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Gut Microbiota and Metabolic Diseases

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Abstract

In this review, the characteristics of gut microbiota changes in 11 metabolic diseases, as well as the research progress on their interventions, are summarized. The gut microbiota contributes to metabolic diseases through intestinal mucosal dysfunction, chronic metabolic inflammatory response, gut brain axis imbalance, gene regulation, insulin resistance, and the action of its metabolites. The researches of cause effect relationship and mechanism are relatively few, need further study, expecting a breakthrough in the future to be a new path in the treatment of some metabolic diseases.

Keywords

Gut Microbiota, Microbiota-Gut-Brain Axis, Metabolic Diseases, Interventions

1. Introduction

Metabolic diseases refer to disorders that occur at some point in the body's metabolism, and mainly refer to a class of diseases caused by abnormal metabolism of glucose, proteins and lipids in the body [1]. It is the result of a combination of genetic and environmental factors [2]. It has been found that a large number of microorganisms inhabit in the human skin, upper respiratory tract, oral cavity, intestinal tract, vagina, and most microorganisms host in the intestine [3], and the intestinal flora balance organism health, and the disturbance of intestinal flora can cause respiratory [4], circulatory [5], digestive [6], urinary [7], reproductive [8], endocrine [9], blood [10], motor [11], immune [12], neurological [13], metabolic diseases [14]. The relationship with metabolic diseases is the earliest studied, within the last 2 years or more, and is of particular interest, because diabetes, obesity, and hypertension, which are currently prevalent coronavirus diseases worldwide, can significantly increase the risk of new coronavirus pneu-

monia exacerbations and associated mortality [15], and the literature linking the gut microbiota with metabolic diseases is now reviewed, increases and expands the thoughts on the pathogenesis of some metabolic diseases, and explores new approaches for the diagnosis and treatment of such metabolic diseases.

2. Overview of the Gut Microbiota

The studies have shown that gut flora is one of the important environmental factors affecting human health [16]. It is the collective term of multiple microbial communities inhabiting the intestine and symbiotic with the host, with bacteria, viruses and fungi, etc. [17], 98% of them are bacteria, weight 0.2 - 2.0 kg, species over 500 - 1000, have 10^{14} colony forming units, about 10 times the number of human cells, 150 times the number of human genes [18], more than 50 bacterial phyla in the intestine, There are five major bacterial phyla: gram negative Bacteroidetes (e.g. Bacteroidetes), gram positive Firmicutes (e.g. Enterococcus and Lactobacillus), Actinobacteria, Proteobacteria, and verrucomicrobia, the first two most common [19]. A dysregulated or inverted Firmicutes/Bacteroidetes ratio suggests an imbalance of gut microbiota [3]. The gut microbiota forms a protective biological barrier and maintains junctions between epithelial cells at the mucosal surface of the intestine, has a role in regulating its permeability [20], promotes the secretion of defensins and immunoglobulin A (IGA) from intestinal epithelial cells, decreases the colonization of pathogenic bacteria, inhibits the binding and invasion of pathogenic bacteria to intestinal epithelial cells, prevents excessive proliferation of pathogenic bacteria and viral infection, It is important for the developmental maturation and maintenance of normal function of the body's immune system [3], as well as improving human metabolism, anti inflammation, antioxidant and anti-aging effects [21]. The gut microbiota is a specific biological factor [22] that mediates neuroendocrine and immune functions, influencing body weight and the development of metabolic diseases [23]. Many observational studies support that alterations in the gut flora are associated with weight gain and obesity, T2DM [24], and prediabetes [25]. Clinical interventions for these conditions through the intake of prebiotics, probiotics, synbiotics as well as healthy diets have been reported [26]. Therefore, it is very necessary to pay more attention to the relationship between gut flora and metabolic diseases.

3. Mechanisms of the Gut Microbiota in Metabolic Diseases

The mechanism is multipathway, with 1 - 2 species and 3 - 4 pathways working together. There are currently relatively well-defined hypothesis: 1) Gut mucosal dysfunction: when the gut microbiota is dysregulated, leading to increased intestinal mucosal permeability, one of the components of the cell wall of gram negative bacteria in the gut, lipopolysaccharide (LPS), enters the blood to bind with lipopolysaccharide binding protein (LBP) to activate the receptor CD14 on the surface of immune cells, CD14 assists LPS recognition and activates CD14/Toll

like receptor 4 (TLR4), which then further activates MyD88/NF-κB signaling pathway that promotes the production of inflammatory response factors (e.g. IL-1, IL-6, TNF-*α et al.*) release, which causes an inflammatory cascade in the body, leading to the migration of macrophages into tissue organs, resulting in the entry of the body into a low-grade inflammatory state and insulin resistance, thereby producing metabolic abnormalities [1], such as Mets, and NAFLD when the target organ is the liver. These inflammatory factors can increase the permeability of the blood-brain barrier and enter the brain tissue, causing neuroinflammation leading to hypertension. An LPS producing pathogen, enterobacter, isolated from obese patients was found to induce the development of obesity and insulin resistance in germ free mice. Clinical studies have proved that probiotic therapy can significantly reduce serum LPS levels, inhibit inflammatory factors, and significantly improve insulin resistance while delaying disease progression in diabetic patients. Increased levels of LPS will cause extensive growth and reproduction of intestinal pathogenic bacteria, and the probiotic activity is inhibited, and effective reduction of LPS levels is of great significance for the prevention and treatment of metabolic diseases. 2) Chronic metabolic inflammatory response: Gut microbiota communicate with systemic immune cells. Evidence indicates that chronic low-grade tissue inflammation, which occurs in adipose tissue, can lead to insulin resistance and T2DM, steatohepatitis. Adipose tissue macrophages,a heterogeneous immune cell population with diverse functions, directly or indirectly regulate obesity and energy storage, are important contributors to the pathogenesis of obesity and associated comorbidities, and are key regulators of obesity related inflammatory and metabolic complications. Macrophages are the major immune cells involved in obesity associated inflammation in mice and humans. Macrophage IRX3 (iroquoise class homeobox protein) promotes metabolic inflammation and accelerates the development of obesity and type 2 diabetes, mice with myeloid specific deletion of IRX3 protect against diet induced obesity and metabolic disease by increasing adaptive thermogenesis, and macrophage IRX3 promotes pro-inflammatory cytokine transcription, which suppresses adipocyte adrenergic signaling and thereby lipolysis and thermogenesis [25], leading to the onset and progression of obesity [26]. 3) Gut brain axis imbalances: The gut microbiota and gut brain axis bidirectional interactions are shaped by cultivation during pregnancy and the first 1000 days of life. The brain influences many gastrointestinal processes, including motility and transit, fluid and mucus secretion, immune activation, gut permeability, and other gastrointestinal microenvironments through the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal (HPA) axis, thereby influencing gut bacterial composition, gut microbial abundance, as well as gene expression patterns of certain pathogenic gut microbes and altering the function of the gut microbiota [27]. At the same time, the gut microbiota can communicate with the brain through hundreds of metabolites, which are sensed by specialized cells in the gut, including enteroendocrine cells, enterochromaffin cells, and primary

