Annals of Nutritional Disorders & Therapy

Austin Publishing Group

Open Access Full Text Article

Review Article

Impact of Prebiotics, Probiotics and Synbiotics on Components of the Metabolic Syndrome

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Received: August 08, 2014; **Accepted:** September 02, 2014; **Published:** September 03, 2014

Abstract

Changes in eating habits are undoubtedly the most important non-pharmacologic factor for the prevention and treatment of risk factors of metabolic syndrome and, therefore, nutritional therapies have been researched. The consumption of prebiotics, probiotics and synbiotics gained recognition from the scientific community due to the promising effects on health and well-documented history of safe use. Thus, this article presents a review of scientific studies investigating clinical responses of patients treated with prebiotics, probiotic or symbiotic, and raises the key issues to be considered by scientists in the search of dietary alternatives for patients suffering from metabolic syndrome.

Keywords: Dysbiosis; Obesity; Dyslipidemia; Insulin resistance; Inflammation

Abbreviations

ALA: Alpha Linolenic Acid; *B: Bifidobacterium;* BMI: Body Mass Index; BP: Blood Pressure; CG: Chitin-Glucan; CRP: C-Reactive Protein; DB: Double-Blind; DBP: Diastolic Blood Pressure; FOS: Fructo Oligosaccharides; GLP-1: Glucagon-Like Peptide 1; HDL-C: HDL Cholesterol; HOMA: Homeostasis Model Assessment; hs-CRP: high-sensitive C-Reactive Protein; IL: Interleukin; IR: Insulin Resistance; *L*: *Lactobacillus;* LDL-C: LDL Cholesterol; Lp(a): Lipoprotein A; LPS: Plasma Lipopolysaccharide; MetS: Metabolic Syndrome; OFS: Oligofructose; OGTT: Oral Glucose Tolerance Test; OxLDL: Oxidized Low-Density Lipoprotein; PYY: Peptide YY; RCT: Randomized Control Trial; RCOT: Randomized Cross-Over Trial; RPCT: Randomized Placebo Controlled Trial; SBP: Systolic Blood Pressure; SCFA: Short-Chain Fatty Acids; T2D: Type 2 Diabetes Mellitus; TAC: Plasma Total Antioxidant Capacity; TC: Total Cholesterol; TG: Triglycerides; TNF-α: Tumor Necrosis Factor-alpha; VLDL-C: VLDL Cholesterol.

Introduction

Metabolic syndrome is a complex disorder represented by a cluster of cardiovascular risk factors associated with central fat deposition, abnormal plasma lipid levels, elevated blood pressure insulin resistance and intestinal dysbiosis [1-4]. Changes in eating habits are undoubtedly the most important non-pharmacological factor for the prevention and treatment of the risk factors of the MetS and various nutritional therapies have been researched [5,6]. Among the nutritional therapies to prevent MetS risk factors, the scientific literature has pointed to the consumption of probiotic, prebiotic and symbiotic products.

The gastrointestinal tract is composed of several connected organs that are involved in nutrient conversion and providing energy sources from the food absorbed. This complex system has a well-known anatomical architecture that is approximately 7m long, comprising 300m2 surface area in adults. The human large intestine has a bacterial flora with total numbers of 1014 cells, (ten times the number of the cells of the human body) more than 1000 species and a biomass superior 1Kg [7,8].

From the mouth to the colon, there is a complex micro biota consisted of facultative and strict anaerobes, including streptococci, bacteroides, lactobacilli and yeasts [9,10]. The micro biome comprises nearly two million genes, being the collective bacterial genome vastly greater than the human genome. The advent of high-through put methodologies and the elaboration of sophisticated analytic systems have facilitated the detailed description of the microbial constituents of the human gut as never before and are now enabling comparisons to be made between health and various disease states [11].

Currently, it has also been recognized that this dynamic yet stable ecosystem plays a role in conditions such as obesity and diabetes as well as in general well-being, from infancy to ageing [7,12-15]. The literature has demonstrated different gut microbial composition between non-diabetics and adults with T2D, and lean and obese individuals [7,16] and suggested that gut microbial composition may affect the metabolism and energy storage [17]. The main functions of the gut micro biota are ascribed into three categories: metabolic, protective and trophic [18].

A consensus definition of the term "probiotics" was adopted after a joint Food and Agricultural Organization of the United Nations and World Health Organization expert consultation. In October 2001, the Organizations experts defined probiotics as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host." The original idea of the probiotics concept (that can be translated in 'probiotics effects'), was defined as: 'the selective stimulation of growth and/or activity (ies) of one or a limited number

Citation: Scavuzzi BM, Henrique FC, Miglioranza LHS, Simão ANC and Dichi I. Impact of Prebiotics, Probiotics and Synbiotics on Components of the Metabolic Syndrome. Ann Nutr Disord & Ther. 2014;1(2): 1009.

