body weight, BMI, FM, FM%, and insulin concentration; positive correlation with HDL	**A**
92	Obese (n = 33)	43 ± 13.85 years	Clinical trial	To identify bacteria affecting host metabolism in obesity during weight loss and to correlate them with changes in body composition	qPCR	After weight reduction: ↑ total bacterial abundance, *Lactobacillus, Akkermansia*; ↓ ratio of Firmicutes/ Bacteroidetes, *Clostridium*; Differences in lactobacilli abundance correlated with differences in weight percentage	**A**
90	Pregnant women (24 weeks of pregnancy) Overweight (n = 16) Normal weight (n = 34)	**Overweight**: 29 years (28.0–33.5) **Normal weight**: 31 years (27.7–34.2)	Cross-sectional	To establish possible relationships between gut microbiota, body weight, weight gain, and biochemical parameters in pregnant women	qPCR	**Obese women**: ↑Enterobacteriaceae; ↑*Escherichia coli*; ↑*Staphylococcus* **Normal weight**: ↑*Bifidobacterium*; ↑ratio of *Bifidobacterium* to *C. coccoides* group **Excessive weight gain**: ↑ *Escherichia coli*; ↑*C. leptum*; ↑*Staphylococcus* ↓*Akkermansia muciniphila*; ↓*Bifidobacterium*	**B**

(*Continued on next page*)

Table 1. (*Continued*)

Ref	Subjects' characteristics	Age	Design	Objective	Methods of detection	Results	Quality
104	Overweight adolescents randomized in low weight loss group (n = 13) or high weight loss group (n = 23) Intervention based on an energy-restricted diet and regular physical activity	14.5 years (13.0–15.0)	Clinical trial	To determine the influence of an obesity treatment program on the gut microbiota and body weight of overweight adolescents	qPCR	**Both**: ↑*Bacteroides fragilis*; ↑Lactobacillus; ↓*Clostridium coccoides*; ↓*Bifidobacterium longum*; ↓*Bifidobacterium adolescentis* ***Bacteroides fragilis* and *Clostridium leptum***: positively correlated with higher weight loss ***Escherichia coli, Clostridium coccoides, Lactobacillus* and *Bifidobacterium***: negatively correlated with higher weight loss	A
82	Obese (n = 20) Anorexia nervosa (n = 9) Normal weight (n = 20)	**Obese**: 17–72 years **Anorexia**: 19–36 years **Normal weight**: 13 –68 years	Cross-sectional	To assess the relative abundance of *Lactobacillus, Methanobrevibacter smithii*, Bacteroidetes, and Firmicutes divisions in the microbiota of obese, lean, and patients with anorexia nervosa	qPCR	***B. breve* and *B. bifidum***: correlated with lower weight loss **Obese**: ↓Bacteroidetes; ↑*Lactobacillus* The anorexic bacterial profile is similar to the lean control group	B
86	15 obese male subjects and 14 non-obese subjects 4 weeks: high-protein low carbohydrate 4 weeks: high-protein moderate carbohydrate	—	Cross-over clinical trial	To examine the relationships between BMI, weight loss, and the major bacterial groups detected in fecal samples	FISH	**Bacteroides**: No difference between obese and non-obese individuals No relationship between changes in the percentage of Bacteroides and weight lost **After diet**: ↓Roseburia+Eubacterium rectale; ↓*Bifidobacteria*; no change in the percentage of Firmicutes; no change in the percentage of Bacteroidetes	B
87	Normal weight (n = 3) Obese (n = 3) Post-gastric bypass (n = 3)	**Normal weight**: 36.7 ± 4.0 years **Obese**: 35.7 ± 4.2 years **Post-gastric bypass**: 43.3 ± 8.1 years	Cross-sectional	To identify specific microbial lineages that may play important roles in the development of obesity and also to determine whether the presence or abundance of these microorganisms changes after successful post-gastric bypass surgery	qPCR	**Obese**: ↑Prevotellaceae; ↑Archaea; ↑Firmicutes **Post-gastric bypass**: ↓Firmicutes, ↑Gammaproteobacteria	B
93	Normal weight (n = 13) Obese (n = 30)	—	Cross-sectional analyses: before (M0), 3 months (M3), and 6 months (M6) after Roux-en-Y gastric bypass	To analyze the impact of RYGB on the modifications of gut microbiota and to examine links with adaptations associated with this procedure	qPCR	**Obese M0**: ↓ Bacteroides/Prevotella; ↓*F. prausnitzii* **Obese M3**: ↑Bacteroides/Prevotella; ↑*Escherichia coli*; ↑*Faecalibacterium prausnitzii*; ↓*Bifidobacterium*; ↓*Lactobacillus/Leuconostoc/Pediococcus* groups; **F. *prausnitzii***: negatively correlated with inflammatory markers **Bacteroides/Prevotella and *E. coli***: correlated negatively with body weight, BMI, body fat mass, and serum leptin concentrations **Bacteroides/Prevotella**: correlated negatively with calorie intake	B
81	Normal weight (n = 12) Obese (n = 9)	**Normal weight**: 32.8 ± 9.2 years **Obese**: 35.8 ± 10.6 years	Cross-over clinical trial	To test how gut bacterial community structure is affected by altering the nutrient load in lean and obese individuals and whether their microbiota is correlated with the efficiency of dietary energy harvest	Multiplex pyrosequencing	97%: Firmicutes + Bacteroidetes **↑20% in Firmicutes and ↓ Bacteroidetes**: energy harvest of ≈150 kcal	A

