A multifaceted examination of hypertension within the African-American community

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Dedication

I would like to dedicate this work to God, family, and friends that have always held me to the highest standards, and have always expected the utmost from me. I would also like to thank you all for the steadfast faith and encouragement that you have showed to me; it has served to invigorate and drive me through to the finish even in my darkest hour. For my late grandmother, Rose, thank you for all the warmth and love over the years; I will miss you deeply.

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Introduction

Background

Hypertension (HTN) is a condition that is extremely prevalent throughout the United States of America. HTN, often known as “the silent killer” has long term implications and complications associated with coronary artery disease (CAD), congestive heart failure (CHF), cerebral vascular accident (CVA), myocardial infarction (MI), chronic kidney disease (CKD), and retinopathy (James et al., 2014). One-third of the adult population have HTN, which equates to about 80 million Americans roughly. African Americans have the highest prevalence of HTN of all ethnic groups in the country. In the United States, 45% of African-American males, aged 20 and older have HTN; while 46% of African American females, aged 20 and older have HTN (Mozaffarian et al., 2015). These raw numbers are staggering, especially considering that 33% of white males and 31% of white females are affected by HTN. The aforementioned statistics are staggering, and show that there is a discrepancy in how HTN effects different ethnic groups in the United States.

Due to the fact that African Americans are effected at more alarming rates compared to Caucasians, the treatment regimen must be approached differently because there is a physiologic difference. Research has been conducted to determine what pharmacotherapies have a more beneficial outcome for specific ethnic groups and groups that have different comorbidities. For example, the Eight Joint National Committee (JNC-8) conducted a study regarding the optimal treatment for African Americans. It was determined that African Americans affected by HTN should either be on a calcium channel blocker (CCB) or a thiazide diuretic (James et al., 2014). According to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), thiazide diuretics are better at preventing and improving cardiac outcomes

compared to angiotensin converting enzyme inhibitors (ACE-I) (Furburg et al., 2002). There was no difference pertaining to management of hypertension between CCBs and thiazide diuretics (Furburg et al., 2002). This specific study hypothesized that hypertensive patients treated with thiazide diuretics or CCBs would have better control of blood pressure more in line with the guidelines set forth by JNC-8 as well as less incidence of end organ damage (Abel et al., 2015). Three hundred and forty-five people were initially included in the study, but 21 were excluded leaving the final number of participants at 323. Four separate groups were created and participants were placed into a group based on if they were on a thiazide diuretic only, CCB only, thiazide diuretic and CCB, or another type of antihypertensive. Systolic and diastolic blood pressures were compared across the four groups and showed no statistically significant difference across the four groups (Abel et al., 2015). Diastolic blood pressures ranged from 80.0-82.3 mmHg. Systolic blood pressure ranged from 128.7-133.5 mmHg, both within optimal range. It was also demonstrated that there was no significant difference in target end organ damage across each group. Target end organ damage does not depend on the type of antihypertensive, but appears to depend on keeping the blood pressure within optimal range. As previously stated, JNC-8 guidelines do not recommend CCBs over thiazide diuretics, but a study conducted by the Jackson Heart Study concluded that hypertension was better treated with a thiazide diuretic compared to CCB (Harman et al., 2013). The efficacy of beta-blockers was compared against CCBs in a study that examined progressing CKD in African Americans. It determined that CCBs had greater efficacy in in the reduction of proteinuria, and slowed the rate of creatinine decline (Bakris et al., 1997).

Problem statement

African Americans are disproportionately affected by HTN and have greater complications as a result of HTN. In the United States, African Americans have a complex of history of disenfranchisement; which creates increased rates of poverty that can lead to low-levels of education and lack of access to healthcare. This unique history has also formed the foundation for dietary habits that are present today in African-Americans; some of which have had disastrous consequences leading to increased rates of HTN and the development of severe diseases as a result; leading to increased mortality. Issues such as access to healthcare, poverty, diet, and other factors have all been explored in great detail with regard to how they contribute to HTN. Although these factors are very important, little research has been done at the cellular level to access if there is an underlying pathophysiological issue that predisposes African Americans to HTN. This needs to be explored in greater detail. As previously illustrated, there has been research conducted about pharmacotherapy that can target African Americans, which is helpful, but little information is known regarding perceptions of HTN and attitudes about adherence in the African-American community

Statement of Purpose

Our aim was to identify underlying pathophysiological factors that cause African Americans to be disproportionately affected and have increased complications related to HTN. Our aim was also to examine the effect exercise has on biomarkers as well as to better understand perceptions about HTN in the African-American community that could lead to non-adherence. Understanding if a culturally and community-based approach can improve adherence and decrease BPs was also an aim of the study.

Research questions

1) Is there underlying pathology that causes increased prevalence of HTN in the African-American community?
2) Is exercise a viable option in reducing potentially elevated biomarkers that contribute to HTN in the African-American community?
3) Do cultural perceptions within the African-American community lead to decreased understanding about HTN?
4) Is a culturally and community-based approach an adequate method in increased adherence and decreasing BP in the African-American community?

Summary

Throughout the research, a literature review was performed in order to first understand the pathophysiology of potential complications that can occur humans. This was completed in order to establish potential complications that could be occurring in African Americans. The literature review examined several factors such as endothelial dysfunction and inflammatory markers to determine if there were any underlying physiological differences that cause a greater prevalence of HTN in African Americans in comparison to other races, mainly Caucasian. The literature review also examined how different exercise techniques elicited changes in biomarkers that have been implicated in causing a disruption in the normal physiology of African Americans. Further review was conducted to determine and understand perceptions regarding HTN and reasons for non-adherence in the African-American community. Finally, a review of

cultural and community-based approaches was examined to determine if there were changes in perceptions, adherence patterns, and BP in conjunction with completion of these interventions.

Methodology

Search words: Hypertension, blacks, African-Americans, Caucasian, qualitative, adherence, community-based, coronary artery calcification, physiology, biomarkers, endothelial dysfunction, oxidative stress, inflammation, poor, urban, nitric oxide synthase, interleukin-10, endothelial cells, genetic, laminar shear stress, resistance training, MMP-9, 8-isprostane dipping status, exercise, nocturnal blood pressure, health literacy, endothelial microparticles, cytokines, and vasodilation.

Databases

PubMed, ClinicalKey, Dynamed, UpToDate, AccessMedicine, and MEDLINE

Inclusion and exclusion criteria for articles

Articles selected for the scholarly project were articles containing information about biomarkers related to the underlying pathophysiology of endothelial dysfunction, inflammation, and other factors associated with increased prevalence in HTN among African Americans. Other articles selected contained information regarding perceptions of HTN within the African-American community, as well as different culturally and community-based interventions that improved adherence within these communities. Articles were carefully examined for validity, with English- language articles selected for inclusion. Articles selected ranged from 1974-2016. Peer reviewed and systematic reviewed- articles were first choice for the body of the literature,

however some review articles were included for background information. Articles that were-non English- language, before 1950, magazines, Wikipedia, not pertaining to the topic, or un-reputable sources were excluded from the literature review.