or secondary afferent nerve endings. SCFAs, BAS, and amino acid derived metabolites and subcellular bacterial components, such as gut flora metabolites such as casein hydrolysate peptidase B (ClpB), LPS, or muramyl dipeptide (MDP) [28], affect the central nervous system (CNS) via endocrine [29], and vagal pathways. Disturbance at any level of the gut brain axis system leads to impairment of inhibitory mechanisms regulating food intake, affecting eating habits, increased appetite and overeating [30], resulting in the onset and progression of obesity and related metabolic diseases. 4) Gene regulation: The gut microbiota also regulates the expression of approximately 10% of the transcribable genes in the host, which affects the body's immunity, proliferation, metabolism and exerts dual influences on environmental and genetic factors of metabolic diseases, and studies have found that individuals with a low abundance of genes in the gut microbiota are more likely to develop metabolic abnormalities such as systemic obesity, lipid metabolism disorders, and insulin resistance than those with a high abundance. A population-based study of gut microbial composition in 123 non obese and 169 obese Danish individuals found: the two groups of individuals differed in the number of gut microbial genes, with individuals with low bacterial gene abundances exhibiting more pronounced overall obesity, insulin resistance and dyslipidemia, and a more pronounced inflammatory phenotype, compared to individuals with high bacterial gene abundances, who may be at higher risk of developing obesity and related complications. The fasting induced Adipocyte Factor (FIAF) gene is primarily responsible for encoding the lipoprotein lipase (LPL) inhibitor, which inhibits triglyceride cycling by inhibiting LPL. Correlation between gut microbiota changes and FIAF, insulin resistance in NAFLD patients studies have shown that the number of Proteobacteria was significantly negatively correlated with the expression level of FIAF and positively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) [1]. Studies of the effects of several Lactobacillus strains on human intestinal epithelial FIAF gene expression found [31]: *Lactobacillus rhamnosus* cncmi-4317 was able to induce expression of human intestinal epithelial FIAF, increasing the body's energy stores. 5) Insulin resistance (IR): Insulin is a peptide hormone secreted by pancreatic β cells in response to hyperglycemia. It exerts anabolic effects by inhibiting lipolysis and hepatic gluconeogenesis, while increasing glucose uptake in liver, muscle, and adipose tissue [32]. Disturbed gut microbiota and its metabolites can lead to chronic inflammation in adipose tissue, mainly due to increased accumulation of pro-inflammatory macrophages in human and mouse adipose tissue, but also other immune cells. Involved in this inflammatory process, these cells are the main immune cells that secrete most inflammatory cytokines (TNFα, IL-6), galectin-3 and exosomes. TNFα has the ability to lead to insulin signaling Reduced transduction and induced local tissue effects, thereby reducing insulin action, can reduce the expression of Irs2 and Glut4, promote inhibitory phosphorylated substrate (IRS) proteins of the insulin receptor, enhance lipolysis in adipocytes, and generate free Fatty acids (FFAs) enter the blood circu-

lation, and the increase of FFA leads to changes in insulin signaling cascades in different organs, thereby worsening IR and creating a vicious circle. Severe IR presents a variety of abnormal metabolic diseases and a higher risk of cardiovascular, renal, and hepatic comorbidities [33]. 6) The role of gut microbiota metabolites: Half of the small molecules in the blood are either produced or regulated by microorganisms [34], the common ones are: dopamine, bile acids (BAs), glutamic acid, 5-hydroxytryptamine (5-HT), γ-aminobutyric acid, Short-chain fatty acids (SCFAs), Trimethylamine N-oxide (TMAO), hydrogen sulfide (H2S). SCFAs signal through G protein-sensitive G protein-coupled receptors, and circulating SCFAs in the blood affect tissue-specific acetylation of histones 3 and 4. It induces epigenetic changes in the genome and is involved in the regulation of host neuroimmune endocrine function, gut homeostasis and energy metabolism. SCFAs are the main metabolites of gut microbiota, play an important role in the pathogenesis of hypertension, and have a significant correlation with blood pressure levels. After SCFAs enter the blood circulation, they enter the Kreb's circulation through acetyl-CoA, which increases the body's energy intake and induces obesity. Animal experiments have shown that the changes in the gut microbiota of rodents caused by high-fat diet Acetate production increases, activates the parasympathetic nervous system, promotes glucose-stimulated insulin secretion, increases growth hormone secretion, and overfeeds, resulting in obesity and related diseases [35]. Conversely, however, it was found that dietary supplementation with acetic acid, propionic acid, butyric acid or their mixtures significantly inhibited high-fat diet-induced weight gain [36], and SCFAs supplementation increased the expression of GPR43 and GPR41 in adipose tissue, increases triglyceride hydrolysis and FFA oxidation in adipose tissue, promotes beige adipocyte and mitochondrial biosynthesis, inhibits chronic inflammatory responses, and further reduces body weight. SCFAs can also promote the secretion of glucagon like peptide 1 (GLP-1), tyrosyl peptide YY (PYY), leptin, and so on by binding to gpcr41 or gpcr43, further inhibiting gastric secretion and gastrointestinal motility, delaying gastric content emptying, while acting on the central nervous system such as the hypothalamus to produce a feeling of fullness and decrease in appetite to improve obesity While also improving insulin resistance. Gut microbiota can metabolize choline food into trimethylamine (TMA), which is absorbed into the liver and oxidized to TMAO by flavin monooxidase. TMAO can prevent cholesterol from flowing out of macrophages, so that cholesterol can be stored in macrophages. Foam cells accumulate continuously, and foam cells accumulate in the vascular endothelium to form arteriosclerosis; TMAO also has a certain degree of blood pressure raising effect. H2S is produced by intestinal sulfate-reducing bacteria [37] and affects blood pressure regulation through ATP-sensitive ion channels. After injecting normal saline and sodium sulfide (H2S donor) into hypertensive and normotensive rats, it was found that, Mean arterial blood pressure was significantly decreased in hypertensive rats. After treatment with neomycin, the levels of H2S derivatives such as thiosulfate

