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REVIEW ARTICLE

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The Prospect of Probiotics to Treat Metabolic Syndrome

Andika Yusuf Ramadhan[1], Dewi Selvina Rosdiana[2]

[1]*Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[2]*Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

Metabolic syndrome remains as a major health problem in the world today, with a prevalence of 23.4% in people aged 26-82 years. A high-fat, high-carbohydrate diet and lack of physical activity are considered as one of the triggers for metabolic syndrome. Dysbiosis is a condition where there is an imbalance between pathogenic and non-pathogenic bacteria in the human gut. Currently, an association has been found between dysbiosis and metabolic syndrome. Dysbiosis causes the generation of fermentation products in the form of active metabolites that can modulate hormones and other physiological functions. In metabolic syndrome, low-grade inflammation, energy metabolism, and disruption of the gut brain axis are thought to be the main mechanisms of the development of metabolic syndrome due to dysbiosis. Probiotics may be a promising therapeutic agent in the treatment of metabolic syndrome, by improving dysbiosis to eubiosis. Based on previously conducted clinical trials, it is currently known that probiotics can improve lipid profiles, fasting blood glucose, homeostatic model assessment for insulin resistance (HOMA-IR), vascular cell adhesion molecule 1 (VCAM-1), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and body mass index (BMI). However, the results found are still varied, so a dose ranging study is needed to determine the duration, bacterial composition and dose of probiotics as a therapeutic agent for metabolic syndrome.

Keywords: *insulin resistance, dysbiosis, gut-brain axis*

Introduction

The prevalence of metabolic syndrome in Indonesia reaches 23.4% in people aged 26-82 years. Insulin resistance is thought to be the primary cause of metabolic syndrome. Metabolic syndrome is characterized by obesity, glucose intolerance, hypertension, and dyslipidaemia. Insulin resistance is defined as the inability of a tissue to respond to normal insulin levels, so that higher levels of insulin are required to maintain normal function. The cause of insulin resistance is believed to be an increase in the consumption of high amounts of fat, leading to obesity. Prolonged insulin resistance could progress into metabolic syndrome.[1,2]

The gut microbiota is considered to play a role in the development of metabolic diseases and insulin resistance. The human gut microbiota consists of over 100 billion microbes that are symbiotic with the human host. The composition of the microbiota consists of several phyla

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Corresponding Author:
Andika Yusuf Ramadhan
Master Program in Biomedical Sciences
Faculty of Medicine, Universitas Indonesia
Jl. Salemba Raya No.6, Jakarta 10430, Indonesia
e-mail: dr.andikayusufr@gmail.com

Cell and Biopharmaceutical Institute

including Bacteriodes and Firmicutes. Throughout human life, these microbiotas are mutually symbiotic to support bacterial growth and also help the digestive process in humans.[1,3] This symbiotic mutualism that already occurs has a wide and broad scope and is not limited to the process of food digestion. The gut microbiota benefits include enhancing gut integrity, forming intestinal epithelium, harvesting energy, protecting against pathogens and regulation of the immune system.[4,5]

Gut microbiota obtain energy through enzymatic processes that aim to obtain energy from the human body, so the diet consumed by the host will affect the proliferation and viability of the microbiota. Changes in dietary patterns can affect the population size and species proportions of the gut microbiota. This imbalance between pathogenic bacterial populations and normal flora is known as dysbiosis. From current research, dysbiosis could give rise changes in gut endocrine functions, such as insulin resistance.[4-6] Dysbiosis resulting changes in neuroendocrine function in human gut, and cause disruption in gut-brain axis. One of the effects is the changes in satiety level in humans, which is thought to be one reason of overeating in obese population. The imbalance of gut microbiota could be the target therapy of metabolic syndrome, which could be resolved by improving bacteria population and insulin resistance.[6,7]

Dysbiosis

The composition of the microbiota in the human gut is strongly influenced by host genotype, environmental factors and diet. Molecular signals and metabolic products from the microbiota influence a wide range of physiological functions in the intestinal organs including visceral sensing, motility, digestion, secretion, membrane permeability, mucosal immunity and intestinal epithelial defence. Under healthy conditions, the microbiota interacts symbiotically with the host, providing protection to the host against foreign bacteria. The microbiota acts as a central line in preventing the colonization of pathogenic bacteria in the digestive system.[8,9] This Defense mechanism is mediated through a process known as barrier effect or colonization resistance. Contact between the intestinal mucosa and the microbiota triggers an interaction between the first-line immune system and the microbiota. Components of the host-microbiota interaction can enter the systemic circulation and travel to and affect the brain, liver and pancreas.[8]

