Accepted Manuscript

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Please cite this article as: Mazidi M, Rezaie P, Kengne AP, Mobarhan MG, Ferns GA, **Gut microbiome and Metabolic Syndrome**, *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* (2016), http://dx.doi.org/10.1016/j.dsx.2016.01.024

Gut microbiome and Metabolic Syndrome

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Abstract

The gut microbiome contributes approximately two kilograms of the whole body weight, and recent studies suggest that gut microbiota has a profound effect on human metabolism, potentially contributing to several features of the metabolic syndrome. Metabolic syndrome is defined by a clustering of metabolic disorders that include central adiposity with visceral fat accumulation, dyslipidemia, insulin resistance, dysglycaemia and non-optimal blood pressure levels. Metabolic syndrome is associated with an increased risk of cardiovascular diseases and type 2 diabetes. It is estimated that around 20-25 percent of the world's adult population has metabolic syndrome. In this manuscript, we have reviewed the existing data linking gut microbiome with metabolic syndrome. Existing evidence from studies both in animals and humans support a link between gut microbiome and various components of metabolic syndrome. Possible pathways include involvement with energy homeostasis and metabolic processes, modulation of inflammatory signaling pathways, interferences with the immune system, and interference with the renin-angiotensin system. Modification of gut microbiota via prebiotics, probiotics or other dietary interventions has provided evidence to support a possible beneficial effects of interventions targeting gut microbiota modulation to treat components or complications of metabolic syndrome.

Key words: metabolic syndrome, microbiome, human gut, diet

Introduction

Human gut microbiome

The human intestine contains approximately 100 trillion microorganisms comprising up to 1000 different species of bacteria, yeasts, and parasites [1, 2], weighting approximately two kilograms and carrying at least 100 times as many genes as the whole human genome [2]. This microbiological population renews itself every 3 days and has an active biomass similar to that of a major human organ [3]. The gut microbiota is essential for the intestinal growth and general health of the host [4-6]. Through competition for resources, established symbionts protect the host from colonization by potentially pathogenic microorganisms [4-7]. The gut microbiota makes otherwise inaccessible, nutrients available, and is intimately involved in mammalian's metabolism [4, 6, 7]. Experiments comparing conventional mice with germ-free mice colonized with human bowel flora indicate that the gut microbiota seems to be involved in the enterohepatic circulation of bile acids and lipid metabolism [7].

Gut colonization by micro-organisms occurs soon after delivery, particularly by facultative anaerobes and anaerobic microbiota. Bifidobacteria have been highlighted as important gut microbiota anaerobes for general health [8, 9]. Bifidobacteria ferment oligosaccharides, which are often liberated from more complex polysaccharides by Bacteroides, to produce short-chain fatty acids such as acetate and lactate, which in turn are converted into butyrate, a key source of energy for the colonic mucosa, by other dominant constituents of the gut microbiota [8-10]. Deviations in the initial establishment of the bifidobacteria gut microbiota has been associated with later development of immunological and inflammatory diseases, as well as obesity [11]. In general, it has been suggested that Gastro-intestinal microbiome may contribute to the etiology of cardiometabolic diseases, and that microbiome modulation has a potential importance in therapeutic interventions targeting metabolic syndrome and related components. In the current manuscript, we aimed to review existing literature on the associations between metabolic syndrome components and gut microbiome.

Metabolic syndrome – A brief overview

The first description of the features of metabolic syndrome was by Hermann Haller in 1977 [12] and Gerald Reaven first coined the term ''syndrome X'' in 1988, to characterize the constellation of cardiometabolic risk factors in the same individual [13]. Over time, several international bodies have used different combinations of cardiometabolic risk factors to define metabolic syndrome (MetS). These include the World Health Organization (WHO)

criteria in 1998 [14], the European Group for the study of Insulin Resistance (EGIR) criteria in 1999 [15], the American Association of Clinical Endocrinologists (AACE) criteria in 2003 [16], the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) criteria in 2001 [17], the American Heart association (AHA) criteria in 2004 [18], the International Diabetes Federation (IDF) criteria in 2005 [19], and the Joint Interim Statement (JIS) criteria in 2009 [20].