Table 1: Human studies considering probiotics and body weight.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the impact of a *L. rhamnosus* CGMCC1.3724 (LPR) supplementation on weight loss and maintenance.	125 obese adults (48 male and 77 female) aged 18-55 years.	LPR supplementation can accentuate body-weight loss and seems to help obese women to maintain healthy body weight.	[27]
A DB, randomized, prospective study to evaluate the impact of perinatal probiotic intervention (*L. rhamnosus* GG - ATCC 53103) on childhood growth patterns and the development of overweight during a 10-year follow-up.	159 women before delivery and 113 children were measured at the ages of 3, 6, 12 and 24 months and 4, 7 and 10 years.	Early gut microbiota modulation with probiotics may modify the growth pattern of the child by restraining excessive weight gain during the first years of life.	[29]
A multicenter, DB, RPCT to evaluate the effects of the probiotic L. *gasseri* SBT2055 (LG2055) - originated from the human gut - on abdominal adiposity, body weight and other body measures.	87 healthy adults (59 men/ 28 women) with BMI of 24.2-30.7 kg/m^2 and abdominal visceral fat area (81.2-78.5 cm^2).	LG2055 consumption promoted a significant reduction in abdominal adiposity, BMI, waist and hip circumference.	[33]
A DB, RPCT parallel pilot study to evaluate the effects of a hypocaloric diet supplemented with a probiotic cheese containing L. plantarum strain TENSIA on obese hypertensive patients.	25 obese hypertensive patients.	The hypocaloric diet supplemented with a probiotic cheese helped to reduce BMI.	[45]
A DB, RPCT to assess the beneficial effects on MetS of functional yogurt NY-YP901 (Namyang Dairy Product Co. Ltd and Nutra R&BT Inc., Seoul, Korea) supplemented with Streptococcus thermophilus, L. acidophilus, B. infantis.	101 healthy adults (70 women and 31 men), 20-65 years.	The functional yogurt NY-YP901 with probiotics reduced body weight and BMI.	[50]

Table 2: Human studies considering probiotics and blood lipids.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the effect of L. salivarius Ls-33 on a series of biomarkers related to inflammation and the MetS.	50 obese adolescents (28 female and 22 male), 12-15 years.	No evidence of any beneficial effect on lipid profile.	[13]
A DB, RPCT to assess the cholesterol-lowering clinical efficacy and safety of microencapsulated L. reuteri NCIMB 30242 supplemented in a yogurt formulation.	114 healthy hypercholesterolaemic adult men and women, 18-74 years.	Microencapsulate L. reuteri yoghurt consumption decreased LDL-C, TC and non-HDL-C.	[28]
A DB, RCT to investigate the effects of probiotic (L. acidophilus La5 and B. lactis Bb12) and conventional yogurt on the lipid profile.	60 adults (23 men and 37 women) with T2D and LDL-C > 2.6 mmol/L, 30-60 years.	Probiotic yogurt improved TC and LDL-cholesterol.	[35]
A RPCT to verify and compare the effects of probiotic (L. casei subsp. casei) and conventional yoghurt on the plasma lipid profile.	33 healthy, non-smoking, normocholesterolemic women, 22-29 years.	The total/HDL and LDL/HDL-C ratios improved in both probiotic and conventional yogurt intake.	[36]
A DB, RPCT to assess the beneficial effects on MetS of functional yogurt NY-YP901 (Namyang Dairy Product Co. Ltd and Nutra R&BT Inc., Seoul, Korea) supplemented with Streptococcus thermophilus, L. acidophilus, B. infantis.	101 healthy adults (70 women and 31 men), 20-65 years.	The functional yogurt NY-YP901 with probiotics reduced LDL-C.	[50]
A triple blind, randomized study to test the effect of probiotic (L. acidophilus La5 and B. lactis Bb12) and conventional yogurt on the lipid profile.	90 women, 19-49 years.	Decrease in cholesterol, increase in HDL-C, decrease in total:HDL-C ratio) were observed in both yogurt groups.	[51]
A single-blind, RCOT to compare the effect of consuming probiotic yogurt (L. acidophilus and B. lactis) with that of ordinary yogurt on serum cholesterol level.	14 adults (10 men and 4 women) 40-64 years with mild to moderate hypercholesterolemia.	Cholesterol-lowering effect.	[52]
A single-blind, RPCT to investigate the effect of probiotic capsules (L. acidophilus DDS-1 and B. longum UABL-14) on plasma lipid concentrations.	55 normocholesterolemic adults (33 premenopausal women and 22 men), 18-36 years.	No evidence of any beneficial effect on plasma lipids.	[53]
A single-center, DB, placebo-controlled study to assess the effects of PCC® L. fermentum on LDL cholesterol and other lipid fractions.	44 adults (16 men and 28 women) 30-75 years.	No major effect of Lactobacillus fermentum on serum lipids.	[54]
A single-blind, parallel group study to demonstrate the effect of milk fermented by B. longum strain BL1 on blood lipids.	32 healthy males with serum TC levels within the range of 220 to 280 mg/dl. 35-52 years.	B. longum yogurt lowered serum TC, especially in subjects with moderate hypercholesterolemia.	[55]
A randomized, DB, placebo-and compliance-controlled, parallel study to investigate the effect of a probiotic milk product containing the culture CAUSIDO® and of two alternative products on risk factors for cardiovascular disease.	70 healthy, weight-stable, overweight and obese adults (20 men and 50 women) 18-55 years.	CAUSIDO® culture reduced LDL-cholesterol.	[56]

of microbial genus (era)/species in the gut micro biota that confer(s) health benefits to the host.' When probiotics and prebiotics are used in combination, they are known as synbiotics [19,20].

The consumption of prebiotics, probiotics and synbiotics has gained recognition from the scientific community due to the promising health effects and well documented history of safe use. Thus, the present review gathers recent and relevant literature found in at least 130 Databases included in the virtual library "Portal CAPES Consortia" (Higher Education Personnel Improvement Coordination –Brazil) published from 1994 to 2014, involving the consumption of prebiotics, probiotics and synbiotics and the components of the MS. There were no restriction groups, but searches have focused on texts written in English.

Probiotics

The modulation of the intestinal microbiota is one of the potential

beneficial health effects of probiotics, and numerous research studies have documented that probiotics can impact the gut microbiota [21]. The mechanisms and efficiency of the probiotic effect depend primarily on the interactions between the probiotic microorganisms and either the microbiota of the host or the immunocompetent cells of the intestinal mucosa [22,23].

