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Probiotics, prebiotics and synbiotics for weight loss and metabolic syndrome in the microbiome era

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Abstract. – OBJECTIVE: Excessive body fat and the associated dysmetabolic consequences affect both developed and emerging countries. An altered gut microbiota composition is an important environmental cause of these conditions. Clinical trials targeting gut microbiome composition or functions with pro or prebiotics to promote a healthier profile are considered a promising tool for excessive body weight treatment and prevention of dysmetabolic complications.

MATERIALS AND METHODS: We searched PubMed and Cochrane Library using combinations of probiotics/prebiotics and synbiotics with obesity/weight loss/metabolic syndrome as the search terms. Clinical studies and significant pre-clinical results showing molecular mechanisms supporting clinical results were also discussed.

RESULTS: Several studies in humans and in animal models have elucidated biological mechanisms supporting the observed clinical efficacy of selected probiotic and prebiotic compounds for weight management. Efficacy appears to be species or strain-specific. Fibers such as inulin or galactomannan promote independent and synergistic beneficial effects.

CONCLUSIONS: Diet supplementation with synbiotics prepared using selected strains (such as *Lactobacillus gasseri* strains) showed to exert weight-reduction and anti-inflammatory activity in large independent studies. Their administration, together with galactomannan and/or inulin fibers, may increase weight management effects due to synergistic effect on short chain fatty acid production and microbiota 're-configuration'.

Key Words
Probiotic, Prebiotic, Synbiotic, Microbiome, Metabolic syndrome, Weight.

Introduction

Excessive body fat and its metabolic consequences are worldwide epidemics affecting both developed and emerging countries (Obesity and overweight: World Health Organization; fact-sheets updated October Available from: http://www.who.int/mediacentre/factsheets/fs311/en/). Metabolic comorbidities more frequently associated with excessive abdominal body fat and obesity are dyslipidemia, insulin resistance, hypertension (the so-called Metabolic Syndrome), diabetes, cardiovascular diseases (CVD), but also cancer[1-7].

However, despite the increased risk to develop metabolic syndrome or CVD, recent data suggest that not the body fat mass alone but a systemic state of increased subclinical low-grade inflammation and local (in the adipose tissue) metabolic dysfunction may explain the pathogenic potential of adipose tissue accumulation despite genetic or environmental causes[8]. It has been proposed that metaflammation is a key feature of the metabolic syndrome, where a leaky intestinal barrier allows translocation of proinflammatory bacterial components (such as lipopolysaccharide released by gram-negative bacteria, LPS). Metaflammation promotes insulin resistance in the liver (eventually leading to non-alcoholic steatohepatitis; NASH) and the release of various inflammatory mediators from adipose tissues[8,9].

Among the environmental determinants of obesity and its comorbidities, the intestinal microbiota has recently been proposed to have a significant impact[10]. Its role in human energy balance has been demonstrated and, in a co-evolutionary perspective, it can be speculated that the increased energy extraction from ingested food obtained by virtue of the vast enzymatic armamentarium of intestinal bacteria (especially for plant-derived complex carbohydrates) is an advantage in conditions of limited food availability[11,12]. Nowadays the increased availability of food in Western countries and changes in the proportion of diet components have markedly changed the composition of our gut microbiota[13-15]. The main responsible for this

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change is the increased intake of fat (especially unsaturated fatty acids) and sugar, the reduction of plant-derived carbohydrates, the consumption of processed food with wide usage of antimicrobial preservatives and the antibiotic abuse (especially at younger ages).

The recent availability of the next generation technology for the massive sequencing of nucleic acid extracted from human samples (sputum, feces, biopsies, etc.) allowed us to reveal changes in the microbiome (when referring to data collected from microbiota sequencing), population and sometimes even variation of very few bacterial species related with increased weight accumulation and with metabolic dysfunctions or systemic inflammation[10,16-21]. In fact, the gut microbiota has important physiologic functions that have direct impact on host metabolism, gut mucosal barrier development and both local and systemic immune functions[4,22-26]. Targeting gut microbiota composition or metabolic functions with natural and safe compounds, such as pro or prebiotics, to promote a healthier "non-obese" profile might, therefore, represent a promising tool for prevention and treatment of obesity and correlated diseases. Indeed, a heterogeneous group of pioneer clinical trials and more recent molecular metagenomic analyses of intestinal microbes have investigated these possibilities[27].

Recently, the ISAPP consensus panel proposed a new definition of a prebiotic that better fits recent data obtained in the "microbiome era": "a substrate that is selectively utilized by host microorganisms conferring a health benefit"[28]. Today, even if new substances are known to influence microbiota composition, fructans (fructooligosaccharides (FOS), inulin) and galactans (galactomannan or other galactooligosaccharides) dominate this group of compounds. Their activity is mainly mediated through enrichment of *Lactobacillus* and/or *Bifidobacterium* species but possibly also through modulation of the metabolism of other beneficial microorganisms, such as *Akkermansia muciniphila, Faecalibacterium prausnitzii* or some *Clostridia* groups[28]. The metabolic activity of gut microbes directly affects host energy homoeostasis and variations of microbiome composition are associated with obesity pathogenesis[10]. Part of these effects may also be due to the fact that humans utilize not only glucose, long-chain fatty acids, and amino acids as energy sources, but also short chain fatty acids (SCFA) produced by these beneficial organisms through fermentation of dietary fibers that reach the anaerobic colon environment.

Probiotics are defined as live microorganisms that confer a health benefit to the host when administered in adequate amounts[29]. *Bifidobacterium* and *Lactobacillus* strains are still the most widely used probiotic genera included in many functional foods and dietary supplements. Next generation probiotics, such as *F. prausnitzii*, *A. muciniphila*, or *Clostridia* strains, were shown to be present in the majority of people's microbiota, but their relative reduction was associated with increased risk of suffering from immunometabolic diseases. However, in part due to complex large-scale production of strictly anaerobe bacteria, they are still lacking clinical trials to support their beneficial usage as supplements[30]. At the same time, the newly discovered or better elucidated beneficial interactions with the host of commercially available probiotics preparation can nowadays lead to a more scientifically robust and evidence-based therapeutic or preventive approach for weight loss, to limit the metabolic consequences of obesity or to maintain and reinforce the efficacy of weight reduction regimens.

