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Gut Microbiota and Metabolic Syndrome (Diabetes)

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Abstract

Role of Gut Microbiota (GM) in the emerging of Metabolic Syndrome (MS) related pathologies including type 2 diabetes mellitus, metabolism of lipids and carbohydrates or obesity have been discussed in recent years. The aim of this chapter is to review and explain the different aspects of the effects of changes in the microbial populations of gut in normal and disease states of human and animal studies. Results of recent studies indicates that many of MS related diseases arising from imbalances in the ratio of beneficial (probiotics bacteria) and detrimental microbial population in the gut. Anti-diabetic effects of known probiotics including *bifidobacterium* and *lactobacillus* have also been reviewed in this chapter. Finally challenges of previously known diabetes risk factors have been explained in the continuation of chapter based on the new facts in the literature. It seems that risk factors like obesity and aging are the results of imbalance in guts beneficial bacteria not as a risk factor for induction of diabetes. Certainly, with comprehensive studies in the future, the role of beneficial bacteria would be illustrated clearly in MS pathologies, which in turn could draw the definitive treatment strategies of diseases including diabetes.

Introduction

Metabolic syndrome and Type 2 Diabetes Mellitus (DM2) are globally pandemic diseases, which occurring with increasing prevalence in both developed and developing countries independent of a definitive relation with their known risk in different ethnicities. Although genetic makeup of humans are important, but environmental factors including socioeconomic situations, cultural and eating habits are considered as very important factors predisposing individuals to the so-called diseases. However, it seems like that the role of probiotics or beneficial GM are very critical than the known risk factors and should be highlighted by scientific societies and clinicians as inducers of MS and many of other pathologies [1]. So, DM2 is a critical worldwide public health challenge, and both of genetic and environmental factors have intervening roles in type 2 diabetes pathogenesis, and among environmental factors GM playing important role than other, because it can the potential of changing metabolism and biological functions of human bodies. In fact, correlations of GM and insulin resistance have been suggested in 2007, and it was found that high-fat diet increased some species of bacteria in gut which in turn increased lipopolysaccharide and inducing insulin resistance. In later studies it was found that the gut micro biome by some of metabolites affecting glucose hemostasis in our body. Very interestingly, probiotics using in a mouse model of diabetes prevented gluconeogenesis. In randomized controlled trials the potential benefits of probiotics have been showed in type 2 diabetic humans. In fact, DT2 is one of the complications of metabolic syndrome with characteristics of hyperglycemia and insulin resistance, which accompanies with metabolic disturbance of blood lipids. It affects very heavily economy and health of humans and families. Different impacts of probiotics on type 2 diabetes metabolic disturbances have been indicated in some studies [2]. However, in spite of recently discovered evidences on the emerging of MS related pathologies, currently, the risk factors like overweight and obesity are considered as the main causes of DM2 between majorities of societies. It is a fact that GM pattern is changing in DM2 patients in comparison with non-diabetics, and GM has nutritional, metabolic and immunological effects on humans [1]. In a study, important role of probiotics have been emphasized in intestinal immunes system modulations [3].

Modifications of GM composition and function in the gut have correlations with the increased risk of DM2 and higher number of Bacteroides and Clostridium. In fact, in the pathologic situations the increasing of Firmicutes/Bacteroidetes ratio in the colon, predisposes the humans to increased opportunistic pathogens, and production of endotoxins of gram-negative bacteria which in turn changing of intestinal permeability and other pathologic effects of MS including slight inflammation by Toll-like receptors and insulin resistance [1]. In relation of the effects of GM or probiotics on lipids, in fact, there are not many studies. However, there was not found any correlation between

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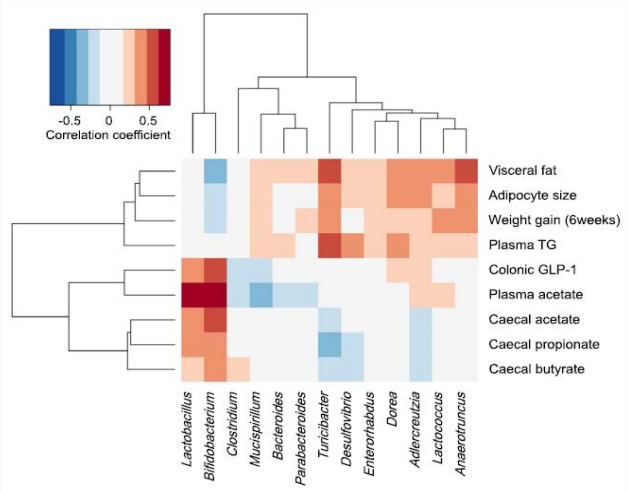

