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Endothelial Dysfunction and Hypertension in African Americans: Overview of the Role of the Gut Microbiome

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Abstract Hypertension (now defined by systolic blood pressure/diastolic blood pressure [SBP/DBP] greater than 130/90 mmHg), is one of the most common cardiovascular disorders and is a critical public health and economic concern. African Americans have the greatest burden of hypertension and elucidating the causes of this racial disparity is important for amending and developing effective treatment strategies. Although studies have provided mechanistic insight concerning characteristics of endothelial dysfunction, which likely precedes hypertension in African Americans, our knowledge is limited concerning internal systems (i.e., gut) that may affect endothelial and vascular health outcomes. Recent studies report that the types, and balance, of microbes in the gut are significant contributors to health and disease. Gut microbial dysbiosis, an unhealthy and poorly diverse gut microbial profile, has been linked to hypertension and other diseases that may disproportionately affect cardiovascular health. Relative to hypertension, dysbiosis has been characterized as a reduced richness of short chain fatty acid (SCFA) producing microbes. SCFAs are significant metabolites produced by gut microbes beneficially impact cellular functions, specifically vascular smooth muscle and endothelial cells. Studies concerning the gut microbiome and cardiovascular disease are limited in humans and grossly underrepresent minority populations. This brief review will overview factors concerning the racial disparity in hypertension and provide insight into the potential role that gut dysbiosis may have in hypertension, highlighting the "gut-vascular axis" concerning cardiovascular health.

Keywords: *racial disparity, endothelial dysfunction, hypertension, gut dysbiosis, short-chain fatty acids*

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1. Introduction

Hypertension (as now defined by systolic blood pressure/diastolic blood pressure [SBP/DBP] greater than 130/80 mmHg), is one of the most common disorders and is a critical public health and economic concern. Hypertension increases the risk for cardiovascular disease (CVD) [1], stroke [2,3], and chronic kidney disease [4] making hypertension a major contributor to death and disability [5]. Hypertension is the leading preventable risk factor for premature death and disability worldwide [6]. The number of years of life lost to hypertension-related diseases in 2010 was estimated to be: stroke (1.9 million), chronic kidney disease, other cardiovascular and circulatory, and hypertensive heart disease (2.2 million combined), and ischemic heart disease (7.2 million) [7]. The overall prevalence of hypertension among US adults from 2015-2016 was 29%, and was similar in men and women [8]. The prevalence of hypertension increases with age such that 63.1% among those 60 and older have hypertension [8,9]. Thus, approximately 85 million adults in the US have hypertension and it is estimated that it the prevalence of hypertension will increase by more than 9%, or 27 million more people, from 2010 to 2030 [10].

In addition to the US health burden, the economic burden of hypertension is extremely high. Estimates using data analyzed from 2001 to 2005 suggest that hypertension is the costliest of all CVDs, with an estimated direct cost of $69.9 billion in 2010 [10]. However, when accounting for the prevalence of hypertension in the US society, hypertension is associated with about $131 billion per year in population-level expenditures [11].

In a special issue of *Circulation* published in 2005, it was reported that significant disparities exist in the prevalence of cardiovascular morbidity and mortality [12]. The same is true for a primary risk factor for CVD, hypertension [12,13]. The prevalence, after adjustment for age, is higher in African Americans (AA) than for any other major race or ethnic group [9]. Data from the National Health and Nutrition Survey from 1988 to 2008 showed that there were significant increases during this

time in the proportions of AA with hypertension compared to their Caucasian (CA) and Hispanic counterparts [9]. AA tend to develop hypertension at an earlier age than CA and in children aged 8–17 years, SBP levels were 2.9 mmHg and 1.6 mmHg higher in AA boys and girls, respectively, compared to age-matched CA boys and girls [14].

