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New Therapeutic Agents to Treat Obesity and Its Related Disorders: Prebiotic, Probiotic and Synbiotic Supplementation

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Abstract

New evidences have shown that the gut microbiota is associated with intermediary metabolism, body weight, and inflammation. So, it could be involved in the pathogenesis of obesity and other metabolic disorders. Microbiota have influences on these disorders through different mechanisms related to host genes, environment, nutrition, appetite, lifestyle and systemic or adipocytes inflammation. Several factors including unhealthy dietary patterns, chronic intake of antibiotics, chronic stress, aging and different infections can disturb the balance between the number of helpful and pathogenic bacteria in the colon. So, consumption of prebiotic, probiotic or synbiotic may be in favor of the host health through alteration of the bacterial imbalance. In this review, we summarized the recent evidences that support the association between pre/pro/symbiotic consumption and prevention or treatment of obesity and the other metabolic disorders.

Keywords: Obesity; Metabolism; Inflammation; Appetite; Microflora; Synbiotic; Prebiotic; Probiotic

Introduction

Recently growing number of evidences shows that the high prevalence of obesity, type 2 diabetes mellitus and other related metabolic disorders cannot be solely attributed to the known factors such as human genome, dietary patterns and physical activity habit or not even absence of nutrition knowledge that we showed the significant effect of it on glycemic and lipidemic control in our previous study[1,2]. The new evidences suggest that gut microbiota has an important role not only in maintenance of human health, but also in occurrence/prevention of some metabolic disorders related to weight gain[3]. Dysbiosis of the gut ecosystem is associated with development of certain complications[4]. Human gut includes 300-500 strains different bacteria that are varied among different people. Gut microbiota includes more than 100 trillion cells that are mostly contained gram positive and anaerobic bacteria. Its composition is unique for each person[1]. Despite this exclusivity, two bacterial phyla named Firmicutes (most of them are gram positive) and Bacteridetes (gram negative) consist more than 90% of total gut bacteria[5,6]. Obesity is the main precursor for some metabolic disorders like metabolic syndrome. So, it can be targeted in developing various therapeutic strategies[7]. There are many evidencesshowing thatobesity and its causes are more complex than previously thought. Microbiota have some influences through different mechanisms related to host genes, environment, nutrition, appetite, lifestyle and systemic or adipocytes inflammation[8]. Therefore, microbiota modification may be a potential nutritional and pharmacological target to manage obesity and its relative disorders[9,10]. According to the recent hypothesis, the composition of microbiota is

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the result of interaction among a complex of factors like dietary pattern, race, genetic and so on[11]. The microbiota composition is different in lean from obese animals and humans[12]. There are some mechanisms by which colon can regulate energy metabolism, including energy extraction from the diet, the synthesis of intestinal hormones involved in energy homeostasis and appetite control, such as GLP-1 and PYY, regulation of fat storage, influence on GLP-2 secretion which is needed to maintain integrity of epithelium barrier, influence on immune system and effect on inflammatory factors such as IL-6, TNF- α via lipopolysaccharide-TLR-4 axis[13,14]. Gut changes may lead to activation of Toll like receptors (TLRs) in the gut that may have profound effects on host metabolism through development of inflammation factors and insulin resistance[15]. Dysbiosis of the microbiota increases gut permeability, increase plasma lipopolysaccharides levels leading to metabolic endotoxemia. Metabolic endotoxemia induces low-grade inflammation that can cause metabolic disorders including obesity, insulin resistance, diabetes, steatosis and oxidative stress[14,16]. There are certain species of Bifidobacterium and lactobacilliphyla that are responsible for make a balance in the intestinal microbiota. This balance is the result of increase in the number of helpful bacteria and decrease in pathogenic bacteria. It disturbs through several factors including unhealthy dietary patterns, chronic intake of antibiotics, chronic stress, ageing and different infections. Probiotics can help to gut health maintenance through releasing antimicrobial substances in the blood flow, protecting against harmful bacteria, preventing of attachment of pathogens to the gastrointestinal tract and improving the activity of brushborder enzymes[17]. Synbioticsare consisting of some probiotic bacteria accompanied with some prebiotic component as energy source for growing probiotics[18]. Synbiotic therapy also named as biotherapeutics. They areamong the new dietary strategies which many people are interested in learning the facts behind these health claims[7]. In order to FAO/WHO definition, probiotics are live bacteria which when administered in adequate amounts confer some health benefits on the host[19]. A prebiotic was defined as a none-digestible food ingredient that affects the health of gut by selectively stimulating the growth and/or activity of beneficial bacteria in the colon, and thus improves host health[20]. Therefore, considering the results of recent researches, treatment of obesity and its related complications like diabetes and metabolic syndrome with pre/pro/synbiotics can be considered as a safe, natural and cost-effective approach. This review have studied researches assessing the effects of these new therapeutic agents on anthropometric, metabolic and inflammatory markers and their association with prevention or treatment of obesity and its related disorders in human and animal studies.

