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Relationship between Hypertension and Gut Microbiota: A Comprehensive Review

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Abstract: Hypertension, one of the most common cardiovascular diseases, has become a global public health problem. The pathogenesis of hypertension has not been fully elucidated to date. Known risk factors for hypertension include atherosclerosis, obesity, dyslipidemia, among others. In addition, physical exercise, diet, traditional Chinese medicine, antibiotics and probiotics also play important roles in the occurrence and development of hypertension. Studies have shown that the gut microbiota can participate in the occurrence and development of hypertension through a series of processes involving the regulation of endocrine and host metabolism. This article provides a brief summary of the current understanding of the relationship between gut microbiota and the occurrence and development of hypertension, aiming to provide new insights for the diagnosis and treatment of hypertension in the future.

1. Introduction

Hypertension is characterized by abnormally elevated systemic arterial blood pressure, with a main clinical feature of exceeding 140/90 mmHg. It is characterized by a wide affected population, unclear pathogenesis, and insidious nature [1-2]. Over the past 30 years, the number of hypertensive patients aged 30-79 years worldwide has doubled. As of 2019, there were approximately 1. 278 billion hypertensive patients [3]. The national prevalence, diagnosis and treatment rates of hypertension are shown in Figure 1. China is currently facing the dual challenges of the prevalence of metabolic risk factors and population aging. The incidence and mortality rates of cardiovascular diseases (CVD) are continuously increasing, making it the leading cause of death in the Chinese population. Hypertension, as a major risk factor for CVD, has a continuously increasing prevalence. The results of the national hypertension prevalence survey over the years are shown in Figure 2. In 2015, there were already 245 million hypertensive patients among individuals aged 18 years and older in China [4]. In 2017, 2. 54 million people in China died from elevated systolic blood pressure, with disability-adjusted life years exceeding 5% [5]. Hypertension has become a significant public health problem in China.

