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Gut microbiota and metabolic syndrome

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Core tip: The present review offers a summary of available studies exploring the pathogenic role of gut microbiota in the development of metabolic syndrome, subdividing experimental evidences coming from animal models and human subjects, since their results are not always comparable. The relative influences of dietary intake on gut microbial composition and functions are also explored, as well as the effects on intestinal microhabitat exerted by diet-induced weight loss and bariatric surgery. Finally a critical evaluation of the available evidences on probiotic and prebiotics is reported, delineating their potential clinical impact.

Abstract

Gut microbiota exerts a significant role in the pathogenesis of the metabolic syndrome, as confirmed by studies conducted both on humans and animal models. Gut microbial composition and functions are strongly influenced by diet. This complex intestinal "superorganism" seems to affect host metabolic balance modulating energy absorption, gut motility, appetite, glucose and lipid metabolism, as well as hepatic fatty storage. An impairment of the fine balance between gut microbes and host's immune system could culminate in the intestinal translocation of bacterial fragments and the development of "metabolic endotoxemia", leading to systemic inflammation and insulin resistance. Diet induced weight-loss and bariatric surgery promote significant changes of gut microbial composition, that seem to affect the success, or the inefficacy, of treatment strategies. Manipulation of gut microbiota through the administration of prebiotics or probiotics could reduce intestinal low grade inflammation and improve gut barrier integrity, thus, ameliorating metabolic balance and promoting weight loss. However, further evidence is needed to better understand their clinical impact and therapeutic use.

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INTRODUCTION

The metabolic syndrome is defined by a combination of interconnected physiological, biochemical, clinical and metabolic factors linked to an increased risk of cardiovascular diseases and type 2 diabetes mellitus^[1]. Raised blood pressure, dyslipidemia (defined by increased triglycerides and reduced high-density lipoprotein cholesterol), raised fasting glucose and central obesity are metabolic syndrome's main features, as defined by the International Diabetes Federation (IDF)^[2].

The worldwide prevalence is variable, ranging from < 10% to 84%, depending on geographical origins and composition of the studied population, as well as the

definition criteria applied^[1]. However, its high economic and social burden is still growing, thus, clinical research is focusing on understanding the complex pathogenesis of metabolic disorders.

Recent evidences have proposed the potential role of gut microbiota as pathogenic factor affecting host metabolic balance and disorders^[3]. In fact, gut microbiota seems to exert a great variety of functional properties impacting human physiology and pathology^[4]: modulation of host nutrition and energy harvest by the production of vitamins and fermentation of food components indigestible by the host; influence of intestinal epithelial homeostasis; development of host immune system; protection against pathogens; drug metabolism^[4-6].

Initial studies on gut microbial composition and function were limited by the difficulty to culture all intestinal microbes^[7]. The recent introduction of analyzing methods, based on bacterial genome sequencing and “metagenome” analysis, has contributed to increase the knowledge about uncultivable microbes, gut microbial functions, its cross-talk with the host and the potential pathogenic role related to host’s diseases^[8].

In the present review, the pathogenic role of gut microbiota on the development of metabolic disorders, such as obesity, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD), as well as the influence of diet on gut microbial composition, will be discussed. Available evidences emerging from studies conducted on animal models and humans are reported separately, thus, underlining that experimental and clinical observations are not always comparable. Finally, the therapeutic implications of gut microbiota manipulation, through the administration of probiotics and prebiotics, are also discussed.

GUT MICROBIOTA AND OBESITY

Experimental studies on animal models

First evidences about the role of gut microbiota on the development of obesity came from studies conducted on germ free mice (GF-mice) compared to conventionally raised mice (CONV-R)^[9]. In basal conditions, the latter have a 40% higher body fat content than GF-mice and this phenomenon was independent from the food intake. Moreover, after colonization of GF-mice with intestinal flora coming from CONV-R mice, a significant increase of body weight, in particular a 60% increase of body fat, a significant increase of hepatic triglycerides synthesis and the development of insulin resistance were observed in recipients (CONV-D), independently from food intake and total energy expenditure^[9]. Several mechanisms have been proposed to explain these observations^[9]: the increased secretion of leptin, observed in CONV-D mice, was associated to reduced insulin sensitivity; the increased monosaccharides absorption in CONV-D mice enhanced hepatic triglyceride synthesis by up-stimulation of lipogenic genes, such as acetyl-CoA carboxylase and fatty acid synthase, through the

activation of carbohydrate response element binding protein and sterol response element binding protein-1; moreover, gut microbiota, inoculated in CONV-D mice, seemed to suppress the expression of fasting-induced adipose factor (FIAF), a central regulator of lipid metabolism, that modulates lipoprotein lipase (LPL) activity in adipose tissue^[10]. The suppression of FIAF, induced by gut microbiota, resulted in enhanced LPL activity and increased fatty acids storage in adipocytes^[9]. Indeed, in their study^[9], Bäckhed and colleagues concluded that gut microbiota represents an environmental factor affecting host’s predisposition to develop obesity and increase adiposity.

In a subsequent study^[11], Bäckhed and colleagues observed that GF-mice, fed with “high sugar - high fat Western diet”, do not seem to develop obesity^[11]. The main mechanisms explaining GF resistance to diet-induced obesity are the enhanced fatty acids oxidation, uncoupled with decreased LPL activity and fatty acids storage^[11]. The first mechanism is promoted by increased AMP-activated protein kinase activity, an activator of mitochondrial enzymes, involved in fatty acid oxidation in skeletal muscle and liver. On the other hand, GF-mice showed elevated levels of FIAF, which suppresses LPL activity^[11].

Moreover, GF-mice colonized with intestinal flora coming from obese mice showed a more evident increase of body weight and of fat tissue than those colonized with gut flora deriving from lean mice^[12]. The speculated mechanism was the increased energy harvest promoted by gut microbiota metabolism, in particular by microbes deriving from obese subjects^[9,12].

The mechanism through which gut microbes contribute to increased energy absorption seems to be the production of short chain fatty acids (SCFAs), resulting from the hydrolysis and the fermentation of dietary polysaccharides. SCFAs, such as propionate, butyrate and acetate, could be absorbed and used as source of energy, but seem to exert more complex metabolic functions influencing host appetite^[13,14], intestinal transit time^[13], energy absorption and energy harvest^[15].

For example, SCFAs increase intestinal absorption of monosaccharides stimulating the expression of sodium/glucose transporter-1^[15].