in rats were significantly reduced, indicating that the content of H2S in rats is related to hypertension. BAs are a group of products of cholesterol catabolism in the liver, which are divided into primary bile acids and secondary bile acids. Hepatocytes convert cholesterol into primary bile acids, which are stored in the gallbladder and released into the small intestine, where the gut microbiota converts primary bile acids into secondary bile acids [1]. This conversion is hindered when the gut microbial structure is altered, resulting in lower levels of secondary bile acids, affecting the expression of farnesoid X receptor (FXR) and G-protein coupled bile acid receptor 1 (GPBAR1) in tissues such as the gut, liver, and pancreas. The binding of bile acid metabolites to GPBAR1 can promote the release of type II deiodinase and increase thyroid hormone levels in the body, elevate fat metabolism and energy expenditure, improve and prevent the development of diseases such as obesity and insulin resistance. The study found that the intestinal FXR knockout mice fed a high-fat diet decreased plasma ceramide levels and showed lower diet-induced obesity and metabolic diseases [38], BAs-can inhibit 11-BHSD and mediate blood pressure elevation through a pseudo-aldosteronism effect, see **Figure 1**.

4. Metabolic Diseases

4.1. Obesity

Obesity, which refers to excessive body fat accumulation and adipose tissue hypertrophy [39], is a complex metabolic disease caused by a variety of non genetic and genetic factors [40], with the intensive study of the gut microbiota in obesity, the results all support that the gut microbiota can serve as a target for obesity treatment, and further exploration is needed. The study of the relationship between obesity and gut flora was the earliest study of the relationship between

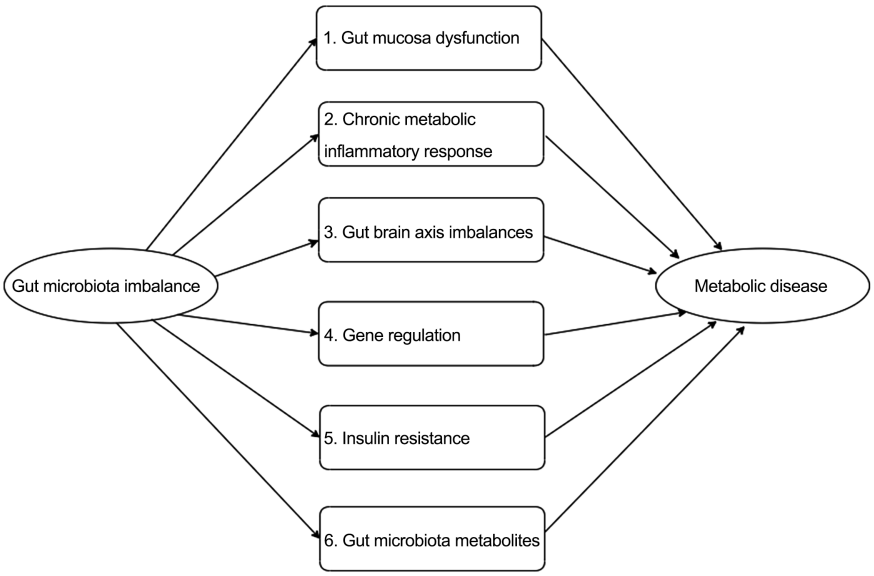

Figure 1. Mechanisms of metabolic disease caused by imbalanced gut microbiota.

human health and gut flora: germ free mice transplanted with normal gut flora were found to eat less and accumulate more fat after transplantation, which illustrated that the gut flora helped the animals to absorb calories from food more efficiently and become fat storing [41]. Recent studies have shown that the ratio of Firmicutes to Bacteroidetes in the gut is significantly higher in obese compared to lean subjects, while Bacteroidetes show the opposite trend, and the decreased number of genes in the gut flora is associated with severe metabolic abnormalities in obese subjects [42]; The microbiota differs significantly between obese and control subjects at different levels. The genera Prevotella, megamonas, Fusobacterium and blautia were significantly increased, while faecalibacterium, parabacteroides, Bifidobacterium and alistipes were significantly decreased in obese subjects; At the species level, nine species were significantly different between obese and control groups, among which Prevotella was significantly increased in the obese group [43]. A systematic review of randomized clinical trials of probiotics and synbiotics for weight loss in obese subjects suggested [44]: Probiotics and synbiotics from the Bifidobacterium genus Lactobacillus associated with other Lactobacillus species and/or species lactobacillus, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus curvatus* strains could help overweight and obese people lose weight and fat mass. However, clinical trials are needed to make more accurate recommendations regarding strain, dose, and timing of intervention.

4.2. Type 2 Diabetes Mellitus (T2DM)

T2DM, a metabolic disease mainly characterized by hyperglycemia and insulin resistance, results from a combination of several factors including genetics, gender, lifestyle, diet, aging and epigenetics [45]. In recent years, an increasing number of studies have proved that intestinal flora is closely related to type 2 diabetes and may be another etiological factor leading to type 2 diabetes [46]. Two large-scale meta genomic analyses investigated the characteristics of the gut microbiota in T2DM patients and healthy individuals: bacteria enriched in Chinese T2DM patients were mainly conditional pathogens such as *Escherichia coli*, some clostridia, *Bacteroides caccae* and *Eggerthella lenta*, and decreased abundances of butyrate producing bacteria, including *Eubacterium rectale*, *Clostridium difficile* SS3/4, *Faecalibacterium prausnitzii* and intestinal Roseburia [24]. Increased abundances of *Lactobacillus gasseri*, *Streptococcus mutans*, some clostridia and lactobacilli and decreased abundances of butyrate producing bacteria, including *Roseburia*, *Eubacterium* IRI, *Bacteroides enterica* and some clostridia, have been reported in European women with T2DM [16]. A meta-analysis showed that probiotics improved HbA1c and fasting insulin in diabetes. The effect of synbiotic supplementation on patients with type 2 diabetes has received increasing attention. A fecal microbiota transplantation (FMT) for 24 weeks of T2DM Double-blind randomized controlled trial results: Repeated FMT increases the level and duration of microbiota engraftment in obese patients with T2DM.

Combining a lifestyle intervention with FMT resulted in more favorable changes in the recipient's microbiota and improved lipid levels and Liver stiffness. The effect of FMT on blood glucose in diabetic patients has not been reported, and further research is needed in the future.

