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THE ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF HYPERTENSION - NEW PATHOPHYSIOLOGICAL AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Background: Hypertension (HT) is a major cardiovascular risk factor, yet traditional models often fail to explain resistant cases. Recent research shifts the focus to the gastrointestinal tract, positioning gut microbiota as a critical modulator of vascular, renal, and neurological functions.

Objective: This study analyzes the role of gut dysbiosis in HT pathogenesis, focusing on gut-vascular and gut-brain axes. It synthesizes evidence on how bacterial metabolites, epigenetic mechanisms, and chronic inflammation affect blood pressure homeostasis, evaluating diet and probiotics as supportive therapies.

Methods: A review of the current literature in PubMed, Scopus, Google Scholar and ESH/ESC guidelines was conducted, analyzing metagenomic data, animal model studies, and clinical trials regarding the impact of molecular mechanism of metabolic signaling, epigenetic and immunological processes influencing vascular and renal blood pressure regulation.

Results: HT patients exhibit a distinct microbiota phenotype, characterized by an increased *Firmicutes/Bacteroides* ratio and reduced butyrate-producing bacteria. Key metabolic regulators include protective short-chain fatty acids and prohypertensive trimethylamine N-oxide. It has been demonstrated that leaky gut syndrome leads to the translocation of lipopolysaccharide, which induces systemic neuroinflammation. Furthermore, bacterial metabolites act as epigenetic regulators in the kidneys by modulating the activity of histone deacetylases.

Conclusion: Gut dysbiosis is an active pathophysiological component of HT. The gut-vascular axis integrates pressure control through immunological hormonal, and neuronal mechanisms. Incorporating targeted diets, probiotics, and psychobiotics into standard protocols offers promising new perspective for HT management.

KEYWORDS

Gut Microbiota, Hypertension, Dysbiosis, Gut-Brain Axis, Gut Bacteria

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Introduction

Hypertension (HT) is currently the most significant modifiable risk factor for cardiovascular mortality, affecting more than 1.3 billion people worldwide [1]. Despite the availability of numerous classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, beta-blockers, calcium channel blockers, and diuretics, a significant portion of the population still fails to achieve target blood pressure levels. Traditional pathophysiological models, focusing mainly on peripheral vascular resistance, renal function and sympathetic activity, appear insufficient to fully explain the cause of primary HT and to understand why standard therapy remains ineffective in many patients.

For this reason, over the past decade, researchers' attention shifted toward the gastrointestinal tract, changing the paradigm of how the gut is perceived- it is no longer treated merely as a digestive organ, but as a complex hormonal and immune system with holistic impact on the body. A key component of this system is the gut microbiota, understood as a multidirectional ecosystem of bacteria, viruses, and fungi. It functions as a newly discovered organ with immense metabolic potential that actively communicates with the host's circulatory system via the so-called gut- vascular axis.

The microbiota produces hundreds of biologically active compounds that enter the systemic circulation and modulate vascular function. Metagenomic studies have shown that patients with HT exhibit a distinctly different bacterial profile compared to individuals with normal blood pressure. A thorough understanding of this relationship paves the way for the development of personalized medicine, in which targeted diets and probiotic therapy may in the future become an integral part of the official guidelines of the European Society of Hypertension/Cardiology (ESH/ESC), supporting the treatment of this condition.

Aim of the Study:

A systematic review of the impact of the gut microbiota on the development of hypertension (HT), with particular emphasis on molecular, metabolic (SCFA, TMAO), epigenetic (HDAC inhibition), immunological (Th17, IL-17A), and neurogenic mechanism.

Methods

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across major databases, including PubMed, ResearchGate, and Google Scholar.

Eligibility Criteria

Studies were included if they met the following criteria:

- Were randomized controlled trials, meta-analyses, controlled clinical trials, or experimental animal studies investigating the impact of gut microbiota, bacterial metabolites, or fecal microbiota transplantation on hemodynamic parameters and vascular function.
- Involved human subjects or experimental animal models.
- Focused on primary, resistant, or salt- sensitive HT.
- Full-text articles published in English.

Exclusion criteria were:

- Non-original research (e.g., reviews, editorials, case reports).
- Studies unrelated to blood pressure regulation or cardiovascular homeostasis.
- Abstract-only publications or conference proceedings.