Effects on weight and appetite

Probiotic bacteria can alter the gut environment, reduce adhesion and cellular invasion. They can also produce antibacterial substances (eg, bacteriocins, hydrogen peroxide, and organic acids). These substances are able to inhibition of pathogen's growth. New evidences introduce probiotics and prebiotics as weight manager via several mechanisms including improving microbial balance, increasing mucosal integrity, decreasing food appetite and decreasing abdominal adiposity[4,7]. The most common and researched probiotic species are belonged to the Lactobacillus and Bifidobacteriumphyla. Manipulation in gut microbiota through pre/pro/synbiotics yields encouraging results for the treatment of obesity and its related disorders like diabetes and NAFLD in animal and in vitro models, but data in humans are still scarce[21]. The effect of the probiotic bacteria on gut microbiota may be different in animals from humans, so it makes difficult comparing the findings on animal studies with the human results[22]. As mentioned before, probiotics are bacteria in some food ingredients that are beneficial to health. There are some possible anti-obesity effects of probiotics, although the underlying molecular mechanisms have not been shown yet[23-25]. Some recent investigations show that the number of Bacteroidetes are reduced in obese people, so that the Firmicutes /Bacteroidetes ratio is different in obese from lean human[26,27], although, the others showed no difference in this ratio between obese and normal weight people[28,29]. Interestingly, some authors have showed an increase in Bacteroidetes and decrease in Firmicutes after adherence to a low calorie diet. Kotzampassi and colleagues showed that Bacteroidetes constitute approximately 3% of the gut bacteria before a low calorie diet and it reaches to approximately 15% after successful weight loss[8]. The similar result has been found after gastric bypass surgery procedure[28,30,31]. Changes in the proportion of Firmicutes and Bacteridetes bacteria lead to change in food energy extraction capacity of microbiota. It means that the increase in Firmicutes bacteria seen in the obese people, increases the fucnction of food energy extraction and lead to less energy wasting in stool[31]. Furthermore, Pil and colleagues suggested that obese mice have a higher proportion of Firmicutes. They also showed that obese mice can extract calories from their diet more efficiently than lean mice, which had a higher percentage of Bacteroidetes[32].

Kadooka and colleagues conducted a multicenter, double-blind, randomized, placebo-controlled intervention trial on 87 Subjects with high body mass index and abdominal visceral fat area (81.2-178.5 cm^2. They were randomly assigned to receive either fermented milk (FM) containing Lactobacillus gasseri SBT2055 (LG2055) (active FM; n=43) or FM without LG2055 (control FM; n=44), and were asked to consume 200 g/day of FM for 12 weeks. Body weight and other measures decreased significantly ($P<0.001$) as follows: body weight, 1.4% (-1.1 (-1.5, -0.7) kg); BMI, 1.5% (-0.4 (-0.5, -0.2) kg/m(2)); waist, 1.8% (-1.7 (-2.1, -1.4) cm); hip, 1.5% (-1.5 (-1.8, -1.1) cm). In the control group, by contrast, none of these parameters decreased significantly. In this study the probiotic LG2055 showed lowering effects on abdominal adiposity, body weight and other measures, suggesting its beneficial influence on metabolic disorders[24]. In the other study conducted by Parnell and colleagues, oligofructose supplementation (21g/day) comparing with maltodextrin as placebo for 12 weeks lead to decrease in calorie intake, weight loss and improvement in glucose modulation through anorexigenic hormones alteration[33]. It seems that microbiota modification lead to decrease in fat accumulation and weight through increase in expression and function of lipoprotein lipase inhibitor factor. This factor is one of the members of angiopoetin like proteins family that expressin epithelial differentiated cells, liver and adipose tissues[34-36].