Literature Review

Pathophysiology in humans

There are many factors and systems that control the regulation of normal blood pressure. Disruption in any of these systems has ramifications that contribute to HTN. Prolonged activation of angiotensin type-1 receptor (AT1) stimulates oxidative stress by formation of a superoxide anion that reacts with the vasodilator nitric oxide synthase (NO) (Oparil, Zaman, & Calhoun, 2003). Through the reaction of NO and the superoxide anion, the activity of NO is reduced, and more vasoconstriction occurs (Rajagopalan et al., 1996). The reduction of nitric oxide not only reduces the amount of vasodilation, but it also causes increased platelet adhesion, aggregation, and suppression of migration and proliferation of smooth muscle cells (Oparil et al.). Dysfunctional release of NO has deleterious effects on the regulation of blood pressure, thrombosis, and atherosclerosis; all of which effect other systems and play an important role in the development and propagation of HTN (Cai &Harrison, 2000). Increased activation of mineralocorticoid receptors that produce aldosterone causes increased interstitial, intra, and perivascular fibrosis; which is thought to contribute to an aspect of HTN (Oparil et al.). An increase in either cardiac output (CO) or peripheral vascular resistance (PVR) can cause an increase in the mean arterial pressure (MAP) (Mayet & Huges, 2003). It is noted that patients with longstanding HTN have an increase PVR in renal, splanchnic, skeletal, coronary, and pulmonary vascular territories. Most often in younger adults (18-40) with elevated blood pressure, PVR is normal and elevated blood pressure is attributed to an alteration in some aspect of cardiac output such as increase heart rate (HR) (Mayet & Huges). A prospective study illustrated that an issue with CO usually occurs in younger patients, and after about 10 years it shifts to that of a problem with PVR (Lung-Johansen, 1994). Structural changes occur in HTN.

When PVR increases, the load on the wall is increased further causing an increase in wall tension (Mayet & Huges). Adaptive changes such as an increase in wall thickness occurs at the arterioles.

Remodeling also occurs at the large conduit arteries. These arteries lose elasticity and become stiff, causing an increase in pulse pressure (Oparil et al., 2003). Endothelial dysfunction not only occurs in response to oxidative stress, but also occurs as a process of aging. A reduction of NO occurs resulting in decreased vasodilation, more endothelial dysfunction, and increased thickness of large-conduit arteries; resulting in systolic hypertension (Oparil et al.). Through the administration of exogenous NO, increased arterial compliance has occurred, leading to reduced systolic blood pressure (Oparil et al.). When blood is ejected from the heart, a pressure wave is created from the left ventricle to the periphery. The speed largely depends on the compliance of the conduit arteries (Oparil et al.). The pulse wave velocity in adults is increased due to the loss of the elasticity of the arteries. Since the speed is much faster, than in younger individuals, the wave reaches the aortic valve before closure, causing elevated systolic blood pressure, pulse pressure, and afterload, all while decreasing diastolic filling time (Oparil et al.). The decrease in diastolic blood pressure can lead to poorer coronary perfusion.

As previously stated, the normal regulation of blood pressure is a delicate balance between the sympathetic and parasympathetic nervous system. It has been noted that in hypertensive patients there is an imbalance between the two systems; with more sympathetic activity occurring (Oparil et al., 2003). The increase in activity is mediated at the levels of the heart, kidneys and peripheral vessels; further leading to increased cardiac output, increased vascular resistance, and fluid retention (Mark, 1996). In patients with HTN, arterial baroreceptors are reset to a higher pressure, which can cause inhibition of sympathetic input,

which is also thought to be caused, centrally, by angiotensin II (Guo & Abboud, 1984). Peripherally, angiotensin II amplifies the effects of norepinephrine, which is released presynaptically (Abboud, 1974).

Endothelial dysfunction

As noted previously, African Americans are disproportionately affected by HTN; with incidence being higher as well as end-organ damage being a major issue. There is a role in genetic difference among African Americans that could partially contribute to the increased prevalence of HTN in this ethnic group. African Americans have dysfunctional endothelial mechanisms compared to Caucasians, as demonstrated by decreased flow in carotid mediated forearm artery vasodilation (Campia et al., 2002; Jones et al. 1999; Perregaux et al., 2000). African Americans also have an increased intima-media thickness (D'agostino, Burke, & O'Leary, 1996; Lange et al., 2002), as well as an increased level of endothelin-1; which is a potent vasoconstrictor released by the epithelium (Evans et al., 1996). Forearm blood flow in normotensive African Americans and Caucasians at rest and after mental stress was studied by Cardillo, Kilcoyne, Cannon, and Panza (1998). Stress-induced blood flow, which is mediated by endothelial cells, was lower in African Americans than in Caucasians. When NG-monomethyl-L-arginine, a NO synthesis inhibitor, was administered, stress-induced blood flow was significantly lower in the Caucasian group. When exogenous NO was administered, the vasodilator response was lower in African Americans than in Caucasians (Cardillo et al.). Isoproterenol, a beta-adrenergic agent that causes the release of endothelial NO, demonstrated decreased vasodilation in normotensive African Americans (Lang et al., 1995). Forearm microvascular function in response to nitroprusside, verapamil, and methacholine, all of which

stimulates NO release, was studied; showing that vasodilation in response to methacholine was decreased in the normotensive African-American group that was studied (Kahn et al., 2002). A contradictory study conducted by Stein, Lang, Nelson, Brown, and Wood (1997) demonstrated that there was a blunted rise in blood flow in normotensive African Americans. These contradictory results from the previous studies indicate that there is variation among African-Americans; indicating that not all African Americans have endothelial dysfunction (Patel, Velazquez, & Arora, 2008). Female gender is thought to have protective qualities in regards to endothelial function, but these qualities are lost among African-American females (Bransford, St Vrain, & Webb, 2001; Perregaux et al., 2000).

As previously stated, nitric oxide is an endogenous vasodilator that is important in inhibiting smooth muscle cell proliferation and migration, adhesion of leukocytes to endothelium and platelet aggregation (Kalinowski, Dobrucki, & Malinski, 2004). Vascular abnormalities can occur from oxidative stress when there is an increased production of reactive oxygen species (ROS), or when the antioxidant system is increasingly unable to remove ROS. African Americans have a lower bioavailability of endothelial NO than Caucasians. This is caused by excess superoxide production, which is known to cause endothelial dysfunction (Guzik, West, & Black, 2000). When there is an increase in superoxide production; it reacts with NO further reducing bioactivity of NO (Kalinowski et al.). As this process occurs, more peroxynitrite, which is an oxidizing agent is produced (Kalinowski et al.). Excess superoxide ion is also thought to be a result of nicotinamide adenine dinucleotide phosphate oxidase (NADPH), which causes uncoupling of endothelial nitric oxide synthase (eNOS) further producing excess superoxide ion (Kalinowski et al.). A combination of these processes are thought to be a cause for increased oxidative stress and endothelial dysfunction.

Campia et al. (2002) sought to investigate racial differences in the function of large-conduit vessels of normotensive African Americans and Caucasians. This was completed using flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) of the brachial artery. In FMD, the brachial artery was visualized, and baseline images and flow measurements were obtained. A blood pressure cuff was inflated and 15 seconds after deflation, blood flood was measured. Diameter measurements were performed between 60 and 90 seconds after the cuff was deflated. After 15 minutes of rest, new baseline images and flow measurements were obtained. After the aforementioned variables were obtained, nitroglycerin spray was administered sublingually and blood flow and images for arterial diameter were recorded after 3 minutes. FMD and NMD was significantly lower in African-American males and females when compared to their racial counter parts. In this experiment, NO-induced vasodilation came from increased endogenous release of NO caused by shear stress, or directly through the conversion of the nitroglycerine tablet into NO. Campia et al. proposed three mechanisms by which these decreased levels of FMD and NMD can occur. They suggested that there could be a generalized defect in the vasculature of African-Americans; caused by structural changes in smooth muscle cells of the arterial wall leading to decreased bioavailability of NO/NTG (Bassett, Duey, Walker, Howley, & Bond, 1992; Hinderliter et al., 1996). Similarly, there could be an overproduction of free-radicals; leading to decreased NO (Morrow et al., 1995). Campia et al. feel that the most likely explanation comes from a defect in the soluble guanylate cyclase/ cyclic guanosine monophosphate signaling system present in the vascular smooth muscle cell (VSMC); leading to impaired vasodilator function. As previously stated, NO has a role in inhibiting vascular proliferation, migration and platelet adhesion. The underlying pathology of VSMC proliferation has an underlying effect related to remodeling of the vessel and atherogenosis (Ross, 1999).