SCFAs also contribute to modulate host appetite and food intake interacting with G-coupled proteins expressed by enteroendocrine cells and promoting the release of glucagon-like peptide-1 (GLP-1) and peptide YY, which directly influence host’s satiety^[13,14].

Moreover, SCFAs influence lipid metabolism by increasing lipogenesis^[9] and inhibiting fatty acids oxidation^[11], as previously reported.

Other studies have reported specific changes of gut microbiota composition in genetically obese mice (*ob/ob* mice), compared to lean counterparts, showing a 50% reduction in the abundance of *Bacteroidetes* and a proportional increase in *Firmicutes*^[16]. These specific changes could contribute to the increased SCFAs production and energy harvest observed both in obese mice and in GF-

mice colonized with *ob/ob* mice microbiota^[12].

However, it's not clear how and why, in obese subjects, gut microbiota seems to extract more energy from ingested food^[17]. Moreover, this mechanism is insufficient to explain the more significant weight gain observed in GF-mice colonized with intestinal flora coming from obese donor, compared to that observed in mice receiving lean donor's microbiota^[12,17]. In genetically obese mice *ob/ob*, leptin deficiency could in part explain the increased efficiency of gut microbiota to extract energy from food; however, it's not clear why the metabolic activity of "obese-gut microbiota" is still increased, also when transferred to wild-type lean donors^[17].

Other putative mechanisms have also been proposed. For example, high-fat diet has shown to increase the proportion of Gram-negative species in gut microbiota, thus, contributing to an increased intestinal absorption of bacterial fragments, such as lipopolysaccharides (LPS). As a consequence, the increased levels of circulating LPS lead to a condition defined as "metabolic endotoxemia"^[18], in which, however, blood LPS levels are lower than those observed in septic shock. The experimentally induced endotoxemia in mice leads to body weight gain, fasted hyperglycemia and hyperinsulinemia, similar to that observed on high-fat-fed mice^[18].

Increasing evidence suggests that high-fat diet promotes changes in gut microbiota composition, but the subsequent development of obese phenotype occurs only in the presence of metabolic endotoxemia^[19].

Fei *et al.*^[20] found that a specific endotoxin-producing bacterium, the *Enterobacter cloacae* B29, isolated from morbidly obese human's gut, induced obesity and insulin resistance in GF-mice, increasing endotoxin circulating levels. The Authors concluded that an increase of endotoxin-producing bacteria in gut microbiota, represents a cause, rather than a consequence, of the host's metabolic balance deterioration. Indeed, these two studies^[19,20] imply that lowering metabolic endotoxemia, could represent a potential treatment strategy for the metabolic disease, even if additional studies are necessary to confirm this assertion.

Metabolic endotoxemia is promoted by increased intestinal permeability and bacterial translocation related to a low grade intestinal inflammation state, resulting from the interaction between luminal bacteria and host's immune system^[18,19,21].

Bacterial antigens are recognized by specific receptors exposed by intestinal dendritic cells, such as NOD1, CD-14 and Toll-like receptor 4 (TLR-4). The interaction between these receptors and bacterial peptidoglycan or LPS activates mucosal inflammation and bacterial translocation^[21], through the activation of the NF- κ B pathway.

Bacterial translocation is prevented in mice lacking the specific microbial pattern recognition receptors NOD1 or TLR-4^[21]. In fact, animal models resistant to high-fat diet induced obesity, showed reduced TLR-4 activation and decreased intestinal translocation^[19].

However, even if some studies have explained the

role of host immune system in promoting metabolic endotoxemia and bacterial translocation^[18,19,21], other studies have underlined the role of immune response in maintain gut homeostasis and prevention of gut dysbiosis^[22,23].

For example, TLR-5 seems to exert a central function in the recognition of pathogen-associated molecular patterns (PAMPs) and in the stimulation of inflammatory response in order to maintain mucosal homeostasis^[22]. TLR-5 deficient mice develop intestinal dysbiosis, hyperphagia, obesity and insulin resistance^[23]; moreover, these traits could be transmitted by colonizing wild type mice with gut microbiota deriving from TLR-5 knock-out mice.

Another mechanism involved in the regulation of gut ecosystem homeostasis is the endocannabinoid system^[24]. In fact endocannabinoid receptors expressed in the gut (eCB1) interact with bacterial LPS, modulating gut permeability, LPS translocation and inducing metabolic endotoxemia^[24].

On the other hand, gut microbiota is essential for host's immune system maturation, gut-associated lymphoid tissue development and a well-balanced T-cells differentiation^[25]. Indeed, GF-mice show an immature gut-associated lymphoid tissue and several systemic immune system dysfunctions. Moreover, an intestinal dysbiosis contributes to an altered differentiation of T-cells, an imbalance between T-helper and T-regulatory lymphocytes, leading to the disruption of immune tolerance and the development of autoimmune diseases^[26].

In conclusion, evidences emerging from studies conducted on animal models have confirmed the pathogenic role exerted by gut microbiota on the development of obesity. In fact, microbial products, mainly SCFAs, regulate several host's metabolic functions, energy absorption and appetite. Moreover, the complex interactions between gut microbes and host's immune system affect gut microbial homeostasis and composition, intestinal dysbiosis, bacterial translocation and the subsequent development of metabolic endotoxemia, which is essential for the development of obese phenotype and insulin resistance.

Human clinical studies

Studies conducted on obese human subjects have confirmed specific changes on gut microbiota composition, such as a reduction of *Bacteroidetes* phylum and a proportional increase of *Firmicutes*^[27,29]. Moreover, a reduction of *Bifidobacterium* and *Bacteroides* and an increase of *Staphylococcus*, *Enterobacteriaceae* and *Escherichia coli* were detected in overweight compared to normal-weight pregnant women^[29].

However, other studies showed conflicting results: Duncan *et al.*^[30] reported no significant differences of the *Bacteroidetes/Firmicutes* ratio between obese and lean subjects, as well as no significant changes of fecal *Bacteroidetes* count during diet induced weight loss. On the contrary, Schwiertz *et al.*^[31] reported a significant increase of *Bacteroidetes* in obese and overweight subjects.