It is estimated that around 20-25 percent of the world's adult population has metabolic syndrome, and people with the condition are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome [21]. The prevalence of MetS has increased substantially in the last two decades particularly in countries where there has been an increase in calorie intake and decreasing levels of physical activity [22, 23]. Components of MetS including obesity, dyslipidemia, glucose intolerance and hypertension are associated with an increased risk for cardiovascular diseases and type 2 diabetes [24, 25].

Microbiome and Obesity

Obesity and its complications are increasing prevalent worldwide, and have become a major health problem [26]. In 2010 alone, excess weight was estimated to have caused 3.4 million deaths, 3.9% of years of life lost, and 3.8% of disability-adjusted life-years around the world [27]. The global population of obese and overweight individuals was estimated to be 2.1 billion in 2013, corresponding to a 2.4 folds increase from the 1980 figures [26]. Intestinal microbiota has been implicated in the development of some metabolic phenotypes such as obesity and insulin resistance [28-31]. Nowadays, considerable attention is been paid to the role of the gut microbiota in the host energy homeostasis and metabolic functions. It has been proposed that the gut microbiota is an important environmental factor involved in the regulation of body weight and energy homeostasis [32-37]. This "exteriorized organ" contributes to the homeostasis through various metabolic functions and different control pathways involved in the extraction of calories from ingested dietary substances and assists the storage these calories in host adipose tissue for future usage [38, 39].

Evidence from experimental animal studies

Evidence to support the role of the gut microbiota in energy homeostasis has been obtained from studies performed in mice lacking gut microbiota [40-42]. Bacteria-free, anexic or germ-

free mice have been reported to be 40% leaner (less body fat) than mice living with normal gut microbiota, although the latter consumed approximately 30% less chow than the axenic mice [43]. Moreover, when axenic mice were conventionalized with microbes collected from the cecum of lean mice, their body weight (total body fat mass) increased within two weeks unless food intake was reduced [43]. Studies in leptin gene deficient obese mouse model (ob/ob) have indicated that the firmicutes (60–80%) and bacteroidetes (20–40%) are the predominant bacterial species in the gut microbiota [44-47]. Furthermore, studies have suggested that these two species may contribute to obesity [37, 45, 46, 48]. Enzymes involved in the breakdown and digestion of dietary carbohydrates as well as in the pathways for starch, sucrose and galactose metabolism are enhanced in ob/ob mice with a firmicutes enriched microbiome [38, 44, 49]. However reports have not been entirely consistent. Some investigators have found that genetically obese (ob/ob) mice have lower Bacteroidetes/Firmicutes ratios compared with lean (ob/+ and +/+ wild-type) litter-mates (39, 40). The transplantation of gut microbiota from the obese (ob/ob) to germ-free mice conferred an obese phenotype; therefore, confirming the transmissibility of metabolic phenotypes [37, 50, 51].

Evidences from studies in human subjects

Several studies have investigated the possible role of gut microbiota in obesity and weight management in humans. Turnbaugh et al. have proposed that although the main reason for obesity is excess caloric intake compared with expenditure, there are differences between humans in energy homeostasis according to their gut microbial ecology [47]. Individuals with a gut microbiota more efficient in energy extraction from the diet, or who have an increased ability to promote adiposity because of changes in the expression of host genes and metabolism; may consequently be predisposed to obesity [47]. This hypothesis predicts that obese and lean individuals will have distinct microbiota, with measurable differences in their ability to extract energy from their diet and to store it in fat tissue [47]. Some published data are in support of this hypothesis [52-55]. Moreover, other studies have shown that microbial changes in the human gut are correlated with an increase in body weight and fat mass; leading to the suggestion of alteration in gut microbiota as a possible cause of obesity [35, 38, 56, 57]. Further investigations have shown that the gut microbiota can alter the expression of genes that influence fatty acid oxidation and fat deposition in adipocytes. For instance, production of the lipoprotein lipase inhibitor angipoietin-like protein 4 (Angptl4) which is also recognized as fasting-induced adipose factor [58], is inhibited by the normal constituents of human gut microbiome. Investigations in germ-free and conventionalized wild-type and

Angptl4−/− animals have shown that microbiota-mediated inhibition of gut epithelial expression of this LPL suppressor induces augmented LPL activity and fat storage in white adipose tissue [7, 59, 60].

