REVIEW ARTICLE

Therapeutic Potential of Gut Microbiota in Hypertension: Mechanisms of Immune Modulation and Inflammation

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Received date: Feb 7, 2025; Revised date: Jul 21, 2025; Accepted date: Jul 23, 2025

Abstract

Emerging evidence links gut dysbiosis to numerous ailments, including hypertension and metabolic diseases. Multi-omics techniques have revealed that hypertensive individuals exhibit distinct alterations in their gut bacterial composition and metabolite profiles. The gut microbiome influences blood pressure through several mechanisms. For instance, microbiota-derived metabolites can have beneficial effects, such as those from short-chain fatty acids (SCFAs), or detrimental ones, like trimethylamine N-oxide (TMAO). These molecules modulate downstream signaling pathways via G protein-coupled receptors or direct immune cell activation. Furthermore, dysbiosis can compromise the gut epithelial barrier, leading to systemic inflammation that activates key regulatory pathways like the renin-angiotensin-aldosterone system (RAAS), the autonomic nervous system, and the immune system. Given these connections, the gut microbiome is a promising therapeutic target for hypertension. This review explores the potential of modulating the gut microbiota to manage blood pressure, focusing on the underlying mechanisms of immune modulation, inflammation, and microbial metabolites. By focusing on the 'how' rather than the 'what' of hypertension, it is identified that immune-mediated inflammation is orchestrated by the gut microbiota, as the core mechanism driving the disease. Gut dysbiosis is triggered by environmental factors like high-salt diets, perpetuates a pro-inflammatory state that undermines the efficacy of conventional antihypertensive drugs and contributes to treatment-resistant hypertension. Consequently, modulating the gut microbiota through targeted interventions, including dietary fiber, probiotics, and fecal transplantation, might represents a critical evolution in treatment. This approach moves beyond managing symptoms to directly correcting the inflammatory dysfunction at the heart of the disease, offering a powerful strategy to complement existing therapies.

KEYWORDS: hypertension, inflammation, gut microbiota, metabolite

Indones Biomed J. 2025; 17(4): 317-34

Introduction

With an estimated 32% worldwide incidence by calendar year 2024, hypertension was impacting 1.28 billion individuals (1,2), which 2/3 of these individuals are from the low-and middle-income countries, including Indonesia (3). An increased blood pressure (BP) can be the main risk factor for worldwide burden of illness in industrialized and undeveloped nations.(2) Over the past ten years, the yearly rise in the global prevalence of hypertension has increased up to 10.8 million or 19.2% of all attributable fatalities came from this cardiovascular (CV) factor.(4) Hypertension increase the risk of various complications, not only CV-related disease but also kidney failure.(5,6) The most significant contribution comes from the aging population,

especially in Western, and high-salt consumption civilizations.(4)

Most people with hypertension fail to reach appropriate BP management even with present anti-hypertensive drugs. Furthermore, a residual risk of CV events and related organ damage exists even with appropriate treatment including stroke, heart failure (HF), myocardial infarction (MI), renal damage, and cognitive impairment.(7-12) These results imply that a fundamental part of the underlying disease is not being addressed by present therapy approaches. New data suggests that immune cells are major players in the genesis and course of hypertension.(13) Pro-hypertensive stimuli like high salt and angiotensin II activate the immune system, which in turn elevates blood pressure and damages organs in a self-reinforcing cycle.(14,15) Clinical studies confirm this process causes vascular damage, a primary type of hypertension-mediated organ damage.(16) This immune activation can also lead to cognitive decline by disrupting critical neurovascular-immune interfaces' in the brain. This disrupts brain perfusion, waste clearance, and synaptic function, linking systemic inflammation directly to neurological impairment.(17)

In hypertension individuals, immune cells become active and infiltrate target organs including the kidney and the vasculature. Reactive oxygen species (ROS), metalloproteinases, cytokines, antibodies produced by these cells induce injury and malfunction of the target organs. These factors induce vasoconstriction, remodelling, and rarefaction in vessels, and produce interstitial fibrosis and glomerular damage in the kidney as well as raise an expression and activity of sodium transporters. In the end, the factors of hypertension and oxidative stress, higher interstitial salt, cytokine generation, and inflammasome promote immune activation in hypertension.(18) Recent studies indicate that the immunogenicity of isolevuglandin-modified self-proteins in antigen-presenting cells (APC), and can stimulate T cell activation and cytokine generation by the cells in which they are produced. Therefore, maintaining a well-balanced immune system and activation can benefit for long-term effects of hypertension and associated cardiovascular diseases (CVD) prevention.(19,20)

Gut microbiota is known to play a role in the development of metabolic diseases (21,22), yet recent studies have also demonstrated that gut microbiota serves as a crucial link between various environmental factors and our eukaryotic body, particularly the internal ecosystem of the human gut bacteria. This connection facilitates the development and progression of numerous diseases, including hypertension, primarily focusing on peripheral vascular remodeling (23-25), and moderating the *in vivo* effects of various drugs (26-29). Much of the current research connecting the gut microbiota to hypertension has concentrated on downstream consequences, such as peripheral vascular remodeling. However, a significant gap remains in our understanding of the upstream molecular triggers. The intricate interplay between specific microbial metabolites, the resulting immune activation, and systemic inflammation as primary drivers of hypertension is less defined. This review addresses this gap by shifting the focus from the 'what' (vascular remodeling) to the 'how', which is the specific mechanisms of immune modulation and inflammation that initiate and sustain elevated blood pressure by exploring the potential of modulating the gut microbiota.

Immune Mechanisms in The Pathophysiology of Hypertension

Recent research reveals that hypertension is caused in part by both innate and adaptive immunity. In the kidney of hypertensive humans animals, inflammatory cells, including macrophages and T cells was accumulated in the artery wall, especially in the perivascular fat. Adoptive T cell transfer restores hypertensive responses to angiotensin II (ANG II) and DOCA-salt challenge; mice devoid of lymphocytes are resistant to the onset of hypertension. In ameliorating end-organ damage and BP increase in experimental hypertension, immune modulating drugs show varied but generally favorable effects. Beginning in the 1970s, multiple studies demonstrated that suppressing immune cells might prevent BP increase; conversely, transferring immune cells from hypertensive animals to non-hypertensive receivers produces or primes hypertension in the recipient.(30,31) Although the exact processes by which hypertension triggers an immune response are yet unknown, they may include the creation of neoantigens activating adaptive immunity that might help prevent and cure this common and terrible diseases.(32) Hypertension and the immune system are locked in a vicious cycle. Initially, the physical and chemical stress of high BP damages blood vessels, creating altered proteins (neoantigens) that the immune system misidentifies as threats. This activates immune cells, particularly T cells, which then travel to and infiltrate key organs like the blood vessels and kidneys. Once there, they release inflammatory signals that cause blood vessels to constrict, impair the kidneys' ability to excrete salt, and increase nerve signals that raise blood pressure. This immune-driven response not

only sustains the existing hypertension but actively worsens it, creating a self-perpetuating loop where high blood pressure and inflammation continually fuel each other.(30)

Traditionally, aldosterone, ANG II, sympathetic tone, renal failure, vascular dysfunction, and in certain cases hyperdynamic conditions were thought to be the pathophysiology of hypertension. Many find it difficult to see how immune cells fit this already complicated picture and have needed a fresh perspective on the interaction between the immune system and conventional prohypertensive elements. Moreover, immune activation by necessity is a highly precise and controlled process.(14)

The immune system's first line of defense is innate immune system, comprises of monocytes, macrophages, dendritic cells (DCs), and neutrophils. They react fast and non-specifically to tissue injury or infection. Innate immune cells also play important roles in stimulating adaptive immune cells, hence producing more specialized responses.(33) Figure 1 describe the innate immune system activated by many stimuli of hypertension. Different roles in the pathophysiology of hypertension are played by circulating monocytes and tissue-resident macrophages. Changes in endothelial function help monocytes and other inflammatory cells to target organs like the heart, kidney and vasculature to be recruited.(34-38) Monocytes can differentiate into macrophages and DCs,or become activated with minimal phenotypic changes during tissue invasion. Remarkable variety of monocyte-derived cells helps them to coordinate complex immune responses and support tissue homeostasis. Monocyte-derived cells are crucial for removing and repairing damaged tissue in response to cellular injury and stress signals, known as damage-associated molecular patterns (DAMPs). The regulation of these pro-inflammatory and pro-resolution phases is highly coordinated. This equilibrium seems to be disrupted during hypertension, which causes longer and disproportionately pro-inflammatory reactions.(38)

In both mouse and human studies, macrophages have been linked to increase in BP and damage of the hypertensive end organs. In mice with a myeloid-specific vitamin D receptor knockout, macrophages exhibit increased sensitivity to prolonged endoplasmic reticulum (ER) stress. The renal infiltration of these macrophages, accompanied by their elevated release of miR-106b-5p, stimulates juxtaglomerular cells to secrete renin, leading to renin-dependent hypertension.(13,39) Same as in human, higher BP usually correlated with increased kidney and macrophages infiltration, which can lead to renal damage and fibrosis.(40) Blunted levels of vascular remodelling, vascular superoxide generation, and retained endothelial function revealed mice lacking macrophages to be shielded against BP increase and vascular injury.(41,42)

Since 1960s, the idea of inflammation and the immune system contribution to hypertension has been concepted. (43,44) It was shown that recipient rats developed hypertension when lymphocytes were transferred from rats with unilateral renal infarction. Immunosuppression lowers BP in rats with partial renal infarction, indicating that an inflammatory response within the vasculature with various forms of hypertension, particularly the periadventitial accumulation of T cells and monocytes, plays a role.(45) In the 1970s, it was discovered that thymectomized or athymic nude mice do not maintain hypertension following renal infarction.(46) In the 1980s, a thymus transplant from a Wistar-Kyoto rat was found to lower BP in a receiver with naturally occurring hypertension.(47) It was also observed that if full immunological restoration was attained, transplanting a suitable thymus into newborn Spontaneously Hypertensive Rat caused notable reduction of BP. These investigations prepared the ground for more current developments on the function of the immune system in hypertension.(47)

Extensive researches were still ongoing in this area, especially to determine exactly the function of myeloid

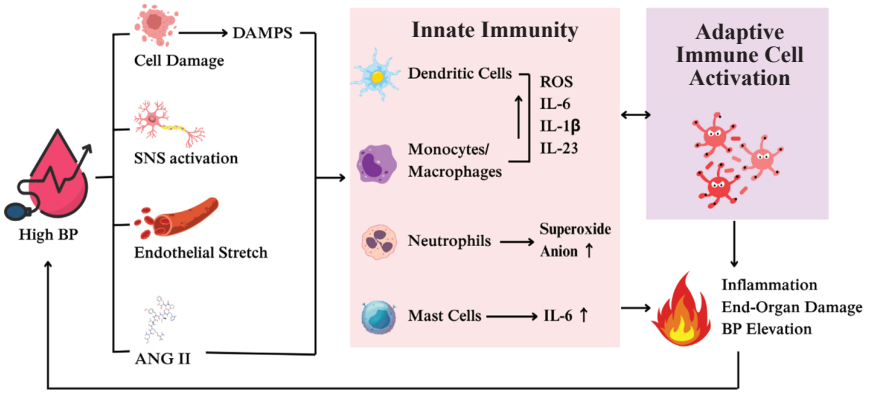

Figure 1. Multiple hypertensive stimuli activate innate immune cells to promote inflammation leading to blood pressure elevations and end organ damage.