The products of microbiota interactions with the host, which can alter the physiological functions of the host, are the basis for the development of research related to the gut microbiota ecosystem. Eubiosis, a desired state of the ecosystem, is a condition when the population of pathogenic and non-pathogenic bacteria is balanced. Eubiosis status in the host can be achieved by an increase in the two main bacterial phyla, which are Firmicutes and Bacteriodetes. Firmicutes and Bacteroidetes mostly represent 90% of total community of gut microbiota.[8,9] On the other hand, the condition where the population of pathogenic bacteria exceeds that of beneficial bacteria is known as dysbiosis.[8] The condition of dysbiosis is found in three main forms consisting of the loss of beneficial bacteria, the overgrowth of potentially pathogenic bacteria and the loss of bacterial diversity.[10] Homeostatic balance in the intestinal microbiota is crucial. This disequilibrium process has been evaluated to be associated with several diseases, including insulin resistance and metabolic syndrome.

Disturbance of microbiota population is hardly recognized. When dysbiosis presents, it could be indicator of several disease or poor health status. Dysbiosis is associated with metabolic syndrome, inflammatory bowel disease, chronic hepatitis, and colorectal cancer. To determine dysbiosis, bacteria population need to be measured. The Genetic Analysis Map Dysbiosis Test is one of the methods to determine and characterize dysbiosis of gut microbiota. This test is covering 6 phyla, including Firmicutes, Proteobacterua, Bacteriodetes, Actinobacterial, Tenericytes, and Verrucomicrobia. However, it is crucial to notice that dysbiosis index is not a sole measurement method to diagnose dysbiosis, other clinical finding is needed to interpret the relation of dysbiosis and diseases.[11]

Host-mirobiota interactions

Host interactions with microbiota have been known for a long time, even interactions between microbiota and unicellular organisms have been found. Microbiota in the human body, in this case the host, forms a complex community consisting of the same species and specific species of microbiota, for example there are microbiota that are normal in certain species but pathogenic in other species, such as *Escherichia coli*.[12]

The host will form a specific construction so that only certain microbiota can live. This dynamic construction forms specific nutrients, body temperature and forms a suitable area for microbes to grow such as pH and diurnal bile acid secretion. An example of the construction of a bacterial ecosystem is certain microbiota that can take

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energy from breast milk and can survive the immune system provided by the mother to the neonate during the breastfeeding period. The transmission of immunity consisting of antibodies immunoglobulin (Ig)A and IgG, as well as $CD4^+$ lymphocyte cells can modulate the growth of bacteria/microbiota in the gut of neonates. The ecosystem of microbiota populations can also be specific to each individual. The growth of microbiota depends on external factors such as body temperature, dietary nutrients, gastric pH, oxygen concentration and the structure of the gastrointestinal system.[12,13]

The first interaction relationship begins with the microbiota providing protection to the host through immune modulatory molecular signals such as short chain fatty acids (SCFA) that can help promote anti-inflammatory responses.[10] In addition, the gut microbiota also produces a variety of active metabolites such as SCFA, secondary bile acids and lipopolysaccharides. These metabolites can modulate gut hormones in the host's digestive tract by interacting with enteroendocrine cells (EEC). This results in the signalling of hormones such as glucagon like peptide 1 (GLP-1), choclecystokinin (CCK), nutrient transport and ion channels.[12]

Microbiota and their secreted metabolites affect the enteroendocrine cells pathway, which consists of EEC cell number, receptor expression, hormone biosynthesis and secretion coupling pathway. Metabolites formed as a result of intraluminal fermentation will cross the epithelium and target several receptors. For example, secondary bile acids that undergo deconjugation will cross the epithelium and target the G protein coupled bile acid receptor located at the basolateral of the EEC.[12,13] Then SCFA can activate the human peptide YY (PYY) promoter through histone deacetylase and stimulate gut hormones through free fatty acid (FFA) receptors. Also, indole compounds secreted by aromatic amino acid catabolism will target EEC volatage gated ion channels and trigger membrane depolarization and calcium influx. Microbiota can also directly affect the number of EEC, such as microbiota can reduce the number of L column cells and increase plasma GLP-1 levels (Figure 1).[13]

The interaction of microbiota with EEC can modulate hormone pathways that play a role in anorexigenic and orexigenic. Both pathways play a role in controlling the appetite of the host. The interaction between these pathways and microbiota also involves the central nervous system through the microbiota-gut-brain axis. The microbiota affects the brain through the production of bioactive molecules such as SCFA, gamma-aminobutyric acid (GABA), serotonin and dopamine. Changes in the composition and diversity

