Gut microbiota and metabolic syndrome

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Abstract

Metabolic syndrome (MetS) describes a set of risk factors that can eventually lead to the occurrence of cardiovascular and cerebrovascular disease. A detailed understanding of the MetS mechanism will be helpful in developing effective prevention strategies and appropriate intervention tools. In this article, we discuss the relationship between the clinical symptoms of MetS and differences in the gut microbial community compared with healthy individuals, characterized by the proliferation of potentially harmful bacteria and the inhibition of beneficial ones. Interactions between gut microbiota and host metabolism have been shown to be mediated by a number of factors, including inflammation caused by gut barrier defects, short-chain fatty acids metabolism, and bile acid metabolism. However, although we can clearly establish a causal relationship between gut microbial profiles and MetS in animal experiments, the relationship between them is still controversial in humans. Therefore, we need more clinical studies to augment our understanding of how we can manipulate the gut microbiota and address the role of the gut microbiota in the prevention and treatment of MetS.

Keywords: Metabolic syndrome; Gut microbiota; Inflammation; Short-chain fatty acids; Bile acids

Introduction

With the widespread Westernization of diet patterns and lifestyles, the occurrence of metabolic syndrome (MetS) has become a worldwide phenomenon at all ages. MetS describes a group of risk factors including obesity, hyperglycemia, dyslipidemia, hypertension, hyperuricemia, and others. If left uncontrolled, it will eventually lead to non-alcoholic fatty liver (NAFLD), obstructive sleep apnea hypopnea syndrome (OSAHS), and other diseases. The pathogenesis of MetS is related to a variety of factors, such as insulin resistance, chronic inflammation, autonomic dysfunction, and oxidative stress.[1,2] In recent years, it has been found that gut microbiota disorder is also a risk factor for the development of MetS. In the human body, the gut microbiota is the most diverse microbial community. During long term co-evolution, it has formed a symbiotic relationship with the host and is deeply involved in regulating gene expression, gut barrier function, nutrition, metabolism, and the overall immune function of the host.[3] The gut microbiota plays a significant role in maintaining the homeostasis of human health, acting as a "second genome," especially during the development of metabolic diseases. Thus, gut microbiota targeted therapies such as probiotics, prebiotics, fecal microbiota transplantation (FMT), metabolic surgery, and drugs may represent effective forms of intervention for the amelioration of MetS. The aim of this study was to review the dysbiosis of gut microbiota in terms of the components of MetS and to assess current potential gut microbiota targeted therapies for the treatment of MetS.

Gut Microbiota in MetS

Up to 1000 species of bacteria inhabit the human colon, together encoding around 3 million genes, which may have an impact on our health. In fact, small molecules produced by gut microbiota play an important role in human blood. Some microbiota-derived metabolites are known to have a positive impact on the host. These include those with anti-inflammatory activity, anti-oxidant activity, and pain relief activity, as well as those acting as vitamins or energy sources, and those that regulate gut barrier function. On the other hand, certain microbiota-derived metabolites are harmful to the host, which include cytotoxins, genotoxins, and immunotoxins.[4,5] The gut microbiota, therefore, plays a key role in maintaining the physiological function of the host, and dysbiosis of the gut microbiota caused by various factors leads to extensive physiological changes and increases the risk of MetS.

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Gut microbiota and obesity

The prevalence of obesity in Western countries and, increasingly, in non-Western countries is a driving force behind the heightened medical interest in the recognition of MetS. Recent studies have shown that the composition of gut microbiota in healthy individuals was significantly different from that in obese individuals, which indicated that gut microbiota might play an important role in obesity.

For example, Tomas et al[6] reported that in mice, a 30-day high-fat diet caused a difference in the gut microbiome, with significantly increased frequencies of the phylum *Firmicutes*, *Proteobacteria*, and reduced frequencies of *Verrucomicrobia*, and *Bacteroidetes*. Thingholm et al[7] investigated the gut microbiota of obese individuals with/ without type 2 diabetes mellitus (T2DM) as well as lean individuals without T2DM in the German population and metabolic disease cohorts. They show that obesity may be related to changes in the composition of the microbiome, the occurrence of individual taxa, and their biochemical functions/outcomes. Specifically, they describe significant changes in *Akkermansia*, *Fecalibacterium, Oscillibacter*, and *Alistipes*, as well as to the levels of serum metabolites related to gut microbial patterns. Fei et al[8] isolated *Enterobacter cloacae B29* from the stool of obese volunteers, and the strain was transplanted to germ-free C57BL/6J mice. As a result, the mice after transplantation developed obesity and insulin resistance on a high-fat diet, but not on a normal diet. However, on a high-fat diet, germfree control mice did not show obesity and insulin resistance. Both serum endotoxin levels and inflammation from the Enterobacter-induced obese mice were negatively affected. Both serum endotoxin levels and inflammation from the Enterobacter-induced obese mice showed a negative side. These studies make it clear that the gut microbiota is an important environmental factor involved in the regulation of fat storage in the host, which ultimately affects the incidence of obesity.

Gut microbiota and hyperglycemia

Hyperglycemia, one of the components of MetS, is highly related to gut microbiota dysbiosis. Recently, Zhou et al[9] conducted a microbiome analysis of four male Zucker diabetic fatty rats. Their results suggested that the progress of age and disease is correlated to changes in fecal microbes. Specific phyla such as *Firmicutes*, *Bacteroidetes*, *Actinomicrobiota*, and *Proteobacteria* comprised the main components of fecal microbes in rats at all stages from 8 to 15 weeks. But *Lactobacillus* and *Turicibacter* were the predominant genera in 8- to 10-week-old rats. *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, and *Allobaculum* were the most abundant genera in 15-week-old rats. The gut microbiota in animals with T2DM shows moderate gut microbiological ecology dysbiosis. Specifically, in T2DM sufferers, the abundance of some metabolically beneficial microbiota is reduced, such as butyrate-producing bacteria, while pathogenic bacteria that are known causes of various other conditions are increased.[10] Butyrate can serve as an energy source for colonocytes and can increase satiety. It can also effectively reduce inflammation, reduce carcinogenesis, reduce oxidative stress, and improve gut barrier function.[11-13] Several studies have found a significant association between hyperglycemia and dysbiosis of the gut microbiota, but the results were inconsistent, highlighting the need for further studies.[14-16]

Gut microbiota and dyslipidemia

Dyslipidemia refers to abnormal concentrations of lipids or lipoproteins in the blood caused by congenital or acquired factors. Both *in vitro* studies and animal experiments have confirmed that dyslipidemia can lead to gut microbiota imbalance, and dysbiosis of the gut microbiota can further aggravate lipid metabolic disorders.