Materials and Methods

The selected studies were reviewed independently by all four researchers. Any disagreement between the investigators was resolved by discussion. The following information were collected: probiotic strain used, study design, duration of intervention, sample size, subjects' characteristics, age, dose of probiotics/prebiotics and composition of the synbiotic preparation, the vehicle used and results of the intervention. The search was limited to human studies for the generation of Tables. Significant pre-clinical results obtained with the bacterial strains present in the probiotic/synbiotic compound described in the selected clinical studies were also analyzed to identify molecular mechanisms explaining clinical results. Studies with probiotics that enrolled less than 50 subjects were not considered, nor those that were not randomized placebo-controlled trials. All results with possible impact on weight loss and dysmetabolic diseases were reported (BMI, body weight, TC, LDL-C, triacylglycerol (TAG), inflammatory markers, the homeostasis model assessment of insulin resistance (HOMA-IR), etc.). We searched PubMed, Cochrane Library, and EMBASE databases from their inception through October 2017, using combinations of probiotics/prebiotics and synbiotics with obesity or weight loss metabolic syndrome, lactobacilli as the search terms.

Plant-Derived Prebiotics: Glucomannan and Inulin-Type Fructans

Not all fibers have the same efficacy and structural characteristics. There are short-chain (oligofructose) and long-chain (polyfructose, such as inulin) fructans typically present in the plant roots where they are used as energy pools[31]. Moreover, their preferential degradation by host or bacterial enzymes in the small or in the large intestine respectively, suggests that enrich our diet with prebiotics supplemented with specific type of fibers can be more beneficial than a generic lifestyle recommendation to eat indistinctly more vegetables. Eating adequate amounts of fibers, especially highly viscous plant-derived fibers such as glucomannan or inulin, was demonstrated to reduce serum triacylglycerols in humans[32].

Among the plant-derived beneficial fibers, glucomannan (KJM), extracted traditionally from the tuber root of *Amorphophallus konjac*, has been used for centuries in Asia as a food source and beneficial healthy remedy[33]. Its safety profile was recently assessed by the Food and Drug Administration and Health Canada, and was approved for general use by the European Union (as E425). More interestingly, in 2010, the European Food Safety Authority (EFSA) approved important health claims related to the usage of glucomannan and reductions in body weight, postprandial glycemia, and blood cholesterol concentrations (EFSA Panel on Dietetic Products, Nutrition and Allergies. EFSA J 2010; 8: 1798). EFSA strictly require assuming at least 1 g three times daily to allow the above mentioned approved claims. Similarly, Health Canada also approved health claims for reductions in cholesterol and postprandial glycemia related to glucomannan supplementation, thus confirming its beneficial metabolic function (Summary of Health Canada's assessment of a health claim about a polysaccharide complex. Ottawa (Canada): Bureau of Nutritional Sciences, Food Directorate, Health Products and Food Branch, Health Canada; 2016. 8. Summary of Health Canada's assessment of a health claim about a polysaccharide complex (glucomannan, xanthan gum, sodium alginate) and a reduction of the post-prandial blood glucose response [updated May 2016]. Ottawa (Canada): Bureau of Nutritional Sciences, Food Directorate, Health Products and Food Branch, Health Canada; 2016.).

Several meta-analyses of large clinical trials[31,34] confirmed that KJM can safely and effectively be used for cardiovascular diseases (CVD) risk reduction, reduction of LDL cholesterol (about 20% total reduction) and non-HDL cholesterol (almost 20-30% reduction) both in adults and children at all doses of KJM used (2.0-15.1 g/d). Several early and more recent investigations[34] have also shown that supplements containing glucomannan, as stated in the EFSA claim promoted weight loss and reduction of postprandial glycemia. Another oligosaccharide with interesting activity and sufficient body of good quality literature is inulin. Even if inulin has not obtained an official claim for weight-loss management, recent meta-analyses of randomized clinical trials that tested the effect of inulin-type fructans on serum triacylglycerols and other dysmetabolic parameters showed that the intake of inulin or oligofructose was associated with a significant decrease (about 20 mmol/L) in serum triacylglycerol concentrations in the vast majority of clinical trials (>80% of trials)[35,36]. Notably, as already observed with galactomannan, the effects were not dependent on the condition of the patients (lipid levels before supplementation). Most effective and safe dosage varies from 3 to 10 g of fibers. Self-supplementation or *ad libitum* administration of larger doses of purified complex fibers (more than 10/15 grams/daily) should be avoided to minimizes gastrointestinal discomfort and bloating, that are otherwise commonly associated side effects that often reduce patients' compliance. The amount of reduction in serum triacylglycerol (7 and 8%) is remarkable, considering that it is obtained in a few weeks of supplementation (4-12) without difficult-to-follow changes in dietary (reduction of carbohydrates, fats, etc.) and behavioral strategies (exercise, etc.) (Table I). Moreover, because inulin fibers are not absorbed in the small bowel, they have no effect on postprandial blood glycaemia and, at the same time, their low-glycemic-index minimally stimulates cholesterol synthesis, thus lowering cholesterol blood concentrations[37,38]. Of note, short chain fatty acids (SCFA) produced during colon fermentation of inulin or galactomannan fibers that reach the colon almost unaltered, specifically bind a series of orphan G protein-coupled receptors. In particular, the free fatty acid receptor 3 (FFA3/GPR41) that is expressed both in the intestine and sympathetic nervous system, recognize SCFA including propionate and butyrate, that trigger several folds higher receptor activation compared to acetate[39,40]. Lack of this GPR41 receptor in mice causes lower energy expenditure and reduced glucose tolerance compared to wild-type mice[41,42]. Other groups have also shown that SCFA are directly involved

Table I. Prebiotics.