4.3. Hypertension (HTN)

HTN, defined as a condition in which arterial blood pressure is persistently high with a blood pressure value ≥ 140/90mmHg, often occurs in the middle-aged and elderly and obese individuals [47], is a cardiovascular syndrome in an evolving state caused by various factors (stress, physical inactivity, obesity, high sodium intake, unhealthy diet and possibly interacting genetic factors, etc.) [48] and is a risk factor associated with heart disease, stroke and chronic kidney disease with high morbidity and mortality, It is estimated that 16% - 37% of the global population has hypertensive disorders [49]. In recent years, increasing evidence has shown that the gut microbiota plays an important role in the development and pathogenesis of HTN and is an important player in the control of blood pressure [50]. Animal studies reported that the variation of fecal flora in essential hypertensive rats greatly exceeded that in normal rats, with a decrease in lipid and butyrate producing flora and a 5-fold increase in the Firmicutes to Bacteroidetes (F/b) ratio, an increase in microbial richness, diversity and even distribution degree and in DNA content per milliliter, and a marked decrease in the Firmicutes to Bacteroidetes ratio after 4 weeks of oral minocycline Administration [51]. In a study of 196 healthy individuals versus hypertensive patients, it was found that the number and diversity of gut microbial genes were significantly lower in the prehypertension group versus the healthy group, Prevotella and Klebsiella were significantly enriched in the prehypertension and HTN groups, some beneficial bacteria such as faecali, Rothia, oscillibacter were enriched in the healthy population and decreased significantly in the prehypertension and HTN groups [52]. In female hypertensive patients, an uncultured genus (erysipelotrichaceae-ucg003) of the family erysipelotrichaceae is present in higher relative abundance and ruminiclostridium 6 in lower relative abundance [53]; These results suggest that the overgrowth of some pathogenic bacteria and the lack of beneficial bacteria may jointly participate in the disease process of HTN. A 3-month multicenter, randomized, placebo-controlled, blinded clinical trial of oral FMT capsules or placebo capsules in 120 patients with grade 1 HTN is currently underway. All recruited patients will be randomized 1:1 to be taken on days 1, 7 and 14 and followed up on days 30, 60 and 90 in anticipation of good results. To date, there are no literature reports on the intervention of synbiotics in HTN.

4.4. Hyperlipidemia

Hyperlipidemia refers to the presence of excess fat or lipids in the blood [2], including increased levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglycerides (TG), and decreased high-density lipoprotein

(HDL) cholesterol [54]. Is a major risk factor for cardiovascular disease (CVD) [55]. The etiology is the result of a combination of genes and environmental factors [56]. The gut microbiota has been reported to play a crucial role in regulating host lipid metabolism [2]. Animal experiments suggest a causative role of gut microbiota in the development of hyperlipidemia [57]. Microbiota associated metabolites such as BAS, LPS, TMAO, SCFA have been shown to modulate hyperlipidemia. Feces of hyperlipidemic children and adolescents had lower levels of SCFA producing bacteria such as those from lachnospiraceae and ruminococcaceae as well as those from akkermansia, Bacteroides, roseobacter and faecalibacterium [58]. A randomized controlled trial showed that feces of patients with metabolic syndrome (characterized by hyperlipidemia) have lower abundance of potential probiotics, such as Bifidobacterium, Lactobacillus, faecalibacterium prausnitzii and Roseburia, but higher abundance of LPS producing Escherichia coli and Enterobacter cloacae compared to feces of healthy individuals [59]. The data show that prebiotics, probiotics, and fecal microbiota transplantation have therapeutic effects on hyperlipidemia, indicating that intestinal flora may be a potential therapeutic target for hyperlipidemia [2].

4.5. Hyperuricemia (HU)

HU, one of the major metabolic diseases caused by purine metabolism disorder, is clinically closely related to many diseases, such as diabetes, HTN, stroke, myocardial infarction [60]. In addition to causing gout attacks, and the prevalence rate has increased year by year in many countries, which has become a common disease that seriously threatens human health [61]. The intestine is the largest organ of the human body and has a huge potential for uric acid excretion [62], and studies have found that probiotic supplementation can reduce uric acid levels, suggesting that probiotics hold promise as a new direction for the treatment of gout and HU [63]. An analysis of gut flora characteristics in asymptomatic Hu (45 cases) versus healthy controls (45 cases) showed [64]: in asymptomatic HU, the abundance of bacteria such as alipipes, dialister, Roseburia, gemmiger and faecalibacterium was relatively high, while the abundance of bacteria such as Bifidobacterium, Klebsiella and Clostridium was relatively low, which was comparable to that of the asymptomatic Hu group α The diversity index was higher in cases than in controls, β Diversity indices also showed significant differences, and unclassified Enterobacteriaceae, Roseburia and faecalibacterium, had good diagnostic values for asymptomatic HU.

4.6. Non Alcoholic Fatty Liver Disease (NAFLD)

NAFLD, a metabolic disease characterized by the presence of hepatic steatosis, hepatic fat accumulation on imaging or histologic testing to exclude alcohol abuse or other causes of indeterminate liver damage [65], is a leading cause of chronic liver disease worldwide [66] and poses a serious threat to human health, which can evolve to nonalcoholic steatohepatitis (NASH), cirrhosis if NAFLD

delays treatment, Even liver cancer [67], which can also present with a wide range of extrahepatic manifestations such as obesity, type 2 diabetes, metabolic syndrome, cardiovascular disease, chronic kidney disease, extrahepatic malignancies, cognitive impairment and polycystic ovary syndrome, is a multisystemic clinical disorder [68]. In recent years, studies on the gut flora, especially the regulation of key components and metabolites on the development and progression of NAFLD, have been conducted. The report of animal studies on the gut microbiota of NAFLD [69] [70] found that *Firmicutes* ↑ *Actinobacteria* ↑ *Deferribacters* ↓ *Bacteroidetes* ↓ *Lactobacillus Murinus*. Studies in patients with NAFLD have found [71] [72] ↑ *Bacteroidaceae* ↑ *Prevotellaceae* ↑ *Proteobacteria* ↑ *Verrucomicrobia* ↑ *Actinobacteri* ↓ *Euryarchaeota* ↓ *Lachnospiraceae* ↓ *Ruminococcaceae* ↓ *Lactobacillaceae*, suggesting that a higher proportion of gram negative bacteria (including Bacteroidetes) is associated with a decrease in short chain fatty acid (SCFA), producing Firmicutes; In children with NAFLD, gram negative bacterial species are overgrown, with increased proportions of gammaproteobacteria and epsilonproteobacteria compared with their obese and lean counterparts [73]. A meta-analysis of 15 randomized controlled trials of probiotics and synbiotics involving 782 patients with NAFLD showed that supplementation with probiotics and synbiotics was associated with significantly lower levels of TG, TC, HDL-C, LDL-C, and TNF-*α*. In general, probiotics/synbiotics are safe and well tolerated, and the long-term protection of NAFLD is sustainable, and further studies are warranted to more clearly elucidate the effectiveness of probiotics/synbiotics in NAFLD management, safety and sustainability.