83	Obese (n = 134) Overweight (n = 38) Normal weight (n = 76) Anorexic patients (n = 15)	**Obese**: 51.8 ± 14.7 years **Overweight**: 54.1 ± 17.8 years **Normal weight**: 49.5 ± 18.6 years **Anorexic patients**: 27.3 ± 10.8	Cross-sectional	To analyze the fecal concentrations of Bacteroidetes, Firmicutes, *Methanobrevibacter smithii*, the genus *Lactobacillus*, and five other *Lactobacillus* species previously linked with lean or obese populations	PCR	**Obese**: ↑*Lactobacillus*; ↑*Lactobacillus reuteri*; ↓Bacteroidetes; ↓*M. smithii*; ↓*Bifidobacterium animalis*; ↓E. *coli* **Overweight**: ↑L. *reuteri* **Positive correlation between**: *L. reuteri* and BMI **Negative correlation between**: *M. smithii* and BMI; *E. coli* and BMI	**A**
79	Overweight (n = 33) Normal overweight (n = 23)	**Overweight**: 54.4 ± 8.2 years **Normal weight**: 45.6 ± 9.6 years	Cross-sectional	To examine the human gut microbiota composition in a Japanese population	Next generation sequencing	**Overweight**: ↓Bacteroidetes; ↑Firmicutes-to-Bacteroidetes ratio; ↑Microbial diversity; ↑*Blautia hydrogenotorophica*; ↑*Coprococcus catus*; ↑*Eubacterium ventriosum*; ↑*Ruminococcus bromii*; ↑*Ruminococcus obeum* **Normal weight**: ↑*Bacteroides faecichinchillae;* ↑*Bacteroides thetaiotaomicron;* ↑*Blautia wexlerae;* ↑*Clostridium bolteae;* ↑*Flavonifractor plautii*	**B**
76	Obese (n = 42) Normal weight (n = 36)	6–16 years	Cross-sectional	To characterize the composition of the gut microbiota in obese and normal weight individuals	PCR	**Obese**: ↓Bacteroidetes; ↑Firmicutes; ↑Firmicutes-to-Bacteroidetes ratio	**B**

LSG: laparoscopic sleeve gastrectomy; qPCR: quantitative polymerase chain reaction; FISH: fluorescent in situ hybridization; FM: fat mass; HDL: high density lipoprotein.

Table 2. Genus and species of bacteria and its relation to obesity.