Microbiota alteration by dietary interventions

Because of the potential effects of gut microbiome on human metabolism and especially on weight modulation, there has been increasing attention on microbiota alteration by dietary interventions [61, 62]. Nowadays, pro- and prebiotics are widely used in order to alter and modify gut microbiota especially in children because of the growing prevalence of obesity and diabetes [63-65]. A probiotic is described typically as a microbial dietary supplement that positively affects the host through its impacts in the intestinal tract [66, 67] and prebiotics are typically non-digestible fiber compounds that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth and/or activity of gut microbiota that colonizes the large intestine by acting as substrate for them [68, 69]. The main probiotic bacteria related to dairy products are *Lactobacillus acidophilus, Lactobacillus casei,* and bifidobacteria [70, 71]. Changes in gut microbiota diversity and composition, for example changes in abundance at the level of phyla, genus or species are associated with the pathogenesis of obesity [29, 72]. Specific phyla, classes or species of bacteria, or bacterial metabolic activities in the form of pre- and probiotic supplements could be beneficial to patients with obesity [63, 65, 73]. Therefore, microbiota alteration by using pro- and prebiotic dietary supplements is a potential nutritional target in the management of obesity and obesity-related disorders.

Gut microbiota therefore play a significant role in host energy homeostasis and metabolism, and it is possible that some of the metabolic-related disorders including obesity may be treated by useful alteration of human microbiome through pharmaceutical or dietary interventions including the use pro- and prebiotic supplements. However, more comprehensive studies are required in order to confirm the association between obesity and human gut microbiota.

Microbiome and dysglycaemia

Dysglycemias which comprise diabetes mellitus, impaired fasting glycaemia and impaired glucose tolerance are increasingly common worldwide, where they contribute a significant proportion of the global deaths. According to the International Diabetes Federation's estimates, about 382 million people around the world had diabetes in 2013, and this figure

was expected to increase by 55% to 592 million by 2035 [74]. There is increasing evidence that the gut microbiota plays a significant role in glucose hemostasis, the development of impaired fasting glucose, type 2 diabetes and insulin resistance [48, 54, 65, 75].

Evidence from experimental animal studies

Lessons from animal studies suggest that impaired glucose metabolism and metabolic disorders including diabetes and obesity are associated with variations in the composition and metabolic function of gut microbiota. Zhou et al. studied the effects of microbiome alteration on insulin resistance and dyslipidemia in mice [76]. Five-week-old male C57BL/6J mice were fed with whole grain oats flour for 8 weeks. They found that Prevotellaceae, Lactobacillaceae, and Alcaligenaceae families of bacteria were increased in the gut microbiota and insulin sensitivity and glucose level were improved. Anhê et al. conducted an investigation to study the protective effects of increased *Akkermansia sp*. Population in the gut microbiota of mice from obesity, insulin resistance and intestinal inflammation through feeding with polyphenol-rich cranberry extracts [77]. Their results indicated that cranberry extracts administration improved insulin sensitivity, as revealed by improved insulin tolerance and decreased glucose-induced hyperinsulinaemia during an oral glucose tolerance test. Cranberry extracts are very rich in polyphenols, especially phenolic acids, flavan-3-ols (eg, catechin, epicatechin) and PAC (proanthocyanidins) [77-79]. It has been shown that these molecules have antibacterial activity and can potentially alter the gut microbiota of obese mice [77, 78, 80]. Although the mechanism of effect of cranberry extracts on the gut microbiota is still unclear, one theory is that phenolic phytochemicals of cranberry extracts decrease the abundance of the species controlling Akkermansia population; therefore increasing the proportion of this specific microbiome [77, 81]. In addition, another theory is that PAC content of cranberry extracts influences the production of mucin and provides enough trophic resources for Akkermansia to thrive [82]. Increased intestinal population of the *Akkermansia sp*. has been associated with protection from the features of metabolic syndrome including insulin resistance [83, 84]. Kang et al. carried out a study to investigate the effects of lactobacillus gasseri BNR17 in high-sucrose diet-Induced obese mice on body weight and insulin levels [85]. In this study, C57BL/6J mice received a diet containing L. gasseri BNR17 for 10 weeks. Their results revealed that the expression of GLUT4 mRNA, an important glucose transporter molecule, was increased in BNR17-fed groups. L. gasseri BNR17, and levels of leptin and insulin in serum decreased. Lactobacillus species have been shown that increase the expression of GLUT4 mRNA through PPAR activation [64, 85]. Other