Fiber	Duration	Population: M/F	Study design	Results	Ref.
Oligofructose-enriched inulin (8 g/day)	16 weeks	42 subjects 24M/18F	Single center, double blind, placebo controlled	Reduced body weight z-score, percent body fat, percent trunk fat, and serum level of interleukin 6	Nicolucci et al[100]
Low calorie diet + Inulin 10 g	12 weeks	59 female subjects	Randomized, controlled, longitudinal	Reduced triglycerides and improved intake of micronutrients	Tovar et al[101]
Galacto-oligo-saccharide (5.5 g)	12 weeks	45 subjects; 16M/29F	Double blind, randomized, placebo controlled, crossover	Decreased: fasting insulin, TC, TG, CRP, fecal calprotectin	Vulevic et al[102]
Inulin (10 g)	8 weeks	49 female subjects	Randomized, triple blind controlled	Decreased: FBG, A1c, malondialdehyde; Increased: antioxidant defense	Gargari et al[103]
Inulin (10 g)	8 weeks	49 female subjects	Randomized controlled	Reduction in FBS, HbA1c, total cholesterol, triglyceride, LDL-c, LDL-c/HDL-c ratio and TC/HDL-c ratio, increased HDL-c	Dehghan et al[104]
Oligofructose-enriched inulin (10 g)	8 weeks	52 female subjects	Triple-blind randomized controlled	Decreased fasting plasma glucose, glycosylated hemoglobin, interleukin-6, tumor necrosis factor-a and plasma lipopolysaccharide	Dehghan et al[47]
Glucomannan/Capsule (0.43 g)	4 weeks	63 subjects	Double-blind crossover, placebo controlled	Reduced total cholesterol, LDL-C, triglycerides and systolic BP	Arvill et al[105]
Glucomannan/Capsule (2 g/d)	8 weeks	40 subjects; 20M/20F	Randomized controlled	Reduced plasma total cholesterol and LDL-C	Martino et al[106]
Glucomannan/Capsule (2 g/d)	8 weeks	40 subjects; 19M/21F	Randomized, double blind, six-arm parallel	Reduced total cholesterol and LDL-C	Martino et al[107]
Glucomannan/Capsule (2 g/d)	8 weeks	60 subjects; 33M/27F	Randomized, double blind	Decrease of alpha-lipoprotein; increase of pre-beta-lipoprotein and triglycerides	Vido et al[108]
Glucomannan/Capsule (3 g/d)	8 weeks	42 subjects; 22M/20F	Randomized, placebo double blind, crossover	Reduced body mass, fat mass, total cholesterol, and LDL-C	Kraemer et al[109]
Glucomannan/Capsule (1.5 g/d)	12 weeks	58 subjects; 12M/46F	Double-blind, placebo controlled	Reduced total cholesterol and LDL-C	Vasques et al[110]

in the so-called 'gut-brain axis', that affects host energy expenditure by directly up-regulating the activity of the sympathetic nervous system via GPR41 and enhancing body energy expenditure[43].

The biological mechanisms by which prebiotics, viscous plant-derived oligosaccharides, exert their health effects (Figure 1)

Highly viscous soluble fibers exert their activity in different districts of the gastrointestinal tract and can affect host physiology and gut barrier function directly or indirectly.

- Delay gastric emptying, thereby affecting nutrient kinetics and satiety[44].
- Enhance intestinal viscosity, that impairing the uptake of dietary cholesterol and reducing bile acids reabsorption[44].
- Increase bacterial fermentation in the colon and promote beneficial bacteria replication and metabolic production of SCFA thus increasing the molar ratio of propionate to acetate, that affect gut barrier integrity and cholesterol metabolism[45].
- Inhibit or down-regulate liver lipogenic pathways through propionic acid production[46].
- SCFA production reduced translocation of Gram-negative bacteria derived Lipopolysaccharide (LPS) systemic metaflammation both in human and animal models[47].
- SCFA production affects the secretion of gastrointestinal hormones such as regulation of incretin hormone GLP-1 and other gastrointestinal peptides (the PYY satiety hormone for example)[48,49].