Previous *in vitro* studies indicate that cGMP and NO both have effects in inhibiting proliferation and migration of VSMC, suggesting that decreased function of this pathway has deleterious effects on regulation of smooth muscle dilation (Jeremy, Rowe, Emsley, & Newby, 1999). L-Name, an inhibitor of cGMP, was placed in presence of the human umbilical vein endothelial cells (HUVECs), and demonstrated that there was an increase in superoxide ion release, this release was greater in Caucasians compared to African Americans (Kalinowski et al., 2004).

Although Campia et al. (2002) suggest that the difference could be a defect in the cGMP signaling pathway, other studies suggest that more of the issues present could be due to the second mechanism mentioned by Campia et al. regarding the overproduction of free-radical ions that is reducing the bioavailability of NO. Kalinowski, Dobrucki, and Malinski (2004) sought to determine if African Americans have a predisposition to vascular compromise due to reduction in NO bioavailability. This was assessed through comparing levels of NO, superoxide ion, and peroxynitrite in HUVECs that was given by a group of African Americans and Caucasians. Results demonstrated that there was a reduction in biologically active NO and an increase in superoxide ion and peroxynitrite in the African-American endothelial cells compared to the Caucasian endothelial cells. The researchers believe that there is not a decrease in bioavailability of NO among blacks, but there is an increase in superoxide ion leading to increased consumption of NO. In the same study, NADPH-oxidase activity was studied in both groups. NADH stimulated more superoxide ions in both African Americans and Caucasians. NADH/NADPH caused more production of superoxide ion in the HUVECs of African Americans compared to Caucasians (Kalinowski et al., 2004). NADPH inhibitors such as apocynin and S17834 both caused a reduction of superoxide ion in both groups. HUVECs were also treated with oxypurinol, meclofenamate, or rotenone; the group treated with meclofenamate was the only group that

decreased the release of superoxide ion in both racial groups. Among the 3 inhibitors, there was still a significant difference in NO, superoxide ion, and peroxynitrite levels, which were more elevated in the HUVECs of African Americans compared to Caucasians. It is thought to act on the xanthine oxidase pathway, which is important in decreasing oxidative stress (Kalinowski et al.). Acetylcholine has effects on muscarinic receptors that cause vasodilation. When muscarinic receptors are stimulated, the release of NO is further stimulated by the endothelium. It was also been demonstrated that African Americans have a decreased vasodilator response to acetylcholine, and have reduced response to NO-independent stimuli (Cardillo et al., 1999). As a result of NO bioavailability being lowered, there is a down- regulation of the downstream target NO, the soluble guanylyl cyclase, which could possibly explain the reduced response to NO-independent stimuli (Mollnau et al., 2002). Similarly, Feairheller et al. (2011) sought to test racial differences in oxidative stress levels *in vitro* and *in vivo*. Results showed that there was no difference in plasma NO levels in African-American and Caucasian adults, but the HUVECs of African Americans had higher levels of NO compared with the Caucasian group. *In vitro* expression of NO was further assessed by testing eNOS and inducible nitric oxide synthase (iNOS); which is activated by pro-inflammatory cytokines, and other markers of inflammation. The HUVECs of African Americans elicited a significantly greater amount of eNOS and iNOS, both of which cause the release of excess NO; creating more free radical damage. NADPH oxidase expression along with subunit p47phox and isoforms NOX2 and NOX4 was also assessed in the same study, and results demonstrated that the HUVECs of African Americans demonstrated greater expression of the subunit and both isoforms; another potential cause of free radical damage in African Americans. It was previously reported that NOX2 and NOX4 isoforms

are directly responsible for increased NADPH-derived oxidative stress and free radical production (Ago et al., 2004; Van Buul, Fernandez-Borja, Anthony, & Hordiik, 2005).

Free radical formation as a part of the underlying pathology in the developmental changes of endothelium has been examined exhaustively, but equally as important is the contribution of antioxidant activity on limiting the damage inflicted by free radicals on the endothelial vessels, especially in African Americans. Superoxide dismutase (SOD) is an important antioxidant that breaks down superoxide ions into either oxygen or hydrogen peroxide (Hayyan, Hashim, & AlNashef, 2016). Total antioxidant capacity is a measure of the sum or cumulative effect of all antioxidant activity that is present in the body (Nagy et al., 2006). Protein carbonyl (PC) formation occurs on side chains of proteins as a result of oxidative stress and free radical production (Dalle-Donne, Rossi, Guistarini, Milzani, & Colombo, 2002). Feairheller et al (2011) demonstrated that African Americans had higher plasma levels of SOD activity in comparison with Caucasians. In the evaluation of HUVECs, there was lower SOD activity in the HUVECs belonging to the African Americans compared to the Caucasians. Increased oxidative stress is associated with increased antioxidant activity in order to counteract superoxide ion production. SOD exist in three isoforms: SOD1, SOD2, SOD3. In humans, there are lower levels of SOD3 in the tissues, but SOD3 accounts for half of SOD activity in circulation. This result could have caused the discrepancy in increased SOD in the plasma of African Americans in contrast to the HUVECs. This was invested further by examining the isoforms, SOD1 and SOD2; both of which showed decreased activity and protein expression (Feairheller et al., 2011). This demonstrates decreased antioxidant activity, which leads to a disruption of the balance between free radicals and antioxidants. Brown, Feairheller, Thakkar, Veerabhadrappa, and Park (2011) demonstrated that basal SOD activity levels were lesser in

African-American HUVECs compared with those of Caucasians. In response to the cytokine, tumor necrosis factor-alpha (TNF-alpha), there was a 79 % increase in SOD activity compared in African Americans compared to a 50% increase in Caucasians. This demonstrates elevated oxidative stress in response to cytokine stimulation, which will be discussed in greater detail in the section about inflammation.

Inflammation

Different inflammatory markers and activation of the inflammatory cascade has been known to contribute to the pathogenesis of HTN. Tumor necrosis factor-alpha (TNF-alpha), is a pro-inflammatory cytokine that has been implicated in the development of different cardiac conditions (Zhao, Chen, Yao, & Chen, 2005). It has pro-coagulatory effects on endothelial cells (Pober & Cotran, 1990). Many events contribute to the activation of TNF-alpha, which is the gateway for many other pathways that can have deleterious effects. TNF-alpha expression can be activated by the deposition of low-density lipoprotein cholesterol on endothelial cells, macrophages, smooth muscle cells, and different types of leukocytes (Gourin &Shackford, 1997; Napoli et al., 1996; Niemann-Jansson et al., 2000). It also has demonstrated the ability to activate several secondary messenger systems in endothelial cells, including the ceramide signaling system, which has been shown to increase endothelial superoxide ion (Madge & Pober, 2001; Zhang, Zou, & Li, 2001). Ceramide is important because of the affect it has on the upstream activation of the mitogen-activated protein kinase (MAPK) family (Mattias, Pena, & Kolesnick, 1998). Previously, TNF-alpha has shown the capacity to reduce the bioavailability of NO in cultured endothelial cells (Kim, Gallis, & Corson, 2001), as well as increasing the production of superoxide ion through the activation of multiple oxidative systems, including NADPH-oxidase;