cells, T cells, B cells, and their different subtypes, however the exact mechanisms is still poorly understood. Interactions with the neurological system and its many mediators demand more research. Of particular importance is now evident that local inflammation can produce afferent signals and a immune reflex; nonetheless, the function of this reflex in hypertension has to be established. Recent data pointed to oxidatively modified proteins which may have antigen properties in hypertension, but the particular proteins or peptides changed in this manner remain unknown. As the foregoing description makes it clear that the immune system is rather interconnected, and the way these many cells and mediators interact in hypertension still has to be clarified.(19)

Inflammation, Kidney Function, and Hypertension

The inflammatory response combats infection and tissue damage. Natural immune cells in tissues, such as macrophages, fibroblasts, mast cells, DCs, and circulating leukocytes (including monocytes and neutrophils), use intracellular or surface-expressed pattern recognition receptors (PRRs) to detect pathogen invasion or cell damage. Either directly or indirectly, these receptors identify pathogen-associated molecular patterns (PAMPs), DAMPs produced from damaged cells and microbial nucleic acids, lipoproteins, and carbohydrates. After then, activated PRRs oligomerize and build big multi-subunit complexes that start signaling cascades releasing molecules that support leukocyte recruitment to the area. DAMPs are produced after necrosis and cause sterile inflammation including adenosine triphosphate (ATP), the cytokine interleukin (IL)-1α, uric acid, calcium-binding, cytoplasmic proteins S100A8 and S100A9, and the DNA-binding, nuclear protein high-mobility group box 1 (HMGB1). PAMPs are pathogen-derived, essential for microbial survival, and structurally diverse. They include bacterial and viral nucleic acids, fungal cell wall components, flagellin, peptidoglycan, and lipopolysaccharide (LPS) from the Gram-negative bacteria.(33)

Inflammatory mediators like histamine and leukotrienes increase vascular permeability, allowing plasma proteins and leukocytes to exit the circulation. Histamine, prostaglandins, and nitric oxide (NO) cause vasodilation, enhancing blood flow and leukocyte recruitment. Cytokines such as tumor necrosis factor (TNF) and IL-1 increase leukocyte adhesion molecules on endothelial cells, promoting leukocyte extravasation. Activated innate immune cells, including DCs, macrophages, and neutrophils, remove foreign particles and host waste via phagocytosis and produce cytokines that influence the adaptive immune response.(33)

Major PRRs in cells, specifically members of the toll-like receptor (TLR) family, recognize bacterial and viral PAMPs either in the extracellular environment (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11) or within endolysosomes (TLR3, TLR7, TLR8, TLR9, and TLR10). These type I transmembrane proteins feature leucine-rich repeats (LRRs). Signal transduction by TLRs is based on a cytoplasmic Toll/IL-1 receptor (TIR) domain, which serves as a docking site for TIR-containing cytoplasmic adaptor proteins. TIR domains in the pro-inflammatory cytokine IL-1 receptor function similarly. Except for TLR3, every TLR interacts either directly (TLR5, TLR7, TLR8, TLR9, TLR10, and TLR11), heterodimeric (TLR1-TLR2 and TLR2-TLR6, and the IL1Rs) or in tandem with the adaptor TIRAP/Mal (TLR1-TLR2, TLR2-TLR6, and TLR4). Along with a TIR domain, MyD88 features a death domain (DD), which helps to modulate interactions with the serine/threonine kinase interleukin-1 receptor-associated kinase 4 (IRAK4).(48)

Chronic low-grade inflammation play basic roles in many human diseases, including hypertension and end-organ damage. While canakinumab, a human monoclonal antibody, reduced inflammatory markers, including high-sensitivity C-reactive protein (hsCRP) and IL-6, and cardiovascular events, it did not affect the link between hypertension and cardiovascular events or prevent the onset of hypertension. This implies that the treatment helps with inflammation and some cardiovascular issues, but it doesn't address hypertension directly.(49-51) A secondary analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial indicated that individuals in the highest BP quartile required greater reductions in major adverse cardiac events, suggesting that those with severe hypertension had elevated levels of inflammation. (52) Many of the 60 genes found were differently expressed in monocytes from hypertensive people and connected to IL-1β and IL-18, the components of the inflammasome.(53) These data suggest a possibly significant contribution of the inflammasome to the pathophysiology of hypertension and CV disease.(4) Statins such as rosuvastatin can also significantly reduce hsCRP up to 37% (54), while colchicine was known to alleviate inflammation and NOD-like receptor family pyrin domain containing 3 protein (NLRP3) inflammation activation.(55)

Strong vasoactive molecules such as endothelin-1, aldosterone, and ANG II act as priming stimuli and can activate the inflammasome during hypertension. ATP-induced K^+ efflux or the generation of ROS, which are classical activators of the NLRP3 inflammasome, trigger its activation and assembly. Elevated nuclear factor-kappa B (NF-κB) activity in hypertension leads to increased levels of proinflammatory cytokines IL-1β and IL-18 in tissues and circulation. The NLRP3 inflammasome plays a significant role in the development and progression of hypertension and other CV disease risks by promoting vascular inflammation and damage. It is a key component of the innate immune system and is involved in the inflammatory response. The priming phase involves stimuli like endothelin-1, aldosterone, ANG II, and sodium chloride (NaCl), leading to the production of pro-caspase-1, apoptosis-associated specklike protein containing a CARD (ASC), NLRP3, and pro-IL-1β. In the activation phase, ATP and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase lead to ROS production and K^+ efflux, forming the NLRP3 inflammasome complex with ASC and pro-caspase-1, which converts pro-IL-1β to IL-1β. This cytokine then contributes to hypertension by causing renal fibrosis, glomerular sclerosis, vascular smooth muscle cell (VSMC) proliferation, vascular remodeling, and vasoconstriction. (56,57) These cytokines affect immune cells like monocytes, macrophages, and DCs, as well as non-immune cells such as vascular endothelium and smooth muscle cells.

The IL-17 family, particularly IL-17A, plays a significant role in the pathogenesis of hypertension and kidney function. IL-17A promotes inflammation by recruiting and activating immune cells, leading to increased blood pressure through mechanisms such as inhibiting endothelial NO production, increasing ROS formation, and promoting vascular fibrosis. IL-17A is produced by various immune cells, including T helper 17 cells (Th17), cytotoxic T cells (Tc17), gamma delta T cells (γδT), natural killer T cells (NKT), and innate lymphoid cells.(58) The important transcriptional factor retinoid-related orphan receptor γδT causes differentiation of Th17 and IL-17-producing γδT cells (γδT17), therefore defining IL-17-producing T lymphocytes.

IL-17 is essential for maintaining ANG II-induced hypertension. Two weeks of ANG II therapy altered the Th17 lymphocyte ratio, and IL-17 knockout mice showed reduced blood pressure. Later, they found that antibodies against IL-17A or IL-17 receptor A, but not IL-17F, lowered blood pressure in ANG II-induced hypertension.(59) The renin-angiotensin-aldosterone system (RAAS) also impact the inflammation response as they are locked in a vicious, self-amplifying cycle that is fundamental to the progression of many chronic diseases. Key RAAS hormones, particularly ANG II and aldosterone, act as potent pro-inflammatory signals, activating pathways like NF-κB and the NLRP3 inflammasome to generate inflammatory cytokines and oxidative stress. In turn, this inflammation feeds back to stimulate the production of RAAS components, especially creating a damaging, localized RAAS within organs like the heart and kidneys. This continuous loop of reciprocal activation drives the pathology of hypertension, chronic kidney disease, and HF by promoting persistent fibrosis, vasoconstriction, and tissue damage, which explains why RAAS-blocking drugs are effective not just for blood pressure control but also for their crucial anti-inflammatory effects.

The role of IL-23 in hypertension has been less explored compared to its downstream mediator, IL-17. Researchers have primarily considered IL-23 as a therapeutic target for atherosclerosis. However, some observational studies have indicated a link between IL-23 and high blood pressure. (60) For instance, individuals with hypertension had higher serum IL-23 levels than healthy controls, and these levels were positively correlated with blood pressure.(61) This finding aligns with other research showing elevated blood IL-23 levels in young obese hypertensive individuals. Additionally, a high salt diet has been associated with increased plasma levels of IL-23 and IL-17 in healthy participants, suggesting that salt intake may promote IL-23R production and Th17 differentiation via SGK1 activation. Moreover, genetic polymorphisms in the IL-23R gene have been linked to susceptibility to coronary artery disease and the presence of hypertension, but not diabetes.(62)

In the context of renal pathophysiology of hypertension, the distinct characteristics of TNF-α receptors in the kidney are a significant area of study. Current researches are examining how different expressions of TNF receptor (TNFR)1 and TNFR2 contribute to salt-sensitive hypertension (SSH) in various experimental mouse models. TNF-α antagonism reduces hypertension in animal models of SSH, but its effectiveness in hypertensive patients has been inconsistent. This variability may stem from the differential activation of TNF-α receptors under various conditions leading to SSH in humans.(63-66)

Future translational research should aim to understand the complex activation patterns of these receptors. This understanding could help explain the differences in BP responses to increased salt intake among the general population. Recognizing the link between TNF-α receptors

and ANG production in the kidney is crucial for determining individual salt sensitivity. Instead of using general anti-TNF-α therapy, which carries a high risk of infection due to broad immune suppression, future studies should focus on targeting specific TNF-α receptors. This approach could lead to more effective treatment strategies for clinical conditions associated with salt sensitivity.(66,67) The most effective future treatments will not be limited to diuretics or traditional blood pressure drugs. Instead, we should look toward precision immunotherapy after assessing the specific immune cells and inflammatory pathways that are over-activated by high salt intake.

The Gut Microbiome and Hypertension

The microbiota, consisting of commensal bacteria, viruses, fungi, and archaea, forms a dynamic and complex network. The number of bacterial cells in a healthy human body (approximately 3.8×10^{13}) is comparable to the number of human cells.(22,68) The human microbiome contains around 9 million genes, which is over 450 times more than the human genome's approximately 20,000 genes. (69) Gut bacteria influence physiological functions through various mechanisms, including priming immune responses, extracting energy and nutrients from the diet, and affecting susceptibility to pathogenic colonization in the colon.(70)

Given their shared risk factors and symptoms, it is evident that gastrointestinal diseases and CV disease are interconnected. For example, patients with HF with preserved ejection fraction exhibit significant gut dysbiosis compared to healthy individuals, with hypertension being a primary risk factor for this condition.(71) Interactions among dietary components, gut microbiota and their metabolites, and BP-lowering medications predominantly occur in the gastrointestinal system. Additionally, the enteric nervous system and gastrointestinal hormones may be regulated by BP. Gut bacteria are thought to impact renal function and hypertension through sympathetic stimulation in the brain, interacting with the neurological, endocrine, and immune systems, thereby increasing blood flow and BP.(72,73)

All animal species, including humans, have co-evolved with diverse microbial communities, forming complex assemblies adapted to their hosts' environments. (74) In particular, the bacteria in the human gastrointestinal tract, or gut, have been extensively studied over the past decade. The human gut flora consists of diverse mutualistic bacteria associated with the host that play crucial roles in the immune system, colonization resistance, and nutrient absorption. These organisms exert a significant influence throughout the human body by producing and modifying a variety of metabolites and chemicals. The gut microbiome and environmental conditions, forms ecological and functional communities that interact bidirectionally with human biological processes, influencing various aspects of health.(75)

Recent data highlight that this connection was influenced by nutritional, environmental, and genetic factors. A higher Firmicutes/Bacteroidetes ratio in two spontaneously hypertensive rats fecal was found with a notable reduction in microbial richness, diversity, and evenness, with fewer butyrate- and acetate-producing bacteria.(76) Similarly, the gut microbiota of hypertensive patients showed reduced richness and diversity. The chronic ANG II infusion rat model also exhibited lower microbial richness and a higher Firmicutes/Bacteroidetes ratio. Oral minocycline was tested in this model and found to lower BP and rebalance gut bacteria by reducing the Firmicutes/Bacteroidetes ratio. These findings suggest that gut microbiota dysbiosis is linked to high BP in both humans and animals, proposing dietary interventions to correct gut microbiota as a potential treatment for hypertension.(77)

Different dietary components, such as fiber, cholesterol, and salt, influence BP regulation through the gut microbiome and their metabolites was briefly described in Figure 2.(78) Fiber metabolized by gut bacteria into short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate. SCFAs interact with the nervous system and reduce inflammation, helping to lower BP. Cholesterol will be converted into bile acids by the liver and further modified by gut bacteria. These bile acids influence immune cells, reducing inflammation and promoting vasodilation, which lowers BP. High salt intake affects gut bacteria that produce trimethylamine (TMA), which is converted into trimethylamine N-oxide (TMAO) in the liver. TMAO influences immune responses, increasing inflammation and vasoconstriction, raising BP.

