



AN OVERVIEW OF VARIOUS MECHANISMS LINKING INTESTINAL MICROBIOTA TO HYPERTENSION

Abdurrahman Omer Cavdar and Hong Fang*

Department of Cardiology, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200065, China

SUMMARY

Cardiovascular disease is the leading cause of disability and premature death worldwide. Hypertension is the most common chronic cardiovascular disease. It is a combination of genetic and environmental factors and is a common chronic non-infectious cardiovascular disease, which is the leading cause of stroke, coronary heart disease, and cardiovascular events. Studies have shown that hypertension is a kind of "cardiovascular syndrome", and it is a disease with many factors, links, stages, and individual differences. Over 60% of the risk factors for hypertension are related to metabolic disorders. Also, many metabolic factors can directly cause vascular dysfunction and elevated blood pressure.

In recent years, animal experiments and clinical trials have found that intestinal microorganisms and their metabolites are strictly related to the occurrence and development of hypertension. By analyzing the effect of changes in intestinal flora structure, composition, and metabolic activity on hypertension, we can reveal the correlation between intestinal microbial activity and hypertension. Gut Microbiota (GM) affects blood pressure by influencing host metabolism and energy absorption, destroying the intestinal barrier, influencing the release of inflammatory factors and other mechanisms. Changing the structure of intestinal flora and adjusting lifestyle may become a potential method to treat hypertension. Intestinal flora plays a vital role in human energy metabolism, substance absorption, and immune regulation. This paper analyzes the correlation between human intestinal microorganism and hypertension risk factors in conjunction with the changes in intestinal flora in patients with hypertension.

Keywords: Hypertension; Gut microbiota; microbiome; Gut pathology; Renin angiotensin aldosterone system; Dysbiosis

INTRODUCTION

General Situation and Physiological Characteristics of GM:

GM is a general term for a large number of microorganisms present in the human intestine. Intestinal microbes are a complex group (1). They are established from birth, coexist with the host, affect the structure and function of the digestive tract, participate in the metabolism of the host, promote the digestion and absorption of nutrients, maintain the normal physiological function of the intestinal tract, regulate the immune system and antagonize the colonization of pathogenic microorganisms (2). It is estimated that the total number of human intestinal microbes is about 10^{13} (3). The intestinal flora is the second genome of the human body. Its total genome size is 100 times larger than that of the human genome. Together with the human genome, intestinal flora affects the physiological metabolism of the human body through interaction with the external environment.

Over 99% of the bacteria in the gut are anaerobes, but in the cecum, aerobic bacteria reach high densities. It is estimated that these gut flora have around a hundred times as many genes in total as there are in the human genome(4).

Many species in the gut have not been studied outside of their hosts because most cannot be cultured (5-7). While there are a small number of core species of microbes shared by most individuals, populations of microbes can vary widely among different individuals (8).

Within an individual, microbe populations stay fairly constant over time, even though some alterations may occur with changes in lifestyle, diet and age (9, 10) . The Human Microbiome Project has set out to better describe the microflora of the human gut and other body locations.

The four dominant bacterial phyla in the human gut are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (9, 11). Most bacteria belong to the genera Bacteroides, Clostridium, Faecalibacterium, (6, 9) Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, and Bifidobacterium (9)(6). Other genera, such as Escherichia and Lactobacillus, are present to a lesser extent (9). Species from the genus Bacteroides alone constitute about 30% of all bacteria in the gut, suggesting that this genus is especially important in the functioning of the host (10)(5).

The Firmicutes and Bacteroides Gates (Firmicutes/Bacteroidetes ratio, F/B) is an important parameter reflecting the intestinal bacterial disorder. Besides, the abundance, diversity, and evenness of intestinal flora are also important indicators reflecting the composition of intestinal flora. Each flora is mutually restricted and interdependent, forming an ecological balance in quality and quantity.

Fungal genera that have been detected in the gut include Candida, Saccharomyces, Aspergillus, Penicillium, Rhodotorula, Trametes, Pleospora, Sclerotinia, Bullera, and Galactomyces, among others (12, 13). Rhodotorula is most frequently found in individuals with inflammatory bowel disease while Candida is most frequently found in individuals with hepatitis B cirrhosis and chronic hepatitis B (12).