which was discussed earlier (Li et al., 2002). Zhang et al. (2006) sought to test the ability of TNF-alpha to stimulate endothelial free radicals through activation of the ceramide-mediated MAPK signaling pathway. These mechanisms were examined through endothelial-dependent, NO-mediated vasodilation; that was further assessed with adenosine in the presence of pressurized porcine coronary arteries. Adenosine, by itself, was found to cause vasodilation in a dose-dependent manner. When TNF-alpha was added to adenosine, basal vascular tone was not altered, but the vasodilator response elicited by adenosine was significantly decreased. The inhibitory properties of TNF-alpha was similar to those elicited by a NO synthase inhibitor (Zhang et al., 2006). Vessels that were treated with TNF-alpha were introduced to desipramine, a sphingomylenase inhibitor, and DMAP, a ceramide-activated protein kinase inhibitor. Both of these agents did not alter basal tone, but increased the vasodilation elicited by adenosine that was previously attenuated. In normal vessels, DMAP had no actions on resting tone response or vasodilation in the presence of adenosine, indicating that the effects of DMAP worked on restoring vasodilation that was related to the presence of TNF-alpha. Three aspects of the MAPK signaling cascade (p38 kinase, ERK, JNK) were assessed in relation to how this pathway interacted and contributed to TNF-alpha-induced impairment of adenosine response. JNK inhibitors, SP600125 or dicumarol, were added to vessels and treated with TNF-alpha. ERK inhibitor PD98059 was added as well as p38 inhibitor SB203580 to TNF-alpha treated vessels. The ERK and p38 inhibitor showed no response in altering vasodilation to adenosine, but the two JNK inhibitors increased the vasodilation response to adenosine. Normal vessels only treated with JNK inhibitors showed no response in altered resting tone or vasodilation, indicating that the JNK inhibitors work on TNF-mediated effects of reduced vasodilation in response to adenosine. To further assess the JNK pathway, immunostaining with anti-phospho-JNK was

completed and showed that in the vessels treated with TNF-alpha, there was a significantly increased fluorescent intensity of phosphorylated-JNK. The effects elicited by TNF-alpha on pathways separate from NO-dependent pathway was also examined. There were no changes in vasodilation in vessels that exhibited vasodilation that was dependent on cytochrome-P450 monooxygenase-mediated agonist bradykinin, when the vessels were pre-treated with TNF-alpha. Adenosine causes vasodilation by activating smooth muscle ATP potassium channels. The affect elicited by TNF-alpha on this channel in the presence of ATP potassium channel opener, pinacidil, was evaluated, and demonstrated no effect on vasodilation. The role of TNF-alpha and superoxide ion production was also examined. The vessel wall under dyhydroethidium oxidative florescent staining demonstrated minor levels of superoxide ion in the vessel wall. TNF-alpha was administered, and showed that there was increased fluorescent signaling in the endothelial and smooth muscle layers; revealing increased levels of superoxide ion. The aforementioned results reveal that TNF-alpha causes endothelial dysfunction through stimulation of the ceramide/JNK/MAPK signal pathway, leading to increased levels of superoxide ion. The results also indicate that TNF-alpha has specificity for endothelial-dependent NO production because there was no effects seen on vasodilation when independent pathways were assessed (Zhang et al., 2006).

It has also been previously demonstrated that TNF-alpha has the ability to stimulate expression of adhesion molecules, tissue factor, interleukin-1 (IL-1), interleukin-8(IL-8), and endothelin-1 (ET-1) (Hummel et al., 2001; Mark, Trickler, & Miller, 2001). ET-1 and NO play a vital role in the homeostasis of endothelial function; as NO bioavailability is decreased, ET-1 has the ability to promote vasoconstriction. ET-1 has an important role in the underlying pathology of hypertension, and its actions are present on the vascular smooth muscle cells, the heart,

coronary vascular smooth muscle cells, the kidneys, and renal mesangial cells (Patel, Velazquez, & Arora, 2008). ET-1 causes vasoconstriction of the kidneys as well as the stimulation of ACE, the RAS, and aldosterone (Patel, Velazquez, & Arora, 2008). Zhao, Chen, Yao, and Chen (2005) sought to examine the effect of TNF-alpha on IL-8 and ET-1 expression in human dermal microvascular endothelial cells (HMECs). The HMECs were treated at dosages of 50, 100, 200, and 400 U/ml for 4 hours. TNF-alpha at each of the previous dosages significantly increased IL-8 mRNA expression by 206%, 252%, 211%, and 158 & respectively (Zhao et al.). HMECs were also evaluated for the effect of TNF-alpha administration on mRNA ET-1 levels, and were treated with dosages of TNF-alpha at 0, 50,100, and 200 U/ml for 4 hours. At the dosages of 50, 100, and 200 there was a significantly increased expression of the ratios of ET-1 and GAPDH mRNA densities of 71%, 82%, and 66% respectively(Zhao et al.). IL-8 is an important chemokine, and is important in the migration of T-cells (Xu et al., 1995). The results of this study indicates that TNF-alpha directly contributes to an increase in IL-8 activity, which has also been shown to be correlated with overproduction of ROS and activation of other transcription factors which have deleterious effects on the vasculature (Yamagishi, Inagaki, Nakamura, & Imaizumi, 2004; Zhao, Stavchansky, & Bowdem, 2003).

Now that the negative role of TNF-alpha has been established, and the disastrous effects on the cells have been demonstrated, it is important to understand how this affects different racial populations, mainly African Americans and Caucasians. Upon the activation of pro-inflammatory cytokines and oxidative stress, endothelial microparticles (EMP) are released from endothelial cells (Combes, et al., 1999). EMP is a biomarker that is elevated in states of endothelial damage and coronary artery disease (Werner, Wassmann, Ahlers, Kosiol, & Nickenig, 2006). EMPs express different surface markers such as CD31, which is a platelet

endothelial cell adhesion molecule that is increased in injury and apoptosis (Feng et al., 2010). When TNF-alpha binds to receptors on endothelial cells, there is increased expression of IL-6 downstream, causing increased aggregation, adhesion, and apoptosis (Brown et al., 2011). Brown et al. sought to observe EMP responses to TNF-alpha in the HUVECs of African Americans and Caucasians. Basal IL-6 concentrations were 2x higher in African Americans when compared to the Caucasian group. Further testing was completed to evaluate if there was a difference in protein expression of IL-6 in African-Americans, and it was also demonstrated that protein expression of IL-6 was significantly higher in African Americans as well. When TNF-alpha was stimulated, there was an increase in in IL-6 in both groups, but there was no significant difference. IL-6 is an important pro-inflammatory cytokine that can increase fibrinogen, PAI-1, and CRP (Ridker, Rifai, Stampfer, & Hennekens, 2000). Previously it has been shown that African Americans have increased systemic inflammation when evaluated by several inflammatory markers (Lampert, Ickovics, & Horwitz, 2005) An increased stress response leading to more inflammation even at basal levels leads to increased production of cytokines, stress, inflammation, and apoptosis; all of which can cause vascular dysfunction and lead to HTN (Brown et al.).