Clear evidence of this was seen in a study that used 16S rRNA analysis to confirm that the gut microbiota of C57BL/6J mice fed a high-glucose (HGD) or high-fructose (HFrD) diet was significantly altered. They found that where there was no change in body weight, both the HGD and HFrD groups showed dyslipidemia. The gut microbiome from HGD- and HFrD-fed mice lost diversity. In the HGD and HFrD groups, the proportion of *Bacteroidetes* was low, and the proportion of *Proteobacteria* was significantly increased. Lipid accumulation was also significantly increased.[17] Separately, Wang et al[18] reported a systemic analysis of the host-genome, the gut microbiome (16S rRNA), body mass index (BMI), and blood lipids in 893 human participants from the LifeLines-DEEP Dutch study cohort. They estimated that the gut microbiome explains 4.5% of the variation in BMI, 6.0% in triglycerides (TGs) and 4% in HDL. Furthermore, the gut microbiome in subjects with unfavorable lipid profiles (high TG and low high-density lipoprotein [HDL] levels) were also characterized by low microbial diversity, a high abundance of some taxa from the phylum *Actinobacteria* and a lower abundance of many taxa from phyla *Proteobacteria* and *Bacteroidetes*. These studies provide evidence for an association between blood lipids and the gut microbiome.

Gut microbiota and hypertension

Hypertension is one of the components of MetS and is the primary risk factor for cardiovascular and cerebrovascular diseases. Studies in animals and humans demonstrate that high blood pressure is associated with gut microbiota dysbiosis.

Yang et al[19] reported that microbial richness, diversity, and uniformity of spontaneously hypertensive rats were significantly reduced, while the thick-walled *Firmicutes*: *Bacteroidetes* proportion increased. These changes are accompanied by a reduction in the microbial population that produces acetic acid and butyrate. In addition, a small group of human hypertensive patients was also found to follow a similar pattern of dysbiosis because their gut microbiota lacked diversity compared to the control group. Li et al[20] reported that compared to the healthy controls, in pre-hypertensive and hypertensive populations, the abundance and diversity of microorganisms was decreased significantly. There are fewer bacteria associated with good health status, but an overgrowth of harmful

bacteria such as *Prevotella* and *Klebsiella*, in both pre-hypertensive and hypertensive populations. The microbiota characteristics of the pre-hypertension group were similar to those of the hypertension group. Pre-hypertensive or hypertensive host metabolic changes are also closely related to a gut microbiota imbalance. In addition, by transplanting feces from hypertensive human donors into sterile mice, we observed that elevated blood pressure can be transferred through the microbiota, confirming the direct effect of the gut microbiota on host blood pressure.

Gut microbiota and hyperuricemia

Hyperuricemia is caused by purine metabolic disorders and/or decreased uric acid excretion. It is the most important biochemical basis for gout and the manifestation of MetS. In animal and human studies, it was found that hyperuricemia was linked to gut dysbacteriosis.

Xu et al[21] reported that at the phylum level, there was a significant reduction in the frequency of *Firmicutes* between a hyperuricemia mouse model and wild-type mice. Simultaneously, the frequency of *Bacteroides* was increased. At the family level, the abundance of *Prevotellaceae, Rikenellaceae, Bacteroidaceae,* and *Bacteroidales* in hyperuricemic mice was increased. At the genus level, some certain bacterial populations were more or less frequent in the hyperuricemia group, including *Lactobacillus, Clostridium, Ruminococcaceae, Clostridium,* and others. Guo et al[22] reported that the gut microbiota of gout patients is highly different from healthy people in terms of organismal and functional structures. In the gut microbiota of gout patients, they found that *Bacteroides caccae* and *Bacteroides xylanisolvens* increased, while *Fecalibacterium prausnitzii* and *Bifidobacterium pseudocatenulatum* decreased.

Gut microbiota and NAFLD

NAFLD has recently become the most common chronic liver disease in the world. NAFLD which has been considered as a hepatic manifestation of MetS, is a range of hepatic related disorders independently associated with a cluster of metabolic abnormalities including abdominal obesity, insulin resistance, T2DM, and dyslipidemia. Gut microbiota imbalance plays an important role in the pathogenesis of NAFLD.

Yuan et al[23] reported that in the Chinese cohort, high alcohol-producing *Klebsiella pneumoniae* (*HiAlc Kpn*) was associated with three-fifths of NAFLD patients. The clinically isolated *HiAlc Kpn* was transferred into NAFLD mice by gavage. Similarly, fecal microbiota was transplanted into mice using a *HiAlc-Kpn*-strain-containing microbiota isolated from non-alcoholic steatohepatitis patients, and NAFLD was induced. The molecular mechanism of NAFLD in *HiAlc-Kpn*-fed mice may be similar to that mediated by ethanol. The NAFLD that occurred in *HiAlc-Kpn*-fed mice might; therefore, be induced with a similar molecular mechanism as that mediated by ethanol. Disruption of the gut barrier can lead to translocation of bacteria and their metabolites and abnormal activation of the immune system, leading to liver inflammation and injury.[24] Therefore, as an important part of connecting the gut tract to the liver, the enterohepatic axis plays a key role in the pathogenesis of NAFLD.

Gut microbiota and OSAHS

OSAHS is a sleep disorder characterized by sudden apnea during sleep, along with a disrupted sleep rhythm. Gut microbiota disorders are involved in the development of OSAHS.