Studies conducted on obese twins have revealed differences on phyla distribution between obese and lean subjects: reduced microbial diversity, such as a relative reduction of *Bacteroidetes* and *Actinobacteria*, were found among obese subjects, but no significant changes in *Firmicutes* proportion emerged^[32]. The identification of a “core microbiome” in obese subjects led to the assumption that functional changes, related to different genes and metabolic pathways expression by gut microbiota, rather than the diversity of organismal assemblage, could explain different physiological states (obese or lean)^[32]; in particular, a preferential increase of genes involved in sugar and carbohydrate metabolism could be present in overweight subjects^[32].

The functional changes in overweight's gut microbiota lead to an increased production of SCFAs^[12,31], with a consequent raised capacity of energy harvest^[12] associated to a preferential increase of propionate^[31].

A more recent study underlined that low genetic richness in gut microbiota, reflecting a reduced microbial diversity and a preferential expression of few metabolic pathways, is correlated with overall adiposity, insulin resistance and a more pronounced inflammatory phenotype^[33]. The qualitative changes in gut microbiota of obese subjects were represented by an increase of *Proteobacteria* and *Bacteroidetes* phyla, a decrease of anti-inflammatory bacteria, such as *Akkermansia muciniphila*, and an increase of pathogens, such as *Campylobacter* and *Shigella*. The changes lead to a decreased production of butyrate, a protective substance affecting intestinal barrier integrity, as well as an increased mucus degradation potential and oxidative stress management^[33].

Qualitative changes of gut microbiota composition have been found also in early stages of life. Two studies^[34,35] conducted on overweight children demonstrated a reduction of beneficial bacteria, such as *Bifidobacteria*^[34], *Desulfovibrio* and *Akkermansia muciniphila*-like bacteria^[35], associated with an increase of pathogens or Gram negative bacteria, such as *Staphylococcus aureus*^[34] and *Enterobacteriaceae*^[35]. Thus, identifying early changes of gut microbiota could predict subsequent development of obesity.

Moreover, gut microbial composition, in overweight adolescents, seems to influence the extent of weight loss, obtained after dietary restriction and increased energy expenditure by physical activity, independently from total food intake^[36]. Indeed, increased total bacteria, *Bacteroides fragilis* group, *Clostridium leptum* group, and *Bifidobacterium catenulatum* group counts, associated to decreased levels of *Clostridium coccoides* group, *Lactobacillus* group and *Bifidobacterium* group before and after dietary interventions are associated to a strongly significant weight loss, independently from total food intake. Thus, gut microbiota could potentially influence the efficacy of dietary interventions^[36].

Several “non-dietary” factors seem to influence gut microbial composition, since the early stages of life. Indeed, delivery mode^[37,38], infant feeding^[39], antibiotic use^[40], gestational age and infant hospitalization are the most im-

portant factors^[37]. In fact, term birth, vaginal delivery, short hospitalization, less exposure to antibiotics and breastfeeding are associated to a more “beneficial” gut microbiota, characterized by higher numbers of *Bifidobacteria* and lower numbers of *Clostridium difficile* and of *Escherichia coli*^[37].

In conclusion, studies conducted on human subjects have confirmed the pathogenic role exerted by gut microbiota. However, the observations emerging from these clinical studies are not always comparable to the results reported in experimental studies conducted on animal models. In fact, the alteration of *Bacteroidetes*/*Firmicutes* ratio in gut microbial composition has not been confirmed in all human studies. The main features characterizing overweight subjects' microbiota are reduced microbial diversity, decrease of bacteria with potential anti-inflammatory properties and increase of pathogens. Recent evidences have underlined the importance of functional changes of gut microbiota, resulting from the alteration of genetic pathways expression, on the pathogenesis of obesity, rather than the simple organismal assemblage.

INFLUENCE OF DIET

Observations in human subjects

Diet seems to strongly influence gut microbial composition since the first stages of life^[41]. De Filippo *et al*^[42] compared fecal microbiota of European children (EU), mostly fed with a “modern western diet”, to gut microbiota of children coming from a rural African village of Burkina Faso (BF), mostly fed with a “high-fiber diet”. BF children showed a significant enrichment in *Bacteroidetes* and depletion in *Firmicutes*, associated to increased abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, compared to EU children. On the other hand, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF compared to EU children. These differences reflect the adaptation of gut microbiota to host's diet, with consequent enrichment of bacterial species hydrolyzing complex polysaccharides in BF group. The results of this adaptation are the maximization of energy extraction from dietary fibers, but also an enrichment of microbial diversity and the potential protection from inflammation and non-infectious colonic disease, observed in rural communities^[42].

On the other hand, high-fat/low-fiber Western diet promotes the overgrowth of gram-negative pathogens, with consequent increased intestinal translocation of bacterial LPS^[18]. LPS interaction with specific receptor of host's immune-system (TLR-4/CD-14) culminates in an inflammatory cascade^[43] that precedes the development of insulin resistance, obesity and diabetes^[18].

Sequencing studies of fecal metagenomes of individuals coming from different countries lead to the identification of three robust clusters, defined “enterotypes”. The three main clusters are dominated by the genera *Bacteroides*, *Prevotella* and *Ruminococcus* (enterotype 1, 2 and 3 respectively). These clusters are indicative of the existence of

limited numbers of well-balanced host-microbial symbiotic states that are not influenced by the geographical origin, but seem to be shaped by the diet^[44].

Regular red meat consumption, as well as the high-fat/low fiber Western diet, is associated to a predominance of *Bacteroides*-rich gut ecosystem, with associated increased expression of genes involved in protein degradation. On the other hand, *Prevotella* species dominate in vegetarians with preferential expression of genes involved in starch break-down^[41,45].

The gut microbiome seems to rapidly respond to specific changes of diet. Indeed, in a study in which “animal-based diet” and “plant-based diet” were assigned to two groups of healthy volunteers, rapid changes of gut microbial composition were observed in both groups^[46]. In particular, the animal-based diet increased the abundance of bile-tolerant and amino-acids metabolizing microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*), while it decreased the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*), thus reflecting the functional and metabolic changes induced by dietary compounds^[46]. However, although these changes appeared within the first 24 h, the overall enterotype identity remains stable^[47].

In conclusion, diet contributes to shape gut microbial composition, creating a stable cluster of microorganisms defined “enterotype”. Diet modification seems to induce rapid changes of gut microbial composition, although enterotype identity is not altered. However, further studies are needed to establish the effect of long term dietary changes on gut microbial composition and function.