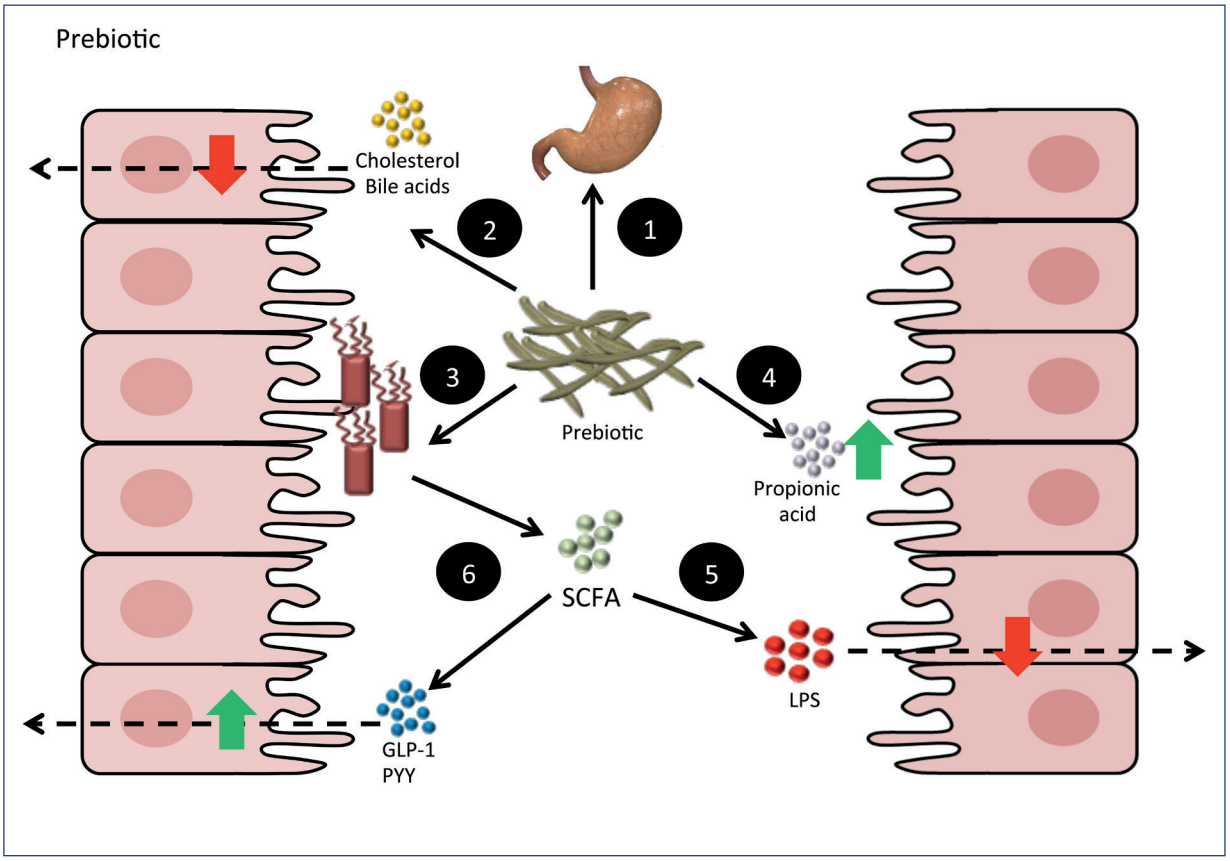

Figure 1. The biological mechanisms by which prebiotics exert their health effects. 1) Delay gastric emptying, thereby affecting nutrient kinetics and satiety. 2) Enhance intestinal viscosity, that impairing the uptake of dietary cholesterol and reducing bile acids reabsorption. 3) Increase bacterial fermentation in the colon and promote beneficial bacteria replication and metabolic production of SCFA thus increasing the molar ratio of propionate to acetate, that affect gut barrier integrity and cholesterol metabolism. 4) Inhibit or down-regulate liver lipogenic pathways through propionic acid production. 5) SCFA production reduced translocation of Gram-negative bacteria derived Lipopolysaccharide (LPS) systemic metaflammation both in human and animal models. 5) SCFA production affects the secretion of gastrointestinal hormones such as regulation of incretin hormone GLP-1 and other gastrointestinal peptides (the PYY satiety hormone for example).

Probiotics

A major obstacle in defining the efficacy of currently available probiotic preparations on weight control and metabolic syndrome treatment reside in the numerous confounding factors that affect both the formulation and, most of the time, also the study design. In fact, under the common definition of probiotics, several microbial strains including yeasts or bacteria were used. Unfortunately, even if bacteria present in different products belong to the same genera or species, they often have important strain-specific phenotypic differences that may modulate their beneficial activity[50]. Different amount of viable bacterial cells in the available commercial preparations were used, sometimes with poorly standardized shelf-life (number of living bacterial cell at time of expiration) determinations. Commercial preparations often lack clear description of the relative representation of each strain when bacterial blends are used. Similarly, different types of formulations, including capsules, sachets, yoghurts etc. were used. Moreover, several comorbidities or co-factors (such as age, sex, autoimmune diseases, diabetes, etc.) today known to be independently associated with microbiota alterations, were not always considered in the exclusion criteria for patient's enrolment nor were they eventually discussed in the analysis of results. However, and despite these biases, several meta-analyses and large review studies clearly suggest that some probiotic strains or synbiotic formulations may exert a beneficial effect on weight loss and on metabolic syndrome management and may help to design improved probiotic or synbiotic formulations. Only very few products containing the probiotic strain alone or in blend were tested in sufficiently large clinical trials in order to promote weight loss, improve lipid metabolism or reduce inflammatory markers in patients with metabolic syndrome (Table II). The majority of results are negative regarding the weight loss effect, with a few of them showing improved lipid or inflammatory markers (Table II). This suggests that the beneficial effects are species, or even strain dependent and cannot be ascribed indistinctly to all available commercial products. This seems especially true if recent analyses will be confirmed, suggesting a deleterious weight-gain effect caused by the majority of probiotic preparations containing very commonly used *Lactobacilli* strains[51]. This may represent an important issue for products containing probiotic blends or for those preparations that indicate the species but not the strain as per good-manufacturing guidelines. This may cause under-supplementation of the beneficial strains or over-supplementation with bacteria with deleterious weight-gain consequences. Some strains are in fact more resistant than others to the industrial processing or at normal storage conditions (such as *Streptococcus thermophilus*). Thus, by the time the commercial preparations reach the shelf, the supplement may still contain a high number of living microbes but with only one or a few single species (personal observation). Moreover, some products commercialized under the same blend name, varied the strains quantity and composition many times (even changing the strains) over the years, thus affecting the scientific reproducibility of previously obtained results or any reliable conclusion.

In many cases probiotics were administered as fermented milk or yoghurt or cheese in human trials not allowing a proper evaluation of the number of living bacteria. Moreover, in this case, products should more properly considered synbiotic preparations, since they contain also prebiotic components that are fermented by the probiotic bacteria or by the host microbiota, that some authors or patients were not probably fully aware (milk oligosaccharides for examples, or other carbohydrates present in yoghurts or in fermented milks or skimmed milk powder excipients that may confer synergistic beneficial effects). In some cases, this bias was addressed by using chemically 'fermented' yoghurt as placebo. For these reasons, these studies are discussed in the Synbiotic session.

As an example, the administration for eight weeks of *L. acidophilus La5, B. lactis Bb12,* and *L. casei* DN001 as yoghurt to patients with high BMI, showed a reduction in BMI, fat percentage, and leptin level and also a reduction in the serum levels of inflammatory markers as well as immunomodulation of PBMCs. The effect was augmented if the supplement was associated with weight-loss diet. The intake of a similar combination of bacteria, (*L. acidophilus La5* and *B. animalis* subsp. *lactis* Bb12) in capsules, did not affect HOMA-IR, blood pressure, heart rate nor the serum lipid concentrations in overweight adults[52,53]. This may suggest a critical role for the presence of the prebiotic milk present in the yoghurt vehicle or to *L. casei* present in only one product. Researches[54,55] that evaluated *Lactobacillus casei* Shirota alone as probiotic in patients with insulin resistance demonstrated that the only

Table II. Probiotics.