Study Selection

Two independent reviewers screened all titles and abstracts for eligibility, followed by a full-text review of potentially relevant articles. Discrepancies were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data extracted from each study included publication year, study design, sample size, patient population, clinical outcomes, microbiota-related changes, and adverse events.

Risk of Bias and Ethical Considerations

All included studies reported adherence to ethical standards such as the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review board approvals and informed consent from participants were documented. Several studies were registered with clinical trial registries. While a formal risk of a bias assessment was not performed, design rigor (e.g., blinding, randomization, control groups) was noted.

Data Synthesis

Due to significant heterogeneity in study designs, clinical guidelines, and microbial analysis protocols, a narrative synthesis approach was used. Data were compared descriptively to identify patterns in the influence of gut-derived metabolites, epigenetic regulators, and immune signaling on blood pressure regulation and vascular function. A total of 53 studies were ultimately included in this review.

Literature Review Results

Hypertension

Definition and Classification

The classification of HT is a key component of diagnosis, enabling a choice between empirical treatment and therapy targeted at the underlying cause of the condition. According to current guidelines from scientific societies (ESH/ESC), HT is divided into two main categories: primary and secondary [2].

Primary HT is characterized by a sustained elevation of blood pressure in which no single, specific organic cause can be identified. It accounts for approximately 90-95% of all clinical cases [3]. Its pathogenesis is multifactorial and results from the complex interaction of genetic predisposition and environmental factors, such as excessive sodium intake, low physical activity, psychophysical stress, or progressive vascular stiffening. Current research emphasizes that in primary HT, subtle disturbances in the renin-angiotensin-aldosterone system (RAAS), sympathetic overactivity and gut dysbiosis play a key role, collectively leading to a sustained increase in peripheral resistance [4].

In contrast, secondary HT is a form of condition in which elevated blood pressure is a direct consequence of diagnosable underlying disease. It affects 5-10% of adult patients, though its prevalence rises sharply in pediatric populations and among patients with severe HT [5]. The most common causes of secondary HT include renal parenchymal diseases, renal artery stenosis, as well as endocrine disorders such as primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma, or thyroid dysfunction. Obstructive sleep apnea and iatrogenic factors- including the use of oral contraceptives, glucocorticoids and nonsteroidal anti-inflammatory drugs- are also significant secondary causes [5].

Resistant HT constitutes a separate, clinically challenging category. It is defined as a condition in which target blood pressure values (typically <140/90 mmHg) cannot be achieved despite the concurrent use of three antihypertensive drugs from different classes at optimal or maximum tolerated doses. One of these three drugs must be a diuretic [6]. Resistant HT is diagnosed only after ruling out so-called pseudo-resistant HT, resulting from patient non-compliance with treatment, the "white coat" effect, or technical errors during measurement. In recent years, it has been emphasized that resistant HT is often a manifestation of undiagnosed changes in the gut-kidney axis, requiring specific intervention beyond standard treatment protocols.

Pathomechanism

The etiopathogenesis of HT is a multifaceted process resulting from hemodynamic, hormonal, and vascular disturbances. The primary mechanism regulating blood pressure remains the RAA system, whose hyperactivity is considered the corenerstone of primary HT development. The key mediator in this system is angiotensin II, which, via type 1 receptor exerts a strong vasoconstrictive effect, promotes sodium retention in the renal tubules, and stimulates the release of aldosterone from the adrenal cortex [7]. Recent studies shed new light on the so-called "local RAA systems" in the heart, blood vessels, and brain, which operate independently of the circulatory system, leading to local fibrosis and left ventricular hypertrophy [8]. Angiotensin II also activates NADPH oxidase in the vascular wall, which generates reactive oxygen species, leading to oxidative stress and secondary endothelial damage [9].

Parallel to the hormonal axis, the autonomic nervous system plays a key role, specifically its chronic hyperactivity. Increased sympathetic influence, stimulated among other things, by afferent signals from chemoreceptors and changes in central brainstem regulation, leads to an increase in peripheral resistance and enhances renin release in the kidneys [10]. Recent reports highlight the release of neuropeptide Y and pro-inflammatory cytokines, including interleukin-6 (IL-6), within blood vessels, which permanently stiffens the arterial wall [10].