While we generally understand how nutrition impacts gut flora, the specific effects and duration of certain dietary components remain unclear. Continuous availability of nutritional substrates is likely essential for bacterial engraftment and multiplication. Sustained influence on the gut microbiota may help achieve a new state of ecological balance. Acute dietary therapies in humans have only lately shown temporary microbial changes in times spanning days to many weeks. Long-term dietary analysis should be included into acute diet treatments in next studies; more dietary data collecting longitudinally would help

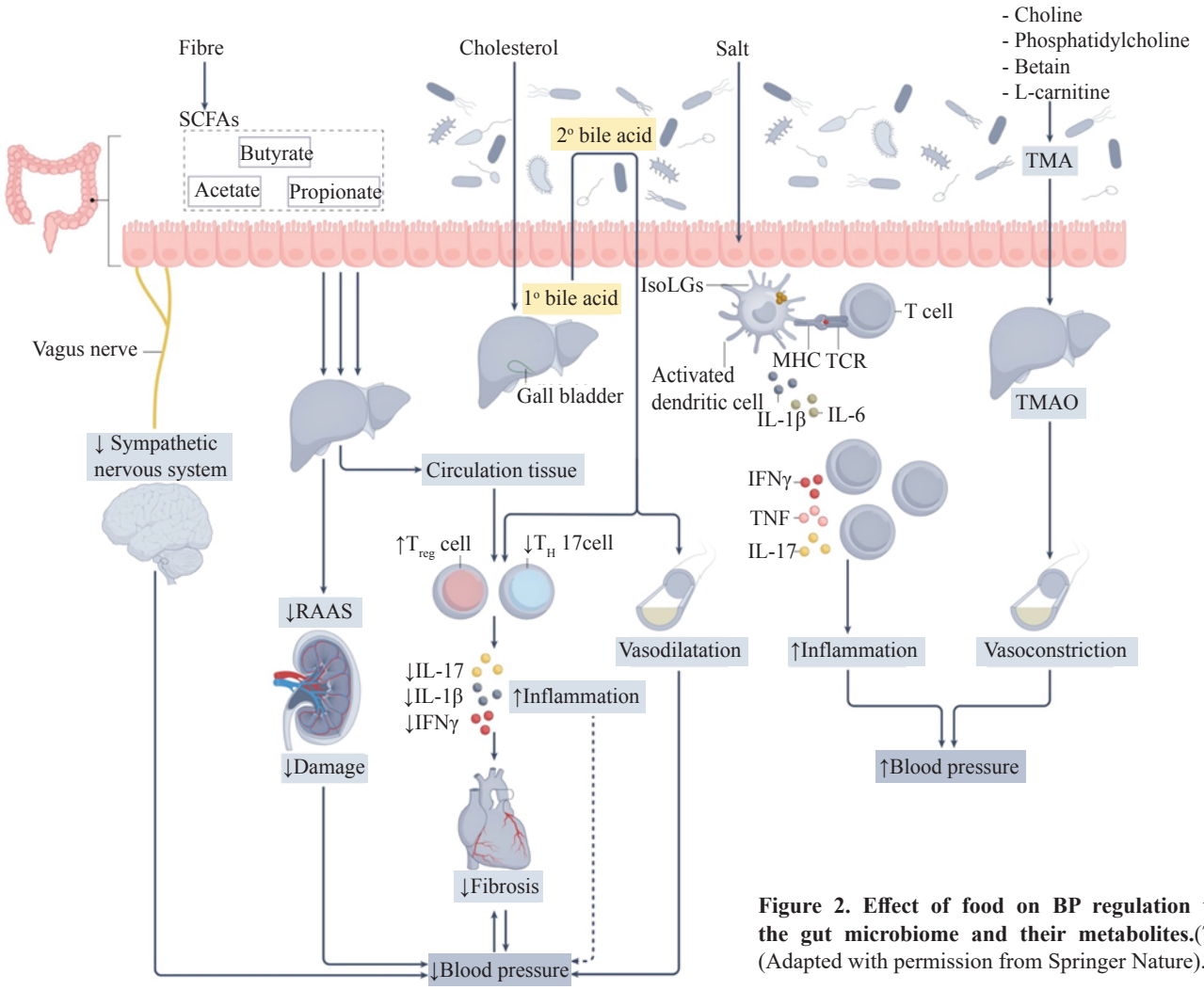

Figure 2. Effect of food on BP regulation via the gut microbiome and their metabolites.(78) (Adapted with permission from Springer Nature).

to enhance the outcomes of the studies. More long-term dietary interventions, including ones with regard to nutrient provenance, are needed to look at the possibility of a permanent diet-induced microbial change. Acknowledging the great variety of individual microbial profiles will help one to investigate tailored therapy approaches.(79)

Therapeutic Targeting of Inflammation in Hypertension

Inflammation and immune activation were first linked to hypertension by Grollman, Okuda, Svendsen, and Olsen. (80,81) Recent research has uncovered mechanisms behind this connection. Studies using animal models with genetic and pharmacological targeting have explored the roles of T cells, γδ cells, monocytes/macrophages, dendritic cells, B cells, NK cells, and other immune-inflammatory components.(82-87) Inflammation in hypertension is triggered by oxidative stress and redox-dependent mechanisms in vascular and renal tissues, leading to the generation of neo-antigens, damage-associated molecular patterns, and neuroimmune mechanisms. These provoke maladaptive immune responses, exacerbating hypertension and related organ damage.(88-90)

Although the specific antigens that activate adaptive immunity in hypertension are not definitively identified, isolevuglandin (isoLG) adducted proteins are potential candidates. IsoLGs, oxidation products of arachidonic acid, bind rapidly to lysines on self-proteins, accumulate in antigen-presenting cells, and are presented within major histocompatibility complexes, activating $CD4^+$ and $CD8^+$ T cells. The isoLG scavenger 2-hydroxybenzylamine has been shown to prevent immune activation and lower blood pressure in animal models of hypertension. Additionally, both animal and human studies have identified HSP70 as a

potential auto-antigen.(91) Numerous animal studies have demonstrated that modulating inflammatory activation and cytokine release can reduce blood pressure increases and mitigate vascular, cardiac, and renal damage.(66,92-96)

Epidemiological and observational data link the immune system to hypertension. For example, hypertensive individuals have a higher risk of death from COVID-19. (97,98) Inflammatory biomarkers like CRP correlate with systolic BP in acute stroke, with each 10 mmHg BP increase raising CRP levels by 72%. Observational and clinical trial data show BP rises with each quartile increase in CRP levels.(99) A nested case-control study of 400 normotensive women found that higher quartiles of IL-6 and CRP were associated with an increased risk of developing hypertension during follow-up.(100) Elevated levels of TNF-α, IL-1β, IL-18, and CCL2 in hypertension promote cell infiltration, affect renal sodium transport, and alter vascular function, leading to sodium retention, increased vascular resistance, and hypertension.(101,102)

GWAS and transcriptome analyses link hypertension to immune cell defense and inflammatory responses (103,104), supported by integrative network analysis and Mendelian randomization. Blood pressure heritability ranges from 33% to 57% (105-107). Several GWAS have implicated the SH2B3/LNK gene in hypertension and myocardial infarction.(103,108-110) SH2B3 encodes a docking protein that modulates T cell activation. Variants of this gene are associated with autoimmune diseases such as multiple sclerosis, coeliac disease, and type 1 diabetes. (110) The SNP rs3184504 in SH2B3 regulates 6 out of 34 blood pressure-related genes identified in a GWAS meta-analysis of 7017 individuals not on anti-hypertensive treatment.(111) These genes are expressed in leukocytes. Integrative network analysis of blood pressure GWAS with mRNA profiles from 3679 participants confirms interactions between SH2B3 and hypertension-related genes.(108)

Notably, T cells, but not B cells, restored the hypertensive phenotype through adoptive transfer, although some studies have shown different results. This alteration in $Rag1^{-/-}$ mice highlights the complexity and adaptability of the immune system. These findings suggest possible alterations in the microbiome and an increase in the population of natural killer (NK) cells, which compensate for the absence of adaptive immune cells by releasing cytokines typically produced by T cells.(4) T cells from LNK knockout mice produce high levels of type I cytokines and show increased sensitivity to ANG II, leading to hypertension, endothelial and renal dysfunction, increased inflammatory cell infiltration, and oxidative stress.(112)

The γδ T cells are a unique subset of T lymphocytes that play a crucial role in hypertension by secreting pro-inflammatory cytokines like IL-17. They respond quickly to cellular stress and damage, contributing to vascular and organ dysfunction associated with hypertension through their interactions with other immune cells and the production of inflammatory signals.(113) γδ T cells are significantly influenced by dietary nutrients. For example, indole-3-carbinol, a tryptophan derivative found in cruciferous vegetables, acts as a high-affinity ligand for the aryl hydrocarbon receptor and is essential for maintaining γδT cells in the skin and gut.(114) Conversely, retinoic acid, a metabolite of vitamin A, boosts γδ intraepithelial lymphocyte (IEL) production of IL-22, which helps reduce colonic inflammation.(115) Fat diet consumption can affect γδ T cell proliferation. A high-fat diet can reduce the proliferation of γδ T cells, leading to decreased numbers in tissues like the gut. In contrast, a ketogenic diet can enhance γδ T cell proliferation and function by increasing levels of β-hydroxybutyrate (BHB), a key metabolite that boosts γδ T cell expansion, cytokine production, and overall metabolic fitness.(116)

Moving forward, it's important to note that anti-inflammatory agents, like traditional anti-hypertensive medications, primarily lower BP in individuals with uncontrolled hypertension. This limitation is due to compensatory mechanisms that prevent further BP reduction beyond normal levels, and these effects may be confined to patients with active pro-hypertensive inflammatory processes. Evidence from studies like Cardiovascular Inflammation Reduction Trial (CIRT), TNF-α inhibitor responders vs. non-responders, and CANTOS suggests that active inflammation is necessary for CV risk reduction through immune modulation. This reduction is achieved not just through BP control but also by addressing oxidative stress, endothelial function, vascular remodeling, and endocrine regulation.