4.7. Alcoholic Fatty Liver Disease (AFLD)

AFLD is a fatty liver disease caused by a large amount of continuous alcohol intake, with a prevalence rate of 6% [74]. If only fat accumulates in the liver, it is called benign or simple fatty liver. Inflammatory reaction is called steatohepatitis. Without treatment or delay in treatment, it can form fibrosis and cirrhosis, and can also develop into hepatocellular carcinoma and liver failure, eventually leading to death. 20% of AFLD patients will develop into progressive liver disease [75]. It is the most common chronic liver disease in the western world and the main cause of liver transplantation [76]. More than 500,000 people worldwide die of alcoholic liver disease every year [77]. Animal studies have shown that three weeks of alcohol exposure will lead to "intestinal leakage", thus increasing the number of bacteroides and verrucae, and reducing the growth of bacteria with anti-inflammatory activity in the cecum, such as chlamydia (genus, such as lactobacillus, lactococcus, Leuconostoc and Pediococcus) [78]. These changes were restored by probiotic *Lactobacillus rhamnosus* GG therapy. Cross study of human shows that drinking red wine will increase the number of bacteroides, enterococcus and bifidobacteria [79]. Research report on intestinal flora of AFLD [80]: ↑ *Olsenella* ↑ *Eubacterium* ↑ *Activibrio* ↑ *Actinobacia* ↑

Firms ↑ *Coriobateriaceae* ↑ *Odoribacteriaceae* ↑ *Clostridiaceae* ↑ *Dora* ↓ *Proteobateria* ↓ *Bacteroides* ↓ *Acinetobacter* ↓ *Anaerotruncus* ↓ *Akkerman sia* ↓ *Blautia*. In addition, fecal transplantation of alcohol fed wild rats in dwarf animals increased liver and intestinal inflammation, indicating that intestinal microbiota participated in AFLD [81]. Research report on intestinal microflora of AFLD [82] ↑ *Candida* spp. ↑ *Candida albicans* ↑ *Candida dubliniensis* ↑ *Proteobasteria* ↑ *Fusobasteria* ↑ *Fusobasteriaceae* ↑ *Enterobasteriaceae* ↑ *Burkholderiae* ↑ *Escherichia Shigella* ↓ *Epicocum* ↓ *Unclassified fugi* ↓ *Galactomycete* ↓ *Debaryomyces* ↓ *Ruminococcaceae* ↓ *Faecaalibacterium* ↓ *ium* ↓ *Lachnospira* ↓ *Agathobacter* ↓ *Ruminococcus*. Because the etiology and pathogenesis of AFLD are basically clear, and alcohol withdrawal is the fundamental method for the treatment of AFLD, there are few reports in the literature on clinical intestinal flora intervention in AFLD.

4.8. Metabolic Syndrome (MetS)

The World Health Organization defined the syndrome and changed its name to MetS [83]: Presence of insulin resistance or glucose > 6.1 mmol/L (110 mg/dl), 2 h glucose > 7.8 mmol (140 mg/dl) (required), along with any two or more of the following: 1) HDL cholesterol < 0.9 mmol/L (35 mg/dl) in men, <1.0 mmol/L (40 mg/dl) in women; 2) Triglycerides > 1.7 mmol/L (150 mg/dl); 3) Waist/hip ratio > 0.9 (men) or >0.85 (women) or BMI > 30 kg/m^2; 4) Blood pressure > 140/90mmHg. In this literature review on obesity, HTN, hyperlipidemia and diabetes, it is shown that these metabolic diseases all have imbalance of intestinal flora, and MetS is bound to have stable intestinal flora, which is characterized by enrichment of potentially harmful bacteria and decline of beneficial bacteria [84].A meta-analysis of the application of probiotics, prebiotics, synbiotics, FMT and other microbial therapies in the treatment of MetS showed that microbial therapy can significantly improve FBG, TC, TG, HDL-C, LDL-C, WC, BMI, HOMA-IR and DBP, but no effect on SBP and HbA1c%.

4.9. Polycystic Ovary Syndrome (PCOS)

PCOS is a common endocrine metabolic disease, which is the main cause of anovulatory infertility in women of childbearing age [85]. Its clinical manifestations include increased secretion of ovarian and/or adrenal androgens, cessation of follicular development [86], and a series of metabolic diseases related to PCOS, such as obesity, T2DM, MetS and gestational diabetes, nonalcoholic fatty liver [87]. The literature reported the changes of intestinal flora of PCOS [14]: Prevotella Bacteroides Streptococcus enrichment, Lactobacillus Ruminococcus Clostridium Akkermania Ruminococcaeae reduction; Animal experiment [88]: αdiversity in PNA animals ↑, β diversity: the PNA animal samples were further apart. *Nocardiaceae* and *Clostridiaceae* ↑, *Akkermansia*, *Bacteroides*, *Lactobacillus*, and *Clostridium* ↓; Results of 38 cases of PCOS and 26 cases of control group [89] *Faecalibacterium*, *Bifidobacterium*, and *Blautia* ↓ *Parabolides*, *Bac-*

teroides, *Lactobacillus*, *Oscillibacter*, *Escherichia/Shigella*, *Clostridium* ↑. These data suggest that PCOS has different degrees of gut microbiota imbalance, and various interventions to alter the stability of the gastrointestinal microbiota may be an effective treatment for PCOS. Numerous prebiotic, probiotic, and synbiotic treatment studies have been reported. So far, there is no report of FMT intervention on PCOS. This is an interesting thing and worth looking forward to.

4.10. Wilson's Disease (WD)

WD, also known as hepatolenticular degeneration, is a disease of copper metabolism disorder and an autosomal recessive inheritance disease caused by ATP7B gene defect [90]. Recent studies have shown that environmental and dietary factors may change the gene expression of WD [91].

Fecal samples from 14 patients with WD and 16 healthy individuals were compared for 16S rRNA sequencing results [92]: the diversity and composition of the gut microbiome were significantly lower in the WD group than in healthy individuals. The WD group showed unique abundances of gemellaceae, pseudomonadaceae and lachnospiraceae at the family level, which were barely detected in healthy controls. Compared with healthy individuals, the WD group had significantly lower abundances of Actinobacteria, Firmicutes, and verrucomicrobia and higher abundances of Bacteroidetes, Proteobacteria, cyanobacteria, and fusobacteria. The Firmicutes to Bacteroidetes ratio was significantly lower in the WD group than in healthy controls. These results suggest that WD has a disturbance of the gut microbiota, is the pathogenesis of WD and a new possible therapeutic target? Due to the small number of WD cases, there is no literature report on the intervention of intestinal flora in clinical and animal experiments. This may provide a new direction for further research on WS.