Moreno-Indias et al[25] studied ten mice which were subject to continuous chronic intermittent hypoxia for 6 weeks, and ten mice that were allowed to have normal oxygen. They took samples from mouse feces, and also analyzed and determined the composition of the microbiome by 16S rRNA pyrosequencing and bioinformatic analysis, the latter using "Quantitative Insights into Microbial Ecology." Compared with the control group, the abundance of *Firmicutes* was higher in mice exposed to intermittent hypoxia, and the abundance of *Bacteroidetes* and *Proteobacteria* was smaller. Along with intermittent hypoxia, the composition and diversity of fecal microbiota in mice were altered, which mimicked the situation in OSAHS. Ko et al[26] obtained fecal samples from 93 patients with OSAHS and 20 controls, and determined the composition of their microbiome. Functional analysis showed changes in the patient's microbiome; in addition, the number of short-chain fatty acids (SCFAs)-producing bacteria decreased, the number of pathogens increased, and interleukin (IL)-6 levels increased. By stratification analysis, they confirmed that *Ruminococcus* was the highest risk factor for the development of OSAHS. These changes in the levels of SCFAs affect the levels of pathogens that play a pathophysiological role in OSAHS and related metabolic comorbidities.

At present, human and animal experiments have shown that the disease indicators of MetS are the result of many intertwined factors. The status of the intestinal flora (and its imbalance) is one of the risk factors for MetS. Different gut microbiome profiles were found in MetS compared to healthy individuals, characterized by the proliferation of potentially harmful bacteria and the inhibition of beneficial ones. However, we must acknowledge that certain bacterial behaviors may be specific to the environment and are determined by a combination of host-related and microbial-related factors. These factors define their combined role as pathogens or symbiotic organisms.[27] For ethical reasons, most of the results on the composition of human gut microbiota are derived from the analysis of human fecal samples. There is a considerable difference between the microbiota in the gut lumen and the mucous layer covering the gut mucosa. Therefore, microbial data based on such analysis cannot represent the specific situation in various gut segments, which might be very different.

Mechanism of Action of the Gut Microbiota With Relation to MetS

Gut barrier and inflammation

A large number of studies have shown that the main pathophysiological basis of MetS is chronic low-grade

inflammation dominated by insulin resistance. Bacteria or their components, such as endotoxins, enter the circulation, causing low levels of inflammation, as a result of an imbalance in the gut microbiota and disruption of the gut barrier.[28,29]

When the metabolism is healthy (eg, in individuals who eat a high-fiber diet), gut microorganisms regulate the integrity of the intestine through a variety of mechanisms of action.[30,31] Dendritic cells extract microbial antigens from the gut lumen and induce the activation of immune cells such as retinoid-related orphan receptor-γt dependent T helper 17 and type 3 natural lymphocytes to promote the secretion of mucus, anti-microbial peptides, and immuno-globulin A.[32-35] The gut epithelium promotes adenosine monophosphate secretion by NOD-, leucine-rich repeat-(LRR-), and domain-containing protein 3 inflammasome-sensing microbiota metabolites.[36,37] The gut microbiota can also be characterized in terms of its metabolites (secondary bile acid and aryl hydrocarbon receptor agonist) with indirect supervision to maintain gut barrier function.[38] Host endogenous factors also determine the integrity of the gut barrier. This includes insulinemia in the blood, which regulates mucus secretion by fatty acid synthase.[39]

The gut microbiota is regulated by environmental and host factors. The imbalance of the gut microbiota caused by diet, diarrhea, heredity, and other factors may increase the expression of lipopolysaccharide (LPS), drive Toll-like receptor signaling, degrade the mucous layer, cause endotoxemia, produce pro-atherogenic trimethyl-amine (TMA) or use other pathways that ultimately cause the metabolic disorder.[40,41] These gut changes cause the translocation of bacterial metabolites, such as phenylacetic acid, TMA, imidazole propionate or mediators of metabolic disorders, and pathogen-associated molecular patterns, such as LPS, which induce chronic low-grade inflammation through pro-inflammatory cytokines such as IL-1β.[42,43] Host blood glycemia induces barrier dysfunction through glucose transporter 2.[44] Other intraluminal mechanisms include increased bile acid concentration and the appearance of exudative diarrhea that disrupts the gut barrier, reducing the thickness of the mucus, putting epithelial cells in direct contact with bacteria.[45] Metabolic inflammation and dysfunction lead to metabolic disease and are closely related. For example, insulin resistance is promoted by metabolic inflammation, including increased IL-6 and tumor necrosis factor. Overall, the gut and gut microbiota promote metabolic inflammation and disorders, which are an important marker of metabolic diseases such as obesity, T2DM, NAFLD, and related atherosclerosis.

In summary, the host-microbial community interface transduces abnormal gut signals from the diet or commensal microbiota to produce a local immune response, leading to barrier disruption. Therefore, it may be reframed as another fight against metabolic inflammation. This disruption of the gut barrier may lead to systemic chronic inflammation and end in organ dysfunction, eventually leading to metabolic diseases in the host.

Energy metabolism

SCFAs

SCFAs are the metabolic end products of microbial fermentation of dietary fibers. SCFAs play an important role in regulating gut homeostasis, adipose tissue, and liver metabolism.[46] SCFAs help to maintain an energy balance by regulating gut hormones such as gut trypsin peptide, glucagon-like peptide-1 (GLP-1), leptin and peptide tyrosine-tyrosine (PYY), thereby preventing the development of metabolic diseases such as obesity, abnormal glucose, and lipid metabolism, hypertension and NAFLD disease.[47]

In the case of a positive energy balance (that is, the energy intake is greater than the energy consumed), adipose tissue exceeds its buffering capacity and cannot store all the excess energy in the form of TGs. As a result, excess fat overflows into the bloodstream. Due to the increased lipid supply of non-fat tissues such as the liver, skeletal muscle and pancreas, ectopic storage of these tissues, and the development of insulin resistance is the result. Our gut microbiota ferments and breaks down food, but the hydrolysis cannot be completed by them due to they lack appropriate enzymes, which leads to the production of SCFAs, including acetic acid, butyric acid, and propionic acid.[48] Butyrate and propionate metabolism is usually performed in the colon and liver, so it mainly affects local gut and liver function. In addition, propionate and butyrate improve glucose and energy homeostasis by inducing gut gluconeogenesis and sympathetic nerve activity. A small amount of propionate, butyrate and a large amount of acetate enter the circulation, which can also directly affect the metabolism and function of surrounding adipose tissue, liver, and muscle substrates. Moreover, acetate in the circulation may be absorbed by the brain and regulate satiety through the central self-regulation mechanism.