Angiopoietin-like 4 (ANGPTL4) is a circulating lipoprotein lipase (LPL) inhibitor that controls triglyceride deposition into adipocytes and has been reported to be regulated by

gut microbes[23]. According to animal studies, selective growth of lactobacillus in colon, lead to reduction of fat mass, through upregulation of Fiaf gene and inhibition of LPL[23,37]. On the other hand, short chain fatty acids (SCFAs) such as propionate and acetate, as fermentation products, are ligands for G protein receptors (Gpr43, Gpr41), and can act as molecular signal[31]. Therefore, changes in activation of these receptors may be considered as a treatment approach[8]. It should be noted that G protein receptors, are expressed in many gut cells and can stimulate secretion of some hormones involved in regulation of energy intake and consumption. When these SCFAs attached to G41, the secretion of PYY and GLP-1 increases and in turn, lead to satiety feeling, delay in gastric depletion and increase in insulin sensitivity[38]. In summary, there are some probable mechanisms in the field of the effects of pre/probiotics on improvement in anthropometric measures, including improve in balance of gut microbiota, decrease in appetite, increase in integration of gut barrier and decrease in inflammatory tone[7]. This has been shown in our previous studies. We found a significant decrease in the mean of anthropometric measurements after 12 weeks supplementation with synbiotic containing 7 strains probiotic bacteria (including *Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus acidophilus, Bifidobacteriumbreve, Bifidobacteriumlongum, Streptococcus thermophiles*) plus Fructo-oligosaccharide as source of prebiotic (TVC: 2×10^8 CFU), twice a day accompanied with a diet adjusting for required calorie for each person (P=0.001). Although we found this reduction in both intervention and placebo groups, the mean changes of antropometric variables including weight, waist circumference, hip circumference, in synbiotic group were significantly more than control group (P=0.001). Interestingly, we found that in synbiotic group, GLP-1 and PYY are increased at the end of the study comparing with the beginning of it (P=0.008 and 0.05, respectively). Moreover, the mean change of GLP-1 in synbiotic group was higher than in placebo group (P= 0.03)[39-42].

Different studies according to metagenomics and biologic approaches have shown that obese people gut microbiota has lower taxonomic diversity than non-obese people; however, controversy in this field may be for the reason of different age, clinical characteristics, obesity degree, diet, sample size and methodology in different studies. Furthermore, different strain of bacteria may play role in this controversy[43]. For example, Indias, et el. showed that lactobacillus plantarum and paracasei are accompanied with weight loss, while lactobacillus Ruteri is related to weight gain[44]. Of anti-obesity mechanisms of lactobacillus are regulation of glucose and lipid metabolism, decrease in adiposity size and regulation of leptin[24,45]. On the other hand, it seems that anti-obesity effects of probiotic, are mostly related to increase in gene expression involved in metabolism and oxidation of fatty acids, instead of decrease in their synthesis[46].

Table 1: Human Clinical trials to assess the effects of pre/pro/symbiotic on anthropometric measurements, metabolic and inflammatory biomarkers and gut hormones