A key component of the pathogenesis is vascular endothelial dysfunction, characterized by an imbalance between vasodilatory and vasoconstrictive factors. Impaired nitric oxide (NO) signaling plays a central role here. Under the influence of high hydrostatic pressure and oxidative stress, the nitric oxide synthase enzyme undergoes denaturation, which instead of producing NO, leads to the generation of superoxide anions. The decrease in NO bioavailability prevents proper relaxation of vascular smooth muscle and promotes the proliferation of these cells, resulting in thickening of the arterial media, narrowing of the vessel lumen, and consequently an increase in peripheral vascular resistance [11]. Research also points to the role of endothelin-1 as the strongest endogenous vasoconstrictor, whose overexpression correlates with the degree of hypertensive resistance to pharmacological treatment [12].

An integral component of HT development is renal dysfunction involving a shift in the pressure-natriuresis curve. Under physiological conditions, an increase in blood pressure should result in increased sodium and water excretion. However, in individuals with HT, the threshold for this mechanism to activate is raised to higher blood pressure values. This phenomenon forces the body to maintain a constant, high blood pressure as the only way to preserve normal sodium-water balance. This effect is caused by changes in intrarenal circulation, including constriction of the afferent and efferent glomerular arterioles and alterations in the expression of sodium transporter due to chronic exposure to cortisol and aldosterone [13]. Epigenetic studies suggest that changes in DNA methylation of the genes encoding these transporters may explain genetic predisposition to salt-sensitive HT [14].

At the molecular level, HT induces vascular wall remodeling, in which matrix metalloproteinases (MMPs) play a key role. Chronic mechanical stress activates MMP-2 and MMP-9, which degrade elastin and promote the deposition of type I collagen in the arterial wall. This process, known as vascular fibrosis, leads to loss of elasticity in large arteries, such as the aorta. This results in an increase in pulse wave velocity and a rise in systolic blood pressure, accompanied by a decrease in diastolic blood pressure. This mechanism is particularly significant in the geriatric population, leading to isolated systolic HT [15].

In summary, the pathomechanism of HT is a dynamic process in which primary dysfunction of neurohormonal and renal regulation is eventually consolidated by structural changes in the vessels. Recently, researchers have been placing increasing emphasis on subclinical vascular wall inflammation and the impact of oxidative stress as targets for new antihypertensive therapies.

Intestinal dysbiosis

Modern HT research, supported by advanced metagenomic tools, is expanding our understanding of the potential mechanisms underlying HT and challenging the view that this condition is solely an isolated hemodynamic defect.

Currently, HT is classified as a condition inextricably linked to a disruption of gut microbiome homeostasis, where dysbiosis acts as an active pathophysiological component rather than merely a passive marker of disease. The strongest evidence for the causal role of microorganisms comes from studies on fecal microbiota transplantation (FMT) in animal models. These experiments have shown that transplanting gut microbiota from hypertensive rats into normotensive individuals induces a significant increase in systolic blood pressure in recipients, averaging 15 to 20 mmHg [16]. This mechanism is associated with a systemic change within the immune system initiated in the mesenteric lymph nodes of individuals with intestinal dysbiosis. It is there that pathological activation of Th17 lymphocytes occurs, which act as a link between intestinal dysbiosis and the vascular system. The key effector of these cells is the cytokine IL-17A, which, upon entering the systemic circulation, induces NADPH oxidase. This leads to a rapid overproduction of reactive oxygen species, which, through the mechanism of oxidative stress, reduces the bioavailability of NO. A drastic drop in NO levels directly reduces the vessels' ability to relax and shifts the hemodynamic balance toward vasoconstriction [17].

At the same time, IL-17A sensitizes vascular smooth muscle cells to the effects of angiotensin II, which potentiates vasoconstriction of resistance vessels and leads to a sustained increase in peripheral resistance. Prolonged exposure to this cytokine also promotes vascular wall remodeling by enhancing collagen deposition, resulting in vascular stiffening. In addition to its vascular effects, IL-17A acts on renal tubule cells, increasing the expression of the sodium-chloride transporter, which enhances sodium reabsorption and increases circulating blood volume [18].