2. Racial Disparity in Endothelial Dysfunction and Hypertension

While AA race is an independent risk factor for vascular disease [15,16], current statistics reported in Heart Disease and Stroke Statistics-2019 Update [17] rates show that the burden is yet increasing. The age-adjusted prevalence of hypertension between the years 2011-2016 was reported to be approximately 57% of adult AA men and 53% of AA women affected, compared to 46% and 38% of their CA peers, respectively. Strikingly, the age-adjusted mortality rates attributed to hypertension (per 100,000) in 2016 was 54.0 for AA males and 36.7 for AA females, compared to 21.1 for CA males and 17.3 for CA females. As AA develop hypertension at younger ages than other groups, they are more likely to develop hypertension-associated complications with nearly a two-fold increase in mortality associated with CVD [18] and end-organ damage compared to CA [13]. Moreover, hypertension control among treated AA is lower than CA despite the higher awareness in this population [17,19]. In AA men only, one study assessed the economic consequences of men's health disparities using data from the 2006 through 2009 Medical Expenditure Panel Survey and the National Vital Statistics Reports and found that the total direct medical care expenditures for AA men were $447.6 billion of which $24.2 billion was excess medical care expenditures [20]. Thus, revealing the epidemiological racial disparity and public health impact regarding hypertension in AA [21,22].

In the Jackson Heart Study cohort of AAs, about 34% had masked hypertension which is higher than other population-based studies of other race/ethnicities [23]. Our group, and others, have previously reported that masked hypertension was associated with elevated levels of low-grade inflammation and diminished endothelial function in AA [24,25]. Essential hypertension is also associated with abnormal endothelium-mediated vasodilation due to decrease nitric oxide (NO) bioavailability in the endothelium [26,27]. Moreover, endothelium-dependent vasodilation is reduced in normotensive subjects with a familial history of hypertension compared to subjects without a familial history of essential hypertension [28]. When assessing vascular function, it was reported that healthy AA exhibited significantly reduced flow-mediated vasodilation (measure of endothelial mediated vascular compliance) compared to their CA counterparts [29,30].

2.1. Endothelial Dysfunction in AA Hypertension

Endothelial dysfunction consists of the endothelium existing in a chronic low-grade inflammatory state and is marked by an exacerbated immune and oxidative stress response during inflammation (reviewed by Cook M.D. [31]). AA have been reported to have greater production of vasoconstricting factors such as endothelin-1 (ET-1) [24] and circulating inflammatory endothelial microparticles [32] (measure of endothelial dysfunction). ET-1 contributes to the development of hypertension and consequent complications by causing systemic vasoconstriction and stimulating the renin-angiotensin system. Concerning endothelial microparticles (EMP), our group has reported circulating EMP burden is associated with hypertension status in multiple publications [32,33,34,35]. The higher prevalence of inflammatory-mediated endothelial dysfunction in this population explains, at least in part, the racial disparity in hypertension [36].