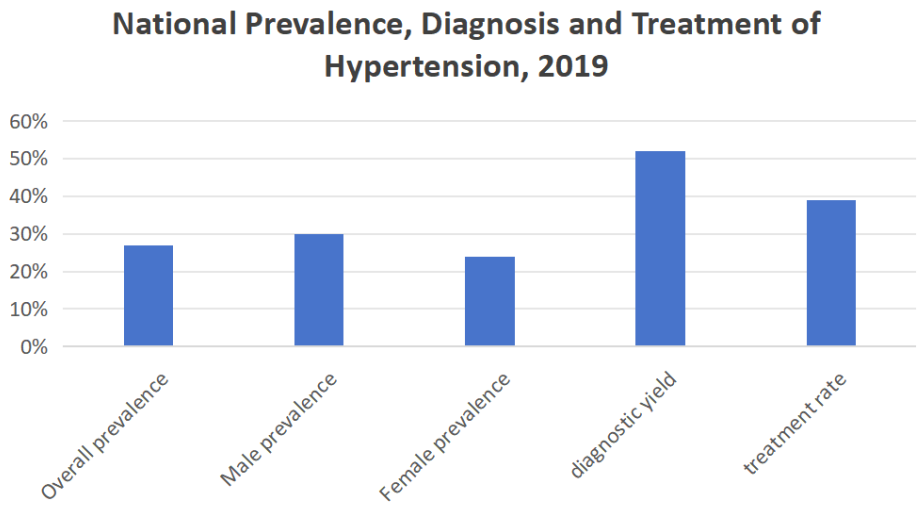

Figure 1: National hypertension prevalence, diagnosis and treatment rates

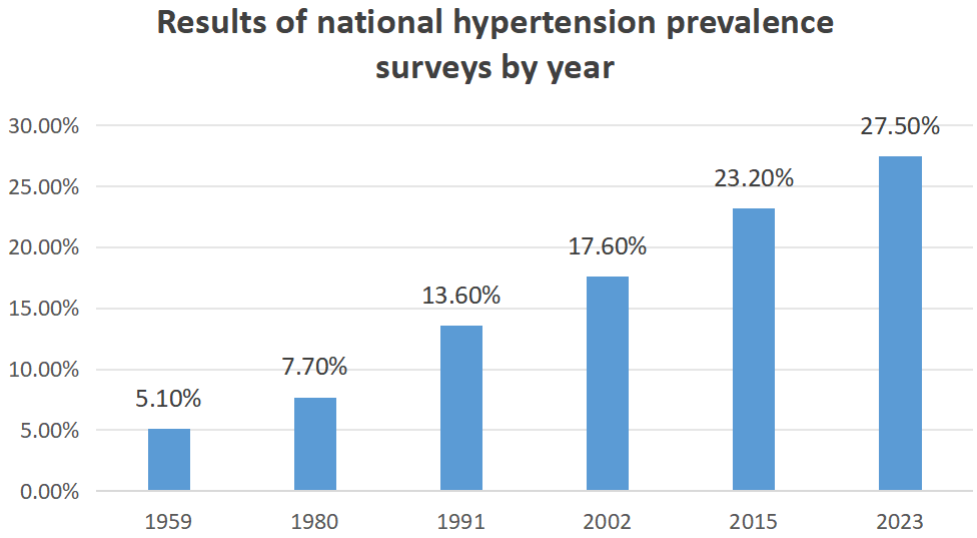

Figure 2: Results of the national hypertension prevalence survey over the years

The gut microbiota, often referred to as the "second genome" of the human body, consists of approximately 10^14 bacteria in normal individuals, belonging to around 1, 000 different species. Increasing evidence suggests that structural changes in specific gut microbiota are closely associated with the occurrence and development of hypertension. These include Ruminococcus, Lactobacillus, Clostridium, and Bifidobacterium, among others [6]. The gut microbiota can produce a variety of metabolites through the absorption and breakdown of nutrients. Some of these metabolites, such as trimethylamine-N-oxide (TMAO), corticosterone, hydrogen sulfide (H2S), and short-chain fatty acids (SCFAs), have been shown to be closely related to the occurrence and development of hypertension [7]. Studies have demonstrated that both hypertensive patients and animal models of hypertension exhibit dysbiosis of the gut microbiota. Clostridium and Ruminococcus are major SCFA-producing bacteria, and by altering their community structure, the types and levels of SCFAs can be changed, thereby affecting blood pressure regulation. Probiotics such as Lactobacillus and Bifidobacterium can improve gut microbiota imbalance and have the potential to prevent and treat hypertension through oral administration [8]. This review summarizes the research progress on the relationship between gut microbiota and the occurrence and development of hypertension, aiming to

provide new references and evidence for related studies on hypertension.

2. Correlation between Gut Microbiota and Hypertension Risk Factors

2.1. Gut Microbiota and Atherosclerosis

The occurrence and development of atherosclerosis (AS) are associated with the gut microbiota. Studies have shown that the human gut microbiota may influence the risk factors of AS and the development of AS plaques, affecting the progression of AS [9]. In patients with AS, there is an increased intestinal mucosal permeability, and bacteria play a role in the formation of AS [10]. When the content of Verrucomicrobia, a phylum of bacteria, is low in the body, it can promote fat accumulation by inhibiting host metabolism, leading to elevated blood lipid levels and the formation of AS. Zang Kaili et al. [11] found that probiotic preparations, such as Bifidobacterium, help reduce blood lipid levels, thereby preventing and delaying the occurrence of AS. Zhang Yanwei et al. [12] confirmed that when intestinal barrier function is impaired, some bacterial endotoxins enter the body, triggering systemic chronic inflammation, causing endothelial damage, and promoting monocyte differentiation into macrophages, thereby driving plaque formation. AS, as one of the major risk factors for hypertension, may be associated with the gut microbiota in its development.