Dysbiosis of the intestinal microbiota has been associated with a growing number of diseases. Some data on the MetS suggest that changes in gut microbiome composition may play a role in the disorder. Recently, fecal microbiota transplant from non-diabetic donors infused into the duodenum of patients with the MetS improved their insulin sensitivity, highlighting the broad potential of this intervention [24]. Since modulation of the composition of intestinal microbiota by probiotics was demonstrated to be possible, this intervention has the potential to counterbalance intestinal Dysbiosis and thus restore health [22].

Probiotics may play a beneficial role in several medical conditions, including diarrhea, gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, cancer, depressed immune function, infant allergies, failure-to-thrive, hyperlipidemia, hepatic diseases, Helicobacter pylori infections, and others [25].

The effects of probiotics are mediated by the role of probiotic bacteria in normalization of intestinal microbiota composition, immunomodulation, and maintenance of gut barrier function. With advancing knowledge of how probiotics interact with the gut microbiome, there is an increasing interest in exploring the effect of probiotics on specific elements of the MetS in humans [26].

Several strains of probiotics improve metabolic parameters such as hypertension, abnormal plasma lipid levels, obesity, inflammation and glucose homeostasis disorders [15,27-30]. The important criteria that have been put forward by FAO/WHO in the selection of food probiotics include identification of strains using state-of-the-art techniques, ability to tolerate gastric juice and bile, maintain stability and, most importantly, prove to be safe and beneficial to the consumer. A number of genera of bacteria are used as probiotics, including *Lactobacillus, Bifidobacterium, Pediococcus, Leuconostoc and Enterococcus* [31]. Amongst probiotics, *L. acidophilus* NCFM / La5, *L. casei* subsp. *casei*, *L. gasseri* SBT2055, *L. helveticus, L. plantarum* 299v, *L. rhamnosus* GG, *L. reuteri* NCIMB, *B. lactis* Bb12 and others, have human health efficacy data with desirable properties and well-documented clinical effects on parameters of MetS [30,32-36].

The physiological effects of probiotics are highly strain-dependent. The variations in outcomes between different studies appear to be due to choice of probiotic strain, route of administration and length of study. Human studies considering probiotics and components of the MetS are still under consideration.

Probiotics and body weight

Numerous studies of the human gut microbiome found evidence of core differences between lean and obese individuals, **reduced diversity of the microbiota in obese individuals** and suggested that gut microbial composition may affect the metabolism and fat storage [17,37-39],

Additionally, studies have recognized that the composition of the gut microbiota has an impact on energy homeostasis and suggested that probiotics have a positive impact on weight loss. However, it is important to mention that the physiological effects of probiotics are highly strain-dependent. Million et al., 2012, conducted a comparative meta-analysis of studies considering the effect of species of *Lactobacillus* on body weight of humans and animals. The authors found that the species *fermentum* and *ingluviei* were associated with weight gain in animals, *plantarum* was associated with weight loss in animals and *gasseri* was associated with weight reduction in animals and humans [40].

Five studies considering the impact of probiotics on body weight were considered for this review. All the studies documented improvements in this MetS parameter after probiotic consumption (Table 1). The mechanisms involved in the reported body weight reduction are not clear, but studies point out to the reduction of adipocyte size [41,42], inhibition of adiposeness [43] and the suppression of energy intake [44].

Probiotics and blood lipids

Guo et al, 2011 conducted a meta-analysis of randomized controlled trials to evaluate the effects of probiotics on blood lipids. The authors found evidence that probiotics decreases plasma LDL and total cholesterol in subjects with normal, borderline high and high cholesterol levels [46]. Similarly, nine out of the twelve studies in this review documented significant improvements in blood lipids after probiotic consumption (Table 2).

Although the mechanisms involved in the cholesterol-lowering effect are not clearly understood, it is accepted that the inhibition of intestinal cholesterol absorption, suppression of bile acid reabsorption [47,48] and production of short-chain fatty acids, which reduce cholesterol synthesis, are involved [49].

Probiotics and glucose homeostasis

Firouzi et al, 2013 conducted a review of studies in animals and humans that considered the impact of probiotics on parameters of glucose homeostasis. The authors found that 16 out of 17 studies in animals, and three out of four studies in humans, had documented significant improvements in at least one glucose homeostasis related parameter [59]. Similarly, in the present review, three out of five studies documented improvements in this MetS parameter after probiotic consumption (Table 3). Currently, it is known that the glucose homeostasis is negatively affected by a low grade chronic inflammatory state promoted by lipopolysaccharide binding to CD14 toll-like receptor-4 [60,61].

Probiotics and inflammatory markers

The pathways involved in the r*eduction* of *inflammation markers are still under investigation. However, it is possible that* increase of glucagon-like peptide-2 production and a resulting improvement of gut permeability [63], decrease of proinflammatory cytokines [64], a toll-like receptor 9 signaling mediation [65] are involved.

One third of the investigations included in this review documented improvements in this MetS parameter after probiotic consumption (Table 4).

Table 3: Human studies considering probiotics and glucose homeostasis.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the effect of L. salivarius Ls-33 on a series of biomarkers related to inflammation and the MetS.	50 obese adolescents (28 female and 22 male), 12-15 years.	No evidence of any beneficial effect on, glucose homeostasis.	[13]
A RPCT to evaluate the influence of fermented milk with L. plantarum in the classical parameters related to MetS and other parameters related to cardiovascular risk.	24 postmenopausal women with MetS, 60-75 years.	L. plantarum consumption decreased glucose levels.	[15]
A DB, RPCT to investigate the effects of the widely applied probiotic strain L. acidophilus NCFM on insulin sensitivity and the systemic inflammatory response.	45 men with T2D, impaired or normal glucose tolerance.	L. acidophilus NCFM intake preserved insulin sensitivity compared with placebo.	[32]
A randomized, prospective, parallel-group intervention study to investigate whether supplementation of probiotics (L. rhamnosus GG, ATCC 53 103 and B. lactis Bb12) with dietary counselling affects glucose metabolism.	256 pregnant women (mean age of 30 years).	Combined dietary counselling and probiotics intervention yielded improved glucose metabolism and insulin sensitivity.	[57]
A DB, RPCT to investigate the effect of a probiotic capsule (L. salivarius UCC118) on maternal fasting glucose.	175 pregnant women with BMI from 30.0 - 39.9 kg/m2. Age > 18 years.	No influence on maternal fasting glucose, metabolic profile or pregnancy outcomes.	[62]