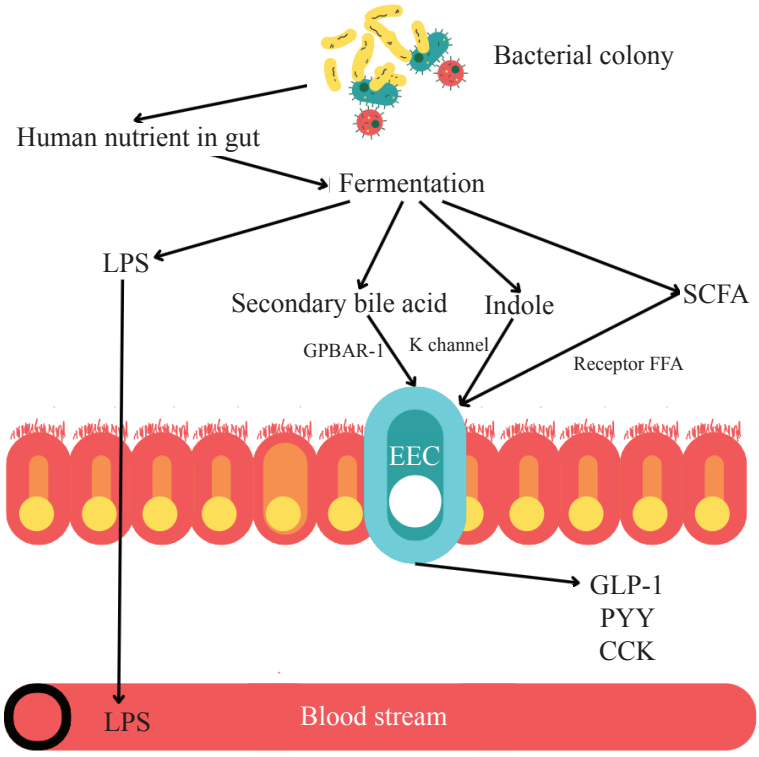

Figure 1. Mechanisms of microbiota interaction with EEC. Undigestible carbohydrate undergoes fermentation process with gut microbiota through metabolic diverse reaction. Result of this fermentation are the formation of SCFA, indole, and secondary bile acid. Three of them are interacting with gut epithelial including enteroendocrine cell and modulate enteroendocrine hormone. LPS: lipopolysaccharides; SCFA: short-chain fatty acid; GPBAR-1: G protein-coupled bile acid receptor 1; FFA: free fatty acid; GLP-1: glucagon like peptide 1; PYY: peptide YY; CCK: cholecystokinin.

of the microbiota affect the secretion of gut peptides and influence the EEC.[14]

Dysbiosis and metabolic syndrome

Food constituent in daily dietary human intake not only provide energy to human body but also play a role in microbiota population. Undigestible food such as non-digestible carbohydrate can be fermented into SCFA through diverse metabolic process.[15,16] Human dietary consists of carbohydrate, protein, lipid, and vitamin have a crucial role in cell proliferation, metabolic process, and human development. Thus, intake also have impact on gut microbiota population. Fiber is one of the dietary compositions that has beneficial impact for gut health. Fiber as human dietary intake classified into several category such as starch resistant, nondigestible oligosaccharide, nondigestible polysaccharide, and chemical synthetic carbohydrate.[17,18] Low gut microbiota diversity is associated with high fat diet, high protein diet, and low fibre intake. Sufficient dietary intake not also promoting gut microbiota diversity, it also helps to maintaining mucus barrier integrity and reduced the risk of pathogen infection.[15,16]

Changes in microbiota composition can alter the pattern of energy extraction from dietary food. Consumption of a high-fat or high-carbohydrate diet may lead to an increase in Firmicutes population and a decrease in Bacteriodetes population. Recent studies have shown that the Firmicutes/Bacteriodetes ratio >1 was found to be higher in overweight people compared to normoweight people.[19] This mechanism is due to the different ability of bacteria to extract energy from the human diet. An increase in Firmicutes microbiota may increase the energy extraction process and trigger weight gain. Whereas an increase in the population of Bacteriodetes can increase fasting-induced adipocyte factor and increase energy expenditure and decrease fat storage, resulting in weight loss.[20,21]