2.2. Gut Microbiota and Obesity

Obesity is also a major risk factor for hypertension, and the fermentation of Sanqi by Lactobacillus plantarum has been found to have anti-obesity effects. Altering the composition of the gut microbiota is considered a key factor in anti-obesity effects, increasing the relative abundance of Bacteroidetes, Erysipelotrichaceae, and Dehalobacterium, while reducing the F/B ratio. Research has shown a negative correlation between Bacteroidetes and the gene expression of peroxisome proliferator-activated receptor γ (PPARγ) in the hypothalamus. Decreased hypothalamic PPARγ gene expression can regulate lipid metabolism [13]. Other studies have confirmed a close relationship between the gut microbiota and obesity, as antibiotics can induce the occurrence and development of obesity by altering the gut microbiota [14-16]. Treatment of 3T3-L1 adipocytes with the cell-free metabolites of Lactobacillus plantarum can inhibit adipocyte differentiation and fat deposition by downregulating key adipogenic transcription factors (PPAR-γ, C/EBP-α, and C/EBP-β) and their downstream targets (FAS, aP2, ACC, and SREBP-1). This leads to reduced fat mass, improved serum lipid profile, and weight reduction in obese mice fed a high-density lipoprotein diet. Lactobacillus plantarum activates p38MAPK, p44/42, and AMPK-α by increasing their phosphorylation, thereby inhibiting the development of obesity in high-fiber-fed mice. Analysis suggests that A29 can regulate the composition of the gut microbiota. Therefore, the potential probiotic strain A29 may slow down the development of obesity and related metabolic disorders by activating the p38MAPK and p44/42 signaling pathways to inhibit PPARγ [17]. Jin Xiaoqin et al. [18] investigated the mechanism of Shenling Baizhu San in treating obesity by studying its effect on the gut microbiota of obese mice. The results showed that compared to the model group, the Shenling Baizhu San group had significantly reduced body weight, blood glucose, and levels of TC, TG, and LDL-C, while HDL-C levels were significantly increased. Gut microbiota analysis showed an increase in species richness and evenness, as well as a significant increase in the number of core operational taxonomic units (OTUs) after treatment with Shenling Baizhu San. The ratio of Bacteroidetes to Firmicutes was reduced. This indicates that Shenling Baizhu San can significantly improve body weight, blood glucose, and blood lipid-related indicators in obese mice and alleviate gut microbiota imbalance. In summary, changes in the composition or structure of the gut microbiota may affect the distribution of body fat and the generation of new fat, leading to the development of obesity.

2.3. Gut Microbiota and Lipid Metabolism

The gut microbiota plays a crucial role in the host's metabolism. Studies have shown that Toll-like receptor 5 (TLR5) deficiency in mice (T5KO) leads to microbiota-dependent metabolic syndrome. The results demonstrate that T5KO mice exhibit elevated neutral lipids, with an increased composition of oleic acid esters [C18:1(n9)] compared to wild-type littermates. The increase in liver lipid content and liver SCD1 expression in T5KO mice depends on the gut microbiota. Analysis of short-chain fatty acids (SCFAs) and (13)C-acetate labeling revealed elevated SCFA levels in the cecum and portal vein blood of T5KO mice, accompanied by increased de novo lipogenesis in the liver. Dietary SCFAs further exacerbate the metabolic syndrome in T5KO mice. Deletion of the SCD1 gene in the liver not only prevents neutral lipid accumulation of oleic acid esters but also improves the metabolic syndrome in T5KO mice. These findings indicate that the gut microbiota-liver axis plays a critical role in the pathogenesis of metabolic diseases [19]. Li Cailiu et al. [20] investigated the effects of Cordyceps polysaccharides on lipid metabolism, inflammatory response, and gut microbiota in high-fat high-cholesterol-induced ob/ob mice liver tissues. The results showed that compared to the model group, high-dose Cordyceps polysaccharides significantly reduced the content of the lipid metabolism-related enzyme fatty acid synthase (FAS) in liver tissues and significantly increased the content of long-chain acyl-CoA dehydrogenase (LCAD). High and medium doses of Cordyceps polysaccharides significantly reduced the expression of C-reactive protein (CRP), inhibited monocyte chemoattractant protein 1 (MCP-1) and serum amyloid A (SAA) expression. Compared to the model group, all three doses of Cordyceps polysaccharides significantly reduced the expression of nuclear transcription factor κB subunit p65 (NF-κBp65) and tumor necrosis factor α (TNF-α). High-dose polysaccharides reduced interleukin 6 (IL-6) levels, while there was no significant difference in the low and medium dose groups. These results suggest that Cordyceps polysaccharides from TaiShan can improve liver tissue lipid metabolism and alleviate inflammation by modulating the gut microbiota. The gut microbiota may play an important role in changes in body mass index and blood lipid levels, independent of age, gender, and genetics. Studies have shown that weight, triglycerides, and high-density lipoprotein can be controlled by altering the gut microbiota [21].