These processes are drastically exacerbated by adverse environmental factors, primarily a high-salt diet. Excess sodium acts as a selective factor eliminating *Lactobacillus* bacteria, thereby negating their natural inhibitory effect on Th17 cells and promoting a pro-inflammatory environment conducive to blood vessel constriction [19].

Gut microbiota phenotype in individuals with HT

Analysis of the taxonomic architecture in patients with primary and resistant HT reveals a characteristic microbiota phenotype based on species-level shifts. A key marker of dysbiosis is an increase in the ratio of *Firmicutes* to *Bacteroidetes*, as determined by the F/B ratio, which reflects a metabolic shift favoring the promotion of systemic inflammation [20]. In individuals with HT, there is a significant depletion of protective commensal bacterial populations, particularly butyrate-producing symbionts such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Coprococcus.* These species show a strong negative correlation with

blood pressure values, and their drastic depletion results in a deficiency of short-chain fatty acids (SCFAs) and weakening of the intestinal mucosal barrier integrity [21].

At the same time, a pathological expansion of pathobionts is observed, including those of the genera *Prevotella* and *Klebsiella*. Studies confirm that the abundance of Klebsiella spp. positively correlates with increased arterial stiffness and thickening of the intima-media complex. These bacteria actively promote a hypertensive phenotype through the synthesis of pro-inflammatory molecules, including IL-6, and the degradation of the vascular glycocalyx, leading to irreversible impairment of endothelial function and progressive organ damage [21].

The identified microbial phenotypes open new perspectives in diagnostics and personalized therapy, allowing for the early detection of individuals predisposed to developing HT and precise stratification of the risk of progression to resistant HT. The use of *shotgun* sequencing is becoming the foundation of pharmacomicrobiomics enabling the selection of appropriate drugs based on their interaction with the patient's individual gut ecosystem [22].

Bacterial metabolites-key mediators of gut-vascular axis

The microbiota's influence on blood pressure homeostasis is primarily mediated by low-molecular-weight signaling molecules that enter the systemic circulation and act on distant target organs, such as blood vessels, the kidneys, and the heart. The best studied mediators include short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO).

Short-chain fatty acids

SCFAs, mainly acetate, propionate, and butyrate, are produced through the anaerobic fermentation of plant polysaccharides by commensal bacteria, including genera such as Bifidobacterium, Lactobacillus, and Faecalibacterium. Their role in blood pressure regulation is determined by their unique interaction with G protein-coupled receptors (GPCRs). As part of vasodilatory mechanisms of GPR41 and GPR43 receptors, activation of GPR41 (FFAR3), located in endothelial cells and the smooth muscle of blood vessels, induces a signaling cascade leading to vasodilation. Recent studies indicate that SCFAs stimulate NO production via activation of the AKT/eNOS pathway, which effectively reduces systemic vascular resistance [23]. In turn, GPR43 (FFAR2) plays a key role in immune modulation by inhibiting the migration of inflammatory cells to the vascular wall, thereby preventing its pathological remodeling and stiffening [23, 24].

An exceptionally unique aspect of SCFA-mediated blood pressure control involves the renal olfactory receptor 78 (Olfr78). Unlike GPR41, Olfr78, located in the juxtaglomerular apparatus, stimulates renin release in response to propionate and acetate, leading to activation of the RAA system and an increase in blood pressure [23, 25]. Physiological homeostasis therefore depends on a precise balance between the hypotensive action of GPR41 and the hypertensive effect of Olfr78. Whereas in a state of dysbiosis, when SCFA levels drop drastically, this homeostasis is disrupted, which contributes to the persistence of high blood pressure [25, 26].