Lessons from animal models

High-fat Western diet contributes to the development of obesity, to weight gain and to the increase of white adipose tissue through the intermediation of gut microbiota. A confirmation comes from experimental studies showing that high-fat diet (HFD) promotes weight gain only in conventional mice but not in germ-free mice^[48].

Moreover HFD promotes the same changes in gut microbiota composition found in obese subjects, influencing the *Bacteroidetes/Firmicutes* ratio^[49]. The colonization of GF-mice with gut microbiota coming from high-fat fed conventional mice is associated to significant weight gain.

de Wit *et al*^[50] found that saturated fatty acids promote weight gain, increased adiposity and the development of fatty liver by modifying gut microbial composition and enhancing lipogenesis.

Moreover, high-fat diet promotes specific changes of gut microbial composition, such as a reduction of *Bacteroidetes* and an increase of *Firmicutes* and *Proteobacteria*, in both obese and lean phenotypes^[51], suggesting its role in shaping intestinal flora, independently from genetically-determined host's phenotype^[51]. Furthermore, the experimental study by Fleissner and colleagues^[52], reported that high-fat diet promotes weight gain, also in absence of gut microbiota. In fact, GF-mice, fed with high-fat

chow, gained more body weight and body fat than their conventional counterpart^[52].

Therefore, these observations demonstrate that a diet rich in lipids, in particular saturated fatty acids, promotes weight gain and increases visceral adiposity, shaping gut microbiota composition and influencing, both directly and indirectly through the intermediation of intestinal flora, energy absorption and harvest^[53].

Other studies have also underlined the role of dietary lipids in promoting low-grade gut inflammation and increased intestinal permeability, as previously described also in GF mice^[48]. Indeed, diet rich in lipids is associated to a significant decrease of *Bifidobacteria*, known to produce butyrate, which exerts anti-inflammatory effects and promotes gut barrier integrity^[54]. Moreover, it is associated to an increase of sulfate-reducing/endotoxin-producing bacteria belonging to the *Desulfovibrionaceae* family, leading to an increased gut inflammation and impaired barrier function^[55]. HFD contributes also to the development of increased intestinal permeability as demonstrated by the reduced expression of genes encoding for components of tight junctions^[56]. Furthermore, the extent of increased gut permeability is correlated to specific microbial changes, such as a reduction of *Lactobacillus* and an increase of *Oscillobacter*^[56].

In conclusion, experimental evidences from animal models demonstrate that HFD promotes weight gain by altering gut microbial composition and by increasing intestinal permeability.

GUT MICROBIOTA AND DIABETES

Experimental studies on animal models

LPS-induced metabolic endotoxemia is the first step for the development of insulin resistance and diabetes^[18]. Indeed, mice fed with high-fat diet have shown increased proportion of LPS-containing microbiota in the gut as well as circulating LPS. Experimental LPS infusion lead to fasted hyperglycemia and hyperinsulinemia. Moreover, CD14/TLR-4 mutant mice, resistant to LPS, were also resistant to high-fat diet-induced metabolic diseases, because, in this animal models, the subsequent expression of inflammatory cascade in liver and fat was significantly reduced^[18,57]. CD14 mutant mice showed insulin hypersensitivity even during normal diet, suggesting the potential role of CD14 to set host's insulin sensitivity in physiological conditions^[18].

The modulation of gut microbiota, through the administration of a broad spectrum antibiotic therapy, ameliorated glucose tolerance in *ob/ob* and diet-induced obese and insulin-resistant mice, influencing inflammatory, and metabolic status of the host, independently from food intake^[58].

Similarly, Cani *et al*^[59] found that antibiotic treatment reduced metabolic endotoxemia and the cecal content of LPS in both high-fat-fed and *ob/ob* mice, with consequent reduction of systemic inflammation and improvement of insulin sensitivity. Similar results were observed

in CD14 mutant *ob/ob* mice, independently from antibiotic treatment.

On the other hand, a recent study^[60] defined the protective role of the bacterium *Akkermansia (A.) muciniphila* against the development of metabolic diseases.

A. muciniphila, a member of the *Verrucomicrobia* phylum, is a mucus-degradating bacteria, located in the mucus layer, representing 1%-4% of the bacterial population in the colon^[61]. The abundance of this mucin-degrading bacterium, is inversely correlated to body weight in rodents and humans^[60], and is negatively associated to type 1^[62] and type 2^[63] diabetes. The normalization of *A. muciniphila* abundance through prebiotic administration is correlated with an improved metabolic profile, reduced fat-mass, metabolic endotoxemia, adipose tissue inflammation and insulin resistance. Moreover, it seems that *A. muciniphila* administration led to increased intestinal levels of endocannabinoids that control inflammation, the gut barrier integrity, and gut peptide secretion^[60]. However, the exploitation of all these effects requires viable bacteria, because treatment with heat-killed cells did not improve the metabolic profile^[60].

In the presence of bacteria producing butyrate or conjugated linolenic acid, such as *Bifidobacteria* or *Lactobacillus*, an improvement of glucose tolerance in association with a decrease of endotoxemia, of circulating pro-inflammatory cytokines and of intestinal permeability, were observed^[59,64].

In conclusion, gut microbiota promotes the development of insulin resistance and diabetes by inducing metabolic endotoxemia. Bacteria with potential anti-inflammatory properties, such as *A. muciniphila*, *Bifidobacteria* and *Lactobacilli*, exert a protective role by enhancing gut barrier integrity and by preventing bacterial translocation.

Human clinical studies

As demonstrated in animals, high energy intake increases levels of circulating LPS also in humans^[65]. Circulating LPS stimulates the TLR-2 mediated inflammatory response and increases the secretion of pro-inflammatory cytokines by the adipose tissue^[32]. LPS levels are significantly increased in diabetic subjects, compared to controls, and seem to decrease with the administration of antidiabetic therapy (rosiglitazone)^[66].

A longitudinal study^[67] found that increased levels of blood circulating bacteria are present before the development of diabetes. Moreover, pyrosequencing analyses conducted on subjects in the early phases of reduced glucose tolerance, identified a core blood microbiota, mostly (85%-90%) composed by *Proteobacteria* phylum, which could represent a potential biomarker for predicting the development of diabetes^[67].

Specific changes in gut microbiota composition have been observed in diabetic subjects: an increase of *Bacteroides* and *Prevotella* was associated to a proportional decrease of *Firmicutes* and *Clostridia*^[68]. Furthermore, a decrease of anti-inflammatory bacteria, such as *Bifidobacteria* was also

observed^[69].