Archaea constitute another large class of gut flora which are important in the metabolism of the bacterial products of fermentation.

Industrialization is associated with changes in the microbiota and the reduction of diversity could drive certain species to extinction; in 2018, researchers proposed a biobank repository of human microbiota (14). The indigenous flora in the intestine is relatively fixed and regularly settled in specific parts of the intestine, which is beneficial to the human body, harmless and necessary. It is called the essential "organ" for providing nutrition. As the "external organ" of the body, the stable composition is the most prominent feature of intestinal flora. Intestinal bacteria exert a "hormone-like" effect by influencing food metabolism and digestive tract function and structure while producing a large number of bioactive metabolic molecules. Many enzymes required for human metabolism are synthesized by normal microorganisms, which participate in the host's material metabolism, promote the digestion and absorption of nutrients, and maintain the normal physiological function of the intestinal tract, regulate immunity and antagonism. Anti-pathogenic microorganism colonization plays a vital role in (15, 16). Normal intestinal flora participates in the whole process of human physiology, biochemistry, pathology, and pharmacology become an essential part of host life and a barrier for health protection. Most of the physiological functions of the human body are results of symbiotic life formed during the co-evolution of human and normal microorganisms (17).

The Complexity of the Mechanism of Hypertension:

At present, it is considered that hypertension is a progressive cardiovascular syndrome caused by many causes, the result of interaction between genetic susceptibility and environmental factors, and the main and common cause. It is also the main and universal cause and cause of cardiovascular and cerebrovascular diseases. The ways of regulating blood pressure include the renin-angiotensin system (RAS), vascular endothelial regulatory factors, and so on. Among them, RAS is the main regulatory pathway, and angiotensin-converting enzyme (ACE) is the key enzyme in this pathway, which catalyzes the formation of angiotensin II and can inactivate vasodilator kinin peptide. However, most of hypertension has no definite cause. Risk factors for hypertension include a sedentary lifestyle, salt sensitivity, alcohol consumption, obesity, hypercholesterolemia, diabetes mellitus, and metabolic syndrome (18). At present, the research on the pathogenesis of hyperactivity of sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), renal water and sodium retention, insulin resistance and other links are explored from the perspective of increased total peripheral vascular resistance(19). The existing studies on the pathogenesis of hypertension mainly focus on the increase of total peripheral vascular resistance, because its hemodynamic characteristics are mainly the relative or absolute increase of total peripheral vascular resistance, which can explain the short-term regulation of blood pressure but cannot fully explain the long-term abnormal regulation of blood pressure. (3) Although the etiology of hypertension is unknown, it is indeed related to many systems and factors of the body. The intervention of any factor may have an impact on blood pressure. The combination of antihypertensive drugs has become an important means to improve the blood pressure compliance rate, which reflects the complexity of the pathogenesis of hypertension.

The Relationship Between Risk Factors of Hypertension and Intestinal Flora:

Various risk factors of hypertension are similar to the pathogenesis of hypertension itself. They are jointly participated by host genetic factors and environmental factors. Intestinal flora plays an important role. The relationship between intestinal flora and cardiovascular diseases has become a hot topic. Firmicutes and Bacteroides are the most abundant intestinal flora in humans and mice (20), and some scholars have pointed out that intestinal flora is related to obesity (21, 22). In ob/ob mice, the relative abundance of intestinal Bacteroides was 50% less than that of lean mice, while the relative abundance of chlamydia was significantly higher than that of lean mice (23). The diversity and richness of bacteria decreased, the ratio of Firmicutes and Bacteroides increased, and the number of bacteria producing acetic acid and butyric acid decreased, and the same changes were observed in the model of hypertensive rats induced by angiotensin II.