Propionate and butyrate might increase non-esterified fatty acid (FFA) uptake, possibly by affecting the lipoprotein lipase (LPL) inhibitor Angiopoietin-like proteins 4.[49] Acetate and propionate can also reduce intracellular lipolysis by reducing HSL phosphorylation via G protein-coupled receptor (GPR) 43. By increasing LPL-mediated TG extraction, propionic acid can increase the lipid buffering capacity of adipose tissue through mechanisms regulated by GPR43, acetic acid, propionic acid, and butyric acid, which then all increase peroxisome prolifer-ators-activated receptors (PPAR) γ-mediated fat formation.[50] Altogether, these effects may help increase TG in adipose tissue and reduce systemic FFA release. Acetate, propionate, and butyrate can prevent chronic low-grade inflammation through various means. For example, they can up-regulate anti-inflammatory Treg cell levels, reduce metabolic endotoxemia, and reduce pro-inflammatory adipocytokines and chemokines.[51] SCFAs can improve the function of the epithelial barrier and gut permeability by regulating the expression of tight junction proteins and mucins.[52] Improving gut barrier function is very important to prevent toxic compounds produced by pathogenic bacteria from leaking into the blood circulation. Metabolic

endotoxemia, especially the increase of circulating LPS, is related to audio-inflammation, chronic low-grade inflammation and dysfunction, insulin resistance and weight gain.[53,54]

SCFAs can also improve insulin sensitivity by improving glucose and oxidative metabolism in skeletal muscle. Acetic acid and butyrate increase FA oxidation in muscle, which may be mediated by the activation of adenosine monophosphate-activated protein kinase (AMPK), PPARδ-dependent mechanisms.[55] In addition, acetic acid and butyric acid may affect glucose metabolism in skeletal muscle in an AMPK-dependent manner and may increase glucose uptake and possibly glycogen storage through a GPR41/GPR43 mediated mechanism.[56] Acetic acid and butyrate can improve the glucose and oxidative metabolism of skeletal muscle, increase lipid metabolism, and improve insulin sensitivity. SCFAs may also indirectly affect muscle insulin sensitivity and glucose metabolism, and regulate muscle microvascular blood volume and flow through gut-derived GLP-1 secretion.[57] This is related to the enhancement of muscle insulin action and the improvement of glucose utilization in the muscle. Animal studies have shown that visceral PYY secretion stimulated by SCFAs may also improve insulin-mediated glucose uptake in skeletal muscle and increase systemic fat oxidation.[58,59]

Bile acids

Bile acid is an endocrine molecule, which not only promotes the absorption of liposoluble nutrients but also regulates many metabolic processes, including the balance of glucose, lipid, and energy.[60] Bile acids play a role in glucose and lipid metabolism by directly or indirectly activating a nuclear receptor: farnesol X (FXR), and a membrane receptor: G protein-coupled membrane receptor 5 (TGR5). Moreover, bile acids can directly or indirectly regulate the composition of gut micro-organisms by activating innate immune genes in the small intestine. Therefore, the metabolism of the host can be affected by changes in bile acid by the micro-organism, which will not only change signals emanating from the bile acid receptor but also change the composition of the microbial community.

The formation of bile acids is a complex process that includes several reaction steps catalyzed by at least 17 different enzymes.[67] Bile acids are synthesized in the liver by two different mechanisms. The classical pathway accounts for at least three-quarters of total bile acid production under normal conditions, which is caused by cholesterol 7a hydroxylation catalyzed by cholesterol 7-alpha hydroxylase (CYP7A1).[61] CYP7A1 is the rate-limiting enzyme that determines the number of bile acids produced. Another pathway is initiated by sterol-27-hydroxylase (CYP27A1). The expression of these enzymes is regulated by gut microbiota.[62,63]

The active reuptake of bile acid transporter (ASBT) from the small intestine is prevented by microbial purification.[64] Bile acid deconjugation is carried out by bacteria with bile salt hydrolase (BSH) activity. Metagenomic analyses demonstrated that functional BSH is present in all major bacterial divisions and archaeal species in the human gut including members of *Lactobacilli, Bifidobacteria, Clostridium,* and *Bacteroides*.[65] In actuality, BSH is more abundant in the gut microbiota than in other microbial ecosystems, and is related itself to increased bile toxicity. The metabolism of bile acids by micro-organisms increases the diversity of bile acids. Generally speaking, it forms a more hydrophobic bile acid pool, which promotes the elimination of bile acids in feces, comprising about 5% in total.[64] In both mice and humans, gut microbial ecology is significantly affected by diet.[66] It not only directly metabolizes bile acids but also affects signal transduction through FXR. This same microbial group can clear away the naturally produced FXR antagonist TBMCA, thus promoting the FXR signal transduction in mice, and can also produce secondary bile acids as TGR5 ligands.[66] TGR5 may play a role in energy balance by promoting the activity of thyroid hormones in cells, thus increasing the heat production of brown adipose tissue. TGR5 signal can control glucose homeostasis by promoting energy consumption of brown adipose tissue and muscle and increasing GLP-1 release from gut L cells. L cells also express FXR, which also regulates the synthesis of GLP-1.[63,67]

When natural bile acids are provided as activators of FXRs, the metabolism of gut microorganisms may produce ligands of TGR5, which emphasizes the importance of studying gut microbiota. The gut microbiota increases the expression of genes involved in lipid uptake in the liver in an FXR dependent manner, thus inducing inflammation in adipose tissue. Dynamic interactions exist between the microbial community and bile acids. This interaction can have beneficial or harmful effects on the metabolism of the host through dietary changes. Metabolic diseases may be caused by interactions among microbiota, bile acids, FXRs, TGR5, and metabolites from micro-organisms and the host metabolism.