Another mechanism that may underlie obesity induced gut microbiota could be the diet harvesting capability of the microbiota that affects the hormonal system of the host. The ability of microbiota to extract indigestible diet triggers the formation of metabolite products that are easily absorbed by the human body such as SCFA: acetate, propionate and butyrate. SCFA have a role in *de novo* synthesis of lipid synthesis (lipogenesis). Butyrate can trigger hypophagia, reduce insulin insensitivity and has obesity-associated anti-inflammatory properties, as well as increase leptin gene expression. Acetate and butyrate also play a role in promoting fatty acid oxidation and energy expenditure through activation of 5-AMP-activated protein kinase.[20]

Obesity is characterized by chronic low-grade inflammation propagated by pro-inflammatory mediators such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 released by adipose cells. These cytokines stimulate the release of cytokines, chemokines and lipogenesis in a paracrine and/or autocrine pattern.[19,20] In obese conditions, there is an increase in gram-negative bacteria such as Prevotellacease which continuously releases lipopolysaccharides (LPS) and stimulates the immune response and increases the permeability of the epithelium, causing bacterial translocation to the systemic circulation. In addition, a high-fat diet can increase the adhesion of gram-negative bacteria to the epithelium of the intestinal mucosa and increase bacterial translocation to the systemic circulation and sequestration in the mesentery lymph vessels due to phagocytosis. LPS can be absorbed by enterocytes into the circulation with chylomicrons and transported to the liver and adipose tissue. This leads to an increase in LPS and bacteraemia in the blood. Endotoxemia then triggers obesity and insulin resistance. The increase in LPS and endotoxemia is followed by a decrease in Bacteroides and Bififobacterium.[19,20]

Obesity is one of criteria diagnosis of metabolic syndrome and a major risk factor for type 2 diabetes melitus (T2DM). Person with obesity is characterized with is level of non-esterified fatty acid, glycerol, and proinflammatory cytokines that involved in insulin resistance.[22] Obesity triggered insulin resistance through mitochondrial dysfunction, hyperinsulinemia, and lipotoxicity. In the term of inflammation, increase visceral adipose tissue release adipose-specific-cytokine such as leptin, adiponectin, and TNF-α, and IL-6. Inflammatory that secreted by visceral adipose tissue alter insulin signalling and contribute to insulin resistance.[23,24] Besides that, excessive and ectopic lipid also promoting insulin resistance through synthesis of toxic metabolic product formation that intervene with insulin resistance, for example the production of ceramide that increase by saturated fatty acid which contribute to insulin resistance.[23,24]

Insulin resistance is major risk factor of pathogenesis of metabolic syndrome. In obesity, lipid promote overactivation of mitochondria through beta oxidation to increase energy in muscle, liver and, brown fat. This mechanism led to increased level of ATP and turn negative feedback on.[24,25] As

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result, adenosin monofosfat protein kinase (AMPK) became inactive to reduced glucose uptake induced by insulin, in order to decrease ATP production. Reduced level of AMPK leads to reduced glucose oxidation and glucose uptake, this process promoting insulin sensitivity even further. Insulin resistance in adipose tissue cause impairment if insulin mediated inhibition of lipolysis, this promote increase level of FFA that induced inhibition of insulin antilipolytic. FFA detains the protein kinase activation and reduced glucose uptake in muscle.[25,26] Increase protein kinase activation also induced gluconeogenesis and lipogenesis. Result of this event led to high level of insulin state, known as hyperinsulinemia. This state is required to maintain normal glucose level. Insulin resistance also contribute in developing of hypertension state due increase activation of sympathetic nerve and increase sodium reabsorption in renal. Insulin resistance also promote prothrombic state and release proinflammatory cytokine from adipose tissue and increase risk of cardiovascular disease (CVD).[24-27]

Metabolic syndrome is a cluster of metabolic disease factors, followed by increased atherosclerosis, heart disease, T2DM, and other forms of morbidity.[17] This condition is associated with dyslipidaemia, hypertension, glucose intolerance, proinflammatory status, and prothrombotic status. Diagnostic criteria of metabolic syndrome state by World Helath Organonization include central obesity (male waist/hip ratio >0.9, female waist/hip ratio >0.85 and BMI >30 kg/m^2), blood pressure >140/90 mmHg, dyslipidemia (triglycerides >150 mg/dL, high density lipoprotein (HDL) <35 mg/dL in men or <39 mg/dL in women), plasma blood sugar disturbances (impaired glucose tolerance, impaired fasting blood sugar or T2DM) and microalbuminuria.[28] Metabolic syndrome results from biophysiological changes that caused by a high fat and carbohydrate diet along with physical inactivity. Firstly, high fat and carbohydrate diet induced changes in normal flora population and caused dysbiosis. Then, dysbiosis induces gut endocrine function and trigger pathophysiological hallmark of metabolic syndrome such as: chronic inflammation, neurohormonal and energy balance disruption.[28-30]