To optimize benefits without adverse effects, it is crucial to identify the optimal checkpoint in the inflammation-hypertension relationship, which has been challenging at a population level. In conclusion, most preclinical studies on the anti-hypertensive effects of immune interventions have focused on treating animals at the onset of hypertension. However, these treatments are usually given to humans with long-standing hypertension, where chronic changes in renal and vascular function reduce their effectiveness. Thus, targeting younger individuals with early-onset hypertension may yield different and potentially more favorable outcomes.

Prospects for Leveraging The Gut Microbiome as Medicine for Hypertension

The relationship between gut microbiota and hypertension has garnered significant attention over the past decade. Early studies identified correlations between microbial dysbiosis and elevated blood pressure, suggesting that gut microbiota could influence CV health.(77) In 2013, a meta-analysis of 14 randomized controlled clinical trials involving 702 hypertensive patients showed that probiotic fermented milk could significantly reduce SBP and DBP. (117) Many studies as discussed previously, discussed on how the Firmicutes/Bacteroidetes ratio and the gut microbiome diversity correlated with hypertension and CV risk stratifications both in human and mice. When the Firmicutes/Bacteroidetes ratio increased, it was associated with a significant decrease in the richness, diversity, and uniformity of microorganisms, as well as the abundance of SCFA-producing bacteria, especially acetate- and butyrate-producing bacteria.(110,118,119)

Subsequent studies demonstrated that high-salt diets and gut-derived metabolites, such as SCFAs and bile acids, significantly impact BP. Salt-sensitive rats had significantly more harmful bacteria in their gut microbiota compared to salt-tolerant rats.(120) The first population-based cohort study publication on the relationship between gut microbiota and hypertension conducted in 2019, finding that the diversity of gut microbiota was negatively correlated with hypertension.

Gut barrier dysfunction refers to abnormal changes in intestinal permeability and structural damage to the intestinal mucosa, leading to the translocation of bacteria and toxic products into the bloodstream, causing systemic inflammation.(119,121) The imbalance of gut microbiota can lead to gut barrier dysfunction, increasing intestinal permeability and allowing pathogenic bacteria and LPS to enter the bloodstream, resulting in systemic inflammation. Patients with hypertension had significantly increased levels of intestinal fatty acid binding proteins, LPS, and pro-inflammatory Th17 cells, indicating heightened intestinal inflammation and permeability.(122)

This imbalance is usually characterized by reduced probiotics and increased harmful bacteria, which promote inflammation and lead to abnormal expression of tight junction proteins, such as zonula occludin-1 (ZO-1) and occludin, impairing gut barrier function.(123) The increased number of pathogenic bacteria can also reduce thoxidae growth of probiotics, further exacerbating the imbalance. These harmful substances enter the blood circulation through the mesentery, triggering chronic inflammation and vascular endothelial damage, resulting in decreased vasodilator factors and increased vasoconstrictor factors. Studies on spontaneously hypertensive rats showed decreased intestinal mucosal thickness, reduced blood flow, fewer glandular goblet cells, shorter intestinal villi, decreased tight junction proteins, and increased intestinal permeability, suggesting that hypertension impairs intestinal barrier function.(121,124) This cascade of events ultimately leads to increased peripheral resistance and elevated blood pressure, contributing to hypertension.(125)

Gut microbiota can also regulate BP via the inflammatory response. Studies have shown a significant increase in the number of harmful Proteobacteria in hypertensive patients, which is closely linked to intestinal inflammation and immune disorders.(117) The sympathetic nervous system's control of inflammation plays a central role, with increased sympathetic drive to the gut exacerbating gut pathology and hypertension. Figure 3 described the comparation between healthy gut and hypertensive gut. Imbalanced intestinal microecology with reduced microbial richness and diversity, increased levels of harmful substances like lipopolysaccharides (LPS) and hydrogen sulfide (H_2S). epithelial damage leading to increased gut permeability ("leaky gut"), and production of pro-inflammatory cytokines was observed in hypertensive gut. This visual representation explains how hypertension can disrupt gut health by altering microbial balance and increasing inflammation.(125)

The gut microbiome influences hypertension through various mechanisms. SCFAs, produced by microbial fermentation of dietary fiber, can lower BP by modulating immune responses and reducing inflammation. Among the various metabolites produced by the gut flora, TMAO, SCFAs, corticosterone, H_2S, choline, bile acids (BAs), indole sulfate, LPS, *etc*., are particularly intimately linked to the development of hypertension. Mostly created by colonic bacteria by digesting indigestible polysaccharides (fibers), SCFAs that is mostly composed of butyrate, acetate, and propionate, are a vital family of gut microbial metabolites. Although the fecal levels of SCFAs in hypertension patients are much greater than those in normal controls, clinical studies have indicated that serum levels of SCFAs are inversely linked with blood pressure.(126) Studies have showed that SCFAs directly widen blood arteries to lower BP. Propionate shown *in vitro* tests might widen human colonic resistance arteries.(127)

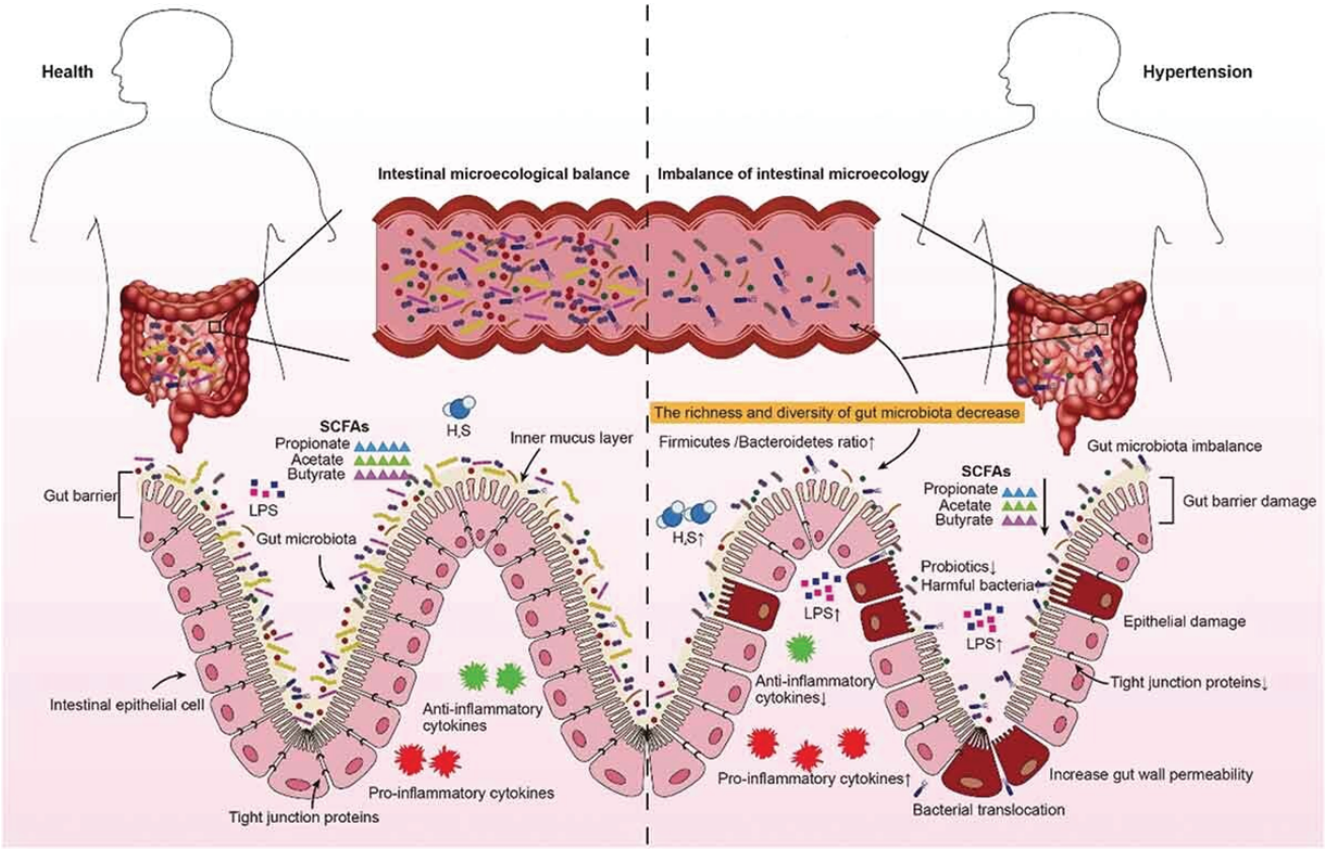

Figure 3. The relationship between gut microbiota and hypertension.(125) (Adapted with permission from Taylor and Francis Group).

Entering the systemic circulation, TMAO influences obesity status, lipid metabolism, platelet activity, and the development of atherosclerosis (128), therefore affecting hypertension. Plasma TMAO levels were linked, in a dose-dependent sense, to the incidence of hypertension according a meta-analysis.(128) The particular process by which TMAO increases BP is still unknown. Research indicates that TMAO increases ANG II-induced vasoconstriction and accelerates ANG II-induced hypertension, which is linked to protein kinase R-like endoplasmic reticulum kinase (PERK).

The major constituents of bile are BAs, which are synthesised and metabolised in part by gut bacteria.(129) BAs control lipid metabolism, speed energy consumption, preserve gut microbiota equilibrium and shield the intestinal barrier, therefore reducing inflammation and avoiding arteriosclerosis.(130) They are endocrine-like signaling molecules. Different pathogenic elements affect the equilibrium of BAs under unbalanced gut flora, which causes several disorders including hypertension to arise and flourish. By means of CV, renal, and TMAO systems, BAs could influence the incidence and course of hypertension. (131) These metabolites interact with the renin-angiotensin system (RAS), nitric oxide (NO) synthesis, and vascular tone, contributing to hypertension management. Studies have shown that SCFAs directly widen blood arteries to lower blood pressure. Propionate, for example, can widen human colonic resistance arteries and lower BP in animal models.(132)

Clinical studies have shown that dietary interventions can significantly improve gut microbiome composition and reduce hypertension. High-fiber diets and acetate supplementation have been found to modify gut microbiota populations, increase beneficial bacteria, and lower BP. For instance, on DOCA hypertensive mice, shown that high-fiber diet and acetate diet led to changes in the gut microbiota by increasing the level of intestinal Bacteroides and acetate concentration, thus played a protective role in CV health, reducing systolic and diastolic BP.(132) Additionally, flavonoid-rich foods like berries and apples have been linked to lower BP and greater gut microbiome diversity. In another study on a rat model of apnea syndrome with hypertension, the number of lactic acid-producing bacteria increased, but the number of Eubacterium, which convert lactic acid to butyrate, decreased exponentially.(133) A fecal transplant from hypertensive rats to normotensive

mice, showed an increase in blood pressure in the recipient mice. This indicates that the gut microbiome can also play a role in "hypertensive transmission".(134)

Advanced diagnostic and supplementation strategies targeting the gut microbiome might hold the future of hypertension treatment. Diagnostic techniques, such as metagenomic and metabolomic analyses, can identify microbial dysbiosis and guide personalized treatments. Current approaches include probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary modifications. (135) In addition to these strategies, repurposing existing drugs offers a promising avenue for hypertension management. Drug repurposing involves finding new therapeutic uses for already approved medications, potentially reducing the time and cost associated with drug development. This approach can leverage existing knowledge about drug safety and efficacy, making it a viable option for addressing complex conditions like hypertension. By targeting the gut microbiome and its interactions with the immune system, repurposed drugs could offer novel treatments that complement current microbiome-based therapies.(136)

Antidiabetes drugs were known to improve metabolic condition by improving gut microbiome. Recent studies showed while sodium-glucose cotransporter-2 (SGLT2) inhibitors and thiazolidinediones (TZDs) have slighter effects, oral antidiabetes medications, including metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and α-glucosidase inhibitors, clearly affect gut microbiota and microbial metabolites.(137-139) Metformin, DPP-4 inhibitors, and α-glucosidase inhibitors have been shown to have similar effects on increased SCFA-producing bacteria and SCFA production (139-145), especially *Akkermansia muciniphila* which may partially explain their beneficial effects in the regulation of insulin sensitivity increase, energy metabolism, and systemic inflammation (142,144), associated to healthy intestinal mucosa and anti-inflammatory effect.