Author, year	Subject	intervention	Variables studied	Significant findings
Hekmatdoost, 2017	50 patients with NAFLD	Symbiotic capsules for 28 weeks, twice a day	Metabolic profile,hepaticsteatosis and fibrosis	-Decrease in FBS most of inflammatory biomarkers
Rabiei, 2015	46 MetS patients	Symbiotic capsules accompanied with a diet adjusted for BMI, for 12 weeks, twice a day	Anthropometric measurements, body composition, BP, metabolic profile, he-CRP, insulin resistance, HOMA-IR, PYY, GLP-1	-Increase in FBS, insulin resistance, HOMA-IR, GLP-1, PYY -Decrease in anthropometric measurements and BP -Decrease in hs-CRP but not significant
Hulstone, 2015	17 healthy men and women	Probiotic milk for 4 weeks twice a day, following with a high fat and high calorie diet for 7 days	Insulin resistance	-No changes in body weight and insulin sensitivity -Increase in FBS
Ostadrahimi, 2015	60 diabetic patients	600 ml Probiotic milk for 8 weeks	FBS, HbA1c	Decrease in FBS, HbA1c
Tajdadi-Ebrahimi, 2014	78 diabetic patients for 12 weeks	Symbiotic bread	Insulin resistance, inflammation	-Decrease in insulin resistance, HOMA-IR -No change on hs-CRP
Mahboobi, 2014	60 pre diabetic patients	Probiotic capsules (500 mg) for 8 weeks	Lipid profile, BP	-No changes in lipid profile -decrease in systolic BP (only before adjustment for confounders)
Asemi, 2014	62 diabetic patients	Synbiotic packages containing inulin, lactobacillus sporogenes for 6 weeks, 3 times a day	Metabolic profile, hs-CRP, oxidative stress	-Decrease in insulin and hs-CRP -Increase in total GSH -No changes in FBS and lipid profile
Hekmatdoost, 2014	38 Mets patients	Symbiotic capsules for 28 weeks, twice a day	FBS,insulin resistance	-Decrease in FBS and insulin resistance
Sharafedtinov, 2013	40 metabolic syndrome	Probiotic cheese accompanied with 1500 kcal diet for 3 weeks	BMI and blood pressure	Decrease in BMI and BP
Gobel, 2012	50 obese adolescents for 12 weeks	Probiotic capsules	MetS determinants and inflammatory biomarkers	-No change in anthropometric measurements, FBS, BP, Insulin, peptide C, CRP, IL-6, TNFα

MetS= metabolic syndrome, BP= blood pressure, FOS= fructooligosacharide, 2hPG= 2 hours postprandial glucose, GLP-1= glucagon like peptide-1, hs-CRP= high sensitive C reactive protein

Effects on glucose and insulin metabolism

There are some studies that suggest that pre/pro/synbioticshave influence on glucose and insulin plasma concentration. They may improve insulin resistance through effect on inflammation pathways[47], increase in pro-glucagon expression[48] and decrease in adiposity[49]. In some animal studies, probiotic consumption leads to improvement in insulin resistance through decrease in hs-CRP inflammatory response. Some of the involved mechanisms in pathophysiology of insulin resistance are as follows: disorder in translocation of GLUT-4 to cell membrane and decrease in glucose uptake in muscles, increase in liver production of glucose, consequently and disorder in function of beta cells leading to decrease in insulin secretion[50,51]. Increase in expression of GLUT4 in skeletal muscles lead to improvement in insulin resistance in obese and diabetic people. Kang, et al. suggested that probiotic may have an antidiabetic function via regulation of GLUT4 and insulin. They have showed that insulin level in probiotic consumers is significantly lower than control group[46], in agreement with our previous studies.We found that the levels of fasting blood glucose and insulin resistance improved significantlyafter 28 weeks of treatment with synbiotic capsules containing 200 million of seven strains of friendly bacteria plus fructooligosaccharide, twice a day[52]. We also found in another our study thatFBS, insulin and HOMA-IR are reduced at the end of the study (12 weeks) comparing with the beginning of it, only in synbiotic group (P=0.001)[40]. There are some studiesthatshowed that a high fat diet changes the gut microbiota and decreases Bifidobacterium. It associates with higher gut permeability and increase in plasma level of lipopolysaccharides. It calls metabolic endotoxemia[16,37]. Lipopolysaccharides lead to production of pro-inflammatory cytokines leading to insulin dysfunction through increase in serine phosphorylation of insulin receptors[53]. Intestinal epithelium, as a physical barrier, usually prevents lipopolysaccharides translocation into blood stream. In animal models with insulin resistance and diabetes type 2, the expression of proteins in tight junctions of epithelium, like ZO-1, is decreased and gut permeability is increased[54,55]. So, metabolic endotoxemia induced by lipopolysaccharides derived from microbiota, is associated with inflammation and insulin resistance[38]. In addition to these well-known mechanisms, changes in microbiotacomposition may play an important role. For example, there are changes in Firmicutes and Bacteridetes ratio as well as proteobacteria family in patients with diabetes type 2 comparing with healthy people[56]. Firmicutesphyla have more genes related to carbohydrate and fat metabolism than Bacteridetesphyla[57]. Some authors have suggested that a high fat diet is associated with increase in the ratio of some gram negative strains of Firmicutesphyla like Veillonella to gram positive bacteria phyla such as Bacteridetes[58]; while consumption of a prebiotic such as oligofructose as dietary fiber, decreases the ratio of gram negative to gram positive bacteria and endotoxemia in rats[59]. On the other hand, some studies on obese rats have showed that increase in bifidobacteria is accompanied with decrease in gut permeability[60]. Increase in bifidobacteria is positively related to improvement in inflammation and glucose intolerance and insulin secretion[59]. Furthermore, we should consider that probiotic bacteria, consume glucose as a primary energy source; so, they can affect serum glucose and insulin level through decrease in glucose absorption in blood stream. Probiotics can also decrease insulin resistance through decrease in inflammation signaling, upregulation of proglucagone and decrease in adiposity[47-49]. There are some other mechanisms for improvement in insulin resistance induced by probiotic consumption, including decrease in JNK (a regulatory kinase by TNF) and decrease in NF-kB binding to DNA. In some animal studies, probiotic consumption lead to improvement in insulin resistance through increase in Natural Killer T in liver cells[61].