The gut microbiota has an effect on the progression and regression of metabolic syndrome. There are bacterial phyla that can trigger worsening of metabolic syndrome and vice versa. Dysbiosis conditions characterized by changes in the ratio of Firmicutes and Bacteriodetes can trigger metabolic changes. The Firmicutes group consists of the genus *Lactobacillus*, *Clostridium* and *Ruminococcus*, while the Bacteriodetes group consists of *Bacteriodetes*, *Prevotella* and *Xylanicacter*.[28]

In metabolic syndrome, patients generally experience changes in dietary patterns in the form of a high-fat diet followed by a high-sucrose diet. Diets high in natural sugars such as glucose, fructose and sucrose can trigger an increase in some bacterial populations such as an increase in Bifidobacteria and a decrease in Bacteriodetes. In addition, a high-sugar diet triggers changes in the structure of the intestinal epithelium and the diversity of the microbiota. Low-fiber diets also lead to a decrease in mucus barrier production, which may lead to translocation of bacteria into the systemic circulation.[29]

The mechanism of dysbiosis on the progression of metabolic syndrome consists of several mechanisms: low-grade inflammation, energy metabolism mechanism, and neurohormonal. Gut barrier and inflammatory mechanisms are considered to be the main basis of metabolic syndrome. Metabolic syndrome is dominated by low-grade inflammation and insulin resistance. In dysbiosis, bacteria and their components such as endotoxins cause low-grade inflammation and disrupt the integrity of the intestinal barrier.[29]

LPS is one of the endotoxin components produced by microbiota. This endotoxin component initiates the inflammatory process that is the initial onset of obesity and insulin resistance. LPS contains lipid A that can structurally penetrate the intestinal barrier or can combine with chylomicrons to enter the systemic circulation.[30] In the systemic circulation, LPS infiltrates liver and adipose tissue and triggers an innate immune response. In the blood plasma, LPS binds to LPS-binding protein (LBP) which causes the activation of CD14 on macrophages. The complex formed causes transduction of several genes encoding inflammatory system effectors such as nuclear factor kappa B and activator protein. LPS in the systemic circulation is found to be high in obese patients. Besides LPS, some microbiota products such as indole also play a role in low-grade inflammation. Indole enters the systemic circulation in the form of 3-indoxysulfate and indole-3-propionate compounds. The 3-indoxysulfate activates the aryl hydrocarbon receptor which regulates the transcription of IL-6 by several cytochrome (CYP) enzymes. Indole-3-propionate will trigger upregulation of junctional proteins or cause downregulation of TNF-α.[31,32]

Probiotics as therapy for metabolic syndrome

Probiotics is a product of living microorganisms that given in adequate amounts can have a health promoting effect towards the host. The components of probiotics include bacteria and/or yeast.[33] Different with probiotic, prebiotic is non digestible food that foster the growth of gut microbiota. Probiotics are currently used as therapeutic agents for several diseases, such as antibiotic-induced diarrhea, infectious diarrhea and constipation. Based on the evaluation of the ability of microbiota to modulate metabolic systems, probiotics are now being used as one of therapy modality in metabolic syndrome. Lactic acid bacteria are microorganisms that used as probiotics with potential beneficial effects. Lactic acid bacteria consist of *Lactobacillus* (*L. plantarum, L. paracasei, L. acidhophillus, L. casei, L. rhamnosus, L. crispatus, L. gaseri, L. reuteri, L. bulgaricus*), Bifidobacterium (*B. longum, B. catenulatum, B. breve, B. animalis, B. bifidum*) and S*accharmyces boulardii*.[32-34]

Probiotic administration is expected to correct dysbiosis state that occurred in metabolic syndrome. Probiotics potentially improve the population of Firmicutes and Bacteroidetes ratio. Beside that, probiotics administration help regulating EEC proliferation, production of gut peptide, and restore energy balance.[6,32-34] Probiotics play a pivotal role in overcoming insulin resistance in metabolic syndrome, one of which is through SCFA synthesis. SCFA has a positive effect on energy metabolism in mammals. SCFA compounds play a role in regulating intestinal homeostasis by regulating pH, increasing calcium absorption, maintaining the function and integrity of the epithelium and having anti-inflammatory effects. The release of SCFA in the gut also inhibit the growth of pathogenic intestinal bacteria such as *E. coli*, *Salmonella* and *Campylobacter*.[35,36] Butyrate is one of the SCFAs that can stimulate *MUC2* gene expression in cell lines and mucin production. The formation of mucin increases the protective barrier against pathogenic bacteria and prevents bacterial translocation to the systemic circulation.[35]