However, Zhang *et al*^[70] found that specific changes of gut microbiota composition could be identified in each progressive stage leading to the development of diabetes. The relative abundances of butyrate-producing bacteria (*Akkermansia muciniphila* and *Faecalibacterium prausnitzii*) seems to decrease along with decreasing glucose tolerance, in association with a decrease of *Verrucomicrobiae*. On the other hand, *Betaproteobacteria* levels show an opposite trend.

Recently, Qin *et al*^[63] have developed a novel gut microbiota analytical platform to identify disease-associated metagenomic markers. Comparing gut microbial metagenome of diabetic to healthy control subjects, the Authors found that in diabetic subjects only a moderate degree of gut microbial dysbiosis was present, characterized by a selective increase in several opportunistic pathogens and a reduction in bacteria producing beneficial metabolites, such as butyrate^[63]. Indeed, it's well known that butyrate may exert a protective role, enhancing the expression of tight junctions genes, promoting gut barrier function and reducing bacterial translocation^[71].

The beneficial effect of butyrate is confirmed by a study from Vrieze *et al*^[72], in which diabetic subjects received a fecal microbiota transplant from lean donors. After the transplant diabetic subjects showed a significant increase of intestinal butyrate-producing bacteria, which was correlated to an improvement of insulin sensitivity^[72].

Similarly, Karlsson *et al*^[73] developed a mathematical model, deriving from metagenome analysis of fecal samples' from 145 European women with different degrees of glucose tolerance, to accurately predict the development of diabetes. Applying this model to a Chinese cohort, the Authors identified different metagenomic predictors for diabetes between European and Chinese people. Thus, they concluded that metagenomic predictive tools for diabetes should be specific for the age and geographical location of the studied population^[73].

In conclusion, human studies confirmed the pathogenic role of metabolic endotoxemia for the development of insulin resistance and diabetes. The progressive development of glucose intolerance and diabetes proceeds along with a corresponding decrease of anti-inflammatory and butyrate-producing bacteria, as well as an increase of pathogens. Indeed, the experimental enrichment of butyrate-producing bacteria is associated to an improvement of insulin sensitivity.

GUT MICROBIOTA AND NAFLD

Experimental studies on animal models

As previously explained, gut microbiota strongly influences energy absorption and storage, in particular by modulating monosaccharides absorption and hepatic de novo lipogenesis through complex pathways which influence expression of genes involved in these specific metabolic reactions^[9]. In fact, GF mice receiving gut

microbial colonization from conventional mice show a significant increase in triglycerides synthesis and fatty storage in hepatocytes^[9].

Although gut microbiota could modulate *per se* lipid metabolic pathways in hepatocytes, specific changes in microbial composition are able to influence the development of fatty liver.

Indeed, although high-fat diet experimentally induced weight gain in conventional mice, not all of them developed reduced glucose tolerance, hyperinsulinemia and overt fatty liver^[74]. A pyrosequencing study revealed that mice developing insulin resistance and fatty liver showed an increased number of *Lachnospiraceae* and *Barnesiella*, associated with a decrease of *Lactobacilli*. These alterations were not observed in mice resistant to diet induced metabolic syndrome^[74].

Moreover, gut microbiota could contribute to the development of fatty liver through the ethanol production^[75]. In fact, in genetically obese mice breath ethanol tested levels were significantly higher than in lean mice and antibiotic treatment could reduce by 50% the cumulative ethanol production^[75].

Other proposed mechanisms through which gut microbiota could influence the susceptibility to develop NAFLD are the alteration of the choline^[76] and the bile acid^[77] metabolisms.

More recently, the role of fructose-rich diet has been explored^[78]: the experimental administration of a 30% fructose solution, for 8 wk, to a group of mice, is associated to the development of hepatic steatosis and a significant increase of hepatic transaminases. The onset of fructose induced-NAFLD is associated to the development of small bowel bacterial overgrowth, increased intestinal permeability, increased circulating endotoxin and the subsequent activation of Kupffer cells mediated hepatic inflammation^[78].

Gut microbiota also exerts a role in the progression from fatty liver to non-alcoholic steatohepatitis (NASH) and the development of hepatic fibrosis. It has been observed that experimentally induced endotoxemia activates hepatic inflammatory response through the recruitment of Kupffer cells by TLR-4 mediated signaling^[79]. Indeed, in TLR-4 deficient mice, as well as after the experimental destruction of Kupffer cells, inflammatory response and liver damage are significantly reduced^[79].

Furthermore, recent studies^[80,81] have underlined the role of cytoplasmic multiprotein complexes, called inflammasomes, in the development of inflammatory liver injury. These inflammasomes are expressed in most liver cells, such as Kupffer cells, liver sinusoidal endothelial cells, periportal myofibroblasts and hepatic stellate cells. The activation of cytosolic inflammasomes, induced by the interaction with LPS or with other microbial antigens coming from bacteria circulating in the portal system, leads to the expression of the pro-inflammatory cascade^[80,81] and modulates hepatic fibrotic tissue deposition^[82].

Although inflammasomes play a critical role in the

pathogenesis of liver disease, inflammasome-deficient mice show a more severe hepatic injury and a faster progression to NASH, probably because these cytosolic complexes may contribute to modulate gut microbial composition, and their dysfunction leads to gut dysbiosis^[83].

In conclusion, gut microbiota affects the susceptibility to develop fatty liver and NASH. Bacterial ethanol production, alterations of choline and bile acids metabolism, the stimulation of hepatocytes' lipogenesis and the development of an increased intestinal permeability leading to metabolic endotoxemia are the main mechanisms involved. The complex interaction between microbial antigens and the cytosolic inflammasomes affects the activation of inflammatory cascade and the development of hepatic fibrosis.

Human clinical studies

Similar mechanisms observed in animals have been proposed to explain the putative role of gut microbiota on the pathogenesis of NAFLD in humans.

In particular, an higher prevalence of small bowel bacterial overgrowth and an increased intestinal permeability have been observed in obese subjects affected by NAFLD, and these variables seem to be correlated with the severity of hepatic steatosis^[84].

Moreover, specific changes in gut microbial composition have been observed in patients affected by NASH, such as a lower percentage of *Bacteroidetes* and higher fecal *Clostridium coccoides* concentrations. However, after adjusting for body mass index (BMI) and dietary intake, only the difference of *Bacteroidetes* fecal concentrations resulted significant. Thus, an inverse association between the presence of NASH and the percentage *Bacteroidetes* in the stools, independent from BMI and diet, was observed^[85].