When the antibiotic minocycline is given, intestinal flora can be restored, the F/B ratio can be reduced, and the state of hypertension could be improved (24). Animal experiments and clinical trial studies have found that the blood pressure of the host reduced after probiotics were given. Similar phenomena were found in the obese population test. The number of Firmicutes was higher than that of the control population, and the number of Bacteroides decreased with the increase of body weight. Reduction of Bacteroides increases the risk of metabolic syndrome.(24)

Obesity and intestinal flora:

Body fat content is positively correlated with blood pressure level. Overweight and obesity are one of the principal reasons leading to elevated blood pressure. Controlling overweight and obesity is a critical way to prevent hypertension. Intestinal flora is associated with obesity, which is one of the important conditions for animal obesity. Obesity also affects the diversity of intestinal flora. Dietary fat and intestinal flora interact to determine dietary obesity in mice (25). A high-fat and high-sugar diet not only changes the intestinal flora structure of pregnant rats but also increases the likelihood of obesity in their offspring (26). The close relationship between intestinal flora and obesity has been a hot topic in recent years, and two viewpoints have attracted much attention. Backhed et al. proposed for the first time that intestinal flora regulates fat storage as an environmental factor by studying the role of intestinal flora in energy metabolism, that is, intestinal flora can help host digest polysaccharides and obtain more energy (27). Cani et al. considered that intestinal flora-induced "metabolic endotoxemia" can induce a long-term low-level systemic inflammatory response in obese patients (28). The hypothesis of metabolic endotoxemia explains the mechanism of chronic low-level inflammation induced by high-fat diet: diet induces changes in intestinal flora, increases the number of opportunistic pathogenic bacteria, decreases the number of bacteria protecting intestinal barrier, affects gene expression of intestinal epithelial cells, leads to increased intestinal permeability, which increases endotoxins entering blood, triggers chronic inflammation, which leads to metabolic disorders such as obesity and insulin resistance (29).

Firmicutes and Bacteroidetes are the dominant beneficial bacteria in the human intestine. The ratio of F / B can be used as biomarkers for evaluating pathological status. Jeffrey I. Gordon, a well-known

bacteriologist, and his colleagues recruited 12 obese people. Compared with slim people, they had more Firmicutes but fewer Bacteroides and higher F/B. Studies have shown that the ratio of Firmicutes to Bacteroides in obese people is significantly higher than that in non-obese people (23). This rate can be reduced after a low-calorie or low-carbohydrate diet. It suggests that we can control weight gain through the regulation of gastrointestinal flora. Studies have shown that gastrointestinal flora is an independent risk factor for weight gain and fat accumulation in mammals other than genetic factors and increased feeding (22). Thus, obesity in both rodents and humans is associated with changes in the intestinal flora. Cellulose and hemicellulose polysaccharides in plants are not digestible, but Bacteroides in the intestinal flora has a series of polysaccharide-digesting enzymes that decompose these polysaccharides to provide energy for humans. Firmicutes, the "obese bacteria" that absorb excess calories from food, deposit excess fat and cause obesity.

Intestinal flora and atherosclerosis:

Intestinal flora imbalance plays an essential role in the development of atherosclerosis. It can indirectly affect the progress of atherosclerosis through interaction with environmental factors and genetic factors. Intestinal flora is involved in the formation of intestinal immunity, and chronic infection of the body can promote the occurrence and development of atherosclerosis. Metabolites of intestinal flora, such as short-chain fatty acids, polyphenols, and methylamine, also have important effects on atherosclerosis.

Abnormal glucose and lipid metabolism and obesity are closely related to atherosclerosis, and have a synergistic effect on the development of atherosclerosis, and can cause hypertension through interaction with other risk factors (30). Elevated levels of trimethylamine oxide (TMAO) are considered to be a new risk factor for atherosclerosis, and the formation of TMAO depends on the intestinal flora (31). First Trimethylamine (TMA) is produced when intestinal flora metabolizes choline and phosphatidylcholine, which is absorbed into the blood and catalyzed by portal vein circulation to the liver, and then produced a new independent atherosclerosis risk factor TMAO via flavin monooxygenase. It raises the risk of cardiovascular disease and promotes the development of atherosclerosis (32).