Considered as exogenous xenobiotics, anti-hypertensive drugs change the makeup of gut bacteria and thereby influence the BP of the host.(146) Inter-individual differences in the gut flora were linked to BP-lowering drugs including angiotensin-converting enzyme inhibitors, β-blockers, and angiotensin II receptor blockers. Although the gut microbial composition is affected by a variety of elements including race, sex, age, food, exercise, and circadian rhythm, the effects of some medicines on distinct bacterial species are yet unknown. Nevertheless, knowing how the gut bacteria affect the response of the host to antihypertensive medications is more relevant than vice versa as the causes of resistant hypertension are yet unknown.(147)

Emphasizing the main gaps in the scientific evidence to boost the consumption of dietary fiber in hypertension therapy, the evidence offers recommendations for incorporating dietary fiber intake in future guidelines on the management of hypertension. But the ignorance of fiber consumption is not limited to hypertension; data shows that it is good for other noncommunicative illnesses such type 2 diabetes, 15 cancer, 15 chronic kidney disease during the lifetime.seventy-six Therefore, we advocate a general review of policies whereby use of fibers would have cross-cutting advantages. The strong data compiled here supports the use of dietary fiber as a potent cardioprotective strategy and auxiliary treatment to decrease BP and CVD risk. Future prospects include developing microbiota-based therapies that leverage specific microbial metabolites and personalized dietary interventions to manage hypertension more effectively. Large-scale clinical trials and further research are essential to establish the efficacy and long-term benefits of these innovative treatments.(148)

Myocardial Interstitial Fibrosis in Hypertensive Heart Disease

Arterial hypertension is the most common modifiable risk factor for early CV mortality. While atherosclerotic events typically define CV risk, it is also important to address nonatherosclerotic hypertension-mediated end-organ damage, such as hypertensive heart disease (HHD). Reducing the impact of HHD is a major goal in modern CV medicine, necessitating better understanding and clinical care. Understanding the mechanisms, diagnosis, and treatment of myocardial fibrosis in HHD is crucial to prevent the progression of both ischemic and non-ischemic chronic heart diseases.(149)

HHD refers to heart conditions caused by long-term high BP. One hallmark of HHD is left ventricular hypertrophy (LVH), where the left ventricle thickens due to chronic high BP. This structural change reduces the heart's ability to pump blood efficiently, leading to systolic and diastolic dysfunction. Other key components include CAD, which accelerates the narrowing of coronary arteries, and HF, where the heart becomes unable to pump blood effectively. These conditions contribute to the overall burden of HHD and its associated complications. The age-standardized global prevalence of HHD has increased in parallel with the rise in the number of individuals with

treated and uncontrolled hypertension over the past two decades.(150)

Myocardial fibrosis is characterized by the excessive accumulation of extracellular matrix proteins, particularly collagen, in the heart muscle. This process is primarily driven by the activation of cardiac fibroblasts, which transform into myofibroblasts in response to various stimuli such as chronic high blood pressure, myocardial infarction, or other cardiac injuries.(151) In patients with HHD, myocardial fibrosis predisposes them to an increased risk of HF, ischemic heart disease, and arrhythmias.

The pathophysiology of myocardial fibrosis involves several key mechanisms. Cardiomyocyte injury triggers an inflammatory response, leading to the activation of fibroblasts. Activated myofibroblasts produce excessive collagen and other matrix proteins, resulting in the stiffening of heart tissue. The type of heart disease influences the predominance and crosslinking of collagen fibers, with type I collagen being stiffer than type III. Stronger crosslinking, mediated by lysyl oxidases (LOX), results in greater stiffness, insolubility, resistance to matrix metalloproteinases (MMPs), and collagen fiber stability. Persistent inflammation further promotes fibrosis by sustaining fibroblast activation and matrix deposition. The accumulation of fibrotic tissue disrupts the normal architecture and function of the heart, reducing elasticity, impairing contractility, and ultimately leading HF.(152,153)

Myocardial fibrosis mostly comes in two forms: replacement myocardial fibrosis and reactive myocardial fibrosis.(154) Formed during a healing phase, the first form is seen as localized macroscopic or microscopic collagen fiber-based scars replacing dead cardiomyocytes following ischemia and non-ischemic assaults. The second form often known as myocardial interstitial fibrosis (MIF), is characterized by thin collagen fiber bands encircling individual cardiomyocytes in the endomysium and bundles of cardiomyocytes in the perimysium. It also includes microscars and widespread thick collagen strands primarily deposited in interstitial areas and around intramyocardial vessels.(155)

Experimental studies in various hypertensive animal models show that elevated BP triggers both adverse left ventricular remodeling and MIF, which then progress in parallel.(156) Resident cardiac fibroblasts detect mechanical stress from left ventricular pressure overload through surface receptors like integrins and discoidin domain receptors, which trigger mechanotransduction pathways and activate fibroblasts and promote their differentiation into myofibroblasts. Furthermore acting as a store of profibrotic signaling molecules ready for release following mechanical stress is the extracellular matrix. (157) Beyond pressure overload from sustained high LV BP nonhemodynamic factors including various inflammatory and noninflammatory cytokines, fibrogenic growth factors, neurohumoral pathways, and epigenetic mechanisms may also contribute to myocardial interstitial fibrosis in HHD, as evidenced by its presence in the right ventricle in experimental models and postmortem studies.(158-160)

The interplay between HF, HHD, and gut microbiota involves a bidirectional relationship where each factor can influence and exacerbate the others. Three different mechanisms in which the gut microbiota and HF are linked have been described by present studies.(161-163) First of all, alterations in microbial makeup could cause HF, and aggravate its development. Second, metabolite levels show a link that could affect the pathophysiology of HF. At last, the state of HF itself and its related symptoms, including fluid retention, can lead to microbial dysbiosis, accumulation of toxic metabolites, and pathogenicity of buildup of pathogenic species.(161)

Clostridium and Dorea were specifically lowered at the genus level; *Eubacterium rectale* and *Dorea longicatena* were specifically lowered at the species level, therefore indicating the possible therapeutic relevance gut bacteria has in the course of HF.(164) A Japanese research found lower SMB53 compared to healthy controls, with higher *Streptococcus* spp. and *Veillonella* spp.(165) In HF patients. Other investigations have shown an imbalance in gut bacteria engaged in the metabolism of toxic and protective compounds including TMAO in individuals with HF.(166) Reduced intestinal blood flow and thicker intestinal walls brought on by this congestion and lowered blood perfusion disturb microcirculation.(167) Bowels ischemia induces hypoxia at the villus tip and damages intestinal epithelial cells in this way. This causes bacterial translocation, which raises the quantity of endotoxins including LPS, which has been seen in oedematous HF sufferers. TNF-α has been found to have a deleterious influence on development of HF by contributing to systemic inflammation induced by LPS. (163) The renin–angiotensin–aldosterone pathway is also upregulated and endothelins are released in HF, therefore producing systemic arterial vasoconstriction, myocyte death, and noradrenaline and anti-diuretic hormone production. (168-170)

Figure 5 summarizes the connection between gut health, diet, medication, and HF. It shows how elements like bile acids, uremic toxins, SCFA, LPS, and TMAO from the gut interact with factors such as diet, medication, prebiotics,

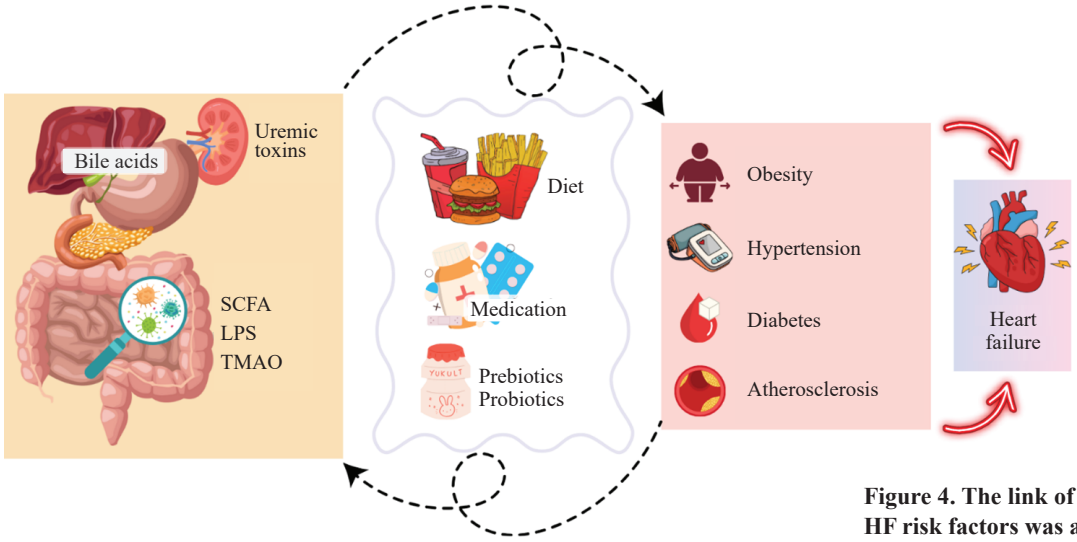

Figure 4. The link of microbiome dysbiosis to HF risk factors was affected by lifestyle.

and probiotics. These interactions can influence conditions like obesity, hypertension, diabetes, and atherosclerosis, which may lead to HF. The arrows in the diagram indicate the relationships between these elements, highlighting the impact of gut health and lifestyle choices on CV health.

Conclusion

By focusing on the 'how' rather than the 'what' of hypertension, this review identifies immune-mediated inflammation, orchestrated by the gut microbiota, as the core mechanism driving the disease. We propose that gut dysbiosis, triggered by environmental factors like high-salt diets, perpetuates a pro-inflammatory state that undermines the efficacy of conventional antihypertensive drugs and contributes to treatment-resistant hypertension. Consequently, modulating the gut microbiota through targeted interventions—including dietary fiber, probiotics, and fecal transplantation—represents a critical evolution in treatment. This approach moves beyond managing symptoms to directly correcting the inflammatory dysfunction at the heart of the disease, offering a powerful strategy to complement existing therapies.

Authors Contribution

AM drafted the original manuscript and critically revised the manuscript manuscript. NMD edited and revised the manuscript. AW proposed and concepted the manuscript topic, and gave critical suggestions to the final draft. All authors have agreed with the final revisions of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest or competing interests related to the content of this manuscript.