A significant increase of circulating levels of ethanol, promoted by intestinal overgrowth of ethanol-producing bacteria, such as *Enterobacteriaceae* and *Escherichia coli*, have been found also in patients affected by NASH^[86].

Alteration of choline metabolism have been proposed as causative mechanism also in human subjects. In fact it's well known that hepatic steatosis, promoted by parenteral nutrition, is partly due to choline deficiency, and its supplementation could reverse hepatic fat accumulation^[87]. More recently the experimental administration of choline deficient diet was associated to variations of the intestinal concentrations of *Gammaproteobacteria* and *Erysipelotrichi*, that were directly associated to changes in liver fat amount^[88].

The development of NASH is associated, also in humans, to increased systemic inflammation, promoted by TLR-4 mediated interaction with circulating PAMPs, with consequent release of pro-inflammatory cytokines^[89].

In conclusion, the development of fatty liver is promoted by small bowel bacterial overgrowth and increased intestinal permeability. Bacterial ethanol production and choline deficiency have been confirmed as pathogenic

mechanisms also in human subjects. Moreover, the development of NASH is affected by the complex interaction between circulating bacterial antigens and host's immune system.

THERAPEUTIC STRATEGIES

Diet induced weight loss and bariatric surgery

Weight loss promoted by calories restricted diet and increased physical activity is associated to significant changes in the composition of gut microflora.

Sotos *et al*^[90] found that nutritional intervention strategy based on an energy restricted diet associated to a physical activity program for 3 mo, on a group of obese adolescents, was associated to a significant reduction of sulphate-reducing bacteria and *Enterobacteriaceae*, which was more pronounced in subjects in which interventions were successful. Moreover, in subjects who didn't reach significant weight loss, the proportion of beneficial bacteria belonging to *Roseburia-Eubacterium* populations remained low^[90]. Furthermore, diet-induced weight loss has also been associated to a reduction of *C. histolyticum*, *C. lituseburensense* and *E. rectale-C. coccoides* and an increase of the *Bacteroides-Prevotella* group^[91].

As previously reported, subjects with a low bacterial gene richness are characterized by more marked overall adiposity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype when compared to high bacterial gene richness individuals^[33]. A recent study of Cotillard *et al*^[92] reported that dietary intervention improves low gene richness and clinical phenotypes in obese subjects, but the treatment strategies seem to be less efficient for inflammation variables in individuals with lower gene richness. Thus, in these latter subjects, dietary interventions could be less effective.

Some studies conducted on subjects submitted to surgical Roux-en-Y gastric by-pass (RYGB) reported a profound change of gut microbiota composition, related to the surgically reverted anatomy of alimentary tube. These changes might contribute to the successful weight loss obtained in these patients.

Zhang *et al*^[93] found that the reduction of gastric acid and the modification of the total length of small bowel contribute to the growth of facultative anaerobes, with a significant increase of *Gammaproteobacteria*. On the other hand, *Firmicutes* and in particular methanogens bacteria, which seem to contribute to the increased energy extraction from fermentation of polysaccharides in obese subjects, are strongly decreased after RYGB^[93].

The increase of *Bacteroides-Prevotella* group was also observed after weight loss promoted by RYGB, in association to an increase of *Faecalibacterium prausnitzii* species, directly linked to the reduction in low-grade inflammation^[94].

The direct transit of carbohydrates to the small intestine, without the prior exposure to gastric acids, promotes the growth of *Proteobacteria* and *Enterobacteria* fermenting complex carbohydrates^[95]. The increased pro-

duction of metabolites deriving from oligosaccharides fermentation is well known to contribute to increased GLP-1 and peptide YY production, which contribute to reduce appetite and to improve beta-pancreatic cell function and insulin secretion^[96].

After RYGB it has been also observed an increase of intestinal gamma-amino-butyric acid production by gut microbes, which also stimulates the release of GLP-1 and peptide YY^[95].

Lips *et al*^[97] also reported that RYGB improves gut hormone release, such as GLP-1 and peptide YY, and glucose tolerance in diabetic subjects. However, it is not sufficient alone to maintain glucose metabolism balance, since calories restriction is the major determinant of short-term benefit in glucose tolerance.

RYGB does not induce only beneficial effects. Indeed, it seems to influence the increase of pathogens bacteria, such as *Escherchia coli*, and the decrease of beneficial bacteria, such as *Lactobacilli* and *Bifidobacteria*^[94]. Moreover, the reduced availability of energy extractable from glucose promotes increased energy extraction from tricarboxylic acid cycle intermediates and from protein catabolism, thus, facilitating the development of renal tubular acidosis^[95].

In conclusion, diet induced weight loss is associated to specific changes in gut microbial composition, in terms of increased beneficial anti-inflammatory bacteria and reduced pathogens. A subgroup of patients with low microbial gene richness has shown a more aggressive clinical phenotype and a less responsiveness to therapeutic strategies.

Bariatric surgery promotes evident changes in intestinal bacterial composition. These changes could reinforce the beneficial effects of the surgical intervention on host's appetite and insulin sensitivity. However, potential negative effects, such as the decrease of beneficial bacteria and the risk of developing renal tubular acidosis, need to be considered.

Probiotics

Probiotics are defined by the Food and Agricultural Organization and the World Health Organization as "live microorganisms which when administered in adequate amounts, confer a beneficial health effect on the host"^[98].

Several studies have demonstrated that probiotic strains, in particular those of the *Lactobacillus* and *Bifidobacterium* genera, exert multiple beneficial effects in subjects affected by metabolic syndrome. Indeed, they seem to promote weight loss and the reduction of visceral adiposity, to improve glucose tolerance, and to modulate intestinal low grade inflammation.

The experimental studies^[98-104] demonstrating the beneficial effects observed in HFD-induced metabolic syndrome, after the administration of probiotics containing *Bifidobacterium* strains, are reported in Table 1.