Species	Genus	Phylum	Characteristics	In obese individuals	Effect associated with obesity
—–	*Bacteroides*	Bacteroidetes	gram -; anaerobic; non-spore-forming	↓ Except in pregnant women	↓absorption of dietary fat[105]; GALT development[106]
Bacteroides vulgatus	*Bacteroides*	Actinobacteria	gram -; anaerobic; non-spore-forming	↓	Part of the core gut microbiota in healthy humans[14]
Bacteroides fragilis	*Bacteroides*	Bacteroidetes	gram -; anaerobic; non-spore-forming	↓	↑IL-10 production[107]
Staphylococcus aureus	*Staphylococcus*	Firmicutes	gram +; facultative anaerobe; non-spore-forming	↑	Trigger of low-grade inflammation[91]
——	*Clostridium*	Firmicutes	gram +; anaerobic; spore-forming	↑	↑Energy storage; ↑low-grade inflammation[85]
Clostridium histolyticum	*Clostridium*	Firmicutes	gram +; facultative anaerobe; produces endospores	↑	Produces acetate, that ↑lipid synthesis[108] Produces cytotoxic proteases:[109]
Akkermansia muciniphila	*Akkermansia*	Verrucomicrobia	gram -; anaerobic; non-spore-forming; mucin-degrading bacterium	↑ Except in pregnant women	↑Degradation of intestinal mucin; ↑pro-inflammatory activity[85]
Escherichia coli	*Escherichia*	Proteobacteria	gram -; facultative anaerobe; non-spore-forming	Disputed	The absence of *E. coli* was an independent predictor of weight gain[83]; ↑harvest energy[88]
L. reuteri	*Lactobacillus*	Firmicutes	gram +; anaerobic; non-spore-forming	↑	↑Gut's ability to absorb and process nutrients[110]
L. plantarum	*Lactobacillus*	Firmicutes	gram +; anaerobic; non-spore-forming	↓	↑Conjugated linoleic acid, which increases energy expenditure and produces an anti-obesity effect[111]
——	*Bifidobacterium*	Actinobacteria	gram +; anaerobic; non-spore-forming	Disputed	↑Insulin resistance, adiponectin ↓Inflammatory adipokine expressions ↑Conjugated linoleic acid[112]
Bifidobacterium adolescentis	*Bifidobacterium*	Actinobacteria	gram +; anaerobic; non-spore-forming	↓	↓Visceral fat accumulation; ↑Insulin sensitivity[113]
Butyrivibrio fibrisolvens	*Butyrivibrio*	Firmicutes	gram +; anaerobic; non-spore-forming	↓	↑Conjugated linoleic acid[114]
Faecalibacterium prausnitzii	*Faecalibacterium*	Firmicutes	gram +; anaerobic; non-spore-forming	↓	Modulates systemic inflammation[115]
E.rectale-C.coccoides	*Eubacterium / Clostridium*	Firmicutes	gram +; anaerobic; non-spore-forming/spore-forming	↑	↑Butyrate; ↑Harvest energy from the diet[116]

differences in the proportion of Bacteroidetes between obese and non-obese individuals (Table 1).[86]

A decrease of Firmicutes was observed after Roux-en-Y gastric bypass (RYGB)[87,88] and after laparoscopic sleeve gastrectomy (LSG).[89] In contrast, Bacteroidetes counts increased after RYGB and LSG[88,89] but after a very low-calorie diet.[89] This phylum decreased with a concomitant increase in the Firmicutes phylum. A decrease in the Firmicutes-to-Bacteroidetes ratio after diet therapy also was observed, and the Bacteroidetes proportion was positively correlated with a percentage of loss of body fat (Table 1).[15]

Obesity related genus changes

The genera *Staphylococcus*[77,84,85,90,91] and *Clostridium*[84,85,89,92] have been shown to be positively associated with obesity. A decrease in the genus *Faecalibacterium* was reported after LSG,[89] while the same genus increased after RYGB.[93] All these genera belong to the Firmicutes phylum (Table 1). The Firmicutes phylum contains many butyrate producing species, and an increase in butyrate and acetate synthesis may contribute to an increase in energy harvest in obese people.[15,94] Furthermore, acetate can be absorbed and used as a substrate for lipogenesis and gluconeogenesis in the liver.[49]

The genus *Bacteroides,* which belongs to the phylum Bacteroidetes, was shown to have an inverse relationship with obesity in overweight/obese women with metabolic disorder[78] after RYGB[88,93] and LSG (Table 1).[89] *Bifidobacterium*, which belongs to the phylum Actinobacteria, was also shown to have an inverse relationship with obesity in pregnant