Table 4: Human studies considering probiotics and inflammatory markers.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the effect of L. salivarius Ls-33 on a series of biomarkers related to inflammation and the MetS.	50 obese adolescents (28 female and 22 male), 12-15 years.	No evidence of any beneficial effect on inflammatory markers.	[13]
A RPCT to evaluate the influence of fermented milk with L. plantarum in the classical parameters related to MetS and other parameters related to cardiovascular risk.	24 postmenopausal women with MetS, 60-75 years.	L. plantarum consumption decreased homocysteine levels.	[15]
A DB, RPCT to investigate the effects of the widely applied probiotic strain L. acidophilus NCFM on insulin sensitivity and the systemic inflammatory response.	45 men with T2D, impaired or normal glucose tolerance.	L. acidophilus NCFM intake did not affect the systemic inflammatory response.	[32]

Table 5: Human studies considering probiotics and blood pressure.

Study	Population	Conclusion	Reference
A DB, RPCT parallel pilot study to evaluate the effects of a hypocaloric diet supplemented with a probiotic cheese on obese hypertensive patients.	25 obese hypertensive patients.	The hypocaloric diet supplemented with a probiotic cheese helped to reduce arterial BP.	[45]
A DB, RPCT parallel group study to evaluate the effects of two doses of lactotripeptides (from Lactobacillus helveticus LBK-16H-fermented milk products) on 24-h ambulatory blood pressure and lipidomics profiles in mildly hypertensive subjects.	89 mildly hypertensive subjects.	Mild, but not significant decrease of blood pressure.	[70]
A DB, RPCT to study the antihypertensive effect of Lactobacillus helveticus FM in prehypertensive and borderline hypertensive subjects.	94 prehypertensive and borderline hypertensive subjects.	No significant antihypertensive effect.	[71]
A DB, RPCT to evaluate the effect and safety of powdered fermented milk with Lactobacillus helveticus CM4 on subjects with high-normal blood pressure or mild hypertension.	40 subjects with high-normal blood pressure and 40 subjects with mild hypertension	Decrease in blood pressure.	[72]
A RCOT to evaluate the effect on BP in subjects with mild hypertension of a new sour milk containing tripeptides (from Lactobacillus helveticus).	60 subjects with mild hypertension (36 men, 24 women).	Modest decrease in blood pressure.	[73]
A DB, RPCT to assess the effect of sour milk, containing two tripeptides (valine-proline-proline and isoleucine-proline-proline), on blood pressure (BP)	6 borderline hypertensive men, 23-59 years.	Decrease in blood pressure.	[74]
A DB, RPCT to evaluate the long-term blood pressure-lowering effect of milk fermented by Lactobacillus helveticus LBK-16H in hypertensive subjects.	39 hypertensive patients.	Decrease in blood pressure.	[75]

Probiotics and blood pressure

In a recent systematic review and meta-analysis of randomized controlled trials, Khalesi et al, 2014 concluded that probiotics moderately reduce blood pressure. The authors found evidence that BP reduction is greater when the intervention has a duration superior to eight weeks, when daily dose of probiotic consumption is greater than (or equal to) 10^{11} colony-forming units, and among individuals with elevated BP. The study also suggests a greater BP-lowering effect when multiple species of probiotics are consumed [66]. In the present review, five out of seven studies documented improvements in this MetS parameter after probiotic consumption (Table 5).

The blood-pressure lowering ability of some probiotics has been related to the release of bioactive peptides that have an Angiotensin-Converting Enzyme (ACE) inhibitor effect [67]. The blood-pressure decrease may also be a result of the reduction of blood lipids [68] and body weight [69].

Safety considerations

Given the growing reports of health benefits of probiotics and the resulting widespread use of these products, *it is important* to *be aware that s*afety data, particularly long-term safety. Studies concerning safety of these products are still very limited and th*ere are n*o established guidelines for this evaluation. Some probiotics have been used for thousands of years without being associated to undesirable effects. However, the health effects are strain-dependent and should not be generalized without prior confirmation. Probiotics contain live organisms and although very rare, may cause infections.

Therefore, there are safety issues particularly amongst individuals with compromised immune systems. *Lactobacilli* strains, for example, have been associated with rare cases of bacterial sepsis in debilitated individuals, *despite of the* long history of safe use. For the general population, probiotics appear to be safe and side effects, if present, tend to be mild and digestive, such as gas or bloating [19,76,77]. Contrarily, some probiotic species have demonstrated beneficial effect in decreasing the symptoms of bloating in patients with irritable bowel syndrome [78].

Another area of concern is that probiotics are commonly commercialized as foods or dietary supplements and, therefore, there is no requirement to demonstrate the purity of these products [76]. Reports of mislabeled number of live organisms and identification of strains *indicate* a *need* for recognized regulations concerning labeling issues and claims, to ensure safety of these products [79, 80].

Prebiotics

Prebiotics are selectively fermented dietary fibers that are found naturally in plants such as asparagus, bananas, berries, chicory, garlic and onions and that promote the growth of beneficial microorganisms such as Lactobacilli and Bifidobacteria in the intestine. Some examples of prebiotics include inulin, oligofructose, fructooligosaccharides, galactooligosaccharides and lactulose. The consumption of nutrients with prebiotics properties is associated with changes in the gut microbiota and improvements in metabolic parameters related to obesity, inflammation, glucose homeostasis disorders and abnormal plasma lipid levels [85-89,97-121]. Additionally, increased satiety has been associated to the intake of prebiotics, which may contribute to weight management [85-87].