Canal *et al*^[105] and Amar *et al*^[21] have demonstrated the putative mechanisms through which *Bifidobacterium* strains could contribute to counteract detrimental effects of meta-

Table 1 Studies conducted on animal models showing effects of probiotics containing *Bifidobacterium* strains on metabolic disorders

Studied animals	Probiotic	Dose	Duration of treatment (wk)	Effects	Ref.
C57BL/6J mice	<i>Bifidobacterium breve</i> B-3	10 ⁹ CFU	8	↓body weight, epididymal fat, serum cholesterol, glucose, insulin and HOMA index ↑expression of FIAF, adiponectin	[99]
C57BL-6 mice	<i>Bifidobacterium pseudocatenulatum</i> CECT 7765		7	↓serum cholesterol, triglycerides, glucose, insulin resistance, leptin, IL-6, monocyte chemotactic protein-1, liver steatosis, adipose tissue ↑glucose tolerance Improvement of immune system functionality	[100]
HFD-fed rats	<i>Bifidobacterium longum</i>			Improvement of HFD induced metabolic disorders through ↓endotoxin levels and intestinal inflammation, ↑expression of Reg 1 genes	[101]
HFD-rats, standard diets fed rats	<i>Bifidobacterium adolescentis</i>		12	↓visceral fat, liver steatosis ↑insulin sensitivity	[102]
Sprague-Dawley rats	<i>B. pseudocatenulatum</i> SPM 1204, <i>B. longum</i> SPM 1205, and <i>B. longum</i> SPM 1207	10 ⁸ -10 ⁹ CFU	7	↓body and fat weights, serum cholesterol, triglycerides, glucose, leptin, AST, ALT and lipase levels	[103]
Sprague-Dawley rats	<i>Bifidobacteria</i> L66-5, L75-4, M13-4 and FS31-12, originated from normal human intestines	10 ⁸ CFU	6	<i>B. M13-4</i> strain ↑body weight <i>B. L66-5</i> strain ↓body weight All strains ↓serum and liver triglycerides, serum and liver cholesterol	[104]

CFU: Colony-forming units; IL-6: Interleukin-6; HFD: High-fat diet; Reg 1 genes: Intestinal regenerating family genes; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; FIAF: Fasting-induced adipose factor; HFD: High-fat diet.

bolic syndrome. The administration of probiotics containing *Bifidobacterium* is associated to an improvement of gut epithelial barrier, promoted by increased expression of tight-junction proteins^[21,105]. Consequently, a significant reduction of bacterial translocation, intestinal inflammation and metabolic endotoxemia have been observed^[18,21].

Other studies^[106-118] have demonstrated the beneficial effects exerted by probiotics containing *Lactobacillus* strains on animals and human subjects, showed in Table 2 and Table 3, respectively.

These studies underline that *Lactobacillus* strains, especially those producing conjugated linoleic acid^[106-108], contribute to body weight loss, reduction of adipocyte size and adipose tissue mass, as well as to improve glucose tolerance, modulating the expression of leptin and fatty acid synthetase.

Other studies reported the positive effects of *Lactobacillus* probiotics in modulating serum lipid profile through the stimulation of fatty acids oxidation^[109-111,115], or by inhibiting lipoprotein lipase activity through Angiopoietin like-4, a microbial regulated protein^[114].

Nerstedt *et al.*^[115] also reported the improvement of gut immune functionality, promoted by *Lactobacillus* strains.

The administration of probiotics combining *Bifidobacterium* and *Lactobacillus* strains, such as VSL#3, significantly improve glucose tolerance and reduce food intake, increasing the production of SCFAs and of butyrate that stimulate the intestinal production of GLP-1^[119].

Moreover, the administration of probiotics containing *Lactobacillus* strains alters gut microbial composition, promoting the expansion of the host's own *Bifidobacteria* population, improving the metabolic functions and reducing the pro-inflammatory activity^[120].

Recently, the role of probiotics as therapeutic strat-

egy for the treatment of hepatic steatosis and NAFLD is emerging^[121]. The putative mechanism involved are the improvement of gut microbial homeostasis of gut barrier function and integrity of the modulation of endotoxemia and of pro-inflammatory response^[121], as well as the improvement of hepatic response against oxidative damage^[110].

However, although encouraging results emerge from meta-analysis evaluating the role of probiotics for the treatment of NAFLD^[122] and the results of most studies seem to be promising, they have to be considered with caution. Indeed, the available evidences suggesting the employ of probiotics for the treatment of obesity are still weak^[123] and, therefore, the therapeutic use of probiotics for the treatment of metabolic disorders has not yet been recommended^[124].

Prebiotics

Prebiotics are defined as non-digestible polysaccharides that promote "the selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefit to the host"^[125].

The most studied prebiotics are the inulin and various types of fructo-oligosaccharides, which enhance the growth of beneficial bacteria such as *Bifidobacteria* or *Lactobacilli*.

Table 4 illustrates studies^[105,126-131] conducted on animal models, employing several types of prebiotics, such as oligofructose, arabinoxylan and inulin and their related effects on the metabolic syndrome.

Prebiotics contribute to modify gut microbial composition, enhancing the growth of *Bifidobacteria*^[105,130,131], *Bacteroides*^[129-131], *Prevotella* and *Roseburia*^[130] and promoting

Table 2 Studies conducted on animal models showing effects of probiotics containing *Lactobacillus* strains on metabolic disorders

Studied subjects	Probiotic	Duration of treatment	Effects	Ref.
C57BL/6J mice	<i>Lactobacillus rhamnosus</i> PL60	8 wk	↓body weight gain, white adipose tissue, hepatic steatosis	[106]
C57BL/6J mice	<i>Lactobacillus plantarum</i> PL62	8 wk	↓body weight, visceral adipose tissue, serum glucose levels	[107]
Sprague-Dawley rats	<i>Lactobacillus gasseri</i> SBT2055	4 wk	↓adipocyte size, leptin levels No significant changes in serum glucose and lipids levels, and liver lipids levels	[108]
Zucker diabetic fatty rats	<i>Lactobacillus fermentum</i> NCIMB 5221	8 wk	↓fasting insulin levels, insulin resistance, serum triglycerides and LDL cholesterol levels, atherosclerosis ↑HDL cholesterol levels	[109]
Male Kunming mice	<i>L. plantarum</i> CA16, <i>L. plantarum</i> SC4	28 d	↓serum total and LDL cholesterol levels, LDL/HDL cholesterol ratio, triglycerides levels, hepatic steatosis ↑serum HDL cholesterol, hepatic anti-oxidant Nrf-2 mediated response	[110]
C57BL/6J mice	<i>Lactobacillus rhamnosus</i> GG	13 wk	↓liver and mesenteric adipose tissue, weight gain ↑glucose tolerance, gluconeogenesis, fatty acids oxidation	[111]
Apoe ^{-/-} mice	<i>Lactobacillus reuteri</i> ATCC PTA 4659 (ATCC), DSM 17938 (DSM), L6798	12 wk	↓body weight gain, insulin levels, hepatic steatosis ↑fatty acids oxidation	[112]
C57BL/6 mice	<i>Lactobacillus plantarum</i> strain No. 14	11 wk	↓adipocyte size, white adipose tissue, serum leptin and total cholesterol levels	[113]
C57B/6J mice	<i>Lactobacillus paracasei</i> ssp paracasei F19	10 d	↓body weight ↑triglyceride load of the lipoprotein VLDL, angiopoietin-like 4 protein that ↓fatty storage	[114]
GF and NMF mice	<i>Lactobacillus paracasei</i> ssp paracasei F19 or <i>Lactobacillus acidophilus</i> NCFB 1748	10 d	↑adipsin, adiponectin, fatty acids oxidation Improvement of efficacy of intestinal immunological barrier ↓resistins like β	[115]