References

1. Valilshchykov M, Babalyan V, Markina T, Kumetchko M, Boiko L, Romaev S. The enalapril use in arterial hypertension stimulates the reparative processes in fractures of the proximal femur. Indones Biomed J. 2022; 14(1): 36-44.
2. World Health Organization [Internet]. Global Report on Hypertension [updated 2023 Sep 19; cited 2024 Dec 14]. Available from: https://www.who.int/teams/noncommunicable-diseases/hypertension-report.
3. Utami SL, Simamora D, Idawati I, Widjaja JH. ACE I/D and A2350G polymorphisms are correlated with body mass index, but not with body weight and essential hypertension: Study in javanese postmenopausal women. Mol Cell Biomed Sci. 2024; 8(2): 96-104.
4. Madhur MS, Elijovich F, Alexander MR, Pitzer A, Ishimwe J, Van Beusecum JP, Patrick DM, Smart CD, Kleyman TR, Kingery J, *et al*. Hypertension. Circ Res. 2021;128:908–933. doi: 10.1161/CIRCRESAHA.121.318052.
5. Ramayani OR. Childhood hyperuricemia as risk factor of hypertension in adulthood. Indones Biomed J. 2012; 4(1): 12-6.
6. Ramadhanti R, Helda. Association of hypertension and chronic kidney disease in population aged ≥18 years old. Mol Cell Biomed Sci. 2021; 5(3): 137-44.
7. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365(9455): 217-23.
8. Murray CJL, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013; 369(5): 448-57.

9. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, *et al*. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 2014; 383(9932): 1899-911.
10. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National health and nutrition examination survey, 2011-2012. NCHS Data Brief. 2013; (133): 1-8.
11. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, *et al*. health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377(1): 13-27.
12. Lawes CM, Hoorn S Vander, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008; 371(9623): 1513-8.
13. Nguyen BA, Alexander MR, Harrison DG. Immune mechanisms in the pathophysiology of hypertension. Nat Rev Nephrol. 2024; 20(8): 530-40.
14. Harrison DG, Patrick DM. Immune mechanisms in hypertension. Hypertension. 2024; 81(8): 1659-74.
15. Berillo O, Schiffrin EL. Advances in understanding of the role of immune cell phenotypes in hypertension and associated vascular disease. Can J Cardiol. 2024; 40(12): 2321-39.
16. Bujanowicz A, Skrzypczyk P. Immunological mechanisms of arterial damage in pediatric patients with primary hypertension. Cent Eur J Immunol. 2023; 48(2): 150-7.
17. Schreiber S, Arndt P, Morton L, Garza AP, Müller P, Neumann K, *et al*. Immune system activation and cognitive impairment in arterial hypertension. Am J Physiol Cell Physiol. 2024; 327(6): C1577-90.
18. Alam R, Ahsan H, Khan S. The role of malondialdehyde (MDA) and ferric reducing antioxidant power (FRAP) in patients with hypertension. Mol Cell Biomed Sci. 2023; 7(2): 58-64.
19. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med. 2018; 215(1): 21-33.
20. Meiliana A, Dewi NM, Wijaya A. Lifestyle modifications and nutraceutical interventions in the prevention and management of metabolic syndrome. Indones Biomed J. 2025; 17(3): 207-32.
21. Ramadhan AY, Rosdiana DS. The prospect of probiotics to treat metabolic syndrome. Mol Cell Biomed Sci. 2024; 8(2): 71-80.
22. Meiliana A, Wijaya A. Gut microbiota, obesity and metabolic dysfunction. Indones Biomed J. 2011; 3(3): 150-67.
23. Dong C, Yang Y, Wang Y, Hu X, Wang Q, Gao F, *et al*. Gut microbiota combined with metabolites reveals unique features of acute myocardial infarction patients different from stable coronary artery disease. J Adv Res. 2023; 46: 101-12.
24. Duan Y, Wu X, Yang Y, Gu L, Liu L, Yang Y, *et al*. Marked shifts in gut microbial structure and neurotransmitter metabolism in fresh inmates revealed a close link between gut microbiota and mental health: A case-controlled study. Int J Clin Health Psychol. 2022; 22(3): 100323. doi: 10.1016/j.ijchp.2022.100323.
25. Miyauchi E, Shimokawa C, Steimle A, Desai MS, Ohno H. The impact of the gut microbiome on extra-intestinal autoimmune diseases. Nat Rev Immunol. 2023; 23(1): 9-23.
26. Wu C, Zhao Y, Zhang Y, Yang Y, Su W, Yang Y, *et al*. Gut microbiota specifically mediates the anti-hypercholesterolemic effect of berberine (BBR) and facilitates to predict BBR's cholesterol-decreasing efficacy in patients. J Adv Res. 2021; 37: 197-208.
27. Zhang X, Yang Y, Zhang F, Yu J, Sun W, Wang R, *et al*. Traditional Chinese medicines differentially modulate the gut microbiota based on their nature (Yao-Xing). Phytomedicine. 2021; 85: 153496. doi: 10.1016/j.phymed.2021.153496.
28. Yang YN, Wang QC, Xu W, Yu J, Zhang H, Wu C. The berberine-enriched gut commensal Blautia producta ameliorates high-fat diet (HFD)-induced hyperlipidemia and stimulates liver LDLR expression. Biomed Pharmacother. 2022: 155: 113749. doi: 10.1016/j.biopha.2022.113749.
29. McCulloch JA, Davar D, Rodrigues RR, Badger JH, Fang JR, Cole AM, *et al*. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. 2022; 28(3): 545-56.
30. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med. 2018; 215(1): 21-33.
31. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, *et al*. Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction. J Exp Med. 2007; 204(10): 2449-60. doi: 10.1084/jem.20070657.
32. Harrison DG, Vinh A, Lob H, Madhur MS. Role of the adaptive immune system in hypertension. Curr Opin Pharmacol. 2010; 10(2): 203-7.
33. Newton K, Dixit VM. Signaling in innate immunity and inflammation. Cold Spring Harb Perspect Biol. 2012; 4(3): a006049. doi: 10.1101/cshperspect.a006049.
34. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, *et al*. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med. 2007; 204(10): 2449-60.
35. Markó L, Kvakan H, Park JK, Qadri F, Spallek B, Binger KJ, *et al*. Interferon-γ signaling inhibition ameliorates angiotensin II-induced cardiac damage. Hypertension. 2012; 60(6): 1430-6.
36. Wei SY, Wang YX, Zhang QF, Zhao SL, Diao TT, *et al*. Multiple mechanisms are involved in salt-sensitive hypertension-induced renal injury and interstitial fibrosis. Sci Rep. 2017; 7: 45952. doi: 10.1038/srep45952.
37. Xiao L, Kirabo A, Wu J, Saleh MA, Zhu L, Wang F, *et al*. Renal denervation prevents immune cell activation and renal inflammation in angiotensin II-induced hypertension. Circ Res. 2015; 117(6): 547–557.
38. Wenzel P. Monocytes as immune targets in arterial hypertension. Br J Pharmacol. 2019; 176(12): 1966-77.
39. Oh J, Matkovich SJ, Riek AE, Bindom SM, Shao JS, Head RD, *et al*. Macrophage secretion of miR-106b-5p causes renin-dependent hypertension. Nat Commun. 2020; 11(1): 4798. doi: 10.1038/s41467-020-18538-x.
40. Hughson MD, Gobe GC, Hoy WE, Manning RD, Douglas-Denton R, Bertram JF. Associations of glomerular number and birth weight with clinicopathological features of african americans and whites. Am J Kidney Dis. 2008; 52(1): 18-28.
41. Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, *et al*. Lysozyme M–positive monocytes mediate angiotensin ii–induced arterial hypertension and vascular dysfunction. Circulation. 2011; 124(12): 1370-81.
42. De Ciuceis C, Amiri F, Brassard P, Endemann DH, Touyz RM, *et al*. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin ii–infused macrophage colony-stimulating factor–deficient mice. Arterioscler Thromb Vasc Biol. 2005; 25(10): 2106-13.
43. Okuda T, Grollman A. Passive transfer of autoimmune induced hypertension in the rat by lymph node cells. Tex Rep Biol Med. 1967; 25(2): 257-64.
44. Gantini L, Bakri S, Wijaya A, Santoso A. Inflammation is associated with vascular remodeling - repairing balances in hypertensive obese subjects. Indones Biomed J. 2011; 3(2): 110-5.
45. Olsen F. Inflammatory cellular reaction in hypertensive vascular disease in man. Acta Pathol Microbiol Scand A. 1972; 80(2): 253-6.
46. Svendsen UG. The role of thymus for the development and prognosis