Gut Microbiota Targeted Therapies in MetS

Probiotics and prebiotics

Probiotics and prebiotics are microbiota-management tools used to improve host health.[68] Probiotics are live microorganisms that confer a health benefit to the host when administered in adequate amounts. Probiotics exert positive effects on the host by regulating the immune function of the host, generating organic acids and anti-microbial products, interacting with the host and its microbiota, and improving the gut microbiota.[69]

Tenorio-Jimenez *et al*[70] reported that they conducted a study of MetS and probiotics, which included 53 newly diagnosed adult patients with MetS. Patients were randomly divided into two groups according to BMI and gender. The experimental group took a capsule containing probiotic *Lactobacillus reuteri V3401* every day, while the control group took a placebo for 12 weeks. During the experiment, they measured anthropometric variables, biochemical, and inflammatory biomarkers, and the composition of the gastrointestinal microbiome. There was no difference in the clinical manifestations of MetS between the two groups. However, they found that IL-6

and soluble vascular cell adhesion molecule-1 in the experimental group were significantly lower than those in the control group.

Prebiotics cannot be digested and absorbed by the host.[71] They play a positive role through selective metabolism in the gut. For prebiotics, some have been proved to be beneficial to the host, such as glucans and fructans, by promoting the growth of beneficial bacteria and transplanting harmful bacteria.[69]

Zhao et al[72] reported that patients with T2DM were randomly divided into two groups. The control group received routine treatment, and the experimental group was treated with a high fiber diet composed of whole grains, Chinese herbs, and prebiotics. Acarbose was used as a basic drug in both groups. Glycated hemoglobin (HbA1c) levels in both groups were significantly lower than baseline and time-dependent; however, from the 28th day, there was a more significant decrease in the experimental group. At the end of the experiment, the blood glucose control rate of the experimental group (HbA1c <7%) was also higher than that of the control group. Compared with the control group, the weight loss of the experimental group was greater and the blood lipid level was better. They obtained the gut microbiota of the same subjects before and after the intervention and then transplanted the microbiota into C57BL/6J mice without bacteria. The metabolic health indexes of the two groups were better than those of the mice before the intervention. It is found that the overgrowth of SCFAs producing bacteria is directly related to the improvement of blood glucose control, in part through the upregulation of GLP-1. Although some studies have shown that probiotics and prebiotics have a positive impact on the host, they were limited based on the influence of the living environment, age, gender, and other factors, the results of the experiment are controversial, and no specific recommendation value can be determined. Therefore, more clinical studies are needed to better understand the role of probiotics and prebiotics in the treatment of MetS.

FMT

FMT, known as "gut microecological transplantation," is a method of transplanting functional microbiota using the feces of healthy people into the gastrointestinal tract of patients, for the treatment of gut and parenteral diseases through the reconstruction of gut microbiota.

Vrieze et al[73] reported that 18 male patients with MetS were randomly assigned to two groups. The experimental group received a gut microbiota transplantation from thin male donors with BMI <23 kg/m^2, and the control group received a gut microbiota transplantation where the microbiota sample came from themselves. Subjects were measured for insulin sensitivity by hyperinsulinemia clamp before and 6 weeks after intervention. The gut microbiota and SCFAs from feces and within the duodenum were also measured before and after the intervention. The results showed that the peripheral insulin sensitivity of the experimental group was improved, and the diversity of gut microorganisms was significantly increased. In the experimental group, 16 groups of bacteria had significantly increased populations. These included the butyrate-producing bacteria Roseburia guts, which increased 2.5-fold. FMT has great potential to treat MetS by reconstructing the gut microbiota. We hope that in the near future, there will be more research to further clarify treatment prospects, in order to create a more comprehensive and optimized diagnosis and treatment strategy using fecal bacteria transplantation.

Metabolic surgery

Medical treatments exist to improve the systemic symptoms of obese patients such as high blood pressure, hyperlipidemia, and hyperglycemia. Metabolic surgery changes the normal anatomical structure of the gastrointestinal tract, thus changing nutrient intake, gastric emptying, and gastric acid secretion, and also affects the gut microbiota and cholic acid structure.[74] Traditionally, methods of metabolic surgery include the use of a bile acid shunt, gastric volume reduction, gut diversion, vagus nerve regulation, and gut hormone regulation. Metabolic surgery can reduce the abundance of butyric acid-producing bacteria and increase the abundance of Proteobacteria. Therefore, alterations in the gut microbiota and functional products (such as endotoxins, bile acids, and branched-chain amino acids) may also be outcomes of metabolic surgery.[75,76]

De Jonge et al[77] reported that 17 obese patients with T2DM received non-surgical duodenojejunostomy bypass. After 6 months of intervention, the weight and glycosylated hemoglobin of the subjects were improved. The number of typical small gut bacteria in the feces was also altered. In particular, the frequency of Proteobacteria, Veillonella, and Lactobacillus species in the feces was increased. However, some studies have shown that as time goes on after the initial intervention, microbiota will return to their baseline level. Weight loss from metabolic surgery may be due to food restriction intake or dietary restrictions, or it may be due to a decreased gastric volume or changes in the gut peptide concentration. The recovery of diversity in the gut microbiota after metabolic surgery may be one of the mechanisms of weight loss after metabolic surgery. The role of gut microbiota in prognosis after metabolic surgery is a subject still in need of studies with a large sample size to confirm these hypotheses.

Drugs

Drugs can affect the composition and function of the gut microbiota. The gut microbiota can directly participate in drug metabolism, affect drug efficacy and toxicity. It can also interact with the immune/metabolic system, indirectly affecting drug response and bioavailability as well.