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein.

Table 3 Studies conducted on humans showing effects of probiotics on metabolic disorders

Studied subjects	Probiotics	Duration of treatment	Effects	Ref.
Overweight humans	<i>Lactobacillus gasseri</i> SBT2055	12 wk	↓body weight, visceral and subcutaneous fat area, BMI, waist and hip circumference ↑serum adiponectin	[116]
Subjects with increased abdominal adiposity	<i>Lactobacillus gasseri</i> SBT2055	12 wk	↓body weight, visceral fat area, BMI, waist and hip circumference, body fat mass	[117]
Women affected by postmenopausal metabolic syndrome	<i>Lactobacillus plantarum</i>	90 d	↓serum glucose and homocysteine levels	[118]

BMI: Body mass index.

the relative decrease of *Firmicutes*^[129,131].

Moreover, they contribute to reduce body weight, body fat and adipocyte size by modulating food intake and appetite, by promoting the production of GLP-1, peptide YY and the decrease of ghrelin, and, at the same time, by decreasing fatty acid storage^[126,127,130,131].

Furthermore, the reduction of intestinal low grade inflammation promoted by the improvement of gut barrier integrity^[128,130] and the decrease of pro-inflammatory^[105] cytokines release, lead to an improvement of glucose tolerance and insulin sensitivity.

Similar effects have been observed in studies conducted on human subjects^[132-136] as reported in Table 5.

A recent meta-analysis, exploring the beneficial effects of prebiotics on subjects with metabolic syndrome, reported a statistically significant reduction of post prandial glucose and insulin levels^[137]. On the other hand, data regarding effects on body weight, total energy intake, sati-

ety, GLP-1 and peptide YY production and inflammatory pattern seem to be controversial^[137].

CONCLUSION

Available clinical and experimental evidence suggests that gut microbiota is a potential pathogenetic factor for the development of metabolic syndrome. The overall expression of its detrimental effects seems to be influenced by complex interactions involving diet, lifestyle, environmental factors, such as antibiotic therapies, genetic predisposition, as well as a complex cross-talk between intestinal microbes and the host's immune system.

Administration of probiotics and prebiotics has been widely used in order to manipulate gut microbiota. However, although several studies reported encouraging results, solid clinical evidence recommending their therapeutic use for metabolic diseases has not emerged, and

Table 4 Studies conducted on animal models showing effects of prebiotics on metabolic disorders

Studied subjects	Prebiotic	Duration of treatment	Effects	Ref.
Wistar rats	OFS	50 d	↓Body weight, food intake, fat mass, serum triglycerides, ghrelin ↑GLP-1	[126]
Wistar rats	OFS	6 wk	↓Food intake, serum glucose and insulin ↑GLP-1, glucose tolerance	[127]
HFD fed mice	OFS	13 wk	↑ <i>Bifidobacterium</i> , glucose tolerance ↓Pro-inflammatory cytokines, endotoxemia	[105]
C57B/6J mice	OFS	4 wk	↓LPS, hepatic inflammatory and oxidative stress markers, intestinal permeability ↑GLP-2	[128]
C57B/6J mice	OFS	8 wk	↓ <i>Firmicutes/Bacteroides</i> ratio, fat mass, oxidative stress, low grade inflammation ↑Glucose tolerance, GLP-1 and leptin sensitivity	[129]
C57B/6J mice	AX	4 wk	↑ <i>Bacteroides</i> , <i>Prevotella</i> , <i>Roseburia</i> , <i>Bifidobacterium</i> spp Improvement of gut barrier function	[130]
Lean and obese JCR: LA.cP rats	Inulin-OFS	10 wk	↓Adipocyte size, fatty acids storage, body weight, serum cholesterol, insulin resistance, low grade inflammation ↓ <i>Firmicutes</i> , food intake ↑ <i>Bacteroides</i> , <i>Bifidobacterium</i> , satiety hormones	[131]

OFS: Oligofructose; GLP-1: GLUCagon-like peptide-1; LPS: Lipopolysaccharides; GLP-2: Glucagon-like peptide-2; AX: Arabinosylose; HFD: High-fat diet.

Table 5 Studies conducted on humans showing effects of prebiotics on metabolic disorders

Studied subject	Prebiotic	Duration of treatment	Effects	Ref.
Healthy men and women	OFS	2 wk	↓Food and energy intake, hunger ↑satiety	[132]
Healthy humans	GOS	12 wk	Significant ↑ <i>Bifidobacterium</i>	[133]
Obese women	Inulin-type fructans	3 mo	↑ <i>Bifidobacterium</i> and <i>Faecalibacterium prausnitzii</i> ↓Circulating LPS, <i>Bacteroides</i> , <i>Propionibacterium</i>	[134]
Obese-dyslipidemic women	Yacon syrup (containing OFS)	120 d	↓Body weight, BMI, waist circumference, serum LDL cholesterol levels	[135]
Overweight and obese adults	OFS	12 wk	↓Body weight, ghrelin, calories intake, serum glucose, insulin ↑peptide YY	[136]

OFS: Oligofructose; GOS: Galactooligosaccharides; LPS: Lipopolysaccharides; BMI: Body mass index; LDL: Low-density lipoprotein.

knowledge about the long term efficacy of this treatment is still lacking. Therefore, additional studies and randomized controlled trials using probiotics and prebiotics, are needed to further understand their clinical impact on gut microbiota manipulation.

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