of hypertension and hypertensive vascular disease in mice following renal infarction. Acta Pathol Microbiol Scand A. 1976; 84(3): 235-43.
47. Ba D, Takeichi N, Kodama T, Kobayashi H. Restoration of T cell depression and suppression of blood pressure in spontaneously hypertensive rats (SHR) by thymus grafts or thymus extracts. J Immunol. 1982; 128(3): 1211-6.
48. Lin SC, Lo YC, Wu H. Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. Nature. 2010; 465(7300): 885-90.
49. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017; 377(12): 1119-31.
50. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, *et al*. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: A secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018; 391(10118): 319-28.
51. Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, *et al*. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. Circulation. 2019; 139(10): 1289-99.
52. Rothman AMK, Macfadyen J, Thuren T, Webb A, Harrison DG, Guzik TJ, *et al*. Effects of interleukin-1β inhibition on blood pressure, incident hypertension, and residual inflammatory risk: A secondary analysis of CANTOS. Hypertension. 2020; 75(2): 477-82.
53. Alexander MR, Norlander AE, Elijovich F, Atreya RV, Gaye A, Gnecco JS, *et al*. Human monocyte transcriptional profiling identifies IL-18 receptor accessory protein and lactoferrin as novel immune targets in hypertension. Br J Pharmacol. 2019; 176(12): 2015-27.
54. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. N Engl J Med. 2008; 359(21): 2195-207.
55. Dalekos GN, Elisaf M, Bairaktari E, Tsolas O, Siamopoulos KC. Increased serum levels of interleukin-1beta in the systemic circulation of patients with essential hypertension: additional risk factor for atherogenesis in hypertensive patients? J Lab Clin Med. 1997; 129(3): 300-8.
56. Rabkin SW. The role of interleukin 18 in the pathogenesis of hypertension-induced vascular disease. Nat Clin Pract Cardiovasc Med. 2009; 6(3): 192-9.
57. Krishnan SM, Sobey CG, Latz E, Mansell A, Drummond GR. IL-1β and IL -18: inflammatory markers or mediators of hypertension? Br J Pharmacol. 2014; 171(24): 5589-602.
58. Gu C, Wu L, Li X. IL-17 family: cytokines, receptors and signaling. Cytokine. 2013; 64(2): 477-85.
59. Saleh MA, Norlander AE, Madhur MS. Inhibition of interleukin 17-A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin ii-induced hypertension. JACC Basic Transl Sci. 2016; 1(7): 606-16.
60. Higaki A, Mahmoud AUM, Paradis P, Schiffrin EL. Role of interleukin-23/interleukin-17 axis in T-cell-mediated actions in hypertension. Cardiovasc Res. 2021; 117(5): 1274-83.
61. Liu W, Chang C, Hu H, Yang H. Interleukin-23: A new atherosclerosis target. J Interferon Cytokine Res. 2018; 38(10): 440-4.
62. Zhang M, Cai ZR, Zhang B, Cai X, Li W, Guo Z, *et al*. Functional polymorphisms in interleukin-23 receptor and susceptibility to coronary artery disease. DNA Cell Biol. 2014; 33(12): 891-7.
63. Elmarakby AA, Quigley JE, Imig JD, Pollock JS, Pollock DM. TNF-α inhibition reduces renal injury in DOCA-salt hypertensive rats. Am J Physiol Regul Integr Comp Physiol. 2008; 294(1): R76-83.
64. Therrien FJ, Agharazii M, Lebel M, Larivire R. Neutralization of tumor necrosis factor-alpha reduces renal fibrosis and hypertension in rats with renal failure. Am J Nephrol. 2012; 36(2): 151-61.
65. Venegas-Pont M, Manigrasso MB, Grifoni SC, Lamarca BB, Maric C, Racusen LC, *et al*. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. Hypertension. 2010; 56(4): 643-9.
66. Zhang J, Patel MB, Griffths R, Mao A, Song YS, Karlovich NS, *et al*. Tumor necrosis factor-α produced in the kidney contributes to angiotensin II-dependent hypertension. Hypertension. 2014; 64(6): 1275-81.
67. Mehaffey E, Majid DSA. Tumor necrosis factor-, kidney function, and hypertension. Am J Physiol Renal Physiol. 2017; 313(4): F1005-8.
68. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016; 14(8): e1002533. doi: 10.1371/journal.pbio.1002533.
69. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, *et al*. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol. 2014; 32(8): 834-41. doi: 10.1038/NBT.2942.
70. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 2012; 489(7415): 242-9.
71. Beale AL, O'Donnell JA, Nakai ME, Nanayakkara S, Vizi D, Carter K, *et al*. The gut microbiome of heart failure with preserved ejection fraction. J Am Heart Assoc. 2021; 10(13): e020654. doi: 10.1161/JAHA.120.020654.
72. Pugh D, Gallacher PJ, Dhaun N. Management of hypertension in chronic kidney disease. Drugs. 2019; 79(4): 365-79.
73. Yang T, Richards EM, Pepine CJ, Raizada MK. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol. 2018; 14(7): 442-56.
74. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nat Rev Microbiol. 2008; 6(10): 776-88.
75. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc Natl Acad Sci USA. 2009; 106(10): 3698-703.
76. Nakai M, Ribeiro RV, Stevens BR, Gill P, Muralitharan RR, Yiallourou S, *et al*. essential hypertension is associated with changes in gut microbial metabolic pathways: a multisite analysis of ambulatory blood pressure. Hypertension. 2021; 78(3): 804-15.
77. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM, *et al*. Gut dysbiosis is linked to hypertension. Hypertension. 2015; 65(6): 1331-40.
78. O'Donnell JA, Zheng T, Meric G, Marques FZ. The gut microbiome and hypertension. Nat Rev Nephrol. 2023; 19(3): 153-67.
79. Leeming ER, Johnson AJ, Spector TD, Roy CIL. Effect of diet on the gut microbiota: Rethinking intervention duration. Nutrients. 2019; 11(12): 2862. doi: 10.3390/nu11122862.
80. Olsen F. Transfer of arterial hypertension by splenic cells from DOCA-salt hypertensive and renal hypertensive rats to normotensive recipients. Acta Pathol Microbiol Scand C. 1980; 88(1): 1-5. doi: 10.1111/j.1699-0463.1980.tb00065.x. PMID: 7376880.
81. Olsen F. Evidence for an immunological factor in the hypertensive vascular disease. Acta Pathol Microbiol Scand A. 1971; 79(1): 22-6
82. Rodríguez-Iturbe B, Ferrebuz A, Vanegas V, Quiroz Y, Mezzano S, Vaziri ND. Early and sustained inhibition of nuclear factor-κb prevents hypertension in spontaneously hypertensive rats. journal of

pharmacology and experimental therapeutics. 2005; 315(1): 51-7.
83. Brands MW, Banes-Berceli AKL, Inscho EW, Al-Azawi H, Allen AJ, Labazi H. Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/ signal transducer and activator of transcription 3 activation. Hypertension. 2010; 56(5): 879-84.
84. Wen Y, Liu Y, Tang T, Lv L, Liu H, Ma K, *et al*. NLRP3 inflammasome activation is involved in Ang II-induced kidney damage via mitochondrial dysfunction. Oncotarget. 2016; 7(34): 54290-302.
85. Huang B, Cheng Y, Usa K, Liu Y, Baker MA, Mattson DL, *et al*. Renal tumor necrosis factor α contributes to hypertension in dahl salt-sensitive rats. Sci Rep. 2016; 6: 21960. doi: 10.1038/SREP21960.
86. McShane L, Tabas I, Lemke G, Kurowska-Stolarska M, Maffia P. TAM receptors in cardiovascular disease. Cardiovasc Res. 2019; 115(8): 1286-95.
87. Nosalski R, Mikolajczyk T, Siedlinski M, Saju B, Koziol J, Maffia P, *et al*. Nox1/4 inhibition exacerbates age dependent perivascular inflammation and fibrosis in a model of spontaneous hypertension. Pharmacol Res. 2020; 161: 105235. doi: 10.1016/J.PHRS.2020.105235.
88. Macritchie N, Grassia G, Noonan J, Cole JE, Hughes CE, Schroeder J, *et al*. The aorta can act as a site of naïve CD4+ T-cell priming. Cardiovasc Res. 2020; 116(2): 306-16.
89. Carnevale D, Perrotta M, Pallante F, Fardella V, Iacobucci R, Fardella S, *et al*. A cholinergic-sympathetic pathway primes immunity in hypertension and mediates brain-to-spleen communication. Nat Commun. 2016; 7: 13035. doi: 10.1038/ncomms13035.
90. Carnevale D, Pallante F, Fardella V, Fardella S, Iacobucci R, Federici M, *et al*. The angiogenic factor PlGF mediates a neuroimmune interaction in the spleen to allow the onset of hypertension. Immunity. 2014; 41(5): 737-52.
91. Rodriguez-Iturbe B, Lanaspa MA, Johnson RJ. The role of autoimmune reactivity induced by heat shock protein 70 in the pathogenesis of essential hypertension. Br J Pharmacol. 2019; 176(12): 1829-38.
92. Nosalski R, Siedlinski M, Denby L, McGinnigle E, Nowak M, Cat AND, *et al*. T-cell-derived miRNA-214 Mediates perivascular fibrosis in hypertension. Circ Res. 2020; 126(8): 988-1003.
93. Hoyer FF, Nahrendorf M. Interferon-γ regulates cardiac myeloid cells in myocardial infarction. Cardiovasc Res. 2019; 115(13): 1815-16.
94. Matrougui K, Zakaria AE, Kassan M, Choi S, Nair D, Gonzalez-Villalobos RA, *et al*. Natural regulatory T cells control coronary arteriolar endothelial dysfunction in hypertensive mice. Am J Pathol. 2011; 178(1): 434-41.
95. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, Harrison DG. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension. 2010; 55(2): 500-7.
96. Kamat NV, Thabet SR, Xiao L, Saleh MA, Kirabo A, Madhur MS, *et al*. Renal transporter activation during angiotensin-II hypertension is blunted in interferon-γ-/- and interleukin-17A-/- mice. Hypertension. 2015; 65(3): 569-76.
97. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, *et al*. COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020; 116(10): 1666-87.
98. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: Sex differences in immune response and cardiovascular comorbidities. Cardiovasc Res. 2020; 116(14): 2197-206.
99. Di Napoli M, Papa F. Association between blood pressure and C-reactive protein levels in acute ischemic stroke. Hypertension. 2003; 42(6): 1117-23.
100. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. Hypertension. 2007; 49(2): 304-10.
101. Zhang J, Rudemiller NP, Patel MB, Karlovich NS, Wu M, McDonough AA, *et al*. Interleukin-1 receptor activation potentiates salt reabsorption in angiotensin ii-induced hypertension via the NKCC2 co-transporter in the nephron. Cell Metab. 2016 Feb 9;23(2):360-8.
102. Litwin M, Kułaga Z. Obesity, metabolic syndrome, and primary hypertension. Pediatr Nephrol. 2021; 36(4): 825-37.
103. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, *et al*. Genome-wide association study of blood pressure and hypertension. Nat Genet. 2009; 41: 677-87.
104. Jermendy G, Horváth T, Littvay L, Steinbach R, Jermendy ÁL, Tárnoki ÁD, *et al*. Effect of genetic and environmental influences on cardiometabolic risk factors: A twin study. Cardiovasc Diabetol. 2011; 10: 1-8. doi: 10.1186/1475-2840-10-96/TABLES/3.
105. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, *et al*. Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the framingham heart study. Hypertension. 2000; 36(4): 477-83.
106. Mitchell GF, DeStefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, *et al*. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: The Framingham Heart Study. Circulation. 2005; 112(2): 194-9.
107. Huan T, Meng Q, Saleh MA, Norlander AE, Joehanes R, Zhu J, *et al*. Integrative network analysis reveals molecular mechanisms of blood pressure regulation. Mol Syst Biol. 2015; 11(1): 799. doi: 10.15252/msb.20145399.
108. Rudemiller NP, Lund H, Priestley JRC, Endres BT, Prokop JW, Jacob HJ, *et al*. Mutation of SH2B3 (LNK), a genome-wide association study candidate for hypertension, attenuates Dahl salt-sensitive hypertension via inflammatory modulation. Hypertension. 2015; 65(5): 1111-7.
109. Devallire J, Charreau B. The adaptor Lnk (SH2B3): an emerging regulator in vascular cells and a link between immune and inflammatory signaling. Biochem Pharmacol. 2011; 82(10): 1391-402.
110. Huan T, Esko T, Peters MJ, Pilling LC, Schramm K, Schurmann C, *et al*. A meta-analysis of gene expression signatures of blood pressure and hypertension. PLoS Genet. 2015; 11(3): e1005035. doi: 10.1371/journal.pgen.1005035.
111. Saleh MA, McMaster WG, Wu J, Norlander AE, Funt SA, Thabet SR, *et al*. Lymphocyte adaptor protein LNK deficiency exacerbates hypertension and end-organ inflammation. J Clin Invest. 2015; 125(3): 1189-202.
112. Gan L, Ye D, Feng Y, Pan H, Lu X, Wan J, Ye J. Immune cells and hypertension. Immunol Res. 2024; 72(1): 1-13. doi: 10.1007/s12026-023-09414-z.
113. Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, Wilhelm C, Veldhoen M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell. 2011; 147(3): 629-40.
114. Mielke LA, Jones SA, Raverdeau M, Higgs R, Stefanska A, Groom JR, *et al*. Retinoic acid expression associates with enhanced IL-22 production by γδ T cells and innate lymphoid cells and attenuation of intestinal inflammation. J Exp Med. 2013; 210(6): 1117-24.
115. Goldberg EL, Shchukina I, Asher JL, Sidorov S, Artyomov MN, Dixit VD. Ketogenesis activates metabolically protective γδ T cells in visceral adipose tissue. Nat Metab. 2020; 2(1): 50-61.