Figure 1: Correlation between the relative abundance of genera and metabolic parameters in mice. Pearson's correlation coefficients are represented by color ranging from blue (negative correlation, -1) to red (positive correlation, 1). Data on genus reads used for the analysis represented 73.7% of the total reads of microbiota.

probiotic consumptions and lipid metabolism improvements in a meta-analysis [2], but, in other studies the relation between probiotic supplementation and reduced total cholesterol and LDL-C level were reported meaningful [4,5].

Diabetes in the world and concept of contagiousness

It seems likely that different frequency of DM2 all over the world have suggesting a kind of contagiousness of diabetes in human populations. Comprehensive study of diabetes incidence in 23 EURODIAB centers of 19 Europe countries in two different periods (1989-1998 and 1999-2008) on 49969 registered new types of Type 1 diabetes in individuals under 15 years old indicated that 3.4% and 3.3% per annum the disease was increased, during 2 separate 10-year periods, respectively [6].

In fact, it can be concluded from this statistics that type 1 diabetes follows a steady state increasing in incidence which mainly unexplainable with genetic causes, and this means that may be environmental factors having a role in its emerging. In author's idea, increasing the incidence of apparently and traditionally accepted a genetically disease is thinkable from viewpoint of causes of disease, and it is logical that the diabetes could be as one of the non-infectious diseases resulting from microbial contacts of humans or other environmental conditions.

Non-uniformity of increasing rate of diabetes in Europe countries also indicate that the disease affecting by different risk factors which is cannot be understandable only by genetic background or apparently accepted risk factors [6]. The similar increasing rate for type 1 diabetes of less than 17 years olds was reported from United States [7]. In other study, it was reported that prevalence and incidence of both type 1 and type 2 diabetes among children and adolescents from 2001 to 2009 was increased in 5 different states of the United States. Researchers suggested that further studies need to be elucidating the causes of this increase [8].

Collectively, it seems like that the epidemicity of MS diseases including diabetes and hypercholesterolemia regardless of ethnicity, race, cultural or other demographics and unexpected incidence or major fluctuations of the so-called diseases all over the world only could be explainable by the contagiousness context of the role of probiotics in gut microbial population and life style.

Statistics of diabetes and challenges of risk factors

Statistics of 2018 showing that diabetes have been affected more than 425 million individuals globally [9-11] which accounts for 12% of health related costs in 2010. Diabetes epidemic is so that many of the countries cannot manage the disease. It is noteworthy that diabetes rate was increased from 1% in 1980 to 10% in 2008, and in urban areas of India reaches to 20% of population that is not explainable with known scientific basic and believes [10]. Type 1 and 2 diabetes are comprising around 10% and 90% of all diabetes cases, respectively [9,11]. Type 1diabetes (autoimmune reaction against insulin producing cells) is causing by combination of genetic and environmental factors, but type 2 is causing mainly by insulin resistance [9]. Frequency of 2 types of diabetes indicates that it is an emerging disease relating to life style, and many of the known risk factors accepted by scientists and clinicians haven't had sophisticated scientific and correct basics. For example, correlation of aging and diabetes apparently seems likely correct, but age itself isn't a direct risk factor of diabetes, because frequency of many of diseases are higher in aged groups and all ethnics which it is likely that originates from weak immune system in aged individuals. Or high prevalence of diabetes in obese individuals as a risk factor really haven't a factual basics, because not only there is not a comprehensive study on the comparison of the disease in lean and obese populations all over the world, but also recent studies indicate that diabetes is not rare in lean peoples in the United states with different ethnicities [12] and in comparison with western population, diabetes occurs in low obesity and Younger's of Asians [13] based on the International Diabetes Federation (IDF) reports in the 2010, the five countries of India, China, the United States, Russia and Brazil, and five others of Nauru, the United Arab Emirates, Saudi Arabia, Mauritius and Bahrain containing the highest counts and the highest prevalence of diabetes in the adult's population. Also in this report it has been emphasized that highest burden of diabetes were seen in low and middle income countries [11]. This point is contradictory to known facts on diabetes risk factors, because obesity is considered as important inducing factor of diabetes, and assuredly obesity cannot be seen in a poor community because of low income and in turn low food resources. It is clear that the frequency of disease in different countries was not explainable with known risk factors, so that, clearly brings accepted risk factors of diabetes including obesity into question that if they are really acting as risk factors? Or instead, scientific society should consider criteria including crudity, population's public health, and severity of microbial transmission between individuals in incidence of some diseases. On the other hand, is obesity itself acts as a direct inducer of diabetes? Or it changes our gut micro biome patters and in turn changing metabolic pathways?