3. Gut Microbiota and Hypertension Treatment

3.1. Exercise

Studies have shown that exercise can help regulate the balance of the gut microbiota in the human body, although the specific mechanisms are not yet clear. In addition to altering the gut microbiota, exercise training can also improve cardiac function to some extent [22]. Researchers have investigated the effects of voluntary exercise (Ex) on the gut microbiota of low-density lipoprotein-fed mice and high-density lipoprotein intraperitoneally injected mice. The results indicate that Ex can cause specific changes in the gut microbiota, which are different from the effects of diet [23]. It is well known that the gut microbiota plays an important role in inflammatory chronic diseases. Campbell et al. [24] found that exercise has a significant impact on gut integrity and the host microbiota, and further mechanistic studies can be conducted on the interaction between specific bacteria in the gut and the host. Intense exercise-induced physical and mental stress can lead to the body's stress response, activating the sympathetic-adrenal medullary axis and the hypothalamic-pituitary-adrenal axis (HPA), resulting in excessive release of catecholamines (norepinephrine and epinephrine) and other neurotransmitters. This can induce gastric acid secretion, gastrointestinal motility, and mucus production through the vagus nerve, impairing gastrointestinal function and subsequently causing dysbiosis in the gut microbiota [25]. Studies have shown that during acute

exercise, the diversity of the gut microbiota increases after the body adapts to the intensity of the exercise. The abundance of Lachnospiraceae, Phascolarctobacterium, and Akkermansia muciniphila increases, while the abundance of Ruminococcaceae decreases [26]. Research has also found that 6 months of endurance exercise can reduce excessive fungal growth in the gut and improve gut barrier function [27].

3.2. Diet

Changes in dietary composition can lead to changes in the gut microbiota. Although the relationship between hypertension and dietary salt intake is well-established, the underlying mechanisms are not fully understood. Research has shown that there is an interaction between dietary salt content, gut microbiota composition, and blood pressure [28]. Possible mechanisms include the impact of a high-salt diet on host immune regulation, gut permeability, and bacterial translocation, which can lead to changes in blood pressure. Additionally, this study found a correlation between a high-salt diet in rats and changes in fecal levels of short-chain fatty acids (SCFAs), highlighting another aspect of the complex interactions between diet, the gut, and blood pressure. These results suggest that dietary interventions may reduce blood pressure by improving the diversity and abundance of intestinal flora. Marques et al. [29] evaluated the effects of a high-fiber diet and the addition of short-chain fatty acid acetates on the gut microbiota and cardiovascular disease prevention by examining the gut microbiota, cardiac and renal structure/function, and blood pressure in sham mice and mice overdosed with mineralocorticoids, and determining the renal and cardiac transcriptomes of mice treated with different diets. The findings suggest that a fiber-rich diet induces changes in the gut microbiota that prevent cardiovascular disease. Therefore, modulating the gut flora structure through dietary interventions may be an innovative strategy for the nutritional treatment of hypertension.