Consumption of prebiotics appears to be effective in the modulation of the components of the MetS. Yacon roots, the most abundant know source of fructooligosaccharides [88], for example, have been related to antiglycemic, hypolipidemic, laxative and slimming effects [89-91].

The exact mechanisms by which prebiotics contribute to the improvement of metabolic parameters are not completely elucidated. The hypotriglyceridemic action seems to be associated to decreased expression of the liver lipogenic pathway [92]. The antilipemic effects have been associated to decreased cholesterol absorption / increased excretion of cholesterol through feces and by the production of short-chain fatty acids such as acetate, butyrate and propionate produced by intestinal micro flora fermentation [93]. The antiobesity and antidiabetic effects are probably related to the binding of SCFA to G-protein coupled receptors and subsequent increase of glucagon-like peptide 1 and peptide YY [94,95]. The antihypertensive effects may be a result of the lowering of cholesterol attributed to the prebiotics [96].

Seven studies considering the impact of probiotics on body weight were included in this review and six of them documented improvements in this MetS parameter after probiotic consumption (Table 6). However, in a systematic review of randomized controlled trials, Kellow et al, concluded that there is insufficient evidence at present to recommend dietary prebiotics for reducing energy intake and body weight. The authors also noted that studies with a duration superior to 12 weeks were more likely to observe reduction in body weight [122].

Studies measuring blood lipids after prebiotics consumption have yielded promising results. Thirteen studies considered the impact of prebiotics on lipids levels in this review, and nine documented significant improvements in this MetS parameter after probiotic consumption (Table 7).

Prebiotics also seem to have positive effect on glucose metabolism. In the systematic review of randomized controlled trials conducted by Kellow et al, the authors found that studies generally supported significant reduction in postprandial glucose and insulin concentrations in healthy and overweight individuals after consumption of prebiotics [122]. Similarly, in the present review, most studies documented improvements these parameters of glucose

Table 6: Human studies considering prebiotics and body weight, energy intake or satiety.

Study	Population	Conclusion	Reference
A single-blinded, crossover, RPCT, pilot study to study the effects of oligofructose on satiety and energy intake in humans.	5 men/5 women, 21-39 years, BMI 18.5-27.4 kg/m2.	Increased satiety following breakfast and dinner, reduced hunger and prospective food consumption following dinner. Total energy intake per day is 5% lower during oligofructose than in the placebo period.	[85]
A two-week DB, parallel, RPCT to examine the effects of prebiotic supplementation on satiety and related hormones during a test meal.	5 healthy men and women (10 subjects).	Increase in plasma concentrations of GLP-1 and PYY.	[86]
A 12-week, DB, RPCT to examine the effects of oligofructose supplementation on body weight and satiety hormone concentrations in overweight and obese adults.	39 healthy subjects (32 women/7 men).	Significantly higher weight loss in oligofructose group than the control group.	[87]
A 120-day, DB, RPCT to verify the effects of yacon (rich in FOS) syrup on obesity and IR in humans.	35 pre-menopausal women, 31-49 years, with no menopausal disorders, obesity with mild dyslipidemia.	Daily intake of yacon syrup produced a significant decrease in body weight, waist circumference and BMI.	[89]
A DB, parallel, RPCT to determine variations on fecal SCFA concentration in obese women treated with inulin-type fructans and to explore associations between Bifidobacterium species, SCFA and host biological markers of metabolism.	30 obese women	Total SCFA, acetate and propionate, which positively correlated with BMI.	[97]
A DB, RCOT to examine the effect of oligofructose supplementation on appetite profiles, satiety hormone concentrations and energy intake in human	31 healthy subjects (10 men/21 women).	Energy intake was significantly reduced with 16 g/d oligofructose compared with 10 g/d, possibly supported by higher GLP-1 and PYY concentrations.	[105]
A DB, RCOT to test the effect of FOS, beta-glucan, or a combination thereof on appetite ratings and food intake over 2 consecutive days.	21 healthy subjects (16 women/5 men).	The addition of beta-glucan, FOS, or a combination thereof did not affect appetite ratings or food intake.	[107]

Table 7: Human studies considering prebiotics and blood lipids.