Genetic background is other most accepted risk factor of diabetes, but any one cannot assure that with even both of parents with diabetes, children's get the disease, and *vice-versa*, in a family free of diabetes, we may witness diabetic children's. so that, based on the American Diabetes Association, in an identical twin with type 1 diabetes, the other twin will get the disease maximum to 50%, but in type 2 diabetes, the second twin may affected by diabetes up to 75%. So, it seems likely that the environmental factors including microbiota composition of individuals gut are very important than

Table 1: Influence of gut micro biome communities on health and disease of humans.

Health	Microbial Products or activities	Disease
Nutrition and energy supply	· SCFA production and vitamin synthesis • Energy supply, gut hormones, & Satiety • Lipopolysaccharides, inflammation	obesity & metabolic syndrome
cancer prevention	• Butyrate production, phytochemical release • Toxin and carcinogen inflammation • Mediates inflammation	Cancer promotion
pathogen inhibition	• SCFA production, intestinal pH, bacteriocins • competition for subtracts and/or binding sites • toxin production, tissue invasion, inflammation	pathogen invasion
GI immune function	• Balance of pro- and anti- inflammatory signals • Inflammation, immune disorders	IBD
Gut motility	Metabolites (SCFAs, gases) from non- digestible carbohydrates	IBS (constipation, diarrhea, bloating)
cardiovascular health	Lipid & cholesterol metabolism	cardiovascular disease

SCFA: Short-Chain-Fatty Acid; IDB: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome

genetic background in diabetes induction. Even exposure to some viruses also has been considered as inducing factors of type 1 diabetes [14]. In relation to diabetes risk factors there are many controversies in scientific literature, for example, in spite of claims of increasing obesity in developed countries as a risk of diseases including dyslipidemia, Cardiovascular Disease (CVD), or type 2 diabetes, [15-17] diabetes develops at younger ages and low body mass indexes of Asians than Caucasians, and recently detected genetic loci were reported insufficient to consider ethnic differences as a diabetes risk [10]. On the other hand there is not a clear-cut correlation between overweight population of the world with diabetes (it is estimated that obesity will be increased from 1.3 billion in 2005 to 2 billion in 2030), and in spite of low population with obesity in Asian countries, diabetes is increasing with developments and urbanization [13,18,19] independent of the obesity. Especially in India, obesity has reverse correlation with diabetes, because this country in spite of having low obesity contains high rate of diabetes [20]. This fact indicates that like other risk factors of diabetes, obesity is also having not a potent basic's as a risk factor, and many of them are very contradictory as etiologies for diabetes. Certainly, scientific and clinicians should change their traditional approaches on the routes of emerging of diseases like diabetes, and it was suggested that many of the diseases have microbial origins and doubtlessly it should be studied by researcher's.

So, bravely it can be said that many of the accepted risk factors of diabetes have not had very strong scientific basics, and in turn, medical science haven't had a consensus on the risk factors, prevention and treatment of diseases like diabetes.