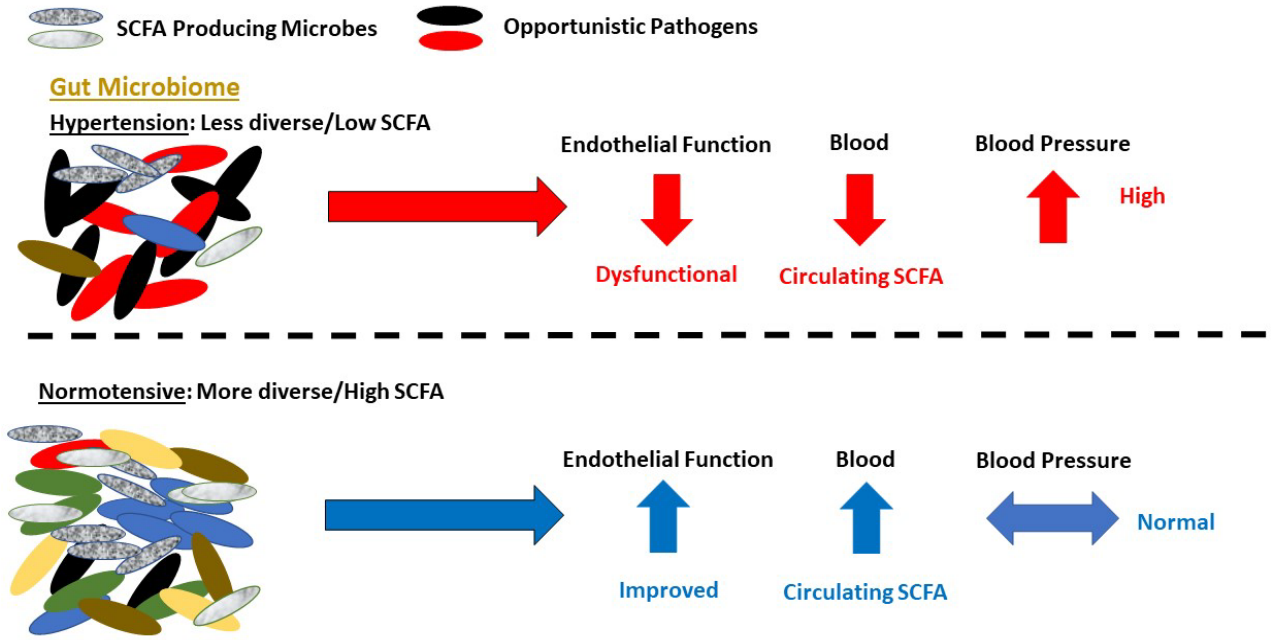

Figure 1. Relationship between Endothelial Dysfunction, Hypertension, and Gut SCFA production - Circulating SCFA

In vitro data from our lab, and others, supports the observed racial difference in endothelial dysfunction. AA endothelial cells exhibited greater basal oxidative stress and heightened inflammation compared to CA endothelial cells [15,37,38]. In Human Umbilical Vein Endothelial Cells (HUVEC) isolated from AA, we reported that AA cells exhibited higher basal expression of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and lower activity of superoxide dismutase (antioxidant capacity) which compromises NO bioavailability [38]. Furthermore, AA HUVECs produce higher basal levels of IL-6, an inflammatory cytokine, than CA HUVECs [37,38]. This state of heightened inflammation stimulates the endothelial cells to release EMP that further trigger endothelial dysfunction by disrupting production of NO and reducing endothelial NO synthase (eNOS) activity, promoting coagulation and inflammation [39]. We have previously shown that, in response to an inflammatory challenge (Tumor Necrosis Factor (TNF)-α stimulation), AA HUVECs had an increase in EMP generation by 89% compared to 8% in CA, highlighting the detrimental effect of inflammation on AA endothelial cells [37]. As endothelial cells are primary cells that make up blood vessels (specifically capillaries which feed our organs), heightened oxidative stress and inflammation initiates a cascade of dysfunctional activities in multiple tissues (i.e., blood vessels, heart, kidneys, intestines, and brain). A reduction in blood vessel function throughout the vascular tree promotes essential hypertension as carotid artery wall thickness and left ventricular mass correlate with reduced endothelium-dependent dilation [40].

Strategies to treat endothelial dysfunction and reduce blood pressure (BP) include drugs targeting the endothelium, such as angiotensin pathway inhibitors, adrenergic receptor blockers, and anti-inflammatory drugs. In a double-blind clinical trial that assessed low-grade inflammation and hemostasis (thrombogenic activity), Ekholm et al. [41] recently reported that both an angiotensin-converting enzyme (ACE) inhibitor and alpha-1 adrenergic receptor blocker reduced BP while reducing thrombin activity and having only minor effects on systemic inflammation. Unfortunately, some drug treatment strategies have been contraindicated in AA (ACE inhibitor therapy) as they lead to worse outcomes [42]. With the etiology of AA endothelial dysfunction rooted in basal inflammation, strategies that suppress endothelial inflammation need to be of greater focus. With this, Grimm et al. [43] performed an *in vitro* study to determine the impact of cyclooxygenase (COX)-1 and COX-2 inhibition in HUVEC (via aspirin and the non-steroid anti-inflammatory drug Celecoxib, respectively). COX is important because it has been shown to regulate prostacyclin (vasodilator) and thromboxane (potent vasoconstrictor) in the endothelium. The balance of prostacyclin/thromboxane regulates vascular homeostasis [44,45]. We reported that COX inhibition alone did not improve inflammatory stimulated reductions in eNOS production. However, COX-2 inhibition improved the prostacyclin/thromboxane ratio as well as a physiologically relevant *in vitro* exercise mimetic (laminar shear stress) in conjunction with COX-1 and COX-2 inhibition, increased eNOS expression and reduced the prostacyclin/thromboxane ratio. Our *in vivo* and *in vitro* data combined support the role of lifestyle interventions (e.g., exercise), and targeted drug therapies, in the maintenance of endothelial health. Lifestyle interventions not only benefit the endothelium but impact a very important tissue that has been noted to impact CV health, the gut microbiome.