Electrolyte regulation

Blood pressure is heavily dependent on the ratio of sodium excretion to potassium excretion, according to the international cooperative INTERSALT study (Stamler et al., 1991). There tends a differences in electrolyte regulation in Caucasian populations when compared to African-American populations; with results showing that African Americans accumulate more sodium with increasing sodium intake when compared to Caucasians (Brier & Luft, 1994). Aviv,

Hollenberg, and Weder (2004) developed a model to explain the discrepancy, and opined that there is increased activity of sodium, potassium, and 2-choloride at the thick ascending limb at the loop of Henle, which causes retention of sodium and water, and decreased potassium excretion. There is also an increase in glomerular capillary hydraulic pressure, causing hyper-filtration of the glomeruli, which causes increased damage to the nephron, potentially causing HTN. This leads to increased colloid osmotic pressure and greater reabsorption at the proximal convoluted tubule. Normotensive and hypertensive African Americans are more salt sensitive when compared to Caucasians (Clark, 1999; Calhoun & Oparil, 1995). Salt-sensitivity is when there is an increased elevation of blood pressure in response to the consumption of salt. African Americans also demonstrated greater falls in blood pressure while undergoing sodium restriction, potentially due to a decrease in the RAA system (He Feng, Markandu, Sagnella, & MacGregor, 1998). African Americans have a diet that is low in potassium, so when this was experimentally duplicated; salt loading caused a mean increase in blood pressure in African Americans. Normotensive African Americans exhibited salt sensitivity; while normotensive Caucasians did not exhibit the same characteristics (Morris, Sebastian, Forman, Tanaka, & Schmidlin, 1999). In the same study when dietary potassium intake was increased to normal levels, salt-sensitivity in normotensive African Americans was mitigated; demonstrating that dietary potassium can have a role in potentially decreasing blood pressure. Dietary potassium has also demonstrated positive results in regards to reversing adrenergic –mediated vasopressor response to stress (Sudhir et al., 1997). It has also been shown that 65 mmol/day of dietary potassium caused a decrease in blood pressure in 32 African-American women that had mild to moderate HTN (Matlou et al., 1986). Elevated salt consumption in African Americans with HTN has also shown decreased levels of plasma nitrate (Campese et al., 1996). ADMA is thought to have a competitive inhibitory effect

on NO. ADMA also causes retention of SALT (Kielstein et al., 2004). African Americans are thought to have higher levels of ADMA than Caucasians (Juonala et al., 2007). In a previous study by Fukiwara et al. (2000) salt loading caused decreased plasma NO, which was reversed after restriction of salt. In contrast, ADMA levels were increased after salt loading and reversed after salt restriction. Endothelium-derived hyperpolarizing factor (EDHF) is another mechanism that causes relaxation of the vessels. NO and EDHF have similar effects of vasodilation, but NO inhibits EDHF. During periods of dysfunction of NO, EDHF is released to cause vasodilation (Bauersachs et al., 1996). EDHF prompts an increase in endothelial intracellular calcium, further propagating opening of two distinct types of potassium channels. Endothelial cells are hyperpolarized which is further transmitted to the smooth muscle cells (Haddy, Vanhoutte, & Feletou, 2006). Potassium is important for the maintenance and functioning of this system. When there are decreased levels of dietary potassium, the system fails to function and vasodilation cannot occur. In a Chinese population, supplementation of potassium has blocked effects of a high-salt diet and ADMA levels (Fang, Mu, He, Wang, &Liu, 2006).

Obesity

There is a greater prevalence of obesity in African-American women when compared to Caucasian women (Kumanyika, 1994). This increased prevalence in obesity causes more comorbidity-related complications among African-American women as well (Dawson, 1985). African-American women also lose weight at a slower rate compared to Caucasian women due to decreased lipolytic rates. There is a higher density of beta-adrenergic receptors in the visceral aspect of adipose tissue; further propagating the activation of adenosine, which causes the suppression of lipolysis (Barakat, Davis, Lang, Mustafa, & McConnaughey, 2006;

McConnaughey et al., 2004). Decreased levels of adiponectin is associated with endothelial dysfunction (Tan et al., 2004). African-American children have lower levels of adiponectin when compared to Caucasian children. This may occur due to increased acute insulin-sensitivity among African-American children (Bush, Darnell, Oster, Goran, & Gower, 2005). African-American boys have elevated levels of androgens, which also lowers levels of adiponectin. This combined with African-American boys entering puberty earlier than Caucasian boys contributes to lower adiponectin levels among African-American boys and potential early endothelial dysfunction (Nishizawa et al., 2002).

The role of exercise

The role of exercise in preventing and improving the cardiovascular disease profile in patients that are at risk for or already have cardiac disease has been examined in great detail. It is widely thought that lifestyle modifications such as exercise is an important non-pharmacologic approach that will decrease the risk for poor cardiovascular outcomes. It is important to examine the role that exercise plays on endothelial dysfunction and other inflammatory-marker abnormalities that are prevalent in African Americans. Babbitt et al. (2013) conducted research regarding the role of aerobic exercise training (AEXT) on potential adaptations and changes that can occur with maximum oxygen uptake (VO_2 max) and other inflammatory markers in African-Americans. In the beginning of the intervention, participants trained 3 times weekly for 20 minutes a session at 50% $VO_{2max.}$ Duration was increased by 5 minutes weekly until 40 % of $VO_{2max.}$ By week 8, the exercise duration and intensity was that of 40 minutes at 65% of $VO_{2max.}$ Heart rate (HR) was recorded every 10 minutes throughout the duration of the training. After completion of the 6 month training intervention, there was a significant increase in VO_{2max}

among the participants. There was a significant decrease in BMI, plasma triglycerides, and fasting blood glucose. There were no significant changes in total cholesterol, LDL cholesterol, HDL cholesterol, and mean systolic and diastolic blood pressure (Babbitt et al.). Ling et al. (2014) also conducted research regarding the role that AEXT exhibits on systolic and diastolic blood pressure in non-dippers. Non-dipping is defined as the absence nocturnal systolic and diastolic blood pressure decline, <10% of daytime value. There were no significant changes in 24 hour, daytime, or nighttime systolic and diastolic blood pressure after the 6 months of AEXT, but there were changes in the blood pressure of non-dippers. After the 6 month intervention, the systolic blood pressure showed significantly increased dipping levels. 33.3% of participants remained non-dippers, but had increased dipping. 44.4% of participants became systolic blood pressure non-dippers. There was a significant increase in VO_{2max} and eGFR following AEXT; fasting glucose levels and circulating levels of hs-CRP showed significant decrease. BMI, triglycerides, and total cholesterol was not significantly changed in this study. In another study FMD was assessed, demonstrating that following AEXT there was a 2.9 % increase in baseline brachial diameter; which was not significant. After 1-minute post-ischemia, the brachial artery diameter significantly increased to 5.6% after AEXT. There was also a 60%, significant increase in brachial artery diameter from baseline to post-ischemia after AEXT (Babbitt et al., 2013). After 12 weeks of aerobic exercise in patients with stable CAD, there was a significant increase in FMD% following the intervention (Cornelisson et al., 2014). Similar research indicated that after 8 weeks of AEXT, there was a significant improvement on FMD in patients with stable CAD (Luk et al., 2012). In patients with hypertension and pre-hypertension, there was a significant improvement in FMD following 12 weeks of swimming exercise (Nualnim et al., 2012).