Sun et al[78] reported that after metformin treatment, the gut microbiota of newly diagnosed T2DM patients changed, where the Bacteroides fragilis population was decreased significantly, and levels of glycoursodeoxycholic acid (GUDCA) and tauroursodeoxycholic acid (TUDCA) were increased. GUDCA and TUDCA are FXR antagonists. Metformin is known to be able to inhibit the growth

of *B. fragilis* and to decrease the activity of BSH enzymes in the bacteria. It has also been reported to increase the level of GUDCA, inhibit the FXR signaling in the gastrointestinal tract and improve metabolism by using an alternative route to the AMPK signaling pathway. Obese mice fed a high-fat diet were given oral GUDCA, which inhibited FXR signaling in the intestine, increasing GLP-1 in the blood and improving blood glucose homeostasis.

Zhao *et al*[79] reported that liraglutide could prevent weight gain by regulating the gut microbiota composition of obese and diabetically obese individuals. Experiments in obese and diabetic obese rats showed that liraglutide significantly improved glucose and lipid metabolism, and its effect of reducing body weight was not affected by blood glucose status. Liraglutide significantly reduced the abundance and diversity of gut microbiota, reducing the microbial phenotype associated with obesity, and increased the phenotype associated with lean mice.

Caparrós-Martín *et al*[80] reported that through the mouse model, they found that the composition of gut microbiota changed significantly after treatment with statins. The diversity and metabolic characteristics of gut microbiota changed significantly and were related to a decrease in butyrate production. The enrichment of *Bacteroidetes* over *Firmicutes* in the gut microbiota after treatment with statins may explain the transition from butyrate to acetate, lactate, and succinate. The size and composition of bile acid pools in the gut are changed by the use of statins.

Conclusions

Current clinical and experimental evidence shows that the gut microbiota is one of the most important pathogenic factors in MetS. MetS itself is a phenotype caused by the interaction of host intrinsic factors such as genetics and the gut microbiome, and extrinsic factors such as diet and lifestyle. MetS is often accompanied by an imbalance of the gut microbiota, inducing a low-grade inflammatory response in the body by destroying the gut barrier, producing insulin resistance through metabolites affecting host metabolism and hormone release, forming a vicious circle that promotes the continuous progress of MetS. Therefore, gut microbiota may be a potential target for the treatment of MetS. However, further research is needed to deepen our understanding of the manipulation of gut microbiota and its role in the prevention and treatment of MetS. This will open new therapeutic strategies.

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Conflicts of interest

None.

References

1. Oda E. Historical perspectives of the metabolic syndrome. Clin Dermatol 2018;36:3–8. doi: 10.1016/j.clindermatol.2017.09.002.

2. Battault S, Meziat C, Nascimento A, Braud L, Gayrard S, Legros C, et al. Vascular endothelial function masks increased sympathetic vasopressor activity in rats with metabolic syndrome. Am J Physiol Heart Circ Physiol 2018;314:H497–H507. doi: 10.1152/ajpheart.00217.2017.

3. Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat Med 2017;23:859–868. doi: 10.1038/nm.4358.

4. Moran-Ramos S, Lopez-Contreras BE, Canizales-Quinteros S. Gut microbiota in obesity and metabolic abnormalities: a matter of composition or functionality? Arch Med Res 2017;48:735–753. doi: 10.1016/j.arcmed.2017.11.003.

5. Zhao L. The gut microbiota and obesity: from correlation to causality. Nat Rev Microbiol 2013;11:639–647. doi: 10.1038/nrmicro3089.

6. Tomas J, Mulet C, Saffarian A, Cavin JB, Ducroc R, Regnault B, et al. High-fat diet modifies the PPAR-gamma pathway leading to disruption of microbial and physiological ecosystem in murine small intestine. Proc Natl Acad Sci U S A 2016;113:E5934–E5943. doi: 10.1073/pnas.1612559113.

7. Thingholm LB, Ruhlemann MC, Koch M, Fuqua B, Laucke G, Boehm R, et al. Obese individuals with and without type 2 diabetes show different gut microbial functional capacity and composition. Cell Host Microbe 2019;26:252–264.e10. doi: 10.1016/j.chom.2019.07.004.

8. Fei N, Zhao L. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. ISME J 2013;7:880–884. doi: 10.1038/ismej.2012.153.

9. Zhou W, Xu H, Zhan L, Lu X, Zhang L. Dynamic development of fecal microbiome during the progression of diabetes mellitus in Zucker diabetic fatty rats. Front Microbiol 2019;10:232. doi: 10.3389/fmicb.2019.00232.

10. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012;490:55–60. doi: 10.1038/nature11450.

11. Lin HV, Frassetto A, Kowalik EJ Jr, Nawrocki AR, Lu MM, Kosinski JR, et al. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS One 2012;7:e35240. doi: 10.1371/journal.pone.0035240.

12. Archer BJ, Johnson SK, Devereux HM, Baxter AL. Effect of fat replacement by inulin or lupin-kernel fibre on sausage patty acceptability, post-meal perceptions of satiety and food intake in men. Br J Nutr 2004;91:591–599. doi: 10.1079/BJN20031088.

13. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther 2008;27:104–119. doi: 10.1111/j.1365-2036.2007.03562.x.

14. Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes 2010;59:3049–3057. doi: 10.2337/db10-0253.

15. Munukka E, Wiklund P, Pekkala S, Volgyi E, Xu L, Cheng S, et al. Women with and without metabolic disorder differ in their gut microbiota composition. Obesity (Silver Spring) 2012;20:1082–1087. doi: 10.1038/oby.2012.8.

16. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 2010;5:e9085. doi: 10.1371/journal.pone.0009085.

17. Do MH, Lee E, Oh MJ, Kim Y, Park HY. High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients 2018;10. doi: 10.3390/nu10060761.

18. Wang Z, Koonen D, Hofker M, Fu J. Gut microbiome and lipid metabolism: from associations to mechanisms. Curr Opin Lipidol 2016;27:216–224. doi: 10.1097/MOL.0000000000000308.

19. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM, et al. Gut dysbiosis is linked to hypertension. Hypertension 2015;65:1331–1340. doi: 10.1161/HYPERTENSIONAHA.115.05315.

20. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome 2017;5:14. doi: 10.1186/s40168-016-0222-x.

21. Xu D, Lv Q, Wang X, Cui X, Zhao P, Yang X, et al. Hyperuricemia is associated with impaired intestinal permeability in mice. Am J Physiol Gastrointest Liver Physiol 2019;317:G484–G492. doi: 10.1152/ajpgi.00151.2019.

22. Guo Z, Zhang J, Wang Z, Ang KY, Huang S, Hou Q, et al. Intestinal microbiota distinguish gout patients from healthy humans. Sci Rep 2016;6:20602. doi: 10.1038/srep20602.

23. Yuan J, Chen C, Cui J, Lu J, Yan C, Wei X, et al. Fatty liver disease caused by high-alcohol-producing Klebsiella pneumoniae. Cell Metab 2019;30:675–688.e7. doi: 10.1016/j.cmet.2019.08.018.

24. Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013;57:601–609. doi: 10.1002/hep.26093.

25. Moreno-Indias I, Torres M, Montserrat JM, Sanchez-Alcoholado L, Cardona F, Tinahones FJ, et al. Intermittent hypoxia alters gut microbiota diversity in a mouse model of sleep apnoea. Eur Respir J 2015;45:1055–1065. doi: 10.1183/09031936.00184314.

26. Ko CY, Liu QQ, Su HZ, Zhang HP, Fan JM, Yang JH, et al. Gut microbiota in obstructive sleep apnea-hypopnea syndrome: disease-related dysbiosis and metabolic comorbidities. Clin Sci (Lond) 2019;133:905–917. doi: 10.1042/CS20180891.

27. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16:35–56. doi: 10.1038/s41575-018-0061-2.

28. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–334. doi: 10.1001/jama.286.3.327.

29. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;542:177–185. doi: 10.1038/nature21363.

30. Cani PD. Human gut microbiome: hopes, threats and promises. Gut 2018;67:1716–1725. doi: 10.1136/gutjnl-2018-316723.

31. Schroeder BO, Backhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 2016;22:1079–1089. doi: 10.1038/nm.4185.

32. Lee JS, Tato CM, Joyce-Shaikh B, Gulen MF, Cayatte C, Chen Y, et al. Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. Immunity 2015;43:727–738. doi: 10.1016/j.immuni.2015.09.003.

33. Stockinger B, Omenetti S. The dichotomous nature of T helper 17 cells. Nat Rev Immunol 2017;17:535–544. doi: 10.1038/nri.2017.50.

34. Brown EM, Sadarangani M, Finlay BB. The role of the immune system in governing host-microbe interactions in the intestine. Nat Immunol 2013;14:660–667. doi: 10.1038/ni.2611.

35. McDole JR, Wheeler LW, McDonald KG, Wang B, Konjufca V, Knoop KA, et al. Goblet cells deliver luminal antigen to CD103+ dendritic cells in the small intestine. Nature 2012;483:345–349. doi: 10.1038/nature10863.

36. Levy M, Thaiss CA, Zeevi D, Dohnalova L, Zilberman-Schapira G, Mahdi JA, et al. Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. Cell 2015;163:1428–1443. doi: 10.1016/j.cell.2015.10.048.

37. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 2012;482:179–185. doi: 10.1038/nature10809.

38. Natividad JM, Agus A, Planchais J, Lamas B, Jarry AC, Martin R, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. Cell Metab 2018;28:737–749.e4. doi: 10.1016/j.cmet.2018.07.001.

39. Wei X, Yang Z, Rey FE, Ridaura VK, Davidson NO, Gordon JI, et al. Fatty acid synthase modulates intestinal barrier function through palmitoylation of mucin 2. Cell Host Microbe 2012;11:140–152. doi: 10.1016/j.chom.2011.12.006.

40. Yoshida N, Emoto T, Yamashita T, Watanabe H, Hayashi T, Tabata T, et al. Bacteroides vulgatus and Bacteroides dorei reduce gut microbial lipopolysaccharide production and inhibit atherosclerosis. Circulation 2018;138:2486–2498. doi: 10.1161/CIRCULATIONAHA.118.033714.

41. O'Neill LA, Golenbock D, Bowie AG. The history of Toll-like receptors - redefining innate immunity. Nat Rev Immunol 2013;13:453–460. doi: 10.1038/nri3446.

42. Hoyles L, Fernandez-Real JM, Federici M, Serino M, Abbott J, Charpentier J, et al. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat Med 2018;24:1070–1080. doi: 10.1038/s41591-018-0061-3.

43. Koh A, Molinaro A, Stahlman M, Khan MT, Schmidt C, Manneras-Holm L, et al. Microbially produced imidazole propionate impairs insulin signaling through mTORC1. Cell 2018;175:947–961.e71. doi: 10.1016/j.cell.2018.09.055.

44. Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science 2018;359:1376–1383. doi: 10.1126/science.aar3318.

45. Suzuki T, Hara H. Dietary fat and bile juice, but not obesity, are responsible for the increase in small intestinal permeability induced through the suppression of tight junction protein expression in LETO and OLETF rats. Nutr Metab (Lond) 2010;7:19. doi: 10.1186/1743-7075-7-19.

46. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol 2015;11:577–591. doi: 10.1038/nrendo.2015.128.

47. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014;156:84–96. doi: 10.1016/j.cell.2013.12.016.

48. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001;81:1031–1064. doi: 10.1152/physrev.2001.81.3.1031.

49. Grootaert C, Van de Wiele T, Van Roosbroeck I, Possemiers S, Vercoutter-Edouart AS, Verstraete W, et al. Bacterial monocultures, propionate, butyrate and H2O2 modulate the expression, secretion and structure of the fasting-induced adipose factor in gut epithelial cell lines. Environ Microbiol 2011;13:1778–1789. doi: 10.1111/j.1462-2920.2011.02482.x.