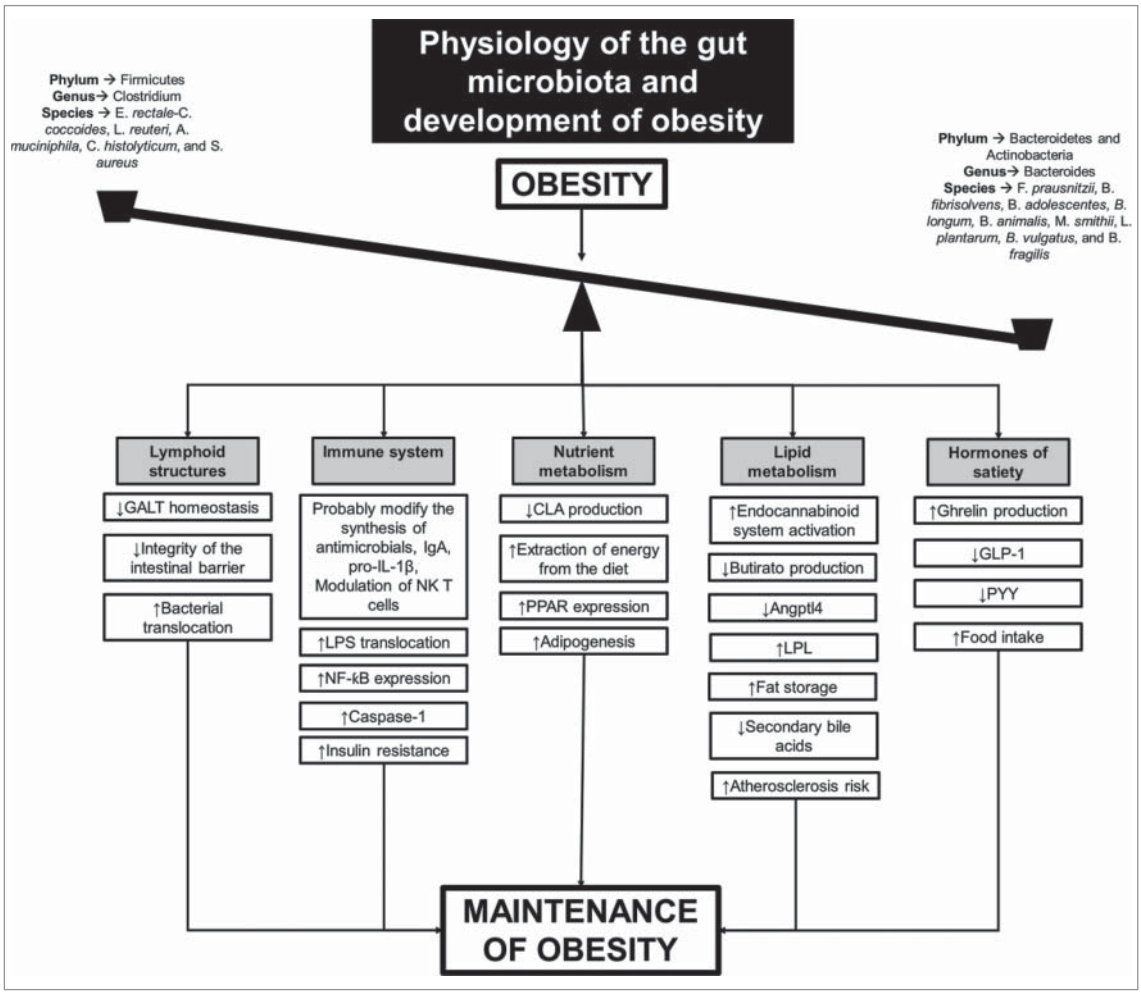

Figure 1. Possible mechanisms that related the obesity and intestinal dysbiosis with the physiological changes that contributed to the maintenance of obesity. GALT: gut-associated lymphoid tissue; IgA: immunoglobulin A; LPS: lipopolysaccharide; NF-κB: nuclear factor kappa B; CLA: conjugated linoleic acids; PPAR: peroxisome proliferator-activated receptor; LPL: lipoprotein lipase; Angptl4: angiopoietin like protein 4; GLP-1: glucagon-like peptide 1; PYY: peptide YY.

women,[84,90] children,[91] and infants of normal weight mothers[85]; however, this genus was decreased in individuals subjected to RYGB.[88,93] *Bifidobacterium* species have been shown to deconjugate bile acids, which may decrease fat absorption.[95] In contrast, strains of the same species can have contradictory effects, as it has been shown that different *Bifidobacterium* strains might increase (strain M13–4) or decrease body weight (strain L66–5).[96]