Studies have shown that TMAO can cause the accumulation of cholesterol in cells by increasing the expression of receptor differentiation antigen 36 (CD36) and scavenger receptor A (SR-A) before atherosclerosis. The genus of intestinal flora directly related to cholesterol metabolism includes bifidobacteria, lactobacilli, Bacteroides, Clostridium, etc... Studies have shown that when applying the same cholesterol feed, The amount of cholesterol accumulated in the blood of sterile animals is twice that of cholesterol in nonsterile animals (33). The metabolism of cholesterol affects the level of atherosclerosis, and arteriosclerosis is one of the most important risk factors for the occurrence and development of hypertension (34).

Further studies have found that the intestinal flora can regulate about 10% of the transcriptional gene expression in the host, and most of these regulated genes are related to immunity, proliferation, and metabolism (35). The intestinal flora can affect the host's metabolism, immune reaction, and inflammatory reaction, and the host's genotype, epigenetics, eating habits and lifestyle play a decisive role in the composition

of the intestinal flora. Therefore, atherosclerosis-related cardiovascular diseases are affected by both environmental and genetic factors, while the intestinal flora participates in the entire process (34).

In short, the intestinal flora is directly or indirectly involved in the entire pathological process of atherosclerosis, a risk factor for hypertension, which affects energy absorption, chronic low-grade inflammatory reactions, and regulation of choline metabolism.

Intestinal flora and glycolipid metabolism:

Abnormal blood sugar and lipid metabolism are generally accepted as important risk factors for hypertension. The abnormal glycolipid metabolism interacts with changes in intestinal flora structure. A high-fat diet can increase the number of Enterobacteriaceae in obese mice, accompanied by chronic low-grade inflammatory reactions; further studies have found that high-fat diet can significantly alter the structure of mouse intestinal flora and cause triglyceride and plasma lipids Deposition in the liver, and this change is associated with the Clostridium cluster XIVa (36). Excessive intake of saturated fatty acids not only changes the structure of the intestinal flora but also damages the intestinal mucosal barrier, causing endotoxin to enter the blood (37).

Lipid metabolic disorder refers to the abnormality of lipids and its metabolites in blood, other tissues, and organs caused by congenital or acquired factors. People have clinically common diseases that as hyperlipoproteinemia, obesity, Ketoacidosis, fatty liver, and neonatal scleredema mostly have the symptoms of functional dyspepsia, but no corresponding organic lesions have been found through relevant auxiliary examinations, and the probiotics represented by Lactobacillus acidophilus and Bifidobacterium are used for treatment of functional dyspepsia associated with lipid metabolism disorders can alleviate symptoms and achieve excellent results (38, 39). In recent years, more and more relevant studies have elucidated the effects of lipid metabolism disorders on the intestinal flora.

Intestinal flora can regulate blood lipid by producing cholesterol oxidase, inhibiting the activity of fatty acid synthase (FAS), regulating the redistribution of cholesterol and affecting the enterohepatic circulation of bile salts. Blood lipid level is closely related to Firmicutes. Adjusting intestinal flora is beneficial to control body mass, ameliorate triglyceride and high-density lipoprotein, and is not affected by host age, sex, and genetic factors (40). Intestinal flora can also prevent the loss of cholesterol in the body by regulating the expression of host genes (41).

The main metabolic pathways of sugar in the body are anaerobic hydrolysis of glucose, aerobic oxidation, pentose phosphate, gluconeogenesis, etc. The intestinal flora plays an essential role in the body's glycometabolism (42). Firstly, Tu Xinming et al. found that compared with sterile mice, the same-age bacterial mice had heavier body weight and lower blood sugar. Also, the body weight and fat content of sterile mice were increased by microbial group transplantation (27). That shows that the existence of intestinal flora does affect the body's sugar metabolism and can cause blood sugar changes, weight gain, fat content increase. Bacterium affect sugar metabolism, which naturally affects body fat and even body weight. Larsen found that the amount of Lactobacillus in the intestinal flora of patients with type 2 diabetes decreased significantly with increasing

blood glucose levels, but according to Xu Xiaojin, the number of Lactobacillus in the intestine of patients with type 2 diabetes mellitus increased while the number of bifidobacteria decreased (43, 44). The study showed that there is a difference in the intestinal flora of type 2 diabetic patients compared with healthy people. Bäckhed et al. showed that normal mice were more prone to insulin resistance than sterile mice, and the cytokines produced by intestinal flora stimulation also affected body's sensitivity to insulin and the efficiency of glucose metabolism (27, 43-45). That may provide a theoretical basis for intestinal flora-induced metabolic diseases.