50. Dewulf EM, Cani PD, Neyrinck AM, Possemiers S, Van Holle A, Muccioli GG, et al. Inulin-type fructans with prebiotic properties counteract GPR43 overexpression and PPARgamma-related adipogenesis in the white adipose tissue of high-fat diet-fed mice. J Nutr Biochem 2011;22:712–722. doi: 10.1016/j.jnutbio.2010.05.009.

51. Al-Lahham S, Roelofsen H, Rezaee F, Weening D, Hoek A, Vonk R, et al. Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. Eur J Clin Invest 2012;42:357–364. doi: 10.1111/j.1365-2362.2011.02590.x.

52. Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. Nat Commun 2015;6:6734. doi: 10.1038/ncomms7734.

53. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 2007;50:2374–2383. doi: 10.1007/s00125-007-0791-0.

54. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L, et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. Diabetes 2010;59:172–181. doi: 10.2337/db09-0367.

55. Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 2009;58:1509–1517. doi: 10.2337/db08-1637.

56. Yamashita H, Maruta H, Jozuka M, Kimura R, Iwabuchi H, Yamato M, et al. Effects of acetate on lipid metabolism in muscles and adipose tissues of type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biosci Biotechnol Biochem 2009;73:570–576. doi: 10.1271/bbb.80634.

57. Chai W, Dong Z, Wang N, Wang W, Tao L, Cao W, et al. Glucagon-like peptide 1 recruits microvasculature and increases glucose use in muscle via a nitric oxide-dependent mechanism. Diabetes 2012;61:888–896. doi: 10.2337/db11-1073.

58. Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. J Physiol Pharmacol 2008;59 (Suppl 2):251–262.

59. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor,

Gpr41. Proc Natl Acad Sci U S A 2008;105:16767–16772. doi: 10.1073/pnas.0808567105.

60. Molinaro A, Wahlstrom A, Marschall HU. Role of bile acids in metabolic control. Trends Endocrinol Metab 2018;29:31–41. doi: 10.1016/j.tem.2017.11.002.

61. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annu Rev Biochem 2003;72:137–174. doi: 10.1146/annurev.biochem.72.121801.161712.

62. Thomas C, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K. Targeting bile-acid signalling for metabolic diseases. Nat Rev Drug Discov 2008;7:678–693. doi: 10.1038/nrd2619.

63. Sayin SI, Wahlstrom A, Felin J, Jantti S, Marschall HU, Bamberg K, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab 2013;17:225–235. doi: 10.1016/j.cmet.2013.01.003.

64. Wahlstrom A, Sayin SI, Marschall HU, Backhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab 2016;24:41–50. doi: 10.1016/j.cmet.2016.05.005.

65. Jones BV, Begley M, Hill C, Gahan CG, Marchesi JR. Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. Proc Natl Acad Sci U S A 2008;105:13580–13585. doi: 10.1073/pnas.0804437105.

66. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559–563. doi: 10.1038/nature12820.

67. Trabelsi MS, Daoudi M, Prawitt J, Ducastel S, Touche V, Sayin SI, et al. Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. Nat Commun 2015;6:7629. doi: 10.1038/ncomms8629.

68. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol 2019;16:605–616. doi: 10.1038/s41575-019-0173-3.

69. Gasbarrini G, Bonvicini F, Gramenzi A. Probiotics History. J Clin Gastroenterol 2016; 50 Suppl 2, Proceedings from the 8th Probiotics, Prebiotics & New Foods for Microbiota and Human Health meeting held in Rome, Italy on September 13-15, 2015:S116-S9. doi: 10.1097/MCG.0000000000000697.

70. Tenorio-Jimenez C, Martinez-Ramirez MJ, Del Castillo-Codes I, Arraiza-Irigoyen C, Tercero-Lozano M, Camacho J, et al. Lactobacillus reuteri V3401 reduces inflammatory biomarkers and modifies the gastrointestinal microbiome in adults with metabolic syndrome: the PROSIR study. Nutrients 2019;11:E1761. doi: 10.3390/nu11081761.

71. Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 2004;17:259–275. doi: 10.1079/NRR200479.

72. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 2018;359:1151–1156. doi: 10.1126/science.aao5774.

73. Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7. doi: 10.1053/j.gastro.2012.06.031.

74. Anhe FF, Varin TV, Schertzer JD, Marette A. The gut microbiota as a mediator of metabolic benefits after bariatric surgery. Can J Diabetes 2017;41:439–447. doi: 10.1016/j.jcjd.2017.02.002.

75. Seganfredo FB, Blume CA, Moehlecke M, Giongo A, Casagrande DS, Spolidoro JVN, et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. Obes Rev 2017;18:832–851. doi: 10.1111/obr.12541.

76. Debedat J, Amouyal C, Aron-Wisnewsky J, Clement K. Impact of bariatric surgery on type 2 diabetes: contribution of inflammation and gut microbiome? Semin Immunopathol 2019;41:461–475. doi: 10.1007/s00281-019-00738-3.

77. de Jonge C, Fuentes S, Zoetendal EG, Bouvy ND, Nelissen R, Buurman WA, et al. Metabolic improvement in obese patients after duodenal-jejunal exclusion is associated with intestinal microbiota composition changes. Int J Obes (Lond) 2019;43:2509–2517. doi: 10.1038/s41366-019-0336-x.

78. Sun L, Xie C, Wang G, Wu Y, Wu Q, Wang X, et al. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. Nat Med 2018;24:1919–1929. doi: 10.1038/s41591-018-0222-4.

79. Zhao L, Chen Y, Xia F, Abudukerimu B, Zhang W, Guo Y, et al. A glucagon-like peptide-1 receptor agonist lowers weight by modulating the structure of gut microbiota. Front Endocrinol (Lausanne) 2018;9:233. doi: 10.3389/fendo.2018.00233.

80. Caparros-Martin JA, Lareu RR, Ramsay JP, Peplies J, Reen FJ, Headlam HA, et al. Statin therapy causes gut dysbiosis in mice through a PXR-dependent mechanism. Microbiome 2017;5:95. doi: 10.1186/s40168-017-0312-4.