Previously, different inflammatory markers, and the contribution made by them was discussed in great detail. Babbitt et al. (2013) also conducted research on the effects of AEXT on biomarkers CD62E+, EMP, and plasma IL-6 and IL-10. Results demonstrated that there was a 47.3% significant decrease in CD62E+, EMPs, and IL-6. Following AEXT, IL-10 increased by 4.9%, which was not significant. After a cardiac rehabilitation program conducted on women with CAD, AEXT showed a significant decrease on IL-6 levels (Beckie, Beckstead, & Groer, 2010). The deleterious effects of EMPs have previously been discussed, and reduction of CD62E+ and EMP through AEXT demonstrates that exercise plays a vital role in decreasing some of agents that contribute to HTN and other cardiac outcomes. IL-10 has previously been discussed for its role in preventing pro-inflammatory cascades from occurring. AEXT was conducted on patients' post-myocardial infarction with elevated inflammatory markers, and demonstrated that AEXT increased IL-10 (Ribeiro et al., 2012). Similarly in another patient population with CAD, AEXT increased plasma levels of IL-10 (Goldhammer et al., 2005). Cook et al. examined differences in markers of inflammation (TNF-alpha, IL-10), markers for vascular remodeling (sICAM, sVCAM, MMP-2, and MMP-9), and markers of oxidative stress (8-isoprostane) in young African-American and Caucasian men. These markers were assessed following resistance training (RT). Baseline circulating levels of sVCAM, TNF-alpha, IL-10, MMP-2, and 8-isoprostane were evaluated and demonstrated no significant difference between the two groups. In African Americans, 8-isoprostane was significantly reduced in comparison to the Caucasian group following RT. At baseline, levels of MMP-9 were reduced in African-American men, and significantly decreased after RT only in the African-American group. RT did not cause any alterations or modifications in IL-10, TNF-alpha, sICAM-1, sVCAM-1, or MMP-2 in either of the groups (Cook, Heffernan, Ranadive, Woods, & Fernhall, 2013). RT has

previously been shown to be effective in lowering central blood pressure (Heffernan et al., 2009). It has also shown to be effective in lowering C - reactive protein (CRP) in young African-American males (Heffernan et al., 2009). RT causes an increase in strength, and an inverse relationship between muscle strength and aortic stiffness and been shown (Fahs, Heffernan, Ranadive, Jae, & Fernhall, 2010). Coutinho, Turner, Mosely, and Kullo (2012) demonstrated that there is a difference in baseline MMPs that exists between African Americans and Caucasians. RT has previously shown capabilities in modulating MMP activity (Urso, Pierce, Alemany, Harman, & Nindl, 2009).

Perceptions of HTN and non-adherence

The increased prevalence of HTN among African Americans has previously been noted. In addition to this problem, there is increased issues with adherence to non-pharmacologic and pharmacologic interventions (Shaya et al., 2009). African Americans also have increased rates of HTN-associated mortality (Mozaffarian et al., 2015). There is potential association between non-adherence and poorer HTN-associated outcomes pertaining to mortality among African-Americans. A random survey of two primary care clinics in Ohio noted that Caucasians were 36% more likely to exercise compared to 17 % of African Americans (Wexler et al., 2008). Perceptions about HTN is suggested to be related to worse outcomes among African Americans (Fongwa et al., 2008; Gatti, Jacobson, Gazmararian, Schmotzer, & Kripalani, 2008). It was previously outlined that CCBs and thiazide diuretics were the pharmacotherapy of choice in African Americans, but many African Americans are prescribed medication that is less effective, leading to poor adherence to the medications (Johnson, 2008). Perceptions of HTN are also believed to be influenced by cultural beliefs about diet, friends and family, as well as other

lifestyle choices. Horowitz, Tuzzio, Rojas, Monteith, and Sisk (2004) found that although some African Americans believed that diet directly contributes to HTN, it was difficult to make the necessary lifestyle choices due to cultural expectations of using salt and other fatty foods. One-third of the focus groups believed that dietary modifications would not help in alleviating HTN, since many were already on a pharmacologic therapy. Other participants felt isolated and ostracized from the greater-community due to making dietary modifications. In one focus group, some of the participants noted the use of herbs, garlic and vinegar to control HTN. Horowitz, Tuzzio, Rojas, Monteith, & Sisk (2004); Heckler et al. (2008); Rose, Kim, Dennison, and Hill (2000); and Webb and Gonzalez (2006) found that some participants thought that anti-hypertensive medications were addictive. When asked about perceptions of HTN at an urban clinic, Fongwa et al. (2008) noted that participants referred to HTN as a headache or the heart working too hard. HTN, known as the silent killer, is also asymptomatic, and many African Americans might stop taking medication; while not feeling any symptoms (Petty et al, 2016). Due to the absence of active symptoms in many patients, there is lack of knowledge regarding the severity of the disease, and potential life-threatening consequences. Even in the presence of certain symptoms such as headache and fatigue, these symptoms are usually attributed to stress (Artinian, Washington, & Templin, 2001). Young et al. (2015) sought to explore the relationship between problems with adherence associated with mortality among a population of low-income African Americans. The relationship between different types of non-adherence to medication was also compared to access to healthcare and attitudes toward being treated. This study included 187 poor African Americans that had severely elevated HTN greater than 180/110 mmHg; with limited access to healthcare. Behaviors regarding adherence were asked and defined as: missing medications prior to admission, failure to refill prescriptions prior to running out of

medications, and typical pill taking behavior. Of the participants, the mean SBP and DBP was 201.9 mmHg and 122.3 mmHg respectively. One-third of the participants had used heroin, cocaine, or both prior to 2 weeks of admission, and over half were smokers. Over 33.3% were uninsured, over 72.7% had missed their medication prior to admission, 42.8 % reported missing a dose of medication within a week, and 33.3% reported not having medications refilled at least 3 times yearly, and of the participants, 19% reported complete adherence, with another 19% reporting complete non-adherence. Of the 187 participants, there were 89 reported deaths, a 47.6% mortality rate, throughout the duration of the research. CVD and ESRD were the two leading causes of death. One of the non-adherence criteria, missing medications at least once weekly was associated with double the likelihood of mortality, but missing medications prior to admission was not significantly related with increased risk of mortality. When surveyed about basic questions related to HTN, 27% answered fever than 80% of the questions correctly, 41% cited forgetting to take medication, 18% reported adverse effects, 15% thought the pills were ineffective, and 9% thought their regimen consisted of too many pills. Patients with increased severity of disease were more likely to take medications before admission, but severity was not associated with the tendency to run out of medications and missing medications throughout the week. A strong association between non-adherence to medication was seen in those with decreased access to healthcare, with the uninsured having been more likely to miss medications before admission or to have run out of medications. Increased knowledge about HTN and medications were strongly associated with adherence and regular pill taking behavior.

The Health Belief Model (HBM) notes that patients need to have a perceived susceptibility; meaning that regardless of being asymptomatic, adherence to medications is imperative. It also suggest that adherence to medications will increase when perceived severity;

the fact that HTN can lead to poor outcomes is understood. Petty et al. (2016) sought to understand perceptions of HTN in 29 African Americans that were all poor southerners without health insurance. Twenty-six participants noted that southern cuisine contributed to HTN. Pork, a popular Southern ingredient, was identified as one of the main antagonist leading to elevated blood pressures along with the use of a lot of salt. “High blood” is a phrase that was used to describe hypertension by one of the participants. Stress was also another identifiable cause of stress in a number of the participants. One of the participants lost his job, and noted this as the cause of his stress. “Unhealthy actions” such as drinking alcohol, not following God’s plans, and using illicit drugs was identified as another cause. One participant noted, “I didn’t focus on God and I was doing what the Devil wanted me to do.” Three participants noted running out of medication, and that life sometimes gets in the way of scheduling appointments for medication refills. “Not eating right, fat, gaining weight” was noted by one participant as a cause for HTN. Heart and kidney problems were identified by three other participants as contributing to their HTN. Although some participants new certain actions such as lack of exercise was connected to HTN, there was no connection between lack of exercise and obesity; demonstrating lack and gaps in knowledge among participants. Participants were also asked about ways to improve HTN. All participants acknowledged that a change needed to occur in eating habits such as reduced salt intake, but this concept was not fully understood. One participant stated, “I try to watch my salt intake, we use like sea salt.” Another participant noted, “I don’t really life salt. I use seasoned salt for flavor but I don’t like salt, period.” One male wanted to reduce pork intake, but still eats pork chops boiled with apple cider vinegar. These raw quotes taken from some of the participants indicate that there is a disconnect between clinicians and patients. It was noted that even though providers were providing information to patients, the patients did not

understand and found directions difficult to follow (Horowitz, Tuzzio, Rojas, Monteith, & Sisk, 2004). In the study conducted by Petty et al. many of the patients described wanting to adhere to medications, but issues with “life” and not being able to schedule appointments caused conflict. Females were prescribed more medications than males, but had less controlled HTN.