4.11. Osteoporosis (OP)

OP is a chronic progressive metabolic osteopathy characterized by decreased bone density and destruction of bone tissue microstructure, which leads to increased bone fragility and easy fracture [93]. At present, there are four main aspects of clinical treatment: lifestyle change, nutritional supplements, drug intervention and surgical treatment [94]. The study on the composition of intestinal microbiota has identified microbial biomarkers related to diseases, which may provide a new direction for the screening, diagnosis and treatment of OP in the future [95]. An association study found that compared with normal BMD patients (N = 60), OP patients (N = 60) had fewer actinomycetes, Egotella, Clostridium group XlVa and Lactobacillus. Compared with osteopenia group (N = 61), the abundance of Escherichia coli/Shigella and Veronella was lower, and there was no statistical difference in diversity indicators between groups [96]; Another study found that the diversity and abundance of dialysis bacteria and fecal bacteria in OP patients (N = 48) were higher than those in normal BMD group (N = 48) [97]; The changes of intestinal microbiota in 44 elderly patients with OP and 64 controls were reported recently: the absolute and relative abundance of Bac-

teroides, Bacteroides and Eisenberg in OP patients were high. In OP group, the absolute abundance of Clostridium, Fecal coccus, Lactobacillus and Egtehela increased, while that of Menera decreased. Clinical observations supplementation with Bacillus subtilis, Lactobacillus and multiple probiotics has beneficial effects not only on the human gut microbiota but also on bone turnover markers and short-term prevention of lumbar spine bone loss [98], animal studies have shown that probiotic supplementation in mice increases trabecular bone formation postoperatively, and two different clinical trials conducted in Sweden have shown that P, Bone loss is significantly reduced in postmenopausal women using probiotics [99]. The interaction of prebiotics with probiotics to reduce osteoporosis through multiple mechanisms, whether the loss of BMD can be prevented in the long term, also needs to be supported by rigorous scientific investigations [100]. To date, there have been no reports on the effects of FMT on bone health. The characteristics of intestinal flora changes in the above 11 metabolic diseases are shown in Table 1.

5. Study on Intestinal Flora Intervention in Metabolic Diseases

Intervention measures for intestinal flora of metabolic diseases include diet and exercise, probiotics, prebiotics, synbiotics,postbiotics, antibiotics and FMT.

5.1. Diet and Exercise

Diet is the main factor of microbiota composition, and different time, diet preference and food materials affect our intestinal ecosystem [101]. Host physiology, immune status and metabolic capacity also regulate bacterial colonization and the existence of specific microbial species [102]. Studies have shown that Mediterranean diet has potential health benefits for human body: Mediterranean diet has anti-inflammatory and regulating effects on intestinal flora, and reduces the ratio of chlamydomonas/bacteroides in patients [103]. Ketogenic diet (KD) can increase the genetic diversity of microbiota and the proportion of Bacteroides and Firmicum [104], reduce the HbA1c of diabetic patients, reduce the demand for insulin [105], reduce weight loss, visceral obesity and control appetite [106], reduce LDL, increase HDL and reduce TG to improve lipid status [107]. The dietary fiber provided by the high dietary fiber diet is mainly fermented by Firmicum and other bacteria, which increases the production of SCFA, such as acetate, propionate and butyrate [108]. Butyric acid is an important mediator of intestinal flora and host metabolic health, affects body weight, body composition and glucose homeostasis, and improves obesity and hyperglycemia/hyperinsulinemia induced by high-fat diet [109].

5.2. Probiotics, Prebiotics, Synbiotics and Postbiotics

Probiotics are living non pathogenic microorganisms. When given enough (at least 10^6 live CFU/g), they are beneficial to the host by improving the microbial

balance in the intestine and participating in metabolism [102] [110]. The role of probiotics [111], see **Figure 2**.

Table 1. Characteristics of gut microbiota changes in 11 metabolic diseases.

Metabolic diseases	Changes of Gut Microbiota	Animal model	Clinical research	Reference
Obesity	Increase in *Prevotella*, *Megamonas*, *Fusobacterium* and *Blautia* Decrease in *Faecalibacterium*, *Parabacteroides Bifidobacterium* and *Alistipes*		yes	[42] [43]
Type 2 diabetes mellitus	Increase in *Escherichia coli*, some *Clostridium species*, *Bacteroides caccae* and *Eggerthella lenta*, *Parabacteroides Enterococcus*, *Enterobacteriaceae*, *Klebsiella* Decrease in *Eubacterium rectale*, *Clostridium SS3/4*, *faecalibacterium prausnitzii* and *Bifidobacterium intestinalis*, *Bacillus lactis*, *Prevotella*, *ruminococcaceae*, *Roseburia*, *faecalibacterium*		yes	[16] [24]
Hypertension	Increase in *Prevotella* and *Klebsiella Erysipelotrichacea-UCG003* Decrease in *faecali*, *Rothia spp.*, *oscillibacter ruminiclostridium*		yes	[51] [52] [53]
Hyperlipidemia	Increase in *LPS producing Escherichia coli* and *Enterobacter cloacae* Decrease in *Bifidobacterium*, *Lactobacillus*, *faecalibacterium prausnitzii* and *Roseburia akkermansia*, *Bacteroides*, *Roseburia* and *faecalibacterium*		yes	[58] [59]
Hyperuricemia	Increase in *Alipipes*, *Dialister*, *Roseburia*, *Gemmiger*, *Faecalibacterium* Decrease in *Bifidobacterium*, *Klebsiella* and *Clostridium*		yes	[64]
Nonalcoholic fatty liver disease	Increase in *Firmicutes Actinobacteria murinus Bacteroidaceae Prevotellaceae Proteobacteria Verrucomicrobia* Decrease in *Actinobacteri Euryarchaeota Lachnospiraceae Ruminococcaceae Lactobacillaceae Deferribacters Bacteroidetes Lactobacillus*	yes	yes	[69] [70] [71] [72]
Alcoholic fatty liver disease	Increase in *Olsenella Eubacterium Acetivibrio ActinobacteriaFirmicutes Coriobacteriaceae Odoribacteriacea Clostridiaceae Dorea Candida spp. Candida albicans Candida dubliniensis Proteobacteria Fusobacteria Fusobacteriaceae Enterobacteriaceae Burkholderiaceae Escherichia-Shigella* Decrease in *Proteobacteria Bacteroidetes Acinetobacter Anaerotruncus Akkermansia Blautia Epicoccum Unclassified fungi Galactomyce Debaryomyces Ruminococcaceae Faecalibacterium Lachnospira Agathobacter Ruminococcus*	yes	yes	[80] [82]
Metabolic syndrome	Increase in *potentially harmful bacteria* Decrease in *beneficial bacteria*		yes	[84]
Polycystic ovary syndrome	Increase in *Prevotella Bacteroides Streptococcus Nocardiaceae* and *Clostridiaceae Parabacteroides*, *Bacteroides*, *Lactobacillus*, *Oscillibacter*, *Escherichia/Shigella*, *Clostridium* Decrease in *Lactobacillus Ruminococcus Clostridium Akkermansia Ruminococcaceae Akkermansia*, *Bacteroides*, *Lactobacillus*, and *Clostridium Faecalibacterium*, *Bifidobacterium*, and *Blautia*	yes	yes	[14] [88] [89]
Wilsons disease	Increase in *Bacteroidetes*, *Proteobacteria*, *cyanobacteria* and *fusobacteria* Decrease in *actinomycetes*, *Firmicutes* and *verrucomicrobia*		yes	[92]
Osteoporosis	Increase in *dialyzers* and *faecalibacterium*, *Clostridium hypervirum*, *faecalibacterium*, *Lactobacillus* and *egtaheira* Declease in *actinomycetes*, *faecalibacterium*, *Clostridium cluster xlva* and *Lactobacillus*, *Veillonella raoullella*		yes	[96] [97] [98]