116. Dong JY, Szeto IMY, Makinen K, Gao Q, Wang J, Qin LQ, Zhao Y. Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2013; 110(7): 1188-94.
117. Dinakis E, Nakai M, Gill P, Ribeiro R, Yiallourou S, Sata Y, *et al*. Association between the gut microbiome and their metabolites with human blood pressure variability. Hypertension. 2022; 79(8): 1690-701.
118. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, Shenoy V, *et al*. Hypertension-linked pathophysiological alterations in the gut. Circ Res. 2017; 120(2): 312-23.
119. Zhou X, Li J, Guo J, Geng B, Ji W, Zhao Q, *et al*. Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction. Microbiome. 2018; 6(1):66. doi: 10.1186/s40168-018-0441-4.
120. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, *et al*. Salt-responsive gut commensal modulates TH17 axis and disease. Nature. 2017; 551: 585-9.
121. Kim S, Goel R, Kumar A, Qi Y, Lobaton G, Hosaka K, *et al*. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. Clin Sci (Lond). 2018; 132(6): 701-18.
122. Larabi A, Barnich N, Nguyen HTT. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. Autophagy. 2020; 1 6(1): 38-51.
123. Jaworska K, Huc T, Samborowska E, Dobrowolski L, Bielinska K, Gawlak M, *et al*. Hypertension in rats is associated with an increased permeability of the colon to TMA, a gut bacteria metabolite. PLoS One. 2017; 12(12): e0189310. doi: 10.1371/journal.pone.0189310.
124. Andersen K, Kesper MS, Marschner JA, Konrad L, Ryu M, Kumar SVR, *et al*. Intestinal dysbiosis, barrier dysfunction, and bacterial translocation account for CKD-related systemic inflammation. J Am Soc Nephrol. 2017; 28(1): 76-83.
125. Yang Z, Wang Q, Liu Y, Wang L, Ge Z, Li Z, *et al*. Gut microbiota and hypertension: Association, mechanisms and treatment. Clin Exp Hypertens. 2023; 45(1): 2195135. doi: 10.1080/10641963.2023.2195135.
126. Chen L, He FJ, Dong Y, Huang Y, Wang C, Harshfield GA, Zhu H. Modest sodium reduction increases circulating short-chain fatty acids in untreated hypertensives: A randomized, double-blind, placebo-controlled trial. Hypertension. 2020; 76(1): 73-9.
127. Mortensen FV, Nielsen H, Mulvany MJ, Hessov I. Short chain fatty acids dilate isolated human colonic resistance arteries. Gut. 1990; 31(12): 1391-4.
128. Duttaroy AK. Role of gut microbiota and their metabolites on atherosclerosis, hypertension and human blood platelet function: A review. Nutrients. 2021; 13(1): 144. doi: 10.3390/nu13010144.
129. Ge X, Zheng L, Zhuang R, Yu P, Xu Z, Liu G, *et al*. The gut microbial metabolite trimethylamine n-oxide and hypertension risk: a systematic review and dose-response meta-analysis. Adv Nutr. 2020; 11: 66-76.
130. Brown JM, Hazen SL. Microbial modulation of cardiovascular disease. Nat Rev Microbiol. 2018; 16(3): 171-81. doi: 10.1038/nrmicro.2017.149.
131. Olalekan SO, Bakare OO, Faponle AS, Okwute PG. A review of gut microbial metabolites and therapeutic approaches in hypertension. Bull Natl Res Cent. 2024; 48: 95. doi: 10.1186/S42269-024-01252-9.
132. Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, *et al*. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. Circulation. 2017; 135(10): 964-77.
133. Durgan DJ, Ganesh BP, Cope JL, Ajami NJ, Phillips SC, Petrosino JF, *et al*. Role of the gut microbiome in obstructive sleep apnea-induced hypertension. Hypertension. 2016; 67(2): 469-74.
134. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, *et al*. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017; 5(1): 14. doi: 10.1186/s40168-016-0222-x.
135. Mahgoup EM. "Gut Microbiota as a Therapeutic Target for Hypertension: Challenges and Insights for Future Clinical Applications" "Gut Microbiota and Hypertension Therapy." Current Hypertension Reports 2025 27:1 [Internet]. 2025 [cited 2025 Apr 28];27:1–13. doi: 10.1007/S11906-025-01331-W.
136. Mei X, Mell B, Manandhar I, Aryal S, Tummala R, Kyoung J, *et al*. Repurposing a drug targeting inflammatory bowel disease for lowering hypertension. J Am Heart Assoc. 2022; 11(24): e027893. doi: 10.1161/JAHA.122.027893.
137. Smits MM, Fluitman KS, Herrema H, Davids M, Kramer MHH, Groen AK, Belzer C, de Vos WM, Cahen DL, Nieuwdorp M, *et al*. Liraglutide and sitagliptin have no effect on intestinal microbiota composition: A 12-week randomized placebo-controlled trial in adults with type 2 diabetes. Diabetes Metab. 2021; 47(5): 101223. doi: 10.1016/j.diabet.2021.101223.
138. van Bommel EJM, Herrema H, Davids M, Kramer MHH, Nieuwdorp M, van Raalte DH. Effects of 12-week treatment with dapagliflozin and gliclazide on faecal microbiome: Results of a double-blind randomized trial in patients with type 2 diabetes. Diabetes Metab. 2020; 46(2): 164-8.
139. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, *et al*. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015; 528(7581): 262-6.
140. Liao X, Song L, Zeng B, Liu B, Qiu Y, Qu H, *et al*. Alteration of gut microbiota induced by DPP-4i treatment improves glucose homeostasis. EBioMedicine. 2019; 44: 665-74.
141. Tong X, Xu J, Lian F, Yu X, Zhao Y, Xu L, *et al*. Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional chinese herbal formula: A multicenter, randomized, open label clinical trial. mBio. 2018; 9(3): e02392-17.
142. Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, *et al*. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut. 2014; 63(5): 727-35. doi: 10.1136/gutjnl-2012-303839.
143. Zhang W, Xu JH, Yu T, Chen QK. Effects of berberine and metformin on intestinal inflammation and gut microbiome composition in db/db mice. Biomed Pharmacother. 2019; 118: 109131. doi: 10.1016/j.biopha.2019.109131.
144. de la Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, Velásquez-Mejía EP, Carmona JA, Abad JM, *et al*. Metformin is associated with higher relative abundance of mucin-degrading Akkermansia muciniphila and several short-chain fatty acid–producing microbiota in the gut. Diabetes Care. 2017; 40(1): 54-62.
145. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, *et al*. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017; 23(7): 850-8.
146. Chen HQ, Gong JY, Xing K, Liu MZ, Ren H, Luo JQ. Pharmacomicrobiomics: Exploiting the drug-microbiota interactions in antihypertensive treatment. Front Med. 2022; 8: 742394. doi: 10.3389/fmed.2021.742394.
147. Kyoung J, Atluri RR, Yang T. Resistance to antihypertensive drugs: Is gut microbiota the missing link? Hypertension. 2022; 79(10): 2138-47.

148. Durgan DJ, Zubcevic J, Vijay-Kumar M, Yang T, Manandhar I, Aryal S, *et al*. Prospects for leveraging the microbiota as medicine for hypertension. Hypertension. 2024; 81(5): 951-63.
149. González A, López B, Ravassa S, San José G, Latasa I, Butler J, *et al*. Myocardial interstitial fibrosis in hypertensive heart disease: From mechanisms to clinical management. Hypertension. Hypertension. 2024; 81(2): 218-28.
150. Dai H, Bragazzi NL, Younis A, Zhong W, Liu X, Wu J, *et al*. Worldwide trends in prevalence, mortality, and disability-adjusted life years for hypertensive heart disease from 1990 to 2017. Hypertension. 2021; 77(4): 1223-33.
151. de Boer RA, De Keulenaer G, Bauersachs J, Brutsaert D, Cleland JG, Diez J, *et al*. Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology. Eur J Heart Fail. 2019; 21(3): 272-85.
152. Shoulders MD, Raines RT. Collagen structure and stability. Annu Rev Biochem. 2009; 78: 929-58.
153. Van Der Slot-Verhoeven AJ, Van Dura EA, Attema J, Blauw B, DeGroot J, Huizinga TWJ, *et al*. The type of collagen cross-link determines the reversibility of experimental skin fibrosis. Biochim Biophys Acta. 2005; 1740(1): 60-7.
154. López B, Ravassa S, Moreno MU, José GS, Beaumont J, González A, *et al*. Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches. Nat Rev Cardiol. 2021; 18(7): 479-98.
155. Ding Y, Wang Y, Jia Q, Wang X, Lu Y, Zhang A, *et al*. Morphological and functional characteristics of animal models of myocardial fibrosis induced by pressure overload. Int J Hypertens. 2020; 2020: 3014693. doi: 10.1155/2020/3014693.
156. Wang Y, Wang M, Samuel CS, Widdop RE. Preclinical rodent models of cardiac fibrosis. Br J Pharmacol. 2022; 179(5): 882-99.
157. Herum KM, Lunde IG, McCulloch AD, Christensen G. The soft- and hard-heartedness of cardiac fibroblasts: Mechanotransduction signaling pathways in fibrosis of the heart. J Clin Med. 2017; 6(5):53. doi: 10.3390/jcm6050053.
158. Díez J. Mechanisms of cardiac fibrosis in hypertension. J Clin Hypertens. 2007; 9(7): 546-50.
159. Nemtsova V, Vischer AS, Burkard T. Hypertensive heart disease: A narrative review series-part 1: pathophysiology and microstructural changes. J Clin Med. 2023; 12(7): 2606. doi: 10.3390/jcm12072606.
160. Mckinsey TA, Foo R, Anene-Nzelu CG, Travers JG, Vagnozzi RJ, Weber N, Thum T. Emerging epigenetic therapies of cardiac fibrosis and remodelling in heart failure: from basic mechanisms to early clinical development. Cardiovasc Res. 2023; 118(18): 3482-98.
161. Tang WHW, Kitai T, Hazen SL. Gut Microbiota in cardiovascular health and disease. Circ Res. 2017; 120(7): 1183-96.
162. Kitai T, Tang WHW. Gut microbiota in cardiovascular disease and heart failure. Clin Sci. 2018; 132(1): 85-91.
163. Zabell A, Tang WHW. Targeting the Microbiome in Heart Failure. Current Treatment Options in Cardiovascular Medicine. 2017; 19(4): 27. doi: 10.1007/s11936-017-0528-4.
164. Kamo T, Akazawa H, Suda W, Saga-Kamo A, Shimizu Y, Yagi H, *et al*. Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. PLoS One. 2017; 12(3): e0174099. doi: 10.1371/journal.pone.0174099.
165. Katsimichas T, Ohtani T, Motooka D, Tsukamoto Y, Kioka H, Nakamoto K, *et al*. Non-ischemic heart failure with reduced ejection fraction is associated with altered intestinal microbiota. Circ J. 2018; 82(6): 1640-50.
166. Cui X, Ye L, Li J, Jin L, Wang W, Li S, *et al*. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. Sci Rep. 2018; 8(1): 635. doi: 10.1038/S41598-017-18756-2.
167. Kamo T, Akazawa H, Suzuki JI, Komuro I. Novel concept of a heart-gut axis in the pathophysiology of heart failure. Korean Circ J. 2017; 47(5): 663-9.
168. Ahmad AF, Ward NC, Dwivedi G. The gut microbiome and heart failure. Curr Opin Cardiol. Curr Opin Cardiol. 2019; 34(2): 225-32.
169. Brahmbhatt DH, Cowie MR. Heart failure: classification and pathophysiology. Medicine. 2018; 46(10): 587-93.
170. Metra M, Teerlink JR. Heart failure. Lancet. 2017; 390(10106): 1981-995.