The Mechanism of GM Regulating Blood Pressure:

The intervention of hypertension first improves lifestyle through exercise, sensible diet, etc. Exercise can adjust or increase gut microbiota diversity (46), and the increase of gut microbiota diversity is important for maintaining the stability and function of the gut ecosystem. Diet is closely related to the type, abundance, and composition of the gut flora. Mediterranean diet can increase the number of intestinal Bacteroides, Firmicutes (Streptococcus, Lactobacillus) and Bifidobacteria, reduce the number of Clostridium in the Firmicutes (47), promote the proliferation of probiotics, inhibit fat production, improve insulin resistance, and chronic inflammatory response. Supplementation of fatty acids can reduce the body weight of obese mice induced by diet and regulate intestinal flora (48). A variety of Lactobacillus with antihypertensive effect has been found, and Lactobacillus helveticus has a good angiotensin-converting enzyme inhibitory activity and antihypertensive effect from traditional fermented dairy products (49).

The mechanism of GM regulating blood pressure is still in the clinical research stage. There is no clear evidence to show which flora plays a vital role in the occurrence and development of hypertension. Wu Zhengjun et al. (50) studied the antihypertensive effect of a bacteria, and the results showed that a small number of lactic acid bacteria have a mild antihypertensive effect in hypertensive patients, and also explained the antihypertensive mechanism of lactic acid bacteria: 1. In the growth process of milk as matrix, through proteolysis, the released bioactive peptides, such as angiotensin-converting enzyme, inhibitory peptide, and opioid peptide, can combine with ACE active center and competitively inhibit ACE activity, so angiotensin I cannot be converted into angiotensin II, thus playing a role in lowering blood pressure; 2. The bacterial constituents of specific lactic acid bacteria, such as polysaccharide peptidoglycan from the cell wall of Lactobacillus casei YIP9018 may have antihypertensive effects; 3. Part of the lactic acid bacteria, especially the lactobacilli that can reach the intestinal tract in the form of live bacteria, promote the body's absorption of some minerals that can regulate blood pressure in the intestinal tract. The current research results indirectly regulate blood pressure in the following ways.

Affects host metabolism and energy absorption:

The metabolic functions of GM include the production of vitamins, amino acid synthesis, and bile acid biotransformation. Bile acid biotransformation is carried out by microbial enzymes. GM can ferment indigestible food and endogenous mucus of the host and convert it into small molecular substances such as SCFA to provide energy for the host. Some GMs such as Lactobacillus and Bifidobacteria stimulate the growth

of bacteria by fermentation and produce SCFA, linoleic acid, gamma-aminobutyric acid, and ACE inhibitory peptides. Studies have shown that these products have potential antihypertensive effects (51). SCFA regulates blood pressure by reducing inflammation, maintaining the epithelial barrier, regulating immune cell function, and reducing sympathetic activity; while abundant dietary fiber reduces the risk of hypertension (52).

One of the characteristics of SCFA is the nutritional effect on the intestinal epithelium. A high-fat diet can significantly change the structure of the intestinal flora of healthy mice and lead to chronic low-grade inflammation. The number of lactobacilli, bifidobacteria, and enterococci in the intestinal tract of mice fed with a high-fat diet is significantly reduced, while the number of Enterobacter in intestine showed an upward trend (53). Elevated serum cholesterol can independently affect blood pressure levels (54). Through simulating human gastrointestinal tract, Lye et al. (55) found that Lactobacillus can remove cholesterol by exogenous binding cholesterol, destroys cholesterol particles, dissociates conjugated bile salts, and affects bile salt hydrolase (BSH) activity. Huang et al. (56) found that probiotics of the genus Lactobacillus, Lactococcus, and Bifidobacterium can express BSH, which can reduce serum cholesterol levels in humans. The competitive or non-competitive binding of ACE inhibitory peptide with ACE can delay the formation rate of angiotensin II and reduce the inactivation of bradykinin. Therefore, the purpose of vasodilation and blood pressure reduction can be effectively achieved. Probiotics are defined by WHO as active microorganisms, which reduce total cholesterol, low-density lipoprotein cholesterol, and blood pressure (57, 58), Taking probiotics to reduce cholesterol can effectively prevent hypertension.