Trimethylamine N-oxide

In contrast to protective SCFAs, TMAO, produced by bacteria, is considered one of the strongest proatherogenic and prohypertensive factors. Its formation is a two-step process. Initially, gut bacteria such as *Prevotella* and *Enterobacteriaceae* convert choline, betaine, and L-carnitine into trimethylamine, which is then oxidized in the liver by flavin monooxygenases to form TMAO. The molecular mechanism of vascular damage caused by TMAO involves several complementary pathways. First, TMAO induces oxidative stress by activating the NLRP3 inflammasome complex in endothelial cells, leading to the overproduction of superoxide anion and a reduction in NO bioavailability [27]. Second, TMAO has been shown to disrupt calcium homeostasis by enhancing calcium release from the endoplasmic reticulum in vascular smooth muscle cells, thereby increasing their responsiveness to neurohormonal vasoconstrictor stimuli such as angiotensin II [28]. Third, chronic exposure to high TMAO concentrations promotes tubulointerstitial fibrosis in the kidneys, which impairs sodium and water excretion [29].

The clinical significance of these findings is confirmed by recent studies. Current meta-analyses indicate that patients in the highest quartile of plasma TMAO concentration have a 40% higher risk of developing treatment-resistant HT [30]. TMAO has thus become an important biomarker for stratifying the risk of cardiovascular events, such as stroke or myocardial infarction, independent of classic risk factors including dyslipidemia or diabetes.

Intestinal barrier

Low-grade chronic inflammation

Modern medicine defines HT not only as a hemodynamic disorder, but increasingly as a state of low-grade chronic inflammation in the body and a disease with a significant immunological basis. A key element of this pathogenesis is the gut-vascular axis, in which microbiota dysbiosis leads to impaired intestinal barrier integrity, referred to as leaky gut syndrome [31, 32].

Mechanism of intestinal barrier degradation

This process is initiated by the degradation of tight junction proteins, such as zonulin and occludin, resulting in a pathological increase in paracellular epithelial permeability. Under physiological conditions, occludin, together with claudins, forms a tight seal between adjacent enterocytes, regulating the flow of ions and molecules. Increased zonulin secretion, e.g., under the influence of dysbiosis, activates EGFR and PAR2 receptors, leading to the phosphorylation of junction proteins and their reorganization within the actin cytoskeleton. Degradation or displacement of these proteins causes the physical barrier to "loosen", opening the way for the translocation of microbial components from the intestinal lumen into the portal and systemic circulation [32].

Lipopolysaccharide

Lipopolysaccharide (LPS)-a potent endotoxin that is a component of Gram-negative bacterial cell walls-plays a special role in this process. The mechanism of LPS action in the pathogenesis of HT is based on the induction of chronic inflammatory response via Toll-like receptors (TLR4). Once it enters the circulation, LPS binds to the lipopolysaccharide-binding protein and is then presented to the TLR4 receptor present on the surface of macrophages, monocytes, and endothelial cells. Activation of TLR4 triggers two main signaling pathways. The first is the MyD88-dependent pathway, leading to the translocation of the NF-κB nuclear factor into the cell nucleus, resulting in massive production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β [20, 33]. The second, however, involves the induction of oxidative stress through the activation of NADPH oxidase in the vascular walls, leading to the overproduction of reactive oxygen species. ROS degrade NO, leading to endothelial dysfunction, increased vascular stiffness, and heightened peripheral resistance [34].

At the same time, the presence of LPS and the accompanying cytokine cascade promotes the aforementioned migration of Th17 lymphocytes to the kidneys, where the IL-17 they secrete induces fibrosis and sodium retention, completing the vicious cycle of immune-mediated HT [35].

Epigenetic mechanisms

The microbiota-butyrate axis

Modern nephrology and hypertensiology are being redefined thanks to discoveries in the field of pharmacomicrobiomics, which provide groundbreaking evidence that the gut microbiota acts as a master epigenetic regulator in the kidneys. This mechanism is primarily based on the modulation of chromatin acetylation by bacterial fermentation metabolites, with a particular focus on butyrate. This compound is not merely an energy substrate for colonocytes but acts as a circulating inhibitor of histone deacetylases (HDACs), mainly classes I and IIa. In the renal contes, this inhibitor activity serves as a key molecular switch controlling water electrolyte homeostasis [36].