Methane-producing archaea (methanogens) have been shown to affect caloric harvest by increasing the capacity of polysaccharide-eating bacteria to digest polyfructose containing glycans, which leads to increased weight gain in mice.[41] A study demonstrated that humans with methane detectable via a breath test have a significantly higher body mass index (BMI) than methane-negative controls (Table 1). This implies a higher amount of *M. smithii* in obese individuals, which was not observed in studies assessing gut archaeal populations.[97]

Gut microbiota and obesity: future perspectives

Although several links have been reported between the gut microbiome and obesity (Table 2), the mechanisms are not yet understood that explain how and when the microbiome affects the obese state. Most studies investigating the relationships between obesity and the gut microbiome use very small sample sizes and use a variety of analytical methods to infer the intestinal microbial composition. Such factors are likely responsible for the considerable heterogeneity observed in the results. For instance, different DNA extraction kits have an impact on the assessment of the human gut microbiota, making it difficult to compare data across studies.[98]

Probiotics, prebiotics, and antibiotics have been evaluated, and they may become new therapeutic possibilities for the treatment of obesity. Oral supplementation with probiotics seems to reduce the concentrations of low-density lipoproteins (LDL) and total cholesterol; to ameliorate atherogenic indices; to improve glycemic control[99]; to reduce body weight, waist circumference, BMI, and abdominal visceral adipose tissue[100]; to improve body composition,[101] and to reduce the concentrations of pro-inflammatory markers such as interleukin 6 (IL-6) and TNF-α[[102] Prebiotics also have been shown to contribute to weight loss and improve metabolic parameters including insulin resistance.[60] Nevertheless, modulations performed with probiotics show results only for specific strains and for the period evaluated, with little data available regarding long-term benefits. In addition, the different ways in which different hosts can react to supplementation make it impossible to carry out generalizations. In the future, the modulation of the gut microbiota may be a way of assisting in the treatment of obesity, but for this idea to become a reality, there is a need to understand the metabolic interactions between the modulated bacteria and the host.

Conclusions

Although there is a large amount of heterogeneity in the data that is available, the following conclusions can be drawn from the literature review: 1) obesity was characterized by the presence of intestinal dysbiosis, marked by the distinct microbiome profile existing between obese and non-obese individuals; 2) the resulting dysbiosis could change the functioning of the intestinal barrier and the GALT, allowing the passage of structural components of bacteria, such as LPS, and activating inflammatory pathways that may contribute to the development of insulin resistance by alteration of insulin receptor signaling by the presence of inflammatory cytokines; 3) intestinal dysbiosis could alter the production of gastrointestinal peptides related to satiety, resulting in an increased food intake and contributing to a self-sustaining cycle; and 4) lipid metabolism could be altered by the changes observed in the gut microbiome, resulting in a stimulus to increase body adiposity (Fig. 1).

Understanding the changes occurring in the gut microbiome of obese individuals and the physiological consequences of these changes is a necessary step in creating modulation strategies that can be used to help treat this condition.

List of Abbreviations

2-AG	2-arachidonoylglycerol
AEA	anandamide
AP-1	activator protein 1
BMI	body mass index
BSH	bile salt hydrolase
CCL20	CC chemokine ligand 20

CCR6	chemokine receptor 6
CLA	conjugated linoleic acid
C-X-C	chemokine
CXCL13	ligand 13 chemokine
GALT	gut-associated lymphoid tissues
GLP-1	glucagon-like peptide-1
GPCR	G protein-coupled receptors
HBD3	β defensin 3 ligand
IFN- γ	interferon-γ
IL-6	interleukin 6
LBP	LPS binding protein
LDL	low-density lipoproteins
LPS	lipopolysaccharides
LSG	laparoscopic sleeve gastrectomy
LTi	lymphoid tissue inducer
MALT	mucosa-associated lymphoid tissue
MyD88	myeloid differentiation factor 88
NF-κB	factor nuclear kappa B
NK	natural killer
NOD1	nucleotide-binding oligomerization domain-containing protein 1
PRR	pattern recognition receptors
PYY	peptide YY
RYGB	Roux-en-Y gastric bypass
SCFA	short chain fatty acids
TCR	T cell receptor
TLR4	Toll-like 4 receptors
TLR5	Toll-like receptors 5
TLRs	Toll-like receptors
TNF	tumor necrosis factor.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Authors' contributions

ACG: drafted the manuscript and performed the design of the study. CH and JFM: drafted and revised the manuscript. All authors read and approved the final manuscript.

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