Obesity is the result of diabetes and micro biome imbalance in gut, not the cause of diabetes

As stated in previous sections, obesity have been accepted as an approved risk factor for diseases like diabetes in scientific literature and clinical guideline's, but based on recent studies it is not clear that gut bacterial imbalances inducing obesity and diabetes, or *vice versa* actually obesity acts as a risk factor of diabetes. However, very interestingly prevalence and incidence of obesity similar to diabetes have been increased substantially in previous three decades, and both of them have not a definite consensus on treatments [21]. Epidemiological data have been suggested the potential environmental exposures, including diet, sleep deprivation, endocrine disruptors, chronic inflammation, and micro biome quality, as risk factors of obesity [22] which among them chronic inflammation is considered as very indexed known factor for induction of obesity and insulin resistance [23]. In fact, micro biome has discussed extensively as a critical factor of inducing obesity in last decade, so, variation in gut bacterial population probably acts as an important role in etiology of obesity similar to other metabolic syndrome related diseases including diabetes [21]. Low quality of microbiota in humans with obesity, insulin resistance and dyslipidemia was reported in some studies [24] although; there is not a standard consensus on microbiota diversity and counts in gastrointestinal tract for differentiating of healthy and pathologic situations. Anyway, prevalence of bacteroidetes in obese individuals is lower, and increasing with weight loss [25] on the other hand, *lactobacillus* species have indicated positive correlations with fasting glucose and HbA1c, whereas, *clostridium* species indicated negative effects on the so-called factors [26]. LPS (endotoxin) derived from bacterial envelope is suggested as one of critical molecules involving in hypertrophy of adipose tissues and developing obesity in humans [27]. On the other hand, animal experiments suggest that high concentrations of LPS in plasma of obese and type-2 diabetic mice could play a role in pathogenesis of insulin resistance [28].

This facts, shows that micro biome and microbial metabolites have very complicated interactions with metabolic related diseases, and of course the absolute treatment of diseases including diabetes, glucose resistance, and in turn many of cardiovascular pathologies would be passed from this channel in the future.

Based on Cani et al. [29] Studies, in both of diabetes and obesity as two important metabolic diseases insulin resistance and a low-grade inflammation having main etiologic roles, and importantly, bacterial Lipopolysaccharide (LPS) has been accused as a triggering factor of insulin resistance, obesity, and diabetes as an inflammatory agents. Two to three times increase in the amount of LPS have been shown after a 4 week high-fat diet, which have been called metabolic endotoxemia in these studies. More significantly, the so-called high-fat diet increased LPS-containing bacteria in the gut. In this study, adipose tissue weight gain was confirmed after both of natural endotoxemia by high-fat diet and continuous subcutaneous infusion of LPS in mice. Induction of liver depended insulin resistance in LPS infused group (metabolic endotoxemia) in a short course confirms the main role of environmental agents in appearance of metabolic syndromes including diabetes, obesity, and hyperlipidemia [29]. In addition, high-fat diet lowered bifidobacteria species in caecal contents of mice, and vice aversely restoration of bifidobacterium quantity was improved the mucosal barrier function and reduced endotoxemia in mice, which in turn, increased glucose tolerance, and glucose related insulin secretion, and normalized inflammatory cytokines [30]. In other study, it was indicated that LPS level in type1 and Type 2 diabetes patients have been raised to 235.7% and 66.4% of non-diabetics, respectively. Researchers finally have not discussed which of the diabetes or endotoxemia have been acting as starting factor for the others [31]. However, in a systematic review, with the

aim of studying therapeutic effects of probiotics on obesity it was reported that some strains of probiotics including *L. gasseri BNR17*, and *L. gasseri L66-5* have slightly reducing and increasing effects on body weight of humans, respectively. Applying *L. rhamnosus GGMCC* was accompanied with positive effect in weight loss in humans. The researchers concluded that some strains of bacterial species with probiotic properties can affect body weight in humans. So, probiotic stores would be imaginable in the future for treatment of many of microbial originating diseases. In this study, it was reported that application of different strains includes *L. plantarum LG42*, *L. gasseri SBT2055* and *L. plantarum* co-therapy with KY103 and *L. curvatus HY7601* had a weight losing effect in animal models [32]. Although, in other studies using animals it was demonstrated that probiotics decreasing blood glucose by intervening with inflammation and preventing pancreatic beta-cells from destruction [33].

Finally, these facts indicate that bacterial diversity and numbers in human gut including genus, and species or microbial metabolites releasing in the gut biosphere might have helpful or devastating to starting of obesity and other metabolic syndrome related diseases. And in fact, this is gut micro biome quality which predisposes humans to obesity not obesity really acts as a risk factor of diabetes.