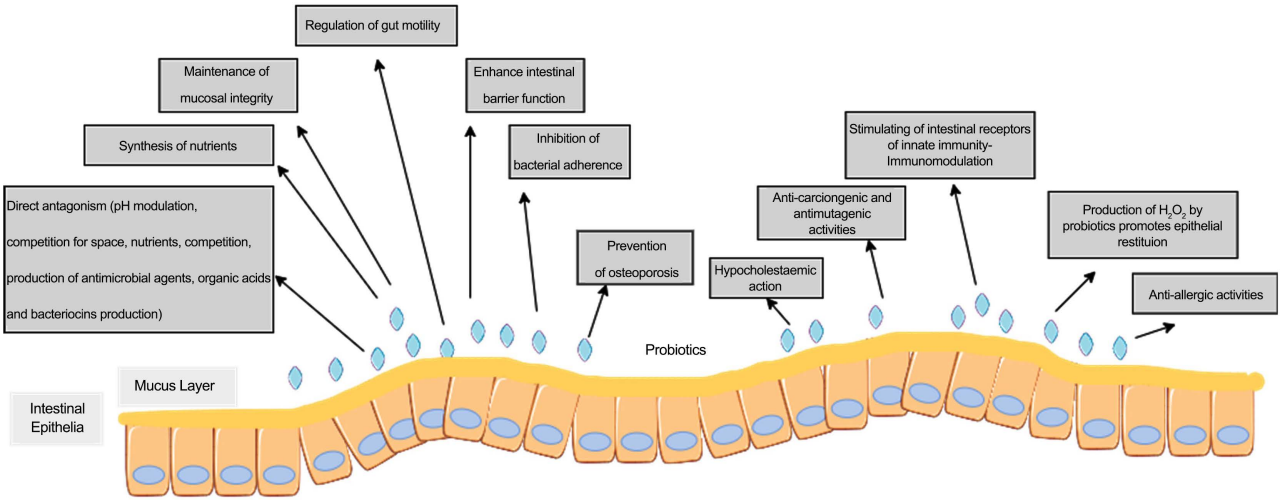

Figure 2. Mechanisms of action and properties of probiotics.

By strengthening the epithelial connection and maintaining the mucosal barrier function, it shows the cytoprotective effect on the integrity of intestinal mucosa, enhances the intestinal barrier function, and regulates intestinal peristalsis [112]. Supplementing probiotics can not only increase bone density, but also prevent primary (estrogen deficiency) and secondary osteoporosis [113], reduce cholesterol, prevent cancer, resist mutagenesis and allergy [114]. It can antagonize pathogenic bacteria through space competition and competition for nutrients in the intestinal cavity and wall [115], produce antibacterial agents, organic acids and bacteriocins, stimulate intestinal flora to produce mucin, and prevent the implantation of pathogens, Enhance the immune regulation of intestinal system and inhibit the production of bacterial toxins [116]. Clinical application of probiotics can improve the symptoms of metabolic diseases. 50 subjects with body mass index over 25 kg/m^2 were randomly divided into probiotics group or placebo group. Each group received unlabeled placebo or probiotic capsules for 12 weeks. Body weight, waist circumference and body composition were measured every 3 weeks. Results: In the placebo group, the percentage of fat, blood glucose and insulin in the intestinal type patients rich in Pleurotus pumilus were significantly increased. The obesity related markers, such as waist circumference, total fat area, visceral fat and the ratio of visceral to subcutaneous fat area, were significantly reduced in the probiotic group. The decrease of obesity related markers in intestinal type patients rich in Plasmobacter spp. was greater than that in intestinal type patients rich in Bacteroides [117]. In patients with type 2 diabetes, probiotics can reduce bacterial translocation and change intestinal microbiota [118]. The effectiveness of probiotics on metabolic diseases needs further observation. Although the safety is good, attention should be paid to the occurrence of adverse reactions. Some people have summarized them into four categories: 1) systemic infection, 2) harmful metabolic activities, 3) excessive immune stimulation, 4) unwanted gene transfer [119]. They should be carefully applied to patients with low immune function.

Prebiotics are undigested carbohydrates in the small intestine, active in the colon, fermented by bacteria in the colon, which affect the production of SCFA, regulate the production of mucin and local inflammatory response of intestinal associated lymphoid tissue, thus stimulating the phagocytosis of macrophages [120]. Compared with placebo, prebiotics supplementation for overweight and obese children can significantly improve satiety ($P = 0.04$), reduce expected food consumption ($P = 0.03$), and significantly reduce energy intake of children aged 11 and 12 ($P = 0.04$). The trend of reducing BMI z score to a greater extent is (−3.4%; $P = 0.09$), which leads to the reduction of energy intake of older but younger children in buffet breakfast [121]; After the intervention of prebiotics on T2DM for two months, anthropometric variables, blood pressure and blood lipids in the treatment group were significantly improved ($P < 0.001$). Serum IL-4, IL-12 and IFN in intervention group γ. The concentration also decreased significantly ($P < 0.001$), and it has some beneficial effects on improving the blood glucose, blood pressure, blood lipid status and immune markers of patients with T2DM [122]; Prebiotic inulin was 10 g/day for 3 months. 75 cases of NAFLD were treated with prebiotic inulin, which improved the fatty liver grade and serum transaminase level [123].