Administration of probiotics such as *Lactobaciilus* induces an increase in beneficial bacteria such as *Akkermansia spp* and *Lactobacillus spp* and increases the production of SCFA metabolites such as butyrate. Butyrate has a role in reducing proinflammatory cytokines in serum and colonic explants. Administration of probiotics such as *Bifidobacterium pseudocatenulatum* CECT 7765 in mice fed a high-fat diet also showed a decrease in endotoxinemia, improved intestinal barrier function and increased metabolism.[35]

Probiotics also have another mechanism in the form of modulating the neurohormonal system in modulation of metabolic syndrome. The results of SCFA fermentation in the gut can directly interact with gut neuroendocrine cells such as EEC. Neurohormone that secreted from EEC systemically, also act as neurotransmitter. Modulation of EEC through G protein coupled (GPR)41 induces increase level of leptin, increased insulin secretion, increased intestinal gluconeogenesis and increased energy use. Modulation through GPR43 cause an increase in GLP-1, increase AMPK activity, stimulate adipogenesis, increase insulin secretion, increase proliferation of B cells and inhibit steatosis. Meanwhile, modulation of GPR109A triggers lipolysis and increases the proliferation of local macrophages (Figure 2).[6,32-34]

Preclinical and clinical studies have been conducted to support the hypothesis of using probiotics as a therapeutic target for metabolic syndrome. A result of preclinical study showed that the administration of *Lactobacillus rhamnosus* PL60 produce linoleic acid in obese mice as a result of its fermentation. Lineloic acid has an antiobesity effect characterized by a decrease in steatosis in the liver and a decrease in mouse body weight. In addition, the fermentation of L. rhamnosus caused significant differences in glucose levels, leptin, and lipid profiles.[36] The administration of *L. plantarum* in obese rats produced fermentation metabolite products in the form of trans-10, cis-12-CLA, which acted as an ant obesity agent based on weight loss, glucose levels, leptin levels, the amount of mesenteric and inguinal perineal adipose tissue.[37]

Currently, there are clinical trials that support the use of probiotics as therapy modality for metabolic syndrome (Table 1). A randomized controlled trial, double-blind in 120 subjects with metabolic syndrome with prediabetes condition randomized received 6 g/day probiotics (*L. acidophilus, B. bifidum, B. longum, and Bifidobater lactis* with CFU of 109), 6 g/day synbiotics (probiotics and inulin), or placebo for 24 weeks. The results of this study shows a significant decrease in the frequency of metabolic syndrome in the group given probiotics and synbiotics compared to placebo (p=0.02). However, there was no significant difference in the central frequency of obesity, hyperglycaemia, hypertension, and hypertriglyceridemia in the three groups.[38]