experimental studies have suggested a probable modulatory role of the microbiome in the control and management of diabetes and insulin resistance [86-88].

Evidences from studies in human subjects

Promising outcomes of experimental animal studies have motivated studies in human studies to investigate the possible role of gut microbiome in development and management of diabetes. Vrieze et al. investigated the effects of infusing intestinal microbiota from lean donors to male recipients with metabolic syndrome on the recipients' microbiota composition and glucose metabolism [89]. Participants were divided randomly into groups that were given small intestinal infusions of microbiota. Results indicated that six weeks after infusion of microbiota from lean donors, an important alteration in intestinal microbiota composition in fecal samples was observed, including a 2.5-fold rise in the quantity of bacteria related to the butyrate producing *R intestinalis* [89, 90]. It has been proposed that butyrate produced in the large and small intestines has energy and signaling roles [91, 92]. Animal studies have shown that SCFA administration (butyrate, propionate, and acetate) in mice protects against diet-induced obesity and insulin resistance [75, 93].

Impact of Microbiota alteration by dietary intervention

Yadav et al. have reported that VSL#3 probiotic induced changes are associated with an increase in the levels of a short chain fatty acid (SCFA) and butyrate [94]. VSL#3 is a high-concentration probiotic preparation of eight live freeze-dried bacterial species that are normal constituents of the human gastrointestinal microbiota, containing four strains of lactobacilli (*Lactobacillus casei, L. plantarum, L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus*), three strains of bifidobacteria (*Bifidobacterium longum, B. breve* and *B. infantis*) and *Streptococcus salivarius* subsp. *Thermophilus* [95]. Moreover, they found that probiotics (similar to VSL#3) altered the gut flora composition; for example decreased firmicutes and increased bacteroidetes and bifidobacteria and caused an improvement in metabolic efficacy. In addition, the change in gut microbiota induced diverse production of SCFAs that in turn stimulate GLP-1 secretion from L-cells, a type of intestinal endocrine cells that is found primarily in the ileum and large intestine [96], to enhance metabolic health and improve insulin sensitivity and diabetes. Furthermore, it is recognized that the anti-inflammatory function of probiotics assists in treating low grade inflammation [97, 98]. Inflammation is associated with obesity, insulin resistance and diabetes [99, 100] and observed reduction in the inflammatory response can be attributed to probiotics in animal models [94].

There has been an increased interest for pro- and prebiotics and dietary interventions in the general public and in the medical community, due to their possible function in improving health condition, and mainly in prevention and treatment of diabetes [65, 101]. Results vary regarding the effects of probiotic consumption on insulin resistance and dysglycaemia. Some investigations have revealed positive effects of probiotics on prediabetes [102-104]; but other studies have reported negative or non-significant impacts of dietary interventions including pre- and probiotics on fasting blood glucose and insulin resistance [105-107]. It has been proposed that altered intestinal microbiota increases intestinal permeability and mucosal immune response, contributing to the development of type 2 diabetes and insulin resistance [57, 108]. Furthermore, it has been shown that modification of intestinal microbiota by probiotics may have a role in the maintenance of a healthier gut microbiota and could be a potential adjuvant in the treatment of insulin resistance and type 2 diabetes [65, 109]. Because of the positive findings in animal trials of probiotics for controlling fasting glucose and insulin resistance [110-112], there has been increasing interest in using probiotics in human studies. Patients with T2DM who consumed 300 g/d of probiotic yogurt containing *L. acidophilus* La5 and *Bifidobacteriumlactis* Bb12 for 6 weeks were found to have a remarkable reduction in fasting glycaemia and hemoglobin A1c [113]. Furthermore, consuming probiotic supplements inhibits mesenteric adipose tissue (MAT) inflammation and prevent high blood glucose levels and insulin resistance [114, 115].