3.3. Traditional Chinese Medicine

Modern medical research has shown that many traditional Chinese medicines have a certain regulatory effect on the gut microbiota and can be used to treat hypertension by modulating the gut microbiota. Dendrobium officinale, known for its nourishing Yin and clearing heat properties, has been found to lower blood pressure through its interaction with the gut microbiota. It improves the gut microbiota in hypertensive rat models, promotes the production, transport, and utilization of SCFAs (short-chain fatty acids), thereby activating the gut-vascular axis SCFA-GPCR43/41 pathway. This pathway regulates metabolic abnormalities, improves endothelial function, and ultimately reduces blood pressure in rats [30]. Zhong Lingyun et al. [31] studied the differences in the pharmacological effects and gut microbiota diversity of different processed products of Pueraria root and Pueraria powder in rats with high-salt water-induced hypertension. The results showed that the vinegar-processed Pueraria root group had the most significant antihypertensive effect compared to the model group. The abundance of Blautia and Prevotella genera was higher in the vinegar-processed Pueraria root group, and these two genera produce more SCFAs, which can promote the growth of beneficial bacteria, alleviate hypertension-related immune-inflammatory reactions, and have a good antihypertensive effect. It has been found that Huangqi Danshen Decoction has a certain antihypertensive effect on spontaneously hypertensive rats. It lowers the F/B ratio, increases the abundance of Lactobacillus, Bifidobacterium, Akkermansia, and Christensenellaceae, suppresses systemic inflammation, reduces blood lipids, and produces antihypertensive substances such as angiotensin-converting enzyme inhibitory peptides, SCFAs, conjugated linoleic acid, and γ-aminobutyric acid, ultimately leading to a decrease in blood pressure [32].

3.4. Probiotics

Probiotics can influence the gut microbiota and its metabolic products. Studies have shown that supplementation of Lactobacillus plantarum DSM15313 fermented blueberry can reduce systolic and diastolic blood pressure in hypertensive rat models [33]. Aoyagi et al. [34] found that regular consumption of fermented dairy products containing Lactobacillus casei strains significantly reduces the risk of hypertension in elderly individuals. Thushara et al. [35] found that ACE inhibition reduces the synthesis of angiotensin II, and probiotics produce bioactive peptides with ACE inhibitory properties during the fermentation process, leading to vasodilation and blood pressure reduction. Proper supplementation of probiotics can influence the function and composition of the intestinal flora, thereby activating the immune system and suppressing inflammation [36]. Probiotics also regulate blood pressure by improving lipid levels, regulating the early dissociation of bound bile acids, and controlling body mass index [37]. These studies indicate that probiotics play an important role in the occurrence, development, and treatment of hypertension. Therefore, the use of probiotics is an effective strategy for the treatment of hypertension.

3.5. Antibiotics

Study shows that oral administration of minocycline to rats with essential hypertension increases gut microbial diversity [38]. It has been found that inhibition of neuroinflammation in the paraventricular nucleus of the hypothalamus via CMT-3 can directly affect the gut microbiota and its pathology, thereby lowering blood pressure [39]. One study confirmed that in rats with hypertension in aged spontaneously hypertensive rats, minocycline and vancomycin can reduce systolic blood pressure by an average of 35 mmHg [40]. This suggests that antibiotics alter the number and type of bacteria directly or indirectly alleviating the process of hypertension.

4. Summary

The results above all indicate that dysbiosis of the gut microbiota is a key factor in the pathogenesis of hypertension. It can be regulated by various methods such as exercise, dietary adjustments, probiotic supplementation, use of antibiotics and fecal microbiota transplantation, thereby playing a role in the prevention and treatment of hypertension. Therefore, restoring the homeostasis of the gut microbiota may be a potential strategy and approach for the future prevention and management of hypertension and reducing the risk of cardiovascular diseases. However, the specific mechanisms underlying the interaction between the gut microbiota and hypertension remain unclear and further in-depth research is warranted. How does the gut flora interact with the host? What are the exact molecular mechanisms by which gut flora modulate host blood pressure? The effectiveness of gut flora-based hypertension treatment strategies such as exercise, diet, herbal medicine, probiotics, antibiotics and fecal transplantation and their mechanisms still need further clinical validation.

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