3. Gut Microbiome, Endothelial Function, and Hypertension: Current Perspectives

The gut microbiome consists of microorganisms that have been shown to have a profound effect on host health. Gut microbes contribute to nearly every aspect of the human growth and development, predispose one to wellness or disease [46], and constantly adapt their composition according to the host and environment (e.g., age, diet, physiological stress (exercise), psychological stress, and disease) [47]. Positively balancing the gut microbial community has been shown to improve CVD risk by reducing cholesterol levels [48], reducing blood glucose and insulin resistance [49], regulating the renin-angiotensin system [50], and lowering BP [51,52].

Gut dysbiosis is an unhealthy and poorly diverse gut microbial profile which is linked to hypertension [53,54], and other prevalent health disparities in AA [55,56]. Genetic programming [57], dietary habits [58,59], environmental stressors [60], and sedentary behavior (e.g., less than 150 minutes of moderate exercise per week) all have a role in the promotion of gut dysbiosis and poorer cardiovascular health [61] in AA. The response of the gut microbes to environment is key to promoting host health. For instance, a diet deficient in fiber promotes an imbalance in gut microbial species that can significantly impact intestinal barrier function and colonic inflammation as microbes' resort to metabolizing colonic mucus as a source of energy. This phenomenon increases intestinal permeability through the breakdown of this barrier and pathogenic microbes and promotes gut inflammation [62]. Gut inflammation is associated with reduced gut SCFA production, poor vascular function, and higher BP [63].

Previous studies have investigated the association of gut flora on the development or control of hypertension when comparing non-hypertensive (control), pre-hypertensive (SBP 120 – 139 mmHg), and hypertensive subjects (SBP ≥140 mmHg). Li et al. [64] reported that control subjects exhibited greater fecal microbial diversity and richness of SCFA producing gut flora comprising of Faecalibacterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, and Butyrivibri. Meanwhile, pre-hypertensive and hypertensive subjects had an underrepresentation of the microbes present in healthy controls and an overrepresentation of Prevotella and Klebsiella. Some species of the genus' Prevotella and Klebsiella are opportunistic pathogens associated with infection, gut inflammation, and antibiotic resistance [65,66]. Individuals with pre-hypertension and hypertension had significantly lower levels of endogenous 3,4,5-tri-methoxycinnamic acid, among other compounds [64]. 3,4,5-Trimethoxycinnamic acid is of particular interest as it has been shown to have anti-inflammatory properties by suppressing the

expression of vascular endothelial cell adhesion molecules [67]. This compound naturally occurs and has been shown to be metabolized and degraded by gut microbes [68] which suggests that gut dysbiosis associated with elevated BP impacts circulating mediators of vascular health.

3.1. Beneficial Metabolites of Gut Microbial Health

SCFA's are the main product of gut microbial fermentation of dietary non-digestible carbohydrates. The majority of SCFA's consist of products ranging from 1-5 carbon (C) molecules and include acetate (2C), propionate (3C), and butyrate (4C). These molecules impact physiological and cellular processes in the gut and systemically. SCFA are absorbed in the small and large intestines, processed by the liver, and released into the systemic circulation if they are not immediately metabolized in the colon. Morrison and Preston [69] provide an excellent review of SCFA and their impact on human metabolism and Pevsner-Fischer et al. [70] report the potential role of the microbiome and BP interactions.