Micro biome and human health

The impact of the human microbiota (micro biome, normal micro floor) on human health have been studied in different studies [34,35]. Microbial composition(microbiota, normal bacteria) of humans body are very diverse composing of mainly of bacteria and viruses playing important role in health and diseases which has been called in some studies as "forgotten organ"[34-36]. Normal bacteria having role in energy harvest and storage and some of metabolic functions such as fermenting and absorbing undigested carbohydrates [36]. Interactions of microbes with each other and host immune system determines the health or disease, and any kind of deviations from normal species (dysbiosis) could be expose humans to different diseases including immune system related disorders, such as allergies, obesity, inflammatory bowel disease, and Crohn's disease [34,36]. Micro biome could be temporarily changed in different body sites of humans and affected by different environmental factors in human's life style [34]. Normal microbes have colonizing in all surfaces and intestinal tract as fingerprint of special bacterial species, and in an individual's body are very different from each other, but microbial population in similar organs for example oral microbes in humans are very similar in comparison with other sites such as skin and mouth of an individual [37-40] and in each of ecologic sites there are many inter-individuals variations in normal bacterial species [41]. Micro biome variations in different sites or body surfaces with the purpose of their role in health or disease have been done in some intensive studies including Human Micro biome Project and Meta HIT [42-44]. Although, it seems that environmental factors playing main role in determining the microbial composition in human body [34], but in some studies it was showed that genetic makeup and some genetic loci also controlling microbial species colonization, and probably having putative pleiotropic impacts on groups of distantly related organisms [45,46] in relation to gut microbiota, three "enterotypes" patterns (Bacteroides, Prevotella, or Ruminococcus) has been suggested based on predominance of bacteria [47]. These patterns affecting by dietary behaviors of humans [48,49] which refers to the critical intricate role of micro biome in health of humans. In fact, determining normal microbial patterns of different ecological niches of body, and effects of environmental factors on it would be from critical discussions in the interpretation of the etiology of many of infectious and non-infectious disease in the future (Table 1). Shows some of the important diseases in which micro biome could have role as starter or accompanying risk factors. As it can be seen, many of the so-called pathologic situations are non-infectious.

Mechanisms of anti-diabetic effects of probiotics

In fact, mechanism of actions of probiotics on treatment of diabetes and other diseases is not clear. One of the anti-diabetic effects which have been proposed is lowering of oxidative stress in hyperglycemic individuals [50,51]. Antioxidant activities of some lactic acid bacteria including *L. acidophilus* and *L. casei* have been reported that effecting on the glucose intolerance, hyperglycemia, and hyper insulinemia by lowering oxidative stress in studied animal models [52-54]. Glucose metabolism is critically affected by immune system, and probiotics may be modulating immune responses and low-grade inflammations which have been seen in diabetics and obese individuals by lowering cytokines, and blocking the NF-κB pathway [55,56]. In this regard, decreasing of acute phase inflammatory factors such as hs-CRP, IL-6, and TNF-α after consumption of probiotics and in turn decreasing of glucose have been reported in some of studies [57-62]. In other studies, it has been indicated that endotoxin as an inducer of inflammation, systemic inflammation, insulin resistance, and hyperglycemia situations was decreased after probiotic consumptions [63-65]. Results of other studies demonstrate that short chain fatty acids, secondary bile acids, LPS, peptidoglycans, indole derivatives, and other bacterial molecules and metabolites have main role on the cells of protecting properties on intestinal microbial commensals and in turn on the metabolic diseases and other intestinal complications. In fact, metabolic diseases starting from the complicated interactions of gut microbiota with gut immune system. So, based on the hologenome theory in strategies for the purpose of glycemia prevention the gut microbial population and its effects on gut immune system should be regarded as critical factors [66].

Effects of diet on gut microbial population and human health

Distal gut is harboring the largest number of microbes in our body. And in a study it was showed that the fecal micro biota-pattern of 154 twins are very similar to their mothers, and in fact, family members have more similar patterns of gut microbial population than unrelated persons. In this study it was also revealed that microbial pattern of monozygotic and dizygotic twins are not very different because of different genetic backgrounds which indicating that environmental exposures are very important than genetic backgrounds in determining predominant bacterial species in gut. This microbial makeup in turn could affect metabolic potentials of individuals and activities including processing and digestion of polysaccharides [67]. More impact of environmental factors on gut microbial patters was also indicated in a study which researchers with transplanting human gut bacteria have produced an established bacterial gut floor in germ-free C57BL/6J mice models [68]. Application of Fecal transplantations have been showed that homeostasis after a bad long course diet-microbiota disorders could be restored which in turn indicates the therapeutic and beneficial importance of gut normal bacteria. So, it could be said that each of the humans harboring a special pattern of gut micriobiota based on life style and encountering's with agents that affecting bacterial population [69].