Under eubiosis conditions, physiological concentrations of butyrate in the renal circulation promote a state of hyperacetylation of histones H3 and H4 in the promoter regions of nephroprotective genes [37]. However, in the course of dysbiosis accompanying HT, a drastic decline in the population of the order *Clostridiales* leads to a butyrate deficit, which releases HDAC activity. Overactivity of these enzymes in distal tubule and collecting duct cells induces chromatin condensation, resulting in the silencing of genes such as DUSP1, responsible for inhibiting inflammatory MAPK pathways. At the same time, the lack of HDAC inhibition to butyrate leads to the paradoxical activation of gene expression encoding key sodium transporters. This mechanism involves increased mRNA stability for the α subunit of the epithelial sodium channel (ENaC) and the sodium-potassium-bicarbonate symporter in the ascending limb of the Henle's loop. This process is further amplified by epigenetic modifications of SGK1-the primary stimulator of ENaC channel insertion into the apical membrane. Consequently, pathological sodium retention occurs, which directly shifts the pressure-natriuresis curve to the right and induces a salt-sensitive hypertension phenotype [36, 38].

Renal remodeling and filtration barrier protection

The epigenetic role of the microbiota extends beyond electrolyte transport alone, directly affecting the structural integrity of the organ. A deficiency in bacterial HDAC inhibitors promotes the activation of renal fibroblasts via the TGF-β1 pathway. Histone deacetylation within the PTEN gene promoter leads to its silencing, which activates the pro-proliferative PI3K/Akt pathway, enhancing the production of type I and III collagen and fibronectin in the peritubular space [39, 40]. This epigenetic etiology of fibrosis and interstitial remodeling explains why patients with dysbiosis exhibit significantly faster progression of chronic kidney disease coexisting with HT [40].

An integral component of this defense system is the effect of butyrate on surface receptors. This metabolite exerts an epigenetic effect by activating the GPR109A receptor, located on podocytes and tubular epithelial cells. This signaling enhances the antioxidant barrier by inducing Nrf2, which effectively protects the glomerular apparatus from damage caused by high perfusion pressure [41]. Thus, the microbiota-butyrate HDAC axis constitutes an integrated protective mechanism, the disruption of which-most often resulting from a highly processed diet or antibiotic overuse-becomes a primary hypertensogenic factor, leading to permanent structural changes in the kidneys.

Effects on Nervous System

The Gut-Brain Axis

Recent studies indicate that the gut microbiota acts as an active modulator of the nervous system, directly influencing central blood pressure regulation. This communication occurs via a bidirectional gut-brain axis, utilizing neural, hormonal and immunological pathways. A key element of this phenomenon is the autonomic nervous system, whose disrupted homeostasis forms the basis of HT with neurogenic component. This main link between the gut and the brainstem is the vagus nerve [42].

Under physiological conditions, SCFAs have an inhibitory effect on excessive neuronal excitability; however, in the states of dysbiosis a decrease in their concentration and the presence of inflammatory mediators activate the afferent terminals of the vagus nerve located in the lamina propria of the intestine [43]. These signals are transmitted to the nucleus of the solitary tract (NTS) in the medulla oblongata, which serves as the primary integrator of autonomic stimuli. Recent reports demonstrate that dysbiosis leads to desensitization of the baroreceptor signal specifically at the NTS level. The consequence of this process is disinhibition of the ventrolateral portion of the medulla oblongata, which is a key regulator of sympathetic activity. Constant stimulation of this part of the medulla oblongata results in a chronic increase in sympathetic tone, which clinically manifests not only as vasoconstriction of resistance vessels but also as increased renin secretion and resting tachycardia [44, 45].

Humoral mechanism and neuroinflammation

In addition to neural transmission, the central nervous system is subjected to constant pressure from humoral signals originating from the dysbiotic gut ecosystem. Disruption of the intestinal barrier allows for the translocation of LPS and pro-inflammatory cytokines, such as IL-1β and TNF-α, into the systemic circulation [45]. These mediators act on the CNS via circumventricular organs, including the organum vasculosum of the lamina terminalis, and the subfornical organ, where the blood-brain barrier is physiologically permeable, allowing direct contact between the brain and molecules circulating in the blood. Activation of the circumventricular organs induces a cascade of local inflammation within the hypothalamus, with particular emphasis on the paraventricular nucleus.

Studies have shown that inflammation in the paraventricular nucleus enhances the expression of NADPH oxidase, generating oxidative stress that permanently shifts sympathetic neurons to a higher baseline activity level. This phenomenon, defined as neuroinflammation, constitutes the key molecular mechanism responsible for the perpetuation of HT [46].