On the other hand, propionate, one of the bacterial fermentation products, causesthe activation of GPR43 in adipocytes and decreases blood glucose[62]. Moreover, some animal studies show that butyrate, as the other products of bacterial fermentation, improves insulin resistance through upregulation of PPARγ expression that increases fatty acids oxidation in muscles[63]. Recently, it has been shown that activation of GPR41 by SCFAs like propionate and butyrate,improves glucose tolerance through induction of intestinal gluconeogenesis via brain-gut-circuit. Such that propionate injunction in portal vein, actives glucose-6-phosphatase in jejunum. It is a rate limiting enzyme in gluconeogenesis pathway[64]. Prebiotics can also decrease post absorption glucose and insulin secretion due to their low glycemic index. Decrease in insulin level leads to upregulation of insulin receptors and increase in tissues sensitivity to insulin through secondarymembrane signaling[65]. Furthermore, SCFAs lead to improvement in liver sensitivity to insulin[66]. Therefore, prebiotics play an important role in reduction of after meal hyperglycemia risk[67]. Sharafedtinov, et al. showed that following a low calorie diet plus probiotic supplemention for 3 weeks, is associated with 18% reduction in blood glucose, both in intervention and control groups. Since thiseffect occurred in both groups, the authors considered the role of a low calorie diet plus probiotic supplementation in reduction of blood glucose[68]. It is partly similar to our previous study. We assessed the effects of synbiotic supplementation plus a weight loss diet in patients with metabolic syndrome. In the beginning of the study, the mean of serum glucose was higher than 126 mg/dl, which is categorized as diabetes. We found a significant decrease in blood glucose at the end of study (after 3 months), however, it was still in the diabetic range (the mean change between end and beginning of the study: -11.65 ± 5.4 in synbiotic group and 13 ± 8.4 in placebo group).We assumed that continue to consume synbiotic supplements more than 3 months, might lead to more decrease in glucose level, until lower than diabetic range[40]. Our study also showed that when a weight-loss diet is accompanied with synbiotic supplementation, the decreases in FBS, insulin, and HOMA-IR will be signifcantly more than when a weight-loss diet is used alone. According to results of a meta-analysis including 26 randomized controlled trials conducted between January 2000 and September 2013, involving 831participants, prebiotic supplementation was associated with reduction in postprandial glucose (–0.76, 95% CI [–1.41, –0.12]) and insulin concentrations (–0.77, 95% CI [–1.50, –0.04]). It also may improve insulin resistance due to increase in hepatic natural killer T cells and reduction in the inflammatory response[25,39,40]. So the beneficial effects of probiotic bacteria on insulin concentration might be mediated through their effect on a surrogate measure of inflammation, high-sensitivity C-reactive protein (hs-CRP)[47]. Some reports have shown that insulin resistance and increased CRP concentrations are significantly associated with several car-

diovascular risk factors, such as hypertension, dyslipidemia, and overweight, which are determinants of metabolic syndrome[61]. So, pre/pro/synbiotic supplementation may be as a potential candidate to treat several important metabolic disorders.