SCFA have anti-inflammatory properties throughout the body. One of the most potent SCFA, butyrate, is important in colon health as it is a significant source of fuel for colonic epithelial cells (colonocytes), regulates cell differentiation, and prevents colon cancer [71]. In a small study including AA, Hispanic, and CA individuals, Hester *et al*. [55] reported that AA had significantly lower levels of fecal butyrate, acetate, and total fecal SCFA that may be related to AA increased risk and incidence of colon cancer. Further, another study reported that lower SCFA gut microbes were significantly related to glucose tolerance and vitamin deficiency in AA [56]. O'Keefe *et al.* [72] reported lower SCFA in AA compared to native Africans. These findings distinguish a link between gut dysbiosis and chronic disorders in AA.

SCFAs produced in the gut have been shown to influence BP [73] and significantly improve endothelial inflammation [74]. Butyrate, a SCFA, is of interest as it has anti-inflammatory and anti-atherogenic properties in EC [74]. Indeed, intestinal cells are the largest consumers of butyrate produced in the gut. However, Van der Beek et al. [75] has shown that intestines release butyrate into the circulation and the liver facilitates measurable amounts in the blood, likely directly proportional to the amount produced in the gut.

A practical intervention by Wilck et al. [76] reported that increased salt intake elicited a depletion in Lactobacillus species and was associated with an increase in gut pro-inflammatory immune cell expansion (T-helper 17) with a concomitant increase in BP in animals and humans. Probiotic strains, such as Lactobacillus species, produce SCFA [77]. Lactobacillus, along with Bifidobactera species, are the majority of most probiotic supplements offered. Their relative abundance, partly due to their role in producing SCFA, are becoming an important marker for gut microbial health.

3.2. Interactions between Vascular Health, the Gut Microbiome, and Exercise

Exercise, a powerful lifestyle modification that impacts vascular health, also influences gut microbial characteristics that promote health in animals [78] and humans [79,80]. Concerning vascular health, Brown et al. [81] discussed the rationale for race dependent exercise-induced changes in endothelial function. Babbitt et al. [32] reported that aerobic exercise training improved endothelial function while reducing circulating inflammatory markers and EMP in AA with hypertension. Increased shear stress on the vascular endothelium (e.g., increased blood flow through the large and small resistance vessels) is a well-documented mechanism associated with improved endothelial function. Additionally, the anti-inflammatory effects of exercise have been documented and further improve vascular health and reduce disease burden [82]. However, recent discoveries suggest a role for exercise-induced changes in gut microbial characteristics for improvements in endothelial function and inflammatory burden.

Table 1. Short Summary of Microbes Currently Associated with Microbial Dysbiosis and Human Hypertension

Study/[Reference]	Highlighted Microbes	Direction	Function(s)
	Phylum		
Yang [53]; Pevsner-Fischer [69];	*Firmicutes*	↑	Acetate, Propionate, Butyrate producers
	Bacteroidetes	↓	Butyrate producers
	Firmicutes/Bacteroidetes ratio	↑	*Greater* in Hypertension
	Proteobacteria	↑	Opportunistic Pathogens
	Genus		
Yang [53]; Yan [54]; Santisteban [63]; Li [64]; Podschun [65]; Ley [66]; Pevsner-Fischer [70]; Wong [71]	*Klebsiella*	↑	Opportunistic Pathogen*
	Key Species: *K. pneumoniae*		
	Prevotella	↑	Opportunistic Pathogen*
	Clostridium	↑	Opportunistic Pathogen*
	Key Species*: C. difficile*		
	Streptococcus	↑	Opportunistic Pathogen*
	Faecalibacterium	↓	Anti-inflammatory microbes
	Key Species: *F. prausnitzii*		Butyrate Producer
	Roseburia	↓	Anti-inflammatory microbes
	Key Species: *R. intestinalis*		Butyrate Producer

Direction: Increased in Hypertensive gut (↑); Decreased in Hypertensive gut (↓)
Key Species: Most notible species and function
* Associated with Inflammatory Bowel Disease.