Therapeutic Perspectives

Diet

Understanding the gut-vascular axis opens up new therapeutic possibilities. The first pillar is dietary modification. The high fiber content in the DASH and Mediterranean diets provides substrates for fermentative bacteria, resulting in the intensive production of SCFAs such as butyrate, acetate, and propionate [47]. These metabolites act systemically, promoting direct vasodilation of blood vessels via GPR41/43 receptors and epigenetically inhibiting inflammatory processes and sodium retention in the kidneys. The synergy between fiber and polyphenols enhances the populations of *Akkermansia muciniphila* bacteria, which tightens the intestinal barrier and prevents the translocation of endotoxins into the bloodstream. By maintaining the integrity of the mucosal layer, the body avoids chronic low-grade inflammation, which is a key factor in vascular stiffness and neuroinflammation. Additionally, the high potassium and magnesium content in the DASH diet supports the function of ion pumps, effectively working in tandem with renal mechanisms regulated by the microbiota [48]. As a result, comprehensive dietary modification permanently lowers blood pressure, addressing the metabolic, immunological, and neurological causes of HT.

Probiotics and psychobiotics

The second pillar of modern HT therapy, alongside diet, is targeted probiotic therapy, which leverages specific interactions between bacteria and the cardiovascular system. Clinical studies suggest that strains such as *Lactobacillus helveticus* and *Bifidobacterium longum* exhibit a moderate hypotensive effect, mediated through unique intra-intestinal mechanisms. A key role here is played by these bacteria's ability to inhibit ACE activity directly in the intestinal lumen and the production of specific vasodilatory peptides that inhibit blood vessel constriction [49].

In light of these findings, the term 'psychobiotics' takes on a completely new meaning in the field of HT. Specific strains such as *Lactobacillus rhamnosus* or *Bifidobacterium infantis*, demonstrate the ability to modulate levels of key neurotransmitters, including GABA and serotonin, directly in the gastrointestinal tract, which contributes to the reduction of systemin inflammation. Recent reports suggest that regular supplementation with these strains may restore normal afferent vagal nerve activity, leading to effective suppression of sympathetic centers in the brainstem [50]. This approach is particularly promising for patients with comorbid anxiety disorders or those exposed to chronic stress, in whom sympathetic overactivity is the dominant cause of resistance to conventional antihypertensive treatment [51].

Antibiotics

Antibiotic resistance is a well-known medical problem; however, in the context of HT, the adverse effects of antibiotic therapy on the microbiota are attracting increasing attention. The unjustified use of broad-spectrum antibiotics leads to a sharp decline in bacterial diversity, which has a direct impact on blood pressure regulation.

Epidemiological studies indicate that frequent use of antibiotic therapy in childhood and early adulthood correlates with a higher risk of developing HT later in life [52]. This mechanism is based on the permanent elimination of Lactobacillus and *Bifidobacterium* strains, which are crucial for maintaining intestinal immune balance. Sudden depletion of the microbiota leads to overgrowth of pathobionts, such as Proteobacteria, resulting in chronic systemic endotoxemia. Furthermore, antibiotics disrupt SCFA production, which-as mentioned earlier-directly impairs vasodilatory function [53].

Discussion

The comprehensive approach to the pathogenesis of HT presented in this study, within the context of the gut-vascular axis, provides impetus for the development of personalized medicine. Traditional models, which focus on the RAAS and peripheral vascular resistance, while remaining the foundation of hypertensology, do not fully explain the mechanisms underlying treatment resistance. Including the gut microbiota as an active metabolic and immunological organ helps fill these gaps, particularly regarding subclinical inflammation and the epigenetic regulation of kidney function.