Table 2: Animal studies to assess the effects of pre/pro/symbiotic on anthropometric measurements, metabolic and inflammatory biomarkers and gut hormones

Author, year	Subject	intervention	Variables studied	Significant findings
Bomhof, 2014	Obese rats	FOS with and without probiotic bacteria for 8 weeks	Metabolic profile, weight, GLP-1	-Decrease in energy intake, weight, insulin and fat mass and increase in GLP-1 in FOS group -Decrease in FBS in FOS with probiotic group
Frossten, 2013	Wistar rats	Fermented milk including Lactobacillus strains	PYY	Increase in PYY
Omidi, 2011	Diabetic rats	Carrots juice inducted with Lactobacillus acidophilus for 14 days	FBS	-Decrease in FBS

Effects on Inflammation

hs-CRP is one of the inflammatory biomarkers related to cardiovascular disease and diabetes; such that considering it in the protocol of metabolic syndrome screening is suggested. hs-CRP level is categorized as below[69]:

Lower than 1 mg/l: low risk; 1-3 mg/l: moderate risk; 3mg/l or higher: high risk. Generally, hs-CRP and IL-6 serum level in patients with metabolic syndrome and diabetes is higher than healthy people[70]. In order to the report of Third National Health and Nutrition Examination, the level of hs-CRP in overweight and obese people is higher than people with normal body mass index[71-73]. It occurs due to increase in cytokines like IL-6 and TNF-α that are expressed in adipose tissues. They are of the main regulators of CRP production in the liver[73,74]. When hypertrophy of adipocytes occurs in response to excess energy intake, production of TNF-α increases in adipose tissues and it leads to stimulation of chemotactic factors and consequently, production of pro-inflammatory macrophages in adipose tissues and increase in production of IL-1 and IL-6[44]. These inflammatory factors are upregulated in insulin target tissues including liver, adipose and muscles and play an important role in insulin resistance[75]. Changes in gut microbiota and thigh junctions of epithelium cells occurring in diabetes type 2, lead to activation of insulin receptors via some gut bacteria and consequently, creation of inflammatory response inducing serine phosphorylation of these receptors and finally, decrease in insulin sensitivity[76]. Microbiota has influence on expression of genes involved in immune system. Disorders in microbiota lead to production of pro-inflammatory molecules and increases macrophages accumulation and inflammation in adipose tissues through TLRs signaling. TLRs are of essential parts of immune system that are expressed by macrophages and epithelial cells. Activation of TLRs in macrophages can significantly disturb glucose homeostasis[15]. Activation of TLR-4 in beta cells may lead to increase in production of pro-inflammatory cytokines both in macrophages and beta cells and disrupt function of beta cells[77]. On the other word, activation of TLR-4 directly lead to decrease in expression and secretion of insulin[78]. On the other hand, as it mentioned before, lipopolysaccharides play an important role in development of inflammation in metabolic syndrome. It creates metabolic disorders induced by low-grade inflammation including insulin resistance, diabetes, obesity, steatosis and oxidative stress. Furthermore, increase in epithelial permeability lead to translocation of bacterial antigens such as lipopolysaccharides into other tissues and blood stream. It in turn leads tochronic systemic inflammation. Lipopolysaccharides in blood stream can cause secretion of pro-inflammatory cytokines via macrophages and B- lymphocytes[14,15]. Lipopolysaccharides can also cause the up regulation of nuclear factor NF-κB and active the pathways mediated by MAPK in adipocytes[78]. They are also strong activators of immune system in mammals. The interactions between these substances and immune cells lead to excess production of reactive oxygen species (ROS), secretion of pro-inflammatory cytokines, weight gain and insulin resistance[79]. Lipopolysaccharides binding proteins initiate monomerization of lipopolysaccharides and create immune response. So, they make a link between inflammatory processes and antigens induced intestine. These inflammatory processes are recognized by plasma level of CRP[76]. Attachment of lipopolysaccharides to TLR-4 creates a cascade signaling that codes pro-inflammatory molecules. Free fatty acids that usually increase as weight increases, active TLR-4 signaling in adipocytes and macrophages, inflammation and insulin resistance[8]. We should note that fat has the most ability for translocation of lipopolysaccharides from gut into blood stream[80]. So, as we mentioned before, a high fat diet increases level of lipopolysaccharides. It also increases gut permeability and induces inflammatory signaling via NF-κB, increase in expression of TNF-α and IL-6[81].