Strain/vehicle (dosage)	Duration	Population: M/F	Study design	Results	Ref.
*L. salivarius*Ls-33/Capsule (10^{10} CFU)	12 weeks	50 obese adolescents	Double-blind, randomized, placebo controlled	Increase in ratios of *Bacteroides*, *Prevotellaceae* and *Porphyromonas*	Larsen et al[59]
*L. salivarius*Ls-33/Capsule (10^{10} CFU)	12 weeks	50 adolescents with obesity: 22M/28F	Double-blind, randomized, placebo controlled	No effect	Gobel et al[58]
Bifidobacteria, Lactobacilli, and *S. thermophiles*/Capsule ($112.5x10^{9}$ CFU)	6 weeks	60 overweight subjects	Randomized, placebo controlled	Improvement in lipid profile, insulin sensitivity and decrease in CRP	Rajkumar et al[56]
*L. paracasei*N19/Sachet ($9.4x10^{10}$ CFU)	6 weeks	58 obese post-menopausal women	Single-blind, randomized, parallel group	No effect	Brahe et al[60]
B. longum BL999 ($1.3x10^{8}$ CFU) *L. rhamnosus* LPR (6.45x10 CFU)/100 mL formula from powder	16 weeks	112 subjects: 54M/58F	Multicentric: prospective, double blind, reference controlled, randomized	Weight gain; daily weight gain on 4 months (g/d)	Chouraqui et al[111]
L. salivarius CECT5713 ($2x10^{6}$ CFU/g) on formula	24 weeks	80 subjects: 39M/41F	Monocentric: prospective, double blind, placebo controlled, randomized	Weight gain on 6 months (g)	Maldonado et al[112]
L. acidophilus ATCC4962 and ATCC4963 (>$5x10^{8}$ CFU), 1 ml to each quart of formula	1 week	800 newborns subjects	Two centers: prospective, randomized	Weight gain; weight gain at one month	Robinson et al[113]
Hydrolyzed casein formula with *L. rhamnosus* strain GG (10^{8} CFU/g of formula powder)	16 weeks	188 subjects: 94M/94F	Multicentric: prospective, double blind, randomized	Growth and tolerance; weight gain (g/d)	Scalabrin et al[114]
L. rhamnosus strain GG ATCC53103/Formula ($1x10^{7}$ CFU)	24 weeks	120 subjects; 60M/60F	Multicentric: prospective, double blind, randomized	Growth and fecal flora on 6 months	Vendt et al[115]

parameter that was clearly ameliorated was insulin sensitivity index, but gut permeability was unfortunately increased despite lack of increased LPS translocation. Other studies tested the effect of a blend containing bifidobacteria, lactobacilli, and *Streptococcus thermophilus* (as capsules) in overweight subjects. The mixture had a significant improvement in their lipid profiles, reducing triacylglycerols, total cholesterol, and LDL-C levels with beneficial effect on high-density lipoprotein cholesterol levels and on insulin sensitivity as well as on inflammatory markers (C-reactive protein, CRP)[56]. Other randomized, double-blind, placebo-controlled studies in overweight and obese subjects designed to evaluate the effects of an *Enterococcus faecium* strain (that unfortunately is a pathobiont, an opportunistic microbe that can cause infections in humans) and two strains of *Streptococcus thermophilus* supplemented as yoghurts, showed a beneficial effect on cardiovascular risk factors including reduction in body weight, blood pressure and LDL-C[57]. Negative results were also obtained by Gobel et al[58] with *Lactobacillus salivarius* Ls-33 on inflammation biomarkers and several dysmetabolic parameters associated with metabolic syndrome in a population of adolescents with obesity. These data are in agreement with more recent findings[59] obtained in a similar population of obese adolescents that showed no effects on weight reduction after 12 weeks of supplementation with *L. salivarius* Ls-33. Other studies showed that *L. paracasei* F19 did not modulate any markers associated with metabolic dysfunctions ((HOMA-IR), C-reactive protein, and lipid profile) when compared with the placebo[60].

The biological mechanisms by which some probiotic strains exert their health effects (Figure 2)

- Competitive adherence to the mucosa and epithelium with proinflammatory microbes[61].
- Regulation of the gut associated lymphoid immune system through intestinal cell pattern recognition receptors, (toll-like receptors and nucleotide-binding oligomerization domain-containing protein-like receptors) or through the release of metabolites or immunomodulating peptides[62].
- Bile-acid deconjugation by some lactobacilli strains, thus reducing lipid absorption and calories intake[63].
- Induction of lipolysis via production of trans-10, cis-12-conjugated linoleic acid[64].
- Increase in sympathetic nerve activity[65].
- Suppression of fat deposition via increased expression of angiopoietin-like 4, a circulating inhibitor of lipoprotein lipase[66,67].
- Induction of transcriptional activation of fatty acid β-oxidation-related genes in the liver and muscle[68,69].
- Inhibition of the transcription of fatty acid synthase in the liver[70,71].
- Improve insulin sensitivity and glucose tolerance through SCFA production and reduction of LPS translocation[72-74].
- Improvement of the gut barrier function, through SCFA production and immunomodulation of gut immune cells[75].
- Modulate the gene expression profile in PBMCs and intestinal immune cells of ROR-gt (down-regulated) and FOXP3 (up-regulated) transcription factors, dampening inflammation and promoting immunomodulation[76].
- Regulation of appetite[77].

Synbiotics

When the probiotic strains are used in combination with prebiotics, the final product can correctly be described as synbiotic if an increased synergistic health benefit is obtained[78]. Some trials were conducted with synbiotics to investigate their combined effects on weight loss and maintenance in obese adults or children. Used preparations contained mainly lactobacilli, more frequently including *L. rhamnosus* (CGMCC1.3724 strain), *L. plantarum*, *L. paracasei* F19, L. *acidophilus* La5 and B. *animalis* subsp. *Lactis* Bb12 together with oligo-fructose and inulin fibers (Table III). Some studies used complex blends of probiotics (5 or more strains) and different amounts of inulin-type fructans. Despite some discrepant results, supplementation with synbiotics appears to confer clear beneficial effects on waist circumference, on BMI, VFA and hip circumference in overweight or obese people (Table III). In women, but not in men, *L. rhamnosus* CGMCC1.3724 + inulin supplementation allowed to obtain a significantly higher weight loss than in the placebo group after the first 12 weeks, with a parallel modification of gut microbiota[79]. The synbiotic induced weight loss was also associated with reductions in visceral fat mass and circulating leptin concentrations. In obese children, the intake of synbiotics resulted in a significant reduction in the BMI z-score, waist circumference, TC, LDL-C and TAG as well as reduction of total oxidative stress serum