Mailing et al. [80] thoroughly reviewed the currently known associations of gut dysbiosis with disease (i.e., colorectal cancer, inflammatory bowel disease, obesity and metabolic disease, and mental health and cognition) and the influence of exercise on the gut microbiome structure and function. In humans, exercise impacts the gut microbiome structure (e.g., increasing diversity and abundance of species) and function (i.e., increasing metabolic capacity for macronutrient turnover, increasing SCFA producing microbes and capacity to generate SCFA). Currently, most studies have been cross-sectional analyses in Athletic and active populations and very few assess or control for dietary intake [80]. In a 6-week (3 day/week; 30-60 min/day) exercise intervention of college-aged lean and obese subjects that controlled for dietary intake before fecal sample collection, we reported that exercise significantly increased the abundance of SCFA producing microbes, SCFA producing capacity (via butyryl-CoA: acetate CoA-transferase (BCoAT) and methylmalonyl-CoA decarboxylase (mmdA) concentrations), and SCFA concentrations in fecal samples [79]. BCoAT and mmdA are two pathways that contribute to the production of butyrate and propionate, respectively. After a post-intervention 6-week wash-out period where participants performed no exercise, the gut microbiome adaptations were lost. Increasing the capacity of the gut to produce anti-inflammatory metabolites (via exercise), such as butyrate, adds another potential mechanism by which exercise may improve CV health risk factors outlined previously in this review. Future studies are needed to assess these associations to identify specific species associated with inflammation and BP specifically in AA.

3.3. Medication and the Gut Microbiome

Medications prescribed for the management of BP target multiple pathways related to the perceived root causes of high BP which include endothelial dysfunction, vascular smooth muscle function, sympathetic nervous system blockers, and enzyme inhibitors. Wilson and Nicholson [83] reviewed the current work that outlines the relationship between the gut microbiome in the metabolism, toxicity, and biotransformation of drugs into their active forms. As the gut microbial community establishes itself to acutely or chronically metabolize drugs, it also adapts to remove byproducts of those processes (i.e., detoxify). Contingent on those byproducts, the shift in gut microbial characteristics may promote an environment that has negative consequences on other biological processes related to macronutrient (eg., fat, glucose, and protein) and micronutrient (e.g., vitamin and mineral) metabolic pathways in tissues and organs [83]. These changes may also elicit unintended side-effects. For example, the non-response and side-effects to ACE inhibitors in AA are noted but it is not known whether gut microbiome has a role in promoting ACE inhibitor therapy ineffectiveness and side-effects in this population. Therefore, efforts to understand the role of chronic medication, such as those related to BP treatment, on gut microbial patterns related to health and disease is essential. With this, the future of drug-managed treatment of chronic disorders will likely include individualized treatment strategies that utilize gut microbial adaptations to drugs to outline their relationship to overall health of the gut microbiome and host.

4. Conclusion

With AA carrying the greatest burden of hypertension and hypertension associated morbidity and mortality, therapies that target the etiology of this CV dysfunction in AA are essential. Research implies that an anti-inflammatory gut microbial profile (i.e., greater SCFA production capacity) would parallel the reduction in systemic low-grade inflammation associated with basal endothelial dysfunction and hypertension status. Future studies should include assessment of interactions between hypertensive medication(s) that initiate drug-induced changes in gut microbial characteristics that may impact drug efficacy (non-response to certain treatments), side-effects, and additional health outcomes. Advocacy to promote the reduction in hypertension should include strategies that improve SCFA capacity in the gut (e.g., exercise and dietary fiber) to suppress low-grade systemic and endothelial inflammation to improve BP control and CV outcomes.

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