On the other hand, AGEs produces in body as productions of normal metabolism, but their level increase in people with chronic high blood glucose, like uncontrolled diabetes[82]. AGEs also increases in metabolic syndrome that is accompanied with oxidative stress[83]. Excess and uncontrolled production of ROS leads to stop glycosylation and produce dicarbonylwhich is necessary for formation of AGEs[84]. Attachment of AGEs to their receptors targets some cascade pathogenic mediators. When AGEs bind to their special receptors, RAGEs, the activity of NF-κB increases and in turn, leads to upregulation of some chemokines like MCP-1 and profibrogenic mediators like TGFβ, in addition to pro-inflammatory cytokines involving in thrombogenesis, vascular inflammation and angiogenesis. Recently it has been shown that AGEs are associated with insulin resistance and can induce low-grade inflammation and dysfunction of beta cells[85]. It seems that AGEs are indigestible by gut enzymes. So, they enter to colon and act as growth factor for harmful bacteria such as clostridiums and bacteriods[86]. In the contrary, supplementation with prebiotics like fructooligosacharides and inulin changes the microbiota composition in favor of selective proliferation of beneficial bacteria producing lactic acid such as Bifidobacterium and lactobacillus. It leads to

decrease in production of ROS and inflammatory markers[9]. Microbiota alteration through prebiotic supplementation decreases AGEs accumulation via different mechanisms, including maintenance of gut barrier function, decrease in oxidative stress, and increase in antioxidant capacity and decrease in hyperglycemia. Prebiotics finally lead to decrease inflammation and insulin resistance[79]. The beneficial effects of microbiota are related to content and activity of SCFAs. Especially, propionate and butyrate have some effects on decrease in inflammation, regulation of proliferation, cell differentiation and hormonal secretions[87]. SCFAs probably show their anti-inflammatory effects through creation of balance between suppression of inflammatory mediators and induction of anti-inflammatory cytokines[78]. Increase in pro-inflammatory cytokines and ROS that are frequently seen in pre-diabetic patients, increase the tightness of intra cellular junctions, destroy the mucosal integrity and increase absorption of large and harmful substances. The changes in microbiota induced by prebiotics, increase endogenous production of GLP-2 which in turn, improve function of gut barrier through increase proliferation of crypt cells[54,88]. Furthermore, prebiotic fermentation products (SCFAs) can decrease gut permeability and decrease exogenous AGEs' absorption[88]. So that SCFAs enter to host blood flow and effect on expression of some genes related to proliferation, differentiation and apoptosis. SCFAs are ligands of G protein receptors in immune cells. These receptors are responsible for down-regulation of pro-inflammatory cytokines, chemokines and ROS produced by immune system[89]. Acetate, propionate and butyrate show their anti- inflammatory effects through suppression of NF-κB, prevention of TNF-α production and suppression of cytokines production[90]. Acetate and butyrate are also involved in epithelial integrity maintenance. Acetate increases colon blood flow and butyrate is the main source of energy forcolonocytes and decreases gut permeability. Furthermore, butyrate increases the expression of genes related to mucin formation that is an important factor for epithelial integrity[91]. It is also inhibitor of histone deacetylase enzyme, so it increases transcription of proteins in thigh junctions, probably[54]. Butyrate is effective on reduction of inflammation, carcinogenesis and oxidative stress[92]. The other mechanism by which SCFAs can act as anti-inflammation factors is down-regulation of adhesion molecules in endothelial cells that leads to suppression of leucocytes migration to inflammatory sites[93]. SCFAs can decrease infiltration of immune cells to adipose tissues through prevention of adhesion and inflammatory cells chemotaxis[94]. It is worth mentioning that hyperglycemia is usually accompanied with oxidative stress. The relative mechanisms to increase in oxidative stress in diabetic patients, are not only included increase in non-enzymatic and auto oxidative glycosylation, but also decrease in antioxidant defense potential[19]. Some clinical trials have shown that prebiotic supplementation can successfully decrease lipopolysaccharides level, markers of lipid peroxidation and production of Ages' precursors, consequently. Pre/probiotics show these beneficial effects through reduction of ROS production and anti-oxidative potential of Bifidobacterium and lactobacillus[95,96].Some species of lactobacillus and Bifidobacterium are effective scavengers for malondialdehyde, i.e. production of lipid peroxidation. So they protect body against excess accumulation of these toxic precursors of AGEs[95]. Moreover, inulin can show the antioxidant activity through its ability to break some linkages in ROSs[97]. Butyrate can also lead to increase production of glutathione. Glutathione is a necessary antioxidant for activation of glyoxalase-1. It is needed to destroy one of the Ages' precursors named methyl glyoxyl. Increase in ROSs leads to depletion of glutathione storages. Prebiotics are involved in upregulation of glyoxalase pathway through reduction of oxidative stress[62]. Totally, many studies have shown that pre/pro/synbiotics decrease inflammatory and immune response and increase insulin sensitivity[76]. In our previous study, hs-CRP level in all participants was in high risk category in the beginning of the study. At the end of the study,it still remained in that category in the placebo group, while it went to moderate risk category in the intervention group who consumed synbiotic for 3 months, although this reduction was not statistically significant but it was important clinically[40]. Our finding is partly consistent with Mazloom, et al. They have showed that probiotic supplementation in diabetic patients is associated to insignificant decrease in hs-CRP and IL-6[19]. In the other our previous study conducted on 52 patients with NAFLD, 28 weeks supplementation with synbiotic(including Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus acidophilus, Bifidobacteriumbreve, Bifidobacteriumlongum, Streptococcus thermophiles, Fructooligosaccharide) comparing with placebo lead to improvement in inflammatory biomarkers as follow: hs-CRP [-2.3 (-3, -1.5) compared with -1.04 (-1.5, -0.6) mmol/L; $P < 0.05$], YNF-α [-1.4 (-1.7, -1.1) compared with -0.59 (-0.8, -0.3) mmol/L; $P < 0.001$], NF κ-B p65 [-0.016 (-0.022, -0.011) compared with 0.001 (-0.004, -0.007) mmol/L; $P < 0.001$]. Generally we showed the beneficial effects of synbiotic supplementation on the main features of NAFLD, partially through reduction in inflammatory markers. These findings show a potential tripartite relation between the gut, diet, and the liver[98,41].