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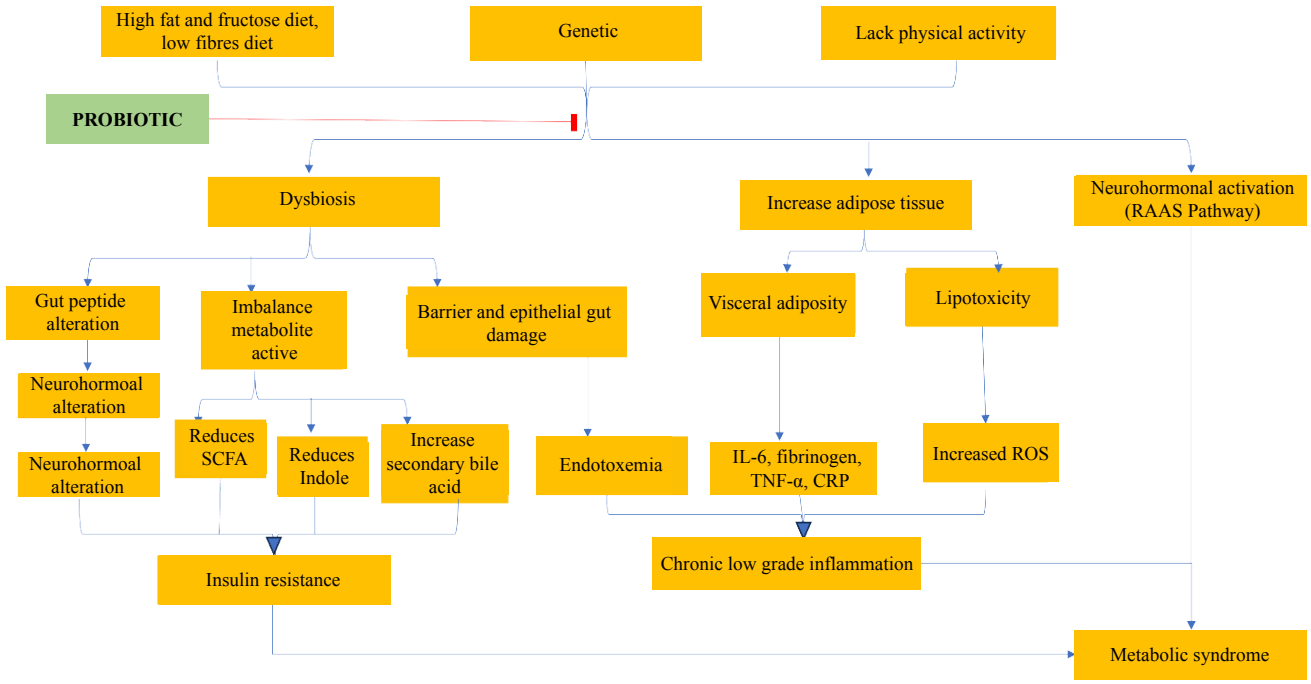

Figure 2. Probiotic roles in metabolic syndrome. Probiotics inhibit metabolic syndrome progression through repairing dysbiosis process, inhibit neurohormonal activation, and reduces adipose tissue. By the end, probiotics help to increase insulin sensitivity and reduced chornic inflammation in metabolic syndrome.

A double-blind randomized clinical trial on 180 subjects with overweight or obese patients with BMI >25 who were given *Lactobacillus fermentum* with strains K7-Lb1, K8-Lb1 and K11-Lb3 1x10^9 CFU for 3 months. The results of this study showed a significant reduction in body fat mass (BFM) in the probiotic group compared to placebo (p=0.039).[39]

In metabolic syndrome perspective, probiotics have hypocholesterolemia effects, antihypertensive, glycemic control, and inflammation modulation. Proposed mechanism of hypocholesterolemia effects mediated by the binding capability of bacteria to cholesterol. It is shows that microorganism can reduced cholesterol absorption in intraluminal tract by binding lipid molecule to probiotic surface.[40,41] Antihypertensive effects of probiotics mediated by several mechanism, such as improvement of vascular oxidative stress and SCFA activity in GPR41 receptor. Oxidative stress and hypertension are closely linked, vascular damage and endothelial dysfunction induced blood pressure abnormality by imbalance of reactive oxygen species (ROS) and nitric oxide (NO). Probiotic such as Kefir can restore the blood pressure abnormality through balancing ROS and NOS. Activation of GPR41R through SCFA (propionate), has hypotensive effects in mice through vascular tension.[42,43] Glycemic control effects of probiotic also proven by reduction of fasting plasma glucose in subject receiving probiotic or synbiotic.[39,44,45]

The results of clinical trials that have been conducted show the administration of probiotics and synbiotics in metabolic syndrome subjects lead to improvement of: lipid profiles (triglyceride, low HDL cholesterol), fasting blood glucose, homeostatic model assessment for insulin resistance (HOMA-IR), vascular cell adhesion molecule 1 (VCAM-1), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and body mass index (BMI). In the clinical trials attached in Table 1, *Lactobacillus* and *Bifidobacterium* are bacteria that are widely used as therapeutic agents in metabolic syndrome cases.[37-39,44-46] A dose ranging study with a longer duration of therapy is needed to determine the optimal dose and exact strain of probiotics in metabolic syndrome therapy.

Conclusion

The gut microbiota can influence the physiological functions of its host. Chronic dysbiosis causes low-grade inflammation and alteration in gut-brain axis that modulates

Table 1. Clinical trial use of probiotic in metabolic syndrome.