Pluznick et al. (59) found that GM mainly affects glomerular filtration rate (GFR) and regulates renin release by the SCFA receptor olfactory receptor 78 (OLFR 78) and GG protein-coupled receptor 41 (Gpr41) in the kidney. Processes such as release mediate the regulation of blood pressure. GM can affect the ability of intestinal chromaffin cells to produce serotonin, dopamine, and norepinephrine, thereby affecting the regulation of blood pressure (60, 61).

The effect of disruption of intestinal barrier on blood pressure:

The role of intestinal resistance to pathogens is achieved through two barrier mechanisms, namely the mechanical barrier and the immune barrier. The gut-blood barrier (GBB) can absorb intestinal nutrition while limiting the passage of enteral nutrition pathogens and toxins through the bloodstream (62). Destruction of the intestinal blood barrier may cause various diseases. Studies have found that commensal microbial communities enhance the integrity of the intestinal blood barrier. The blood-brain barrier (BBB) is another physiological barrier that controls the molecular pathway between the brain parenchyma and the blood. Biancardi et al. (63) found that elevated angiotensin II in the circulation through the disrupted BBB caused the subfornical organ (SFO) to activate the para-ventricular nucleus (PVN) and the rostral ventrolateral medulla (RVLM), thereby activating neurohumoral regulation. Eventually, it leads to the occurrence of high blood pressure.

Affect the release of inflammatory factors:

Bomfim et al. (64) found that the expression of TLR-4 protein in the mesenteric artery was increased in SHR, and decreased blood pressure by reducing serum interleukin (IL) 6 level and arterial TLR-4 protein

during the subsequent 15 days of treatment. Studies have shown that inflammatory factors are strictly related to the occurrence and development of hypertension (65). Sesso et al. (66) C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder. Karbach et al (67) compared sterile mice with conventional mice and found that GM promotes angiotensin II-induced vascular dysfunction and hypertension through the infiltration and inflammation of vascular immune cells driven monocyte chemoattractant protein 1 (MCP-1) and interleukin 17 (IL-17), which indicates that GM inhibits the production of inflammatory cytokines through its consumption and ultimately leads to hypertension.

CONCLUSION

Microorganisms are essential for human survival and participate in and influence human life activities. GM itself and its metabolites can help the host to complete a variety of physiological and biochemical functions. The occurrence of diseases is due to the breakdown of microecological balance. In the long-term co-evolution, the host and GM form a mutually beneficial relationship, which together constitutes the intestinal micro-ecosystem. Hypertension is a chronic disease caused by multiple factors, multiple links, and multiple phases. There may be some difference in the intestinal micro-ecosystem between hypertension patients and healthy individuals, because the state of hypertension may affect the micro-ecosystem in the body. More and more evidence shows that there is a direct or indirect correlation between gut microbiota and hypertension, Although there is no clear causal relationship between intestinal flora and hypertension, whether intestinal flora causes hypertension or hypertension leads to changes in the intestinal flora. The intestinal activity and intestinal physiology and pathology associated with hypertension found in animal models provide us with a new idea and target for the treatment of hypertension. Dietary intervention to correct GM may be a new strategy for the integrated management of hypertension. GM may be a potential new target for the treatment of hypertension and has excellent clinical application prospects, but the application of GM biological agents still needs much clinical evidence. Future research needs to clarify the relationship between specific microbial lineages and hypertension further, identify specific intestinal flora that regulates blood pressure, determine the risk of hypertension in individuals by detecting the composition of GM. Antihypertensive therapy targeting the intestinal flora is an up-and-coming treatment model, but it still requires a large amount of basic research and clinical research to explore and verify.

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