Study	Population	Conclusion	Reference
A 6-week, DB, RPCT to evaluate the efficacy of chitin-glucan, alone and in combination with a potentially anti-inflammatory olive oil extract, for reducing OxLDL in subjects with borderline to high LDL-C levels.	130 subjects aged 21-70 years, BMI of 18.5–34.9 kg/m2, fasting serum levels of LDL-C 3.37–4.92 mmol/l.	CG (4.5 g/day) reduced OxLDL. CG was associated with lower LDL-C levels in the 1.5 g/day group.	[98]
A 12-week DB, crossover, RPCT to study the effect of a galactooligosaccharide mixture on markers of MetS, gut microbiota, and immune function.	45 overweight adults with ≥3 risk factors associated with MetS.	Decrease in plasma TC, TG, and TC/HDL-C ratio.	[102]
A 3-month, RCT to evaluate the efficacy of a partial meal replacement with inulin on weight reduction, blood lipids and micronutrients intake in obese Mexican women.	144 women aged 18–50 years with BMI ≥ 25 kg/m2	Reduced TG and improved intake of micronutrients during caloric restriction.	[103]
A one-month, DB, RCT to evaluate the response of the cardiovascular risk profile in obese patients after inclusion in the diet of an ALA, FOS and inulin enriched-cookie.	36 obese subjects (BMI >30).	Improved TC and LDL-C levels in obese men.	[104]
A DB, RCOT to evaluate the effects of the daily consumption of inulin-enriched pasta on lipid and glucose metabolism as well as on gastrointestinal motility in young healthy subjects.	22 healthy men.	Improved lipidic profile (HDL-C, TC/HDL-C ratio and TG) in healthy young subjects.	[106]
A 3-week DB, crossover, RPCT study to asses the effects of a moderately high-carbohydrate, low-fat diet plus an oral placebo or 10 g high-performance inulin/day on hepatic lipogenesis and plasma triacylglycerol concentrations.	8 healthy subjects.	Decreased plasma TG concentrations and hepatic lipogenesis.	[113]
A 3-week, DB, RCOT to assess the effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men.	12 hypercholesterolemic men.	Daily intake of 20 g of inulin significantly reduced serum TG.	[115]
A DB crossover design to study the effects of the chronic ingestion of FOS on plasma lipid and glucose concentrations, hepatic glucose production and IR in T2D.	10 subjects with T2D (6 men/4 women)	4 weeks of 20 g/d of FOS had no effect on lipid metabolism in T2D subjects.	[116]
A single-blind, RCOT to study the effects of FOS on blood glucose, serum lipids, and serum acetate in patients with T2D.	20 patients with T2D (9 men /11 postmenopausal women).	No major effect on serum lipids.	[117]
A DB, RCOT to study the effect of consuming three servings per day of inulin-containing foods, compared to similar foods without inulin, on serum lipid profiles among hypercholesterolemic men and women.	21 subjects with baseline LDL-C of 3.36-5.17 mmol/L.	No differences were found between any of the lipid variables when the values at the end of the inulin and control periods were compared.	[118]
A RCOT to investigate the effect of a breakfast cereal containing inulin on blood lipids and colonic ecosystem in normolipidemic young men.	12 healthy men.	Plasma TC and TG significantly decreased.	[119]
A Latin square, DB, RCOT to study the effect of the intake of 15 g non-digestible oligosaccharides per day on various parameters of large-bowel function, as well as on blood lipid concentrations and glucose absorption in man.	12 healthy men.	The consumption of 15 g non-digestible oligosaccharides does not seem to alter blood lipid concentrations in young healthy adults.	[120]

homeostasis after prebiotics consumption (Table 8).

Although there is not enough evidence to recommend the use of prebiotics to improve inflammatory markers, measures of antioxidant capacity and blood pressure, all of the studies considered in this review reported improvements for these markers (Tables 9 and 10). Therefore, further studies and more detailed clinical trials are needed to support these clinical findings.

Synbiotics

Synbiotics are defined as 'a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract' [123]. Studies on the effects of synbiotics on metabolic health still are limited. It is worth mentioning that the health effect will likely depend on the symbiotic combination. Therefore, although synbiotics seem promising for the modulation of the gut microbiota composition, the effects remain to be confirmed by human trials, once very few human studies considering synbiotics and components of the MetS have been published (Tables 11-15).

Studies considering the impact of symbiotic supplementation on body composition or energy intake have yielded mixed results. Only two out of the five studies considered for this review documented improvements of these markers (Table 11).

Only one study considered for this review evaluated changes in blood pressure after consumption of synbiotics. A significant decrease in systolic blood pressure was documented (Table 12).

Similarly to probiotics and prebiotics, studies generally support significant improvement on blood lipid profile following synbiotics supplementation. In this review, six out of seven studies documented improvement of at least one blood lipid (Table 13).

Although the number of studies is still very limited, symbiotic consumption seems to have a positive effect on glucose homeostasis. Two out of three studies considered for this review documented improvements in this parameter after the consumption of dietary synbiotics (Table 14).

Even though there is not enough evidence to recommend the use of prebiotics to improve inflammatory markers, most studies considered for this review documented improvements in at least one inflammatory marker after the consumption synbiotics (Table 15).

Conclusion

A diet rich in prebiotics, probiotics and synbiotics might confer numerous health benefits to the host possibly due to positive gut microbiota modulation. However, further studies should provide reliable mechanistic, safety and clinical evidence before recommending prebiotics, probiotics and synbiotics to individuals with the MetS.

Table 8: Human studies considering prebiotics and glucose homeostasis.

Study	Population	Conclusion	Reference
A DB, parallel, RPCT to determine variations on fecal SCFA concentration in obese women treated with inulin-type fructans and to explore associations between Bifidobacterium species, SCFA and host biological markers of metabolism.	30 obese women	Fasting insulinemia and HOMA, were lower.	[97]
An 8-week parallel, DB, RCT to evaluate the effects of inulin supplementation on inflammatory indices and metabolic endotoxemia in patients with T2D.	49 women with T2D.	Decrease in fasting insulin, HOMA-IR.	[99]
A 3-month, DB, RPCT to study the contribution of the gut microbiota to the modulation of host metabolism by dietary inulin-type fructans in obese women.	30 obese women.	Decreased post-OGTT glycaemia.	[100]
A 2-month, triple-blind RCT, to evaluate the effects of high-performance inulin supplementation on blood glycemic control and antioxidant status in women with T2D.	49 women with T2D.	Decrease in fasting plasma glucose, glycosylated hemoglobin and malondialdehyde levels.	[101]
A DB, RCOT to evaluate the effects of the daily consumption of inulin-enriched pasta on lipid and glucose metabolism as well as on gastrointestinal motility in young healthy subjects.	22 healthy men.	Improved glicidic metabolism (fasting glucose level, fructosamine and HbA1c) as well as IR in healthy young subjects.	[106]
An 8-week, DB, RCOT to asses the effect of daily ingestion of OFS in seven patients with nonalcoholic steatohepatitis.	7 men with nonalcoholic steatohepatitis confirmed by liver biopsies.	Decrease of insulin level.	[110]
A two-month, DB, sequential RCOT to evaluate the effects of moderate intake of short-chain-FOS on glucose and lipid metabolism in individuals with mild hypercholesterolemia.	30 subjects (20 men/10 women), with plasma cholesterol 5.17-7.76 mmol/l and plasma triglycerides <3.45 mmol/l.	Reduction of the postprandial insulin response.	[111]
A 3-week, DB, RCOT to assess the effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men.	12 hypercholesterolemic men.	An increase in insulin and glucagon levels at 1-hour post glucose load was found.	[115]
A DB crossover design to study the effects of the chronic ingestion of FOS on plasma lipid and glucose concentrations, hepatic glucose production and IR in T2D.	10 subjects with T2D (6 men/4 women)	4 weeks of 20 g/d of FOS had no effect on glucose metabolism in T2D subjects.	[116]
A single-blind, RCOT to study the effects of FOS on blood glucose, serum lipids, and serum acetate in patients with T2D.	20 patients with T2D (9 men /11 postmenopausal women).	No major effect on blood glucose.	[117]
A Latin square, DB, RCOT to study the effect of the intake of 15 g non-digestible oligosaccharides per day on various parameters of large-bowel function, as well as on blood lipid concentrations and glucose absorption in man.	12 healthy men.	The consumption of 15 g non-digestible oligosaccharides does not seem to alter glucose absorption in young healthy adults.	[120]
A DB, RCOT to study the effects of chronic ingestion of short-chain FOS on hepatic glucose production, insulin-mediated glucose metabolism, erythrocyte insulin binding, and blood lipids in healthy subjects.	12 healthy men, 19-32 years.	Decreased basal hepatic glucose production but no detectable effect on insulin-stimulated glucose metabolism.	[121]