Despite the mentioned mechanisms about the effects of pre/pro/synbiotics on reduction of inflammatory markers, several studies found different results. For example, Kelishadi, et al. have showed that synbiotic supplementation in obese children is associated with significant decrease in TNF-α and IL-6 but only before adjusting for BMI. It shows that the effect of synbiotic on inflammation is depend on weight loss[99]. Tajadadi-Ebrahimi have showed synbiotic bread consumption containing lactobacillus sporogenes (1× 108 CFU) and inulin does not have any effect on hs-CRP in diabetic patients[100]. In the study conducted by Gobel, et al. probiotic consumption for 12 weeks in adolescents with metabolic syndrome did not have any effect on hs-CRP and IL-6, too[101]. Despite these studies, Zarrati, et al.[102] and Rajkumar, et al[103] have showed that probiotic yogurt in healthy people is associated with decrease in hs-CRP. Moreover, Asemi, et al. showed that synbiotic supplementation for 8 weeks in diabetic patients decreases these inflammatory factors[104]. Duration of intervention, clinical characteristics of participants, type of supplement, dose of supplementation and sample size in different studies may partly explain these inconsistent findings. Furthermore, in most of the studies, including our studies, situations including occurrence of different diseases like a cold or other diseases leading to inflammation and exposure to stressful situations during the study did not considered, although the same situations can affect inflammatory markers. Therefore, it is recommended that for the future studies to consider these situations. Furthermore, due to the antioxidant effects of vitamin A,

E, C and their beneficial effects on immune system, assessing the intake of these vitamins is suggested in the future clinical trials, since these vitamins prevent oxidative changes induced by ROSs and other free radicals. So, they may be as confounder factors when we are assessing the effects of pre/pro/synbiotics on inflammation[105].

Conclusion

Generally, there are many studies reveal that the gut microbiota may have specific functions in the body weight, metabolism and hormonal and immune systems. On the other words, gut microbiota is associated with obesity and related disorders. So, the advance in the field of gut manipulating could be valuable to improve therapeutic strategies to manage obesity and its associated metabolic disorders. Making the balance in gut microbiota through pre/pro/synbiotic supplementation, might have beneficial effects on reduction of fat storages, secretion of satiety peptides, and decrease in body weight, improvement in glucose and insulin metabolism and reduction in inflammatory biomarkers. This finding provides new opportunities to design improved dietary intervention strategies to prevent or treatment of obesity and its associated disorders, especially diabetes and metabolic syndrome.

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