It is correct that diet doesn't have direct impact on diseases induction, instead could change our microbiota population and

in turn starting metabolic related diseases as indicated in different animal models [67,69]. For example, in the study of Chao et al. [70], an 8 week high-salt diet of C57BL/6J mice was resulted in increasing of *Firmicutes*/*Bacteroidetes* ratio with high frequency of genera *Lachnospiraceae* and *Ruminococcus*, but decreased the counts of *Lactobacillus*. Whereas, epidemiological facts indicate that salt consumption may increase non-infectious diseases including hypertension, stroke or heart related diseases. And in animal models it was indicated that high-salt diet could cause as an exacerbating factor for tissue inflammation and autoimmune diseases. Although, there is not many studies on the role of salt on gut microbiota, but in some cases effects of high-salt diet have been reported as a risk factor of colitis and changing gut microbial population. Even it was reported that high protein intake may be inducing the growth of *Clostridium perfringens*, and vice versa reducing probiotic *bifidobacteria* in feces [70].

Role of probiotic bacteria in MS (diabetes and insulin resistance)

The efficacy of probiotics including *bifidobacterium* and lactobacillus in improving of glucose and lipid metabolism (from distinctive characteristics of diabetes and other metabolic syndrome related diseases), insulin sensitivity, inflammation and endotoxemia have been proven by their ability to lower fasting glucose, insulin levels, and insulin resistance in preclinical settings as well as in human trials or animal models [71-77]. Probiotics similar to other bacteria entering to humans gut after delivering neonates, and reaching to adult's diversity in 2-3 years old. Because of high number and impacts of normal bacteria in human body, it was referred to as separate endocrine or forgotten organ [36].

Important role of micro biome on the metabolic pathways and diseases including diarrhea, bacterial vaginosis, autoimmune and allergies, irritable bowel, metabolic syndrome and diabetes have been discussed in different studies. In fact, changing life style and behavior's like antibiotics consumption, highly processed diets free of prebiotics and other foods or travel behaviors have changed our normal gut bacteria, which in turn resulting in pathologic situation called dysbiosis, and emerging of metabolic diseases including diabetes, obesity, and lipid related pathologies [71,72]. There is no doubt that gut microbial population and diversity is different in type-2 diabetic and non-diabetics [74], it is also indicated that dysbiosis of the microbial population of gut could increase the risk of insulin resistance and opportunistic pathogens, and decreasing butyrate producing bacteria, which in turn increasing the risk of type 2 diabetes [72,75,78]. In this regard, in a recently conducted RCT study, included patients were divided in two groups of (receiving multiprobiotic "Symbiter" containing of 14 probiotic bacteria genera *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Propionibacterium* or placebo) for a 8-week period. Results of study on Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), HbA1, and inflammatory markers of TNF-α and IL-1β showed that in probiotic treatment group the insulin resistance was improved in comparison with placebo [79].