Table 9: Human studies considering prebiotics and inflammatory or oxidative stress markers.

Study	Population	Conclusion	Reference
An 8-week parallel, DB, RCT to evaluate the effects of inulin supplementation on inflammatory indices and metabolic endotoxemia in patients with T2D.	49 women with T2D.	Decrease in hs-CRP, TNF-α, and LPS.	[99]
A 2-month, triple-blind RCT, to evaluate the effects of high-performance inulin supplementation on blood glycemic control and antioxidant status in women with T2D.	49 women with T2D.	Increase in TAC and superoxide dismutase activity.	[101]
A 12-week DB, crossover, RPCT to study the effect of a galactooligosaccharide mixture on markers of MetS, gut microbiota, and immune function.	45 overweight adults with ≥3 risk factors associated with MetS.	Increase in fecal secretory IgA and decrease in fecal calprotectin and plasma CRP.	[102]
A one-month, DB, RCT to evaluate the response of the cardiovascular risk profile in obese patients after inclusion in the diet of an ALA, FOS and inulin enriched-cookie.	36 obese subjects (BMI >30).	Improved CRP levels in obese men.	[104]
A DB, RCOT to evaluate the effects of inulin-enriched pasta on lipid profile and on Lipoprotein(a) in young healthy subjects.	22 healthy men.	Lipoprotein(a) concentrations decreased.	[108]
A 12-week, DB, RCT to evaluate the effect of nutritional supplementation with oligosaccharides on gut bacteriology and immunology and inflammatory parameters in older persons at risk of malnutrition.	74 elderly subjects (age superior 70 y; 84 +/- 7 years) either undernourished or at risk of undernutrition.	TNF-α mRNA and IL-6 mRNA decreased.	[109]

Table 10: Human studies considering prebiotics and blood pressure.

Study	Population	Conclusion	Reference
A 12-week DB, RPCT to examine the effect of dietary fiber intake on blood pressure (BP).	110 subjects with high but untreated BP or stage-1 hypertension, 30-65 years.	A moderate reduction in SBP and DBP was found.	[112]
An 8-week-long randomized study of factorial design to determine if dietary protein and fiber had additive effects on blood pressure reduction in hypertensives	36 subjects ≥20 years old receiving drug therapy for hypertension.	A significant reduction in SBP.	[114]

Table 11: Human studies considering synbiotics and body weight, energy intake or satiety.

Study	Population	Conclusion	Reference
A 28-week, DB, RPCT to evaluate the effects of synbiotic supplementation (Protexin*) on IR and lipid profile in individuals with the MetS.	38 subjects with the MetS.	No significant changes in waist circumference, BMI and energy intake.	[125]
A 3-month DB study to evaluate some effects of synbiotic supplementation (FOS/L. paracasei, L. rhamnosus, L. acidophilus and B. lactis) on inflammatory markers and the body composition of the elderly at risk of frailty.	17 elderly subjects fulfilling at least one frailty criterion (grip strength).	No significant changes in body composition.	[126]
A 30-day DB, RPCT to investigate the effects of synbiotic supplementation (Protexin*) on lactating mothers' energy intake and BMI, and infants' growth.	80 lactating women.	Synbiotic supplementation was associated with a slight increase in mean energy intake, weight and BMI on lactating mothers and weight gain on infants.	[127]
An 8-week, triple-masked, RCT to assess the anti-obesity and lipid-lowering effects of a synbiotic supplement among children and adolescents.	70 overweight or obese children and adolescents aged 6-18 years.	Decrease in BMI Z-score, waist circumference, and waist-to-hip ratio.	[128]
A DB, RCOT to investigate the effect of daily consumption of a synbiotic yogurt on gastrointestinal function in a sample of healthy adults. The yogurt contained *B. lactis* Bb12, *L. acidophilus* La5, *L. casei* CRL431 and inulin.	65 healthy adults.	Energy, fat and protein intakes were decreased from baseline. Dietary fibre intake was higher POST-treatment with synbiotic versus control.	[129]

*Protexin: probiotics: *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus* and prebiotics: fructo-oligosaccharide.

Table 12: Human studies considering synbiotics and blood pressure.