Synbiotics are a combination of prebiotics and probiotics [120]. *Bifidobacterium brevis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, 10^9 CFU/g plus 35 mg oligosaccharide for 8 weeks. 76 Obesity improves serum insulin level and insulin resistance [124]; Bifidobacterium W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus casei* W56, *Lactobacillus brevis* W63, *Lactobacillus salivarius* W24, *Lactococcus lactis* W58, *Lactococcus lactis* W19, plus galactooligosaccharide P11 and fructooligosaccharide P6 1.5×10^{10}CFU plus 8 g, 6 months, T2DM, diabetes improved hip circumference, zonulin and lipoprotein, and did not affect glucose metabolism [125]; *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, with chicory inulin 7×10^9 CFU with chicory inulin 100 mg 4-month 28 NAFLD improves fatty liver Grade and inflammation, antioxidant status [126].

Postbiotics are preparations of abiotic microorganisms and/or their components that are beneficial to the health of the host; postbiotics are not purified microbial metabolites and vaccines, but are not limited to inactivated probiotics; The beneficial effects of epigenetic elements on the target host and the use safety must be confirmed; The five mechanisms of postbiotics: 1) beneficial regulation of microbiome; 2) Enhancing epithelial barrier function; 3) Regulate local and systemic immunity; 4) Regulate systemic metabolism; 5) Sending signals through the nervous system; The target of postbiotics is not limited to the intestinal tract, but must be administered on the host surface, such as oral cavity, intestinal tract, skin, urogenital tract or nasopharynx. Injection does not belong to the scope of postbiotics [127]. Animal experimental study on metabolic diseases: *Lactobacillus*

plantarum L-14 extracellular polysaccharide upregulates TLR2-AMPK pathway in obese mice [128]. Butyric acid upregulates GPR43-NLCR3-TRAF6 pathway in experimental animals with type 2 diabetes [129]. Butyric acid increased ZO-1 expression and decreased endotoxin level in NAFLD mice [130]. Clinical observation: supplementation of hydroxybutyrate methyl ester, leucine, glutamine and arginine to 34 patients with diabetes related sarcopenia can inhibit skeletal muscle catabolism and improve digestive tract function [131]; Results of butyric acid treatment on 80 patients with dysentery with metabolic disorder: it can reduce the pathological damage of colon mucosal barrier and enhance the release of antimicrobial peptides [132].

5.3. Antibiotics

Minocycline is an antibiotic of the tetracycline family. It can be absorbed quickly in the intestine, easily penetrate the blood brain barrier, and has been clinically applied for decades. It has good safety performance and dual characteristics of antibiotic and anti-inflammatory. Minocycline can rebalance the intestinal microbiota composition of hypertensive rats to that of normal blood pressure animals [133]. In experimental colitis and other intestinal inflammatory diseases, the drug has good efficacy, can induce mucosal healing and reduce intestinal inflammation [134]. Minocycline can prevent the occurrence of diabetic retinopathy in rodent models [135]: an observational study on patients with T2DM showed that in a group of patients withT2DM, it reduced glycosylated hemoglobin, lowered blood pressure, improved vision and symptoms related to neuropathy [136]. An open label study of minocycline on patients with high risk and refractory HTN [137] showed that 16 of 26 patients (62%) responded to minocycline, the daily dynamic mean systolic pressure decreased (135/74 to 124/68 mmHg), the daily dynamic systolic pressure decreased, and minocycline treatment reduced the number of intestinal inflammatory cells. These observations suggest that minocycline may be beneficial to neuroinflammation, intestinal microorganisms and their pathophysiology, intestinal immunity and other mechanisms [137].

5.4. Fecal Microbiota Transplantation (FMT)

FMT is a strategy to transplant the whole intestinal microbiota of healthy donors to diseased recipients [138]. Research shows that FMT can widely affect the intestinal microbiota of recipients, and it is the most effective choice to regulate the intestinal microbiota. Since 2013, FMT has been recommended to treat recurrent Clostridium difficile infection resistant to standard nursing care [139], and is an effective method to treat recurrent Clostridium difficile infection. It has potential therapeutic effect on gastrointestinal diseases and nervous system diseases. FMT is mainly applied to common metabolic diseases (such as MetS, Obesity and T2DM [140], HTN [141]). A double-blind randomized controlled trial of fecal microbiota transplantation (FMT) for treatment of type 2 diabetes mellitus for 24 weeks showed that repeated FMT could improve the level and

time of microbiota implantation in obese T2DM patients. The combination of lifestyle intervention and FMT can make more favorable changes in the microbiota of the recipient, and improve the blood lipid level and liver hardness. The impact on blood glucose has not been reported, which needs further research in the future [142]. In the animal experiment of ischemic cerebrovascular disease, gavage of mice with normal microbiota can reduce the infarct volume [143]. Compared with receiving fecal bacteria from old mice, stroke mice receiving fecal bacteria from young mice improved several behavior tests, reduced mortality and infarct area, and reduced proinflammatory cytokines [144]. A study on the treatment of HTN patients with washing intestinal flora transplantation (WMT) showed that WMT had effect of lowering blood pressure on HTN patients, especially those with WMT through the lower digestive tract and those without anti-hypertensive drugs [141].

6. Existing Problems and Future Trends

Recently, Microbe-seq [145], a new microbial high-throughput single-cell sequencing method, can obtain a large amount of single microbial genome information from complex communities without culturing, and resolve high-quality microbial genomes at strain resolution. There are also studies on the application of artificial intelligence and synthetic biology technology to human gut microbiota [146], which will play a crucial role in regulating the therapeutic and nutritional potential of probiotics. It is necessary to continuously develop new technologies and their application in the study of microflora in order to fully understand the impact of gut microbiota on the human body. At present, the research on the intestinal flora is still at the initial stage, and most of them focus on the changes of the flora when the disease occurs. Basic research should be carried out on what is a healthy microbiota, what structural and functional characteristics a healthy microbiota should have, as well as the interaction between microflora and so on; There are few studies on the mechanism. Only by breaking through the mechanism research can the intestinal flora be precisely regulated [147]. In addition to strengthening the study of the relationship between bacteria in the gut microbiota, we should also study the viruses, fungi and other microorganisms in the gut, deeply study the mechanism and medical transformation of intestinal microbial metabolites on human body; strengthen the study of multiple factors affecting intestinal flora, such as age, diet, race, environment, exercise, etc.; Causal relationship research is the focus and one of the difficulties of flora research. At present, most of the literatures are related studies, and it is not difficult to understand if the clinical intervention effects are contradictory. The effectiveness and safety of clinical intervention trials should adopt the method of RCT. The results and conclusions of RCT are reliable and the level of clinical application evidence is high.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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