In the study of Ryo et al. [76], anti-metabolic syndrome (anti-MS) effects of two different strains of *bifidobacterium* (*B. animalis ssp. lactis GCL2505*; BlaG, and *B. longum* ssp. Longum JCM1217; BloJ) were comparatively studied in experimental mice. BLaG, a fast growing strain in the gut has very positive effects on visceral fat accumulation and glucose tolerance, but BLoJ was reported affectless. In addition, BLaG increased acetate, glucan-like peptide-1, and SCFAs (short-chain fatty acids) levels in gut and plasma of animals. It was explained in this study that high level of acetate plays a main role in Anti-MS Activity of BLaG. So, it can be suggested that relation between MS and microbiota is very delicate that kinds of strains, speed of growth in gut, and their metabolites having role in control of gut functionality and metabolism, and in turn could have beneficial or devastating effects. Correlation between presence of different bacterial strains and their metabolites have been brought in (Figure 1) [76]. Although, in some of the studies it was not reported a positive correlation between probiotics and diabetes indexes [77]. on the other hand, improving effects of probiotic consumption on some characteristics of metabolic syndrome including Fasting Plasma Glucose (FPG), glycosylated Hemoglobin (HbA1c), HOMA-IR, and insulin concentration was assessed in a study. Researchers concluded that probiotic have a moderate effect on glucose metabolism, but with intervention of higher than 8 weeks and using different probiotic species the so-called effects increasing significantly [80] and in a meta-analysis of 12 RCTs (including 684 type 2 diabetes patients) it was confirmed that supplementation of probiotics lead to significant improvement in HbA1c and fasting insulin levels [2]. In other meta-analytic studies the improving effects of probiotics have been reported on insulin resistance and decreasing of HbA1c levels [81-83]. In very recent meta-analyses, it was reported also that probiotics supplementation intensely reduced FPG, HbA1c, insulin, and decreased HOMA-IR in diabetic patients [2] and Very importantly, in a comprehensive collection of randomized controlled trials with different diabetes patterns it was concluded that probiotic consumption in comparison with placebo, intensively decreased fasting glucose, fasting plasma insulin and HOMA-IR [84].

In relation to mechanisms of probiotics effects on diabetes and, metabolic syndrome, many studies have been done all over the world, in a study by Naito et al. feeding obese mice with *L. casei* strain Shirota showed that insulin resistance was improved by decreasing amounts of lipopolysaccharide-binding protein in the plasma (an indicator of endotoxemia), or in study of Chen et al. [63] it was reported that *B. Longum* supplementation of rats (with high fat diet) resulted in decreased intestinal inflammatory activity index which can be one of the mechanisms of effects of probiotics on glucose and lipid metabolism.

As it could be seen in the (Figure 1), effects of different genus of bacteria is different in anatomical sites, for example, *lactobacillus* and *bifidobacterium* have the best positive correlations with plasma acetate, whereas, *Turicibacter* and *Anaerotruncus* showing the best positive correlations with plasma Triglyceride and visceral fat, respectively. This fact indicates that a mathematic ratio of different strains of bacteria could have beneficial or pathologic roles in gut. And repairing and restoring the good bacterial population could be a standard therapeutic strategy in definite treatment of MS related diseases in the future.

Conclusions

Many important and recent studies were discussed about relation of gut microbiota, and probiotics with MS and related diseases in this chapter. It was cleared that changing of gut microbiota in life could affects metabolism of critical molecules including lipids and sugars and modification of gut bacterial profile by probiotic supplementation may be a useful method of inhibition and control of hyperglycemia and MS related problems in clinical cases. Several chronic disorders,

including diabetes, obesity, dyslipidemia, and cardiovascular diseases have been proposed as a result of abnormal glucose metabolism which beneficial bacteria have been indicated to restore the so-called diseases. Beneficial effects of probiotics have been indicated on the immune functions, decreasing blood pressure, and improving lipid profiles in blood of patients. Researches on animal models were also showed that probiotics can decrease blood glucose and insulin resistance.

And importantly, in many studies role of gut normal bacteria in treatment diabetes and metabolic syndrome was suggested in studies, so, it was cleared that diabetic patients have abnormal patterns of gut bacteria in comparison with non-diabetics. As a result, very scientists are interesting to study the role of probiotics to changing gut microbiota, and in fact correcting the gut microbial population for lowering glucose in diabetic patients for treatment purposes. Although, the results of studying the effects of probiotics on glucose level in clinical trials were not reliable in some studies, and were reported from no meaningful to improving glucose level in patients' blood. In this regard, huge number of studies has been done for analysis of the effects of gut microbial population imbalance or impairments, or substitution with anaerobes including ratio of *bacteroidetes* species in the gut with the aim of the induction or treatment of diabetes and other metabolic subjects. Interestingly, it was claimed that diseases like diabetes may be reversible with repairing gut microbial population, and dietary supplementation of probiotics in diabetic rat models had recuperated glucose and lipid metabolism, and had healing effects on glucose intolerance and starting of hyperglycemia, hyper-insulinemia, dyslipidemia, and oxidative stress. Certainly, with these brilliant beneficial results of probiotics, many of MS related pathologies would be definitely curable in the future decades.

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