In conclusion, many studies have shown a potential effect of intestinal microbiota composition on host metabolism as well as development of insulin resistance and diabetes. However more studies are still required to establish the mechanism by which gut microbiota controls these diseases.

Microbiome and lipid profile

There may be a role of human gut microbiome in modifying the lipid profile and therefore dietary modification of intestinal microbiota could be a therapeutic target alongside current pharmaceutical treatments for dyslipidemia [116, 117]. Dyslipidemia in individuals with metabolic syndrome may contribute to the increasing the risk of atherosclerosis and, by extension, the risk of cardiovascular disease [118, 119].

Evidences from experimental studies

It has been proposed that lipid metabolism by gut microbiota promotes atherosclerosis and cardiovascular diseases [120, 121]. Recent findings have shown that microbial metabolism of lipids in the gut yields products [choline, trimethylamine N-oxide (TMAO) and betaine] that promote atherosclerosis [120, 121]. Investigations using germ-free mice found a significant role

of dietary choline and gut microbiome in TMAO production from trimethylamine (TMA), increasing macrophage cholesterol accumulation and foam cell formation; consequently promoting atherosclerosis [120-122]. These investigations concluded that the production of TMAO from dietary phosphatidylcholine is dependent on the metabolism by the intestinal microbiota, in addition elevated TMAO levels are connected with an increased risk of occurrence of adverse cardiovascular events [120-122]. The source of TMA production through the gut microbiota seems to originate from L-Carnitine [123, 124]. Therefore, it has been shown that metabolism by intestinal microbiota of dietary L-Carnitine, a trimethylamine abundant in red meat, also produces TMAO and promotes atherosclerosis in mice [123, 124].

Modulating inflammatory signaling pathways and influencing host immune system by gut microbiota are other proposed mechanisms through which human intestinal microbiome promotes cardiovascular diseases [125-127]. Toll-like receptors (TLRs) are a family of integral membrane pattern-recognition receptors that have an important function in the innate immune system [128]. It has been found that deficiency in functional TLR4 and TLR5 respectively promotes and inhibits the development of features of MetS including dyslipidemia and glucose metabolism in mice [126, 129, 130]. The microbiota is a source of many other pro-inflammatory molecules including peptidoglycan, lipoproteins and flagellin that bind to TLRs [131]; in addition metabolic systems are closely interconnected with pathogen-sensing systems (e.g. TLRs), which interfere with insulin signaling [127]. Therefore, the gut microbiota may influence host metabolism by altering inflammatory signaling pathways [126, 127]. It is interesting that these deficiencies in TLRs are transmissible and it has been shown that transplantation of the microbiota from TLR5-deficient to germ-free mice leads to obesity and decreased insulin sensitivity [126, 132, 133].

Impact of microbiota alteration by dietary interventions

Because of the effects of gut microbiome on lipid profile and their potential role in promoting cardiovascular events, it has been proposed that manipulation of commensal microbial composition could be a novel therapeutic approach for the prevention and treatment of dyslipidemia and atherosclerosis. Hence, considerable attention is been paid to the alteration of human gut microbiome by pro- and prebiotics dietary supplements [134-136]. Cavallini et al. investigated the effects of probiotic soy product on fecal microbiota and its connection with cardiovascular risk factors in animal models [137]. Their findings indicated that consumption of the probiotic soy product was associated with a significant increase in the population of *Lactobacillus sp.*, *Bifidobacterium sp.* and *Enterococcus sp.* as well as a reduction in the

enterobacteria population. Moreover, it has been found that populations of *Enterococcus sp.*, *Lactobacillus sp.* and *Bifidobacterium sp.* were negatively associated with total cholesterol, non-HDL-cholesterol, autoantibodies against oxidized LDL (oxLDL Ab) and atherosclerotic lesion size. In addition, HDL-C levels were positively associated with *Lactobacillus sp.*, *Bifidobacterium sp.*, and *Enterococcus sp.* populations. Other studies have shown hypolipemiant and anti-atherogenic properties of soy in several animal models and clinical experiments [116, 138].