Bacteria	Parameter	Method	Result	Reference
Lactobacillus acidophilus La5 and *Bifidobacterium lactis* Bb 12	Fasting glucose, serum insulin, HOMA-IR and beta cell function HOMA, VCAM-1, ICAM-1, and PAI	Randomized clinical trial, double-blind with placebo control. Subjects, 44 patients with metabolic syndrome, were given 300 g probiotics and regular yogurt or regular yogurt for 8 weeks. Before-after measurements and comparison with control were conducted.	Significant reduction in fasting blood glucose in the probiotic + regular yogurt group (-4.81 mg/dL) compared to regular yogurt (-0.82 mg/dL), p =0.001. Decreased VCAM-1 levels in the probiotic yogurt group compared to regular yogurt (-463.39 ng/m, p =0.001). Other parameters were not found to be significantly different.	44
Lactobacillus casei , *Lactobacillus rhamnosus* , *Lactobacillus acidophilus* , *Lactobacillus bulgaricus* , *Bifidobacterium longum* , *Bifidobacterium breve* , and *Streptococcus thermophiles*	Fasting blood glucose, insulin, HOMA IR, HOMA-B, IGR, hs-CRP, SGPT, ALP, triglycerides, total cholesterol, LDL, and HDL	Randomized clinical trial, double-blind with placebo control. Subjects, 65 patients with metabolic syndrome in each group, were given 1000 mg containing probiotics and 38.5 g FOS for 12 weeks.	Fasting blood glucose was significantly lower in the synbiotic group (-14.7 mg/dL) compared to the placebo group (-8.22 mg/dL), p =0.007. Other parameters were found not significantly different.	45
Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum and *Streptococcus thermophiles*	Blood pressure, anthropometric measurements, fasting glucose, triglyceride, cholesterol, HDL, and LDL	Randomized clinical trial, double-blind with placebo control. Subjects, 60 patients with metabolic syndrome, were given probiotics once a day for 8 weeks.	Decreased BMI in the probiotic group (-0.65 kg/m^2) compared to the placebo group (0.09 kg/m^2), (p =0.003). Decreased triglyceride levels in the probiotic group (-0.16 mmol/L) compared to the placebo group (0.09 mmol/L), p =0.02. Other parameters were found to be not significantly different.	46
Lactobacillus acidophilus, Bifidobacter bifidum, Bifidobater lactis and *Bifidobacter longum*	Fasting blood glucose, anthropometry, blood pressure, HDL, and cholesterol	Randomized clinical trial, double-blind, with placebo control. Subjects, 120 patients with prediabetes, were given 6 g/day of probiotics, 6 g/day of synbiotics (probiotics and inulin), or placebo for 24 weeks.	A significant decrease in the frequency of metabolic syndrome in the group given probiotics (-17.1%) and synbiotics (-23.4%) compared to placebo (-1.9%), p =0.02. Significant reduction in the frequency of low HDL in the synbiotic group (-10%), probiotics (0.8%) compared to placebo (8.4%), p =0.02. Other parameters were found to be not significantly different.	38
Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum , and *Lactobacillus bulgaricus*	Anthropometry, IL-6, CRP, insulin resistance, HOMA-IR, GLP-1, and PYY	Randomized clinical trial, triple blind, with placebo control. Subjects, 46 patients with metabolic syndrome, were given once daily 250 mg synbiotic capsules with 2x10^8 CFU or placebo for 12 weeks.	Decreased BMI (-1.3 kg/m^2 *vs.* -0.7 kg/m^2), fasting glucose (- 11.6 mg/dL *vs.* 13 mg/dL), insulin (-7.4 µIU/mL *vs.* -0.7 µIU/mL, and HOMA IR (-3 *vs.* 0.5); increased GLP-1 (2.1 ng/mL *vs.* 0.3 ng/mL) and PYY (30.9 pg/mL *vs.* 21.6 pg/mL) levels compared to the placebo group. Other parameters were found to be not significantly different.	40

*HOMA-IR: homestatic model of insulin resistance; VCAM-1: vascular cellular adhesion molecule-1; ICAM-1: intracellular adhesion molecular-1; PAI: plasminogen activator inhibitor; CRP: C-reactive protein; HDL: high density lipoprotein, LDL: low density lipoprotein; FOS: fructooligosaccharides; GLP-1: glucagon like peptide-1, PYY: peptide YY; SGOT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase, IGR: impaired glucose regulation.

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anorexigenic and orixogenic pathways, leading to increased risk of metabolic syndrome. There is a tendency to improve metabolic status after probiotic administration in metabolic syndrome patients. Probiotics could be a promising alternative therapy in cases of metabolic syndrome. However, further studies were still needed to obtain the optimal dose, duration, and bacterial composition of probiotic administration for metabolic syndrome.

Authors Contribution

AYR and SDR were involved in concepting of manuscript topic and prepared the manuscript draft. AYR designed the figures and tables. All authors took parts in giving critical revision of the manuscript.

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