Petty et al. (2016) also demonstrated that cultural perceptions contribute greatly to ideals about HTN in African Americans. Traditions, family members, and friends contribute greatly to how African Americans perceive HTN. Due to the important contribution by the aforementioned factors, understanding and implementing interventions in African-American culture can be beneficial in increasing adherence. Throughout the centuries, African-American culture has relied heavily on storytelling (Victor et al., 2011). Previous research conducted by Houston et al. (2011) demonstrated that stories were effective in improving blood pressure control among African Americans. Stories have also demonstrated great value in the management of diabetes (Campbell, Dunt, Fitzgerald, & Gordon, 2015). A study was conducted by Bokhour et al. (2016) in order to show if African Americans respond more favorably to a DVD with didactic information about controlling hypertension compared to a videotaped DVD containing stories by African Americans about successfully controlling HTN. The stories-intervention DVD elicited a significantly greater emotional response than the control DVD. In participants with decreased literacy levels, there was a significantly increased emotional engagement by the stories-intervention DVD. There was also a significantly increased intention to use salt substitutes, become more physically active, remember to take BP medication, and talk openly with clinician in those patients that viewed the stories-intervention DVD. In contrast, the stories-intervention DVD elicited more mind wandering in patients with greater health literacy.

A culturally-based approach is an effective way for clinicians to connect with patients regarding the disease process and promote adherence to medications. In communities with poor access to healthcare, a community-based intervention may prove to be extremely beneficial. In lower-income areas with increased rates of crime, BP checks are less frequent due to issues with transportation, clinic waiting-times, and high-turnover of health care providers (Artinian, Washington, & Templin, 2001). One effective community-based approach has been the use of home BP telemonitoring, which is when hypertensive patients self-monitor at home, and transmit their results over the phone to server. The sever will then create reports; which are sent to health care providers. When feedback occurs, it allows for clinicians to provide feedback to the patients and intervene by giving recommendations on lifestyle modifications or proper use of medications. Artinian et al. (2001) sought to explore if participants in home BP telemonitoring program managed by nurses in addition to usual care or if participants in a community-based monitoring program also managed by nurses would have greater improvements with BP compared to participants that receive usual clinic-based care from baseline to 3 months. There were 26 participants in this study with over half (53.9%) reporting income levels below $9999. Participants could fulfill 1 of 3 of the following criteria: take 2 BPs 5 minutes apart, 3 times weekly in the morning, or 3 times weekly at a community center. There were to be 60 total BPs measured between a 10 week interval between week 1 and week 12. Participants who were in 100% compliance had all 60 BP measurements; in the current study there was a mean 67% and 89% compliance rates for the telemonitoring group and community group respectively. Results indicated participants in the telemonitoring and community-based groups had greater improvement in baseline to final BP when compared to the group that received usual clinic-based care. The home telemonitoring group had a baseline SBP and DBP of 148.8 mmHg and 90.2

mmHg respectively. Both of these dropped and improved to 124.1 mmHg and 75.58 mmHg respectively. The community-based group had a baseline SBP and DBP of 155.52 mmHg and 89.92 mmHg respectively. After 3 months, SBP and DBP both dropped to 142.3 mmHg and 78.25 mmHg respectively. The group receiving usual clinic-based care had a baseline SBP and DBP of 142.83 mmHg and 91.22 mmHg respectively; that remained relatively unchanged after the 3 months to 143.33 mmHg and 89.05 mmHg respectively. The results illustrated by both the home telemonitoring group and community-based group were statistically significant when compared to the usual clinic-based group. In another patient population with HTN in Boston, adherence rates were measured through implementation of a program to see if automated telemonitoring and counseling would lead to increased rates of adherence (Friedman et al., 1996). Participants were placed in either a group that received usual in-clinic care along with a computer-controlled telemonitoring symptom, or a group that received only usual clinic based care. The program lasted for 6 months and demonstrated there was a 17.7 % and 11.7 % increase in mean antihypertensive medication adherence score (measured by pill count) among the telemonitoring group and group that received usual care respectively. The telemonitoring group also demonstrated a mean decrease of 5.2 mmHg in DBP compared to 0.8 mmHg in the group that received usual care. Another study was conducted in a community containing people with HTN. The study sought to examine if tracking and outreach interventions such as: barrier reduction to care, assisting patients with locating providers, appointment reminder letters, and rescheduled appointments for every missed appointment, would provide greater adherence and build a stronger relationship within the community (Krieger, Collier, Song, & Martin, 1999). Participants demonstrated increased likelihood in follow-up appointments.

Discussion/Conclusion

The methodology, research design, sample sizes, and even purpose of these different studies were all different in nature, but they all sought to address the overarching issue of the complexities and severity of HTN in the African-American community. Each research study reviewed, contained a different piece of the puzzle pertaining the issue of HTN in the African-American community. In this literature review our aim was to coalesce each piece of this complex issue and construct a clearer picture of the issue of HTN in the African-American community. Each piece of research was able to give in-depth insight pertaining to the increased prevalence of HTN in African Americans compared to other communities, strategies for potentially reducing HTN in the African-American communities, and perceptions and attitudes contributing to non-adherence in these communities. The literature review demonstrated that African Americans have increased intima-media thickness, and anatomic abnormality contributing to increased prevalence of HTN in the African-American community. Underlying pathophysiological differences leading to endothelial dysfunction were present as well, such as decreased vasodilator response to NO. When agents that stimulated NO release were used, there was still a blunted response in NO release even in African-American patients without HTN, although this was in opposition to other research. As previously stated, this demonstrates that although endothelial dysfunction is present in some African Americans, it is not present in all African Americans. Part of the endothelial dysfunction occurring in African Americans is due to decreased levels of eNOS, but research demonstrates that there are increased levels of free radical damage, which causes endothelial dysfunction and reduction of NO. Antioxidant activity which serves to counteract oxidative stress and free radical activity, showed lower levels in African Americans as well. Several inflammatory markers and their signaling systems

demonstrated that African Americans have increased basal and protein levels of IL-6, an inflammatory marker, leading to proliferation, migration, and aggregation; causing leading further endothelial dysfunction, thus contributing to HTN. These increased inflammatory stress levels have a deleterious effect on African Americans. When both African Americans and Caucasians have increased sodium intake, African Americas accumulate more sodium due to physiologic differences in the kidneys. Similarly, in normotensive and hypertensive African Americans, both have elevated blood pressures in response to salt intake when compared with Caucasians. In terms of weight loss, African-American women lose weight at a slower weight compared to Caucasian women, contributing to HTN. In children, African Americans have lower levels of adiponectin; contributing to endothelial dysfunction. All of the aforementioned findings corroborates that there is underlying pathology present in some African Americans that lead to increased prevalence among the African-American population.