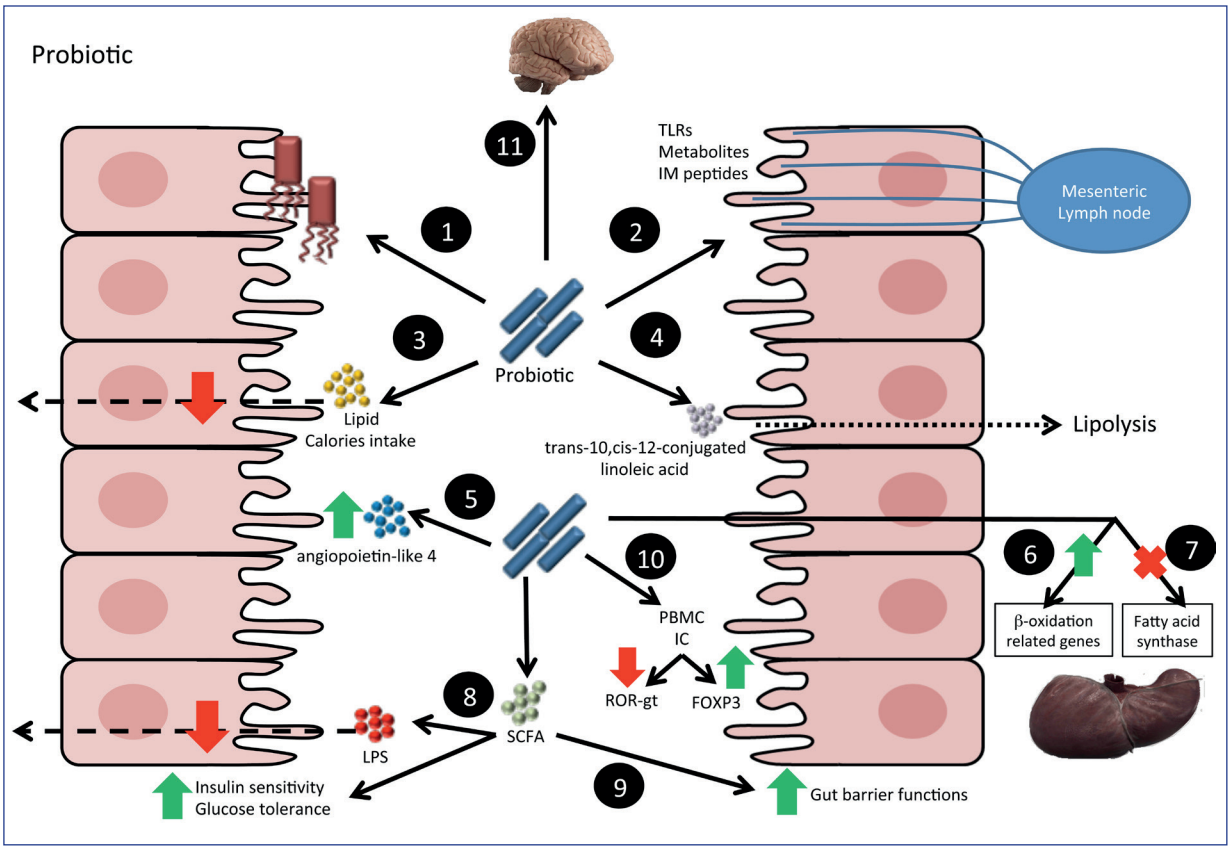

Figure 2. The biological mechanisms by which probiotics exert their health effects. 1) Competitive adherence to the mucosa and epithelium with proinflammatory microbes. 2) Regulation of the gut associated lymphoid immune system through intestinal cell pattern recognition receptors (toll-like receptors and nucleotide-binding oligomerization domain-containing protein-like receptors) or through the release of metabolites or immunomodulating peptides. 3) Bile-acid deconjugation by some lactobacilli strains, thus reducing lipid absorption and calories intake. 4) Induction of lipolysis via production of trans-10, cis-12-conjugated linoleic acid. Increase in sympathetic nerve activity. 5) Suppression of fat deposition via increased expression of angiopoietin-like 4, a circulating inhibitor of lipoprotein lipase. 6) Induction of transcriptional activation of fatty acid β-oxidation-related genes in the liver and muscle. 7) Inhibition of the transcription of fatty acid synthase in the liver. 8) Improve insulin sensitivity and glucose tolerance through SCFA production and reduction of LPS translocation. 9) Improvement of the gut barrier function through SCFA production and immunomodulation of gut immune cells. 10) Modulate the gene expression profile in PBMCs and intestinal immune cells of ROR-gt (down-regulated) and FOXP3 (up-regulated) transcription factors, dampening inflammation and promoting immunomodulation. 11) Regulation of appetite.

levels suggesting an overall protection against CVD risk factors[80,81]. Patients with insulin resistance supplemented with synbiotic capsules (seven strains plus fructo-oligosaccharide) showed a significant improvement of fasting blood sugar and insulin resistance as compare with the placebo group[82]. Recently, a randomized study on the use of a synbiotic that contains five probiotics (*L. plantarum, L. delbrueckii spp. bulgaricus, L. acidophilus, L. rhamnosus, B. bifidum* and inulin) over 6 months in adult patients with NASH was associated with a significant decrease in IHTG[83,84]. The evaluation of supplementation with a synbiotic containing *L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum, L. bulgaricus* and fructo-oligosaccharides, in a study with 52 adults over 28 weeks, demonstrated that synbiotic supplementation dampened NF-kB and reduced TNF-a production. This observation suggests that the reduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), may have improved insulin resistance and reduced hepatic inflammatory cell recruitment observed in metabolic syndrome and NASH[85]. Two *L. gasseri* strains supplemented in synbiotic preparations (SBT2055 and BNR17 in yoghurt, fermented milk or with skimmed milk powders) have shown significant anti-obesity effects in independent well-designed clinical trials with medium to low risk of biases in study design[86-88].

Table III. Synbiotics.