A key focus of this article is to identify specific molecular pathways linking dysbiosis to elevated blood pressure (Table 1). Among the main mechanisms influencing blood pressure, we can highlight the disrupted balance between protective SCFAs and prohypertensive TMAO. SCFA deficiency abolishes the vasodilatory effect of GPR41/43 receptors and promotes renal sodium retention, whereas excess TMAO-through activation of the NLRP3 inflammasome and disruption of calcium homeostasis-drastically increases vascular reactivity to angiotensin II. The coexistence of these phenomena creates the metabolic backdrop for resistant HT, suggesting that restoring the balance between these mediators may be the key to therapeutic success. The epigenetic mechanism in which bacterial butyrate acts as an HDAC inhibitor sheds entirely new light on renal sodium homeostasis. This demonstrates that environmental factors, via microbial metabolism, can directly modify the expression of ENaC transporter genes, which permanently shift the pressure-natriuresis curve to the right. Concurrently, the description of the immunological axis-in which leaky gut syndrome stimulates the Th17 lymphocyte lineage and thereby the release of interleukin-17A-allows us to understand how intestinal inflammation translates into structural vascular stiffening. This picture is completed by the neurogenic component, where the microbiota, via neural pathways-particularly the vagus nerve-and humoral mechanisms (e.g., LPS) permanently modulates sympathetic activity in brainstem centers, perpetuating HT.

Table 1. Summary – The role of the gut microbiota in the pathogenesis of hypertension.

The area of analysis	Key mechanisms and factors	Impact on blood pressure
Microbiota phenotype	Increase in the Firmicutes/Bacteroidetes ratio (F/B ratio).	A reduction in bacterial diversity is associated with increased arterial stiffness and resistance to drug treatment.
Bacterial metabolites	Decrease in short-chain fatty acids (SCFAs) Increase in trimethylamine N-oxide (TMAO)	SCFA: Vasodilatory effects, anti-inflammatory effects, regulation of renin release. TMAO: Induction of oxidative stress, activation of the NLRP3 inflammasome, renal fibrosis.
Intestinal barrier	Leaky gut syndrome: degradation of tight junction proteins (zonulin, occludin).	Translocation of lipopolysaccharide into the circulation. Low-grade chronic inflammation. Activation of TLR4 receptors, overproduction of pro-inflammatory cytokines, and decreased NO bioavailability.
Renal epigenetics	Inhibition of histone deacetylases (HDACs).	Modulation of ENaC channel and SGK1 protein expression. Pathological sodium retention and a rightward shift in the pressure-natriuresis curve.
Gut-brain axis	Signal transmission via the vagus nerve and periventricular structures.	Neuroinflammation in the periventricular nucleus of the hypothalamus. Desensitization of baroreceptors in the NTS. Chronic increase in sympathetic tone.

Despite their high scientific value, the implementation of these findings into clinical practice faces significant barriers. Most evidence for the causal role of the microbiota, such as the spectacular effects of fecal microbiota transplantation, comes from animal models, which requires caution regarding direct application to the human body. Furthermore, the moderate hypertensive effect of probiotics suggests that these interventions should be viewed more as valuable metabolic support rather than a standalone alternative to conventional pharmacotherapy. The economic and technical aspects of pharmacomicrobiomics also remain a challenge-the

cost of shotgun sequencing and the immense individual variability of the microbiome hinder the standardization of the bacterial profile for patients with HT.

An extremely important conclusion drawn from the text is the need to consider the patient's pharmacological history, especially in the context of current or past antibiotic therapy. Side effects related to microbiota may become a hidden risk factor for resistant HT, and the lack of clear guidelines regarding microbiome restoration in adults remains a significant therapeutic gap.

In summary, integrating knowledge from immunology, neurology, and epigenetics creates a coherent and interdisciplinary picture of the gut-vascular axis. It points to new avenues for understanding the etiology of HT and enables further research aimed at new therapeutic possibilities. Although further multicenter clinical trials in humans are necessary, the presented paradigm provides a solid foundation for future ESH/ESC guidelines. The introduction of microbiome analysis into standard cardiovascular risk stratification may soon become the key to effectively combating the HT epidemic.

Conclusions

The gut microbiota is not merely a passive observer of disease processes but an active regulator of blood pressure. The relationship between dysbiosis, intestinal barrier, permeability, and immune system activation is a key element of modern knowledge regarding HT. Although most evidence comes from preclinical models and cohort studies, the direction of change is clear. The incorporation of microbiome assessment into clinical practice may revolutionize the approach to the prevention and treatment of HT in the coming years, making it more precise and personalized.

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