At the moment, as recommended by JNC-8, CCBs and thiazide diuretics are the pharmacotherapy interventions that should be started in African Americans, as they target specific physiological differences that are more effective in reducing HTN. In the literature review, non-pharmacological interventions were addressed, and showed promising outcomes in reversing some of the inflammatory markers that were mentioned in the aforementioned paragraph. AEXT demonstrated elevation in maximum oxygen uptake. Following AEXT, there was a significant improvement in brachial artery diameter. Swimming improved flow mediated dilation in patients that were hypertensive and pre-hypertensive. Inflammatory biomarkers CD62E+, EMP, and plasma IL-6 all demonstrated a significant decrease after AEXT. IL-10, which counteracts inflammation showed a decrease in IL-6, but it was not significant. RT showed reductions in vascular remodeling marker 8-isoprostane. These results demonstrate that

different types of exercise, is a viable option for decreasing inflammatory biomarkers that are associated with the increased prevalence of HTN in the African-American community.

Throughout this literature review another aim was to better understand cultural perceptions in the African-American community, and if this further contributes to decreased knowledge about HTN. There was a pervasive attitude among patients in different studies that there were symptoms associated with have HTN such as a headache. It was not frequently understood that HTN was insidious, and that unless treated, end organ damage or death could occur. If patients were not experiencing symptoms, non-adherence increased. Culture plays a huge role in the African-American community, and perceptions about HTN are heavily influenced by family and cultural practices. Many patients felt ostracized when having to change diet. Participants understood bad elements, of their diet, but did not exactly understand what to do next to make improvements, which can be seen as breakdown in communication between the clinician and the patient. Interviewing the participants demonstrated that many participants referred to cultural recommendations that have been handed down in order to treat HTN such as garlic or apple cider. Some participants understood there was a link between not exercising and HTN, but did not connect that exercise also helped obesity.

Reviewing the literature allowed us to better understand the contribution of African-American culture to lifestyle habits and potential efforts to change. Cultural considerations play a huge role in the Africa-American community, and understanding this allows for better options in implementing interventions that may work in increasing knowledge about HTN and increasing adherence rates. Cultural practices such as stories play a huge role in the African-American community. The literature demonstrated that participants that had low health literacy levels showed a significantly increased level of emotional engagement while watching a DVD that had

stories about HTN. Intention to become more physically active, remember to take BP medication, and talk openly with clinician significantly increased in patients that viewed the DVD with stories. Opening the line of communication with the clinician allows the clinician to greater connect and understand the needs of the patient. It demonstrates compassion and allows the patient to feel that the concerns expressed are being taken seriously; giving the patient more access. More access extends to the community, and several studies demonstrated that a community-based approach could also increase adherence in medication usage; leading to decreased blood pressures. Home telemonitoring demonstrated to be an important intervention allowing patients to report their daily blood pressures and receive feedback from nurses and other clinicians. This increased access and ultimately proved to be an effective intervention in decreasing blood pressure.

Research questions

1) Is there underlying pathology that causes increased prevalence of HTN in the African-American community?
2) Is exercise a viable option in reducing potentially elevated biomarkers that contribute to HTN in the African-American community?
3) Do cultural perceptions within the African-American community lead to decreased understanding about HTN?
4) Is a culturally and community-based approach an adequate manner in increased adherence and decreasing BP in the African-American community?

The literature reviewed indicates that there is underlying pathology that contributes to the increased prevalence of HTN in African Americans compared to Caucasians and other ethnic groups. The literature reviewed also indicates that different types of exercise are viable options

in reducing some of the biomarkers that contribute to the increased prevalence of HTN in African Americans. Cultural perceptions also contribute to decreased understanding in the HTN in the African-American community that can cause adverse outcomes. Finally, a culturally and community-based approach is adequate in changing perceptions, building trust, and increasing adherence in the African-American community.

Future research and limitations

Although recent guidelines published by JNC-8 mandate that the first-line treatments for African Americans are CCBs and thiazide type diuretics, future research needs to be conducted on new pharmacologic interventions that can address some of the underlying pathology in African-Americans. Future research should look to larger sample of African Americans from around the country and from the diaspora to address if some of the underlying pathology is specific to African Americans in the United States, or if vascular dysfunction is intrinsic to all people of African descent. In many of the articles reviewed, African Americans in lower socioeconomic standings were studied, but future research should expand to incorporate perceptions and adherence practices among African Americans of different socioeconomic status, to determine if there are any overarching beliefs that contribute to incorrect perceptions about HTN. Different forms of culturally and community-based approaches need to be investigated in greater detail, and a plan needs to be established about how to implement some of the ideas in different offices across different communities. Cost-effectiveness of different community-based approaches should be explored, calculated, and compared with the expenditures associated with end-stage organ damage. There were also some limitations present in some of the literature reviewed. In the study that examined differences in oxidative stress, it

was noted that there were no differences between races in human plasma NO (Feairhellar et al., 2011). One of the limitations to the aforementioned result is that participants were aged 18-25, without and cardiovascular risk factors for HTN. There were limitations regarding cells intubated with TNF-alpha. Cells were only intubated for 4 hours to avoid apoptosis, but in humans levels of inflammation could occur far longer. Brown et al. (2011) also noted not directly measuring levels of superoxide radical. Babbitt et al. (2013) noted limitations in size of sample population, and that presently there are no standardized methods for measuring microparticles. This means different investigators use different techniques to measure microparticles. Finally, women were the only participants, so results cannot be expanded to other sectors of different ethnic groups (Babbitt et al.). Ling et al. (2014) noted that there was no control group present for non-dippers. Replication of results is also difficult due to other daily factors that influence HTN. Petty et al. (2016) noted that medical records could not be located for three participants and that the sample size was at one-faith based clinic with poor African Americans. Young et al. (2015) noted limitations in self-reported adherence. Adherence was only measured at only one point, so changes in time could not be accounted for. The study only focuses on one specific population at one urban hospital, so results may not be applied to other communities and population groups

Relevance to the PA profession

Understanding the underlying pathophysiology of HTN is extremely important in the treatment of any at-risk population. Due to the increased prevalence in certain populations, knowing and understanding that there are pathophysiological differences present gives increased insight to clinicians and provides a start point for different pharmacological interventions. While the treatment aspect is extremely important, it is more important for clinicians to get a more

holistic understanding of the patient, because as evidenced via the literature review, simply prescribing medications for the patient is not going to solve the problems regarding knowledge and perceptions about HTN in not only African Americans, but other ethnic groups affected by certain diseases. Personalization of care is extremely important within each patient because it builds rapport, trust, and mutual understanding on both sides. When this is accomplished, patient's attitudes will be better understood and enriched, and adherence rates will be increased. For each clinician practicing in their own community, telemonitoring may not be a viable option. None of the options discussed throughout the literature review may be viable options due to availability or financial reasons, but the idea is for clinicians to get creative and implement their own systems for connecting with patients in order to build relationships, increase adherence rates, and reduce negative outcomes for not only HTN, but other chronic diseases.

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Abstract

Objective: Our aim was to examine and identify underlying pathophysiological biomarkers associated with the increased prevalence of HTN within the African-American community, understand the role of exercise on the biomarkers, understand if perceptions and attitudes within the African-American community contribute to decreased knowledge about HTN, and examine if a culturally and community-based intervention can increase adherence and decrease BP. **Methods:** Databases searched included: PubMed, ClinicalKey, Dynamed, UpToDate, AccessMedicine, and MEDLINE. **Results:** Original research and systematic review articles were reviewed and selected based on containing pathophysiological biomarkers, exercise trials, perceptions about HTN, and cultural and community-based interventions. Traditional review articles demonstrating background information were also selected. **Conclusion**: African Americans have underlying pathophysiology that contributes to HTN,AEXT decreased inflammatory biomarkers, perceptions lead to decreased knowledge about HTN, and a culturally, and community-based approach is effective in increasing adherence and decreasing BP. Future research should address implementation of effective interventions within the African-American community.

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