Study	Population	Conclusion	Reference
A DB, RCT to investigate the influence of a functional food product containing *L. plantarum* 299v/oat flour on lipid profiles, inflammatory markers, and monocyte function in heavy smokers.	36 healthy subjects (18 women and 18 men) aged 35–45 years.	Decrease in SBP.	[130]

Table 13: Human studies considering synbiotics and blood lipids.

Study	Population	Conclusion	Reference
A 28-week, DB, RPCT to evaluate the effects of synbiotic supplementation (Protexin*) on IR and lipid profile in individuals with the MetS.	38 subjects with the MetS.	No significant changes in LDL.	[125]
An 8-week, triple-masked, RCT to assess the anti-obesity and lipid-lowering effects of a synbiotic supplement among children and adolescents.	70 overweight or obese children and adolescents aged 6-18 years.	Decrease in serum TG, TC and LDL-C.	[128]
A 9-week, DB, RCT to evaluate the effects of the daily consumption of synbiotic bread (*L. sporogenes*/inulin) on blood lipid profiles of patients with T2D.	78 diabetic patients, aged 35-70 years.	Decrease in serum TG, VLDL-C; TC/HDL-C ratio and an increase in serum HDL-C levels. No significant effect of on TC, LDL-C and non-HDL-C levels.	[131]
A DB, RCT, to evaluate the effects of daily consumption of a synbiotic food (L. sporogenes/inulin) on blood lipid profiles and biomarkers of oxidative stress in pregnant women.	52 primigravida pregnant women, aged 18 to 35-year-old at their third trimester.	Reduction in TG and VLDL levels. No effects on serum TC, LDL and HDL.	[132]
A 12-week DB, parallel-designed, RPCT to investigate the effect of a synbiotic product containing L. gasseri and inulin on lipid profiles of hypercholesterolemic men and women.	32 hypercholesterolemic men and women	Lower concentration of TG in the very low, intermediate, low, and high-density lipoprotein particles.	[134]
A cross-over study to assess the hypocholesterolemic effect of yogurt supplemented with L. acidophilus 145, B. longum 913 and oligofructose in women.	29 (15 normocholesterolaemic and 14 hypercholesterolaemic) women, aged 19-56 years.	Daily consumption of 300 g yogurt over 21 weeks (control and synbiotic) increased the serum concentration of HDL-C.	[135]
A DB, two-way, cross over, RPCT to study the effect of a fermented milk product containing L. acidophilus/FOS on blood lipids.	30 healthy men aged 33-64 years.	Lower values for serum TC, LDL-C and LDL/HDL-ratio. Levels of serum HDL-C and TC remained unchanged.	[136]

*Protexin: probiotics: *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus* and prebiotics: fructo-oligosaccharide.

Table 14: Human studies considering synbiotics and glucose homeostasis.

Study	Population	Conclusion	Reference
A 6-week, DB, RCOT to investigate the effects of synbiotic (L. sporogenes/inulin) food consumption on metabolic profiles, hs-CRP and biomarkers of oxidative stress in diabetic patients	62 diabetic patients aged 35-70 years.	Decrease in serum insulin levels.	[124]
A 28-week, DB, RPCT to evaluate the effects of synbiotic supplementation (Protexin*) on IR and lipid profile in individuals with the MetS.	38 subjects with the MetS.	Levels of fasting blood sugar and IR improved significantly.	[125]
A DB, two-way, cross over, RPCT to study the effect of a fermented milk product containing L. acidophilus/FOS on blood lipids.	30 healthy men aged 33-64 years.	Levels of blood glucose remained unchanged.	[136]

*Protexin: probiotics: *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus* and prebiotics: fructo-oligosaccharide.

Table 15: Human studies considering synbiotics and inflammatory or oxidative stress markers.

Study	Population	Conclusion	Reference
A DB, RCT to investigate the influence of a functional food product containing *L. plantarum* 299v/oat flour on lipid profiles, inflammatory markers, and monocyte function in heavy smokers.	36 healthy subjects (18 women and 18 men) aged 35–45 years.	Decreases in IL-6.	[30]
A 6-week, DB, RCOT to investigate the effects of synbiotic (L. sporogenes/inulin) food consumption on metabolic profiles, hs-CRP and biomarkers of oxidative stress in diabetic patients	62 diabetic patients aged 35-70 years.	Reduction in serum hs-CRP levels.	[124]
An 8-week, triple-masked, RCT to assess the anti-inflammatory effects of a synbiotic supplement (Protexin*) on inflammation markers in overweight and obese children and adolescents.	56 overweight or obese children and adolescents aged 6-18 years.	Decrease in mean values of TNF-α and IL-6 and increase in adiponectin before adjustment for BMI. No significant change in the mean values of hs-CRP.	[126]
A 4-week DB, crossover, RPCT to investigate the effects of synbiotic consumption (*B. longum*/inulin) on the colonic microbiota, immune function and health status in older people.	43 elderly subjects.	Reduced TNF-α in peripheral blood.	[133]
A 3-month DB study to evaluate some effects of synbiotic supplementation (FOS/L. paracasei, L. rhamnosus, L. acidophilus and B. lactis) on inflammatory markers and the body composition of the elderly at risk of frailty.	17 elderly subjects fulfilling at least one frailty criterion (grip strength).	No significant changes in inflammatory cytokines.	[126]

*Protexin: probiotics: *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus* and prebiotics: fructo-oligosaccharide.

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Ann Nutr Disord & Ther - Volume 1 Issue 2 - 2014
ISSN : 2381-8891 | www.austinpublishinggroup.com

Citation: Scavuzzi BM, Henrique FC, Miglioranza LHS, Simão ANC and Dichi I. Impact of Prebiotics, Probiotics and Synbiotics on Components of the Metabolic Syndrome. Ann Nutr Disord & Ther. 2014;1(2): 1009.