Strain/vehicle (dosage)	Duration	Population: M/F	Study design	Results	Ref.
L. rhamnosus CGMCC1.3724/ Capsule ($1.6x10^8$ CFU)	36 weeks	125 obese subjects: 48M/77F	Double-blind, randomized, placebo controlled	Weight loss and reduction in leptin. Increase in Lachnospiraceae	Sanchez et al[79]
L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum, L. bulgaricus, and FOS	8 weeks	70 children and adolescents with high BMI	Randomized, triple-masked controlled	Decrease in BMI z-score and waist circumference	Safavi et al[80]
L. acidophilus, L. rhamnosus, B. bifidum, B. longum, E. faecium, and FOS	4 weeks	77 obese children	Open-label, randomized, controlled study	Changes in anthropometric measurements. Decrease in TC, LDL-C	Ipar et al[81]
L. gasseri SBT2055/Yoghurt ($5x10^{10}$ CFU/g)	12 weeks	87 subjects with high BMI: 59M/28F	Multicenter, double-blind, randomized, placebo controlled	Reduction in BMI, abdominal VFA. Increase in adiponectin levels	Kadooka et al[88]
L. gasseri SBT2055/Yoghurt (10^8 CFU/g)	12 weeks	210 adults with large VFA: 105M/105F	Multicenter, double-blind, parallel group randomized controlled	Reduction in BMI, waist, abdominal VFA and hip circumference	Kadooka et al[87]
L. gasseri BRN17/Capsule (10^{10} CFU); filler powder (50% trehalose, 25% skim milk and 25% FOS)	12 weeks	57 subjects: 22M/35F	Randomized, double blind, controlled	Body weight, BMI e waist and hip circumferences decreased in test group	Jung et al[93]
L. acidophilus, L. casei, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophilus, (109 CFU) and 100 mg FOS	8 weeks	54 patients with T2D (35-70 years)	Double-blind, randomized, placebo controlled	Increased HOMA-IR and TGL plasma level: reduced CRP in serum	Asemi et al[116]
L. sporogenes/Bread ($1x10^8$ CFU) and Inulin/ Bread (0.07g/1 g)	8 weeks	81 patients with T2D	Double-blinded, randomized, controlled	Significant reduction in serum insulin levels, HOMA-IR, and homeostatic model assessment-cell function	Tajadadi-Ebrahimi et al[117]
L. sporogenes/Bread ($1x10^8$ CFU) and Inulin/Bread (0.07g/1 g)	8 weeks	78 patients with T2D: 15M/63F	Double-blinded, randomized, controlled	Decrease in serum lipid profile (TAG, TC/HDL-C) and increase in HDL-C levels	Shakeri et al[118]
L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum, L. bulgaricus, and FOS/ Capsule ($2x10^8$ CFU)	30 weeks	52 adult individuals with NAFLD: 25M/27F	Double-blind, randomized, placebo controlled	Inhibition of NF-kB and reduction of TNF-α	Eslamparast et al[82]
Bofutsushosan herb + DUOLAC7 *(L. acidophilus, L. plantarum, L. rhamnosus, B. lactis, B. longum, B. breve, S. thermophiles)* (5x109 CFU)	8 weeks	50 female subjects	Randomized, double blind, placebo controlled	Increased HDL, increased *B. Breve, B. Lactis, B. rhamnosus, B. Plantarum*	Lee et al[119]
Inulin 1.08 g + *L. sporogenes* ($2.7x10^8$ CFU)	6 weeks	62 subjects: 19M/43F	Randomized, double blinded, crossover controlled	Decreased hsCRP: increased GSH, Uric acid	Asemi et al[120]

Continued

Table III. Synbiotics.

Strain/vehicle (dosage)	Duration	Population: M/F	Study design	Results	Ref.
FOS 2.5 g + B. longum W11 (5x109 CFU)	24 weeks	66 subjects: 33M/33F	Randomized, double blind, placebo controlled	Decreased LDL, CRP, TNF-α, LPS, Steatosis	Malaguarnera et al[121]
L. acidophilus La5, B. lactis Bb12, and L. casei DN001/ Yoghurt (10^8 CFU/g)	8 weeks	75 subjects with high BMI	Double-blind, randomized, placebo controlled	Changes in gene expression in PBMCs as well as BMI, fat percentage and leptin levels	Zarrati et al[76]
E. faecium, two strains of *S. thermophiles*/Yoghurt ($6x10^7$ – $1x10^9$ CFU/g)	8 weeks	70 overweight and obese subjects: 20M/50F	Double-blind, randomized, placebo and compliance controlled, parallel	Reduction in body weight, systolic BP, LDL-C, and increase on fibrinogen levels	Agerholm-Larsen et al[57]
L. acidophilus La5, B. animalis subsp. Lactis Bb12/Yoghurt-capsule ($3x10^9$ CFU)	6 weeks	156 overweight adults: 96M/60F	Double-blind, randomized, parallel study	Reduction in fasting glucose concentration and increase in HOMA-IR	Ivey et al[52,53]
L. acidophilus La5 and B. lactis Bb12/Yoghurt ($7.23x10^6$ and $6.04x10^6$ CFU/g)	6 weeks	60 patients with T2D: 23M/37F	Double-blinded, randomized controlled	Reduced fasting blood glucose and antioxidant status	Ejtahed et al1[22]
L. acidophilus La5 and B. lactis Bb12/Yoghurt	6 weeks	60 patients with T2D: 23M/37F	Double-blinded, randomized controlled	TC and LDL-C improvement	Ejtahed et al[123]
L. acidophilus La5 and B. breve subsp. lactis Bb12/Yoghurt	8 weeks	72 patients with NAFLD: 33M/39F	Double-blinded, randomized, controlled	Reduced serum levels of ALT, ASP, TC, and LDL-C	Nabavi et al[124]
Lactobacillus curvatus (2.5×10^9 CFU) and *L. plantarum* (2.5×10^9 CFU)/powder containing 1.24 g of cellulose, 0.5 g of lactose, 0.06 g of blueberry flavoring	12 weeks	95 subjects: 34M/61F	Double blind, Placebo controlled, randomized	Body weight, BMI, waist circumference and subcutaneous fat mass decreased in test group	Jung et al[125]
L. amylovorus CP1563/Powder (skim milk, citrate, flavors, sweeteners, soybean polysaccharide, food emulsifier and 200 mg of *L. amylovorus*)	12 weeks	200 subjects: 100M/100F	Randomized, double blind, placebo controlled	Body fat percentage, visceral fat area and whole-fat area decreased in test group	Nakamura et al[126]
S. thermophilus, L. acidophilus, B. infantis/Yoghurt (10^9-10^{10} CFU)	8 weeks	101 subjects: 31M/70F	Randomized, double blind, placebo controlled, parallel	Reduced LDL-cholesterol, body weight and BMI	Chang et al[127]
L. acidophilus L-1/Yoghurt ($5x10^9$ to $3x10^{10}$ CFU d)	2 weeks	78 subjects: 22M/56F	Monocentric; prospective, double blind, randomized	Lipid profile and body weight change; weight change difference (kg)	De Roos et al[128]
L. acidophilus La1 and *Bifidobacterium. lactis* Bb12/ Yoghurt ($4x10^7$ CFU)	6 weeks	90 female subjects	prospective, double blind, randomized	Lipid profile; weight change (kg)	Sadrzadeh-Yeganeh et al[129]