A study on the effects of probiotic yogurt supplementation containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* on lipid profile in individuals with type 2 diabetes mellitus [139], found non-significant variations from baseline for serum triglyceride and high-density lipoprotein cholesterol (HDL-C) in the probiotic group. Interestingly, investigators reported that the total cholesterol: HDL-C ratio and LDL-C: HDL-C ratio meaningfully declined in the probiotic group compared with the control group. Other studies in humans have confirmed the contribution of pro- and prebiotic dietary supplementation in the improvement of dyslipidemia and cardiovascular risk factors [102, 117, 140, 141]. The currently available literature suggests that oral probiotics have useful effects on total cholesterol and LDL cholesterol for subjects with high, borderline high and normal cholesterol levels [142-144].

Microbiome and blood pressure

High blood pressure is one of the key features of metabolic syndrome (5, 6). Hypertension is considered as one of the major risk factors for cardiovascular diseases in individuals with metabolic syndrome and in the general population [145, 146]. Some studies have indicated that the microbiome is involved in the regulation of blood pressure [147, 148]. Previous studies have shown that consumption of inorganic nitrate (found in high levels in leafy vegetables) in the diet increases plasma nitrite levels and decreases blood pressure [149, 150]. Results of a meta-analysis of 14 randomized placebo-controlled clinical trials indicated that probiotic fermented milk meaningfully decrease blood pressure in pre-hypertensive and hypertensive patients [149, 151]. It has been revealed that probiotics strains including Lactobacillus and Bifidobacterium produce peptides with ACE-inhibitory activity through the proteolysis and fermentation of milk proteins [149, 152, 153].

Generally, the regulation of blood pressure has been connected with the renin-angiotensin system (RAS) which involves angiotensin-converting enzyme (ACE) [148]. Accordingly, it has been stated that the proteinases from various probiotics during fermentation are capable of

releasing ACE inhibitory peptides and thus producing a blood-pressure lowering effect [152, 154]. Moreover, ACE-inhibitory peptides have also been found in yogurt, cheese and milk fermented with *L. casei* ssp. *rhamnosus*, *L. acidophilus* and bifidobacteria strains and it has been revealed that soy peptides with inhibitory activity against ACE could be produced by fermentation with probiotics [155-158]. Furthermore, the role of estrogen in positive control of hypertension is well recognized in both animal and human experimental studies [148, 159, 160]. Food-derived phytoestrogens which are enriched with probiotics to increase its influence and potency are natural substitute for estrogen [148, 160]. Considering the structural similarities between phytoestrogens and mammalian estrogens, soy isoflavanoids may interact with the estrogen activity pathways in the body and cause identical responses in vascular functions as estradiol [148, 161, 162]. It has been reported that gut microbiota or probiotics promptly hydrolyze the main isoflavonoid glucosides in legumes including genistein and daidzein, into bioactive aglycones [148, 159, 162]. Isoflavone aglycones are absorbed faster and in greater amounts. Therefore, another potential role of probiotics in positive control of hypertension should be considered.

Conclusion

Recent publications have shown an association between gut microbiome and components of metabolic syndrome. In addition, the benefits and therapeutic potentials of consuming pro- and prebiotics are supported by several investigations and these can possibly be used alongside pharmaceutical treatments in order to control some MetS-associated diseases including diabetes and CVD. However, more clinical studies are still needed to reach definitive conclusions on the potential applications of human gut microbiome in the treatment of the patients with MetS-associated diseases.

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