Lactobacillus gasseri strains are probiotic lactic acid bacteria isolated from the gastrointestinal tract or sometimes from the vagina of healthy subjects. *L. gasseri* SBT2055 strain was examined in two studies[86-88] using a cohort of Japanese adults with large visceral fat areas (VFA). The participants received increasing amounts of *L. gasseri* SBT2055 for 12 weeks. The results showed a reduction in body mass index (BMI), waist, abdominal VFA and hip circumferences. In obese individuals, the difference was clinically relevant since an average weight loss of 6 kg (3-6%) was obtained in overweight patients in a few weeks[86-88].

Both studies with *L. gasseri* strains observed decreased visceral fat. This is an important achievement since visceral fat is associated with insulin resistance, cardiovascular risk and diabetes mellitus[86,87]. *In vitro* and preclinical data suggest that these genera of Lactobacilli strains suppress lipogenic gene expression and accumulation of lipids in adipose cells[89,90]. This is also in agreement with Kawano et al[91] findings that demonstrated, in rats, that *L. gasseri* strain SBT2050 reduced gut permeability in mice fed with high fat diet, thus possibly ameliorating gut barrier function and reducing bacterial translocation and the associated low-grade systemic inflammation[86,92]. *L. gasseri* BRN17 was also associated with weight loss in humans (even if not statistically significant) and with reduced adipose tissue accumulation under a carbohydrate-rich diet in animal models[72,93-95]. *Lactobacillus gasseri* BNR17 has recently received the South Korean FDA approval as functional ingredient for body fat reduction[93]. Other authors showed that LG2055 supplementation decreases lymphatic triacylglycerols (TAG) absorption, increases fecal fatty acid excretion in animal models and decreases postprandial TAG absorption in humans. This may be explained in part by the strong bile salt hydrolase (BSH) activity of some lactobacilli, including *L. gasseri* strains, that may help to reduce bile-acid re-adsorption[63]. Bile salts are conjugated with glycine or taurine in the liver and stored in the gall bladder and released into the small intestine where they help to absorb lipids[96]. The BSH enzyme hydrolyzes conjugated bile salts into a deconjugated form that is much less soluble and thus not absorbed by intestinal cells. Elimination of deconjugated bile salts, results in *de novo* synthesis of bile acid from cholesterol in the liver, thereby lowering both lipid absorption from the bowel and serum cholesterol levels[86,97]. Other mechanisms demonstrated in animal models probably involve increased energy expenditure and improved glucose tolerance by synbiotic *L. gasseri* supplementation[98].

Conclusions

In the pre-microbiome era, almost none of the trials were designed to identify the molecular mechanisms underlying the beneficial effects observed in humans supplemented with pre/pro/synbiotic preparations on weight loss and metabolic syndrome dysmetabolism. Nevertheless, more recent studies on human and animal models have in part elucidated several biological mechanisms supporting their usage in these clinical conditions. Future studies attempting to demonstrate a beneficial role for synbiotics in clinical trial will have to evaluate accurately the gut microbiota composition and functions to confirm already described mechanism of actions or to identify new beneficial microbe-host interactions affecting local and systemic inflammation and metabolic pathways. Characterization of baseline microbiome composition in patients' enrolled in future clinical trial may help to understand the individual responses to synbiotic supplementation and may indeed guide to more effective weight-management treatments and results interpretation. Some results obtained in early studies appear indeed controversial, but several reasons may explain some discrepancies. In fact, heterogeneous amounts of bacterial cells, complex mixtures of bacteria strains and different dosages of prebiotic fibers were used (Tables I-III). In fact, the weight control activity appears to be a species or even a strain-specific characteristic and some probiotic strains such as *L. acidophilus, L. ingluviei, L. fermentum* and *delbrueckii* (and probably other endogenous Lactobacillus species that increase in obese patients) were linked to a paradoxical significant weight-gain effect both in animal or human studies[51]. Therefore, diet supplementation only with synbiotics, prepared using selected strains (such as *Lactobacillus gasseri* strains) that showed to exert weight-reduction and anti-inflammatory activity in large independent correctly designed studies, together with galactomannan and/or inulin fibers, may exert more powerful anti-obesity effects due to synergism in SCFA production and microbiota 're-configuration'. Novel synbiotics may reduce insulin resistance, cardiovascular risk and type-2 diabetes development through VFA reduction. Better-designed syn-

biotics may promote not only weight loss but they may also help to maintain the beneficial results of weight reduction regimens through the promotion of a persistently healthier microbiota composition. Obese-type gut microbiota, in fact, induces neurobehavioral changes even in the absence of obesity and data on the effects of the gut microbiota on host behavior showed that microbiota composition and some microbial metabolites can regulate host appetite[99]. This further suggests that synbiotic preparations may exert their beneficial effect on weight control also through the gut-brain axis by activating host satiety pathways and affecting host control of appetite[99]. Probiotic strains may indeed interact with the brain-gut axis, by producing, upon fibers fermentation, SCFA or specific molecules that have evolved to regulate host nutrient intake or energy expenditure[98,99]. Further investigations to evaluate the best dose-response effect and the length of probiotics and synbiotics supplementation are also needed, to evaluate if the persistence of their potential beneficial effects is maintained after interruption or if continuous supplementation should be used for an efficient treatment or dysmetabolic diseases prevention.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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