

Managing hypertension: relevant biomarkers and combating bioactive compounds

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ABSTRACT

Hypertension is one of the most common chronic diseases affecting many people of a higher age group. The standard definition that is offered to the general public has a minimum age of 18 years to be diagnosed with hypertension. Many studies have been conducted in the hopes of finding consistent data that provides information on the biomarkers of hypertension and effective forms of treatment. However, there is a tendency for skewed data due to the ineffectiveness of diagnosing hypertension, because of the reasons of variability in technique or even negligence. Interestingly, research has indicated that there are connections to certain biomarkers of hypertension, however the results have been deemed inconclusive. Moreover, the results provide promising data for future studies with an emphasis on biomarkers. The biomarkers that have been consistently brought to researchers' attention are: circulating C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), urinary albumin:creatinine ratio (UACR), and aldosterone:renin ratio (ARR). These four biomarkers have become the foundation of multiple hypertension studies, yet the only formal conclusion that could be drawn is that there is a wide range of variables that have some kind of influence on hypertension. More recently, treatment options for hypertension have increasingly become an emphasis of studies; and research has predicted that nutrition plays a key role in the managing of diseases. Furthermore, the role of bioactive compounds has gained traction in hypertension research, as it has been loosely correlated to managing specific biomarkers. Ultimately, these correlations to bioactive compounds like, antioxidants, would demonstrate that certain functional foods have the capacity to help treat hypertension. The modality is to find an alternative option for managing or treating hypertension through natural sources of food or food products fortified with ingredients to combat the known biomarkers. This is why the research of functional foods will provide hypertensive patients with an opportunity to affordably manage their chronic disease.

Keywords: hypertension, bioactive compounds, functional foods, vitamins

INTRODUCTION

Chronic diseases such as, hypertension, are very commonly diagnosed in patients that exceed a normal threshold for systolic and diastolic blood pressure. “The National Heart, Lung, and Blood Institute has classified hypertension for adults (aged 18 years or above) into four main categories. Normal blood pressure (BP) is defined as a systolic BP (SBP) of less than 120 mm Hg and a diastolic BP (DBP) of less than 80 mm Hg, while prehypertension has been defined as SBP of 120–139 mm Hg and DBP of 80–90 mm Hg. Those who are at the risk of stage one progression hypertension are defined as those with SBP of 140–159 mm Hg and DBP of 90–99 mm Hg, while stage two includes those with SBP of above 160 mm Hg and DBP above 100 mm Hg.” [1]. Diagnosing hypertension is difficult for several reasons—one example being, BP in hypertensive patients is often measured without technique [2-4]. Over the years, the intent of understanding the mechanisms of hypertension and the effectiveness of certain treatments has been the primary intent. Functional foods have recently become a topic that was introduced as a method for managing hypertension because of the curative properties of certain bioactive compounds. It is the macronutrients and micronutrients that are responsible for preventing, controlling, or treating hypertension through biological mechanisms [5]. Many researchers have shown an interest in bioactive compounds like: antioxidants, probiotics, vitamins, etc. to treat hypertension by means of manipulating biomarkers. The primary biomarkers that are consistently associated with hypertension from case to case are: CRP, PAI-1, ARR, and UACR. More obvious biomarkers and mechanisms that are affected include: total cholesterol levels, LDL concentration, and the most common, elevated blood pressure. Each of these biomarkers plays a pivotal role in the body’s overall function, as well as the healthiness of blood flow within the capillaries of the body. Granted, an overall unhealthy lifestyle is not limited to the diagnosis of hypertension. From an overall perspective, the lifestyle a patient leads may further put one at risk for such diagnosis. Due to genetics, environmental causes and prescription drug use, the general population may be affected by macro- and micronutrient deficiencies that lead to hypertension [5]. Connections are constantly being discovered between the role of nutrition and hypertension. The AHA recommends a diet rich in fruits and vegetables to be the most effective form of non-pharmacological therapy in hypertension [6-7]. This strategy will optimize the reduction of CVD (cardiovascular disease) in both men and women of all ages, as it is a general template that could be individualized to meet the preference of both genders and all ages [7]. Thus, the emphasis of research focused on the roles of bioactive compounds in relation to hypertension is acutely inherent.

Background of Hypertension

First and foremost, hypertension is classically defined as a blood pressure measurement exceeding a threshold of 120 mm Hg/80 mm Hg. Granted that is only just a microcosm of what hypertension actually is as a disease. A blood pressure reading of that level would certainly indicate that an individual would clinically have bouts with hypertension. Although, this definition does not provide any qualitative analysis of what is to be expected when an individual’s blood pressure is that high. Therefore, an examination of affected structures and mechanisms would surely provide better insight than quantitative data. Hypertension is said to have no known symptoms that could measure when an individual’s blood pressure is rising or increased. Given this information, the question becomes how can there be treatment for a disease if there are no symptoms to guide medical professionals besides a blood pressure reading? So, where does this qualitative analysis come from? Hypertension is widely considered to be an asymptomatic condition, many studies since the seventies have focused on patients’ beliefs about hypertension [8]. Although unorthodox to evaluate a condition such as this through patient intuition, the case of hypertension treatment has always been a difficult one without tangible concrete data. This sort of methodology would greatly affect the consistency or effectiveness of treatment, if it were based on an arbitrary feeling of comfort or discomfort. Symptoms related to hypertension that stem from a thought or belief will

greatly impact the adherence of hypertension treatment [8]. Some studies have found that there is no significant relationship between reported symptoms, mood, and fluctuations in blood pressure [8-11]. More importantly, knowing what happens at a micro-level and understanding the structures affected should help increase the consistency of treatment.

Although it is not a disease in which it could easily be detected by a physical symptom, it is the main concern for hypertension management. There is plenty of data from previous studies that suggest hypertension is associated with systemic inflammation [12]. Systemic inflammation is one of the symptoms of hypertension and is a very important factor to keep a close eye on during management. By not monitoring inflammation, especially what occurs beneath the skin's surface, will inevitably host issues far worse than the initial problem. "In turn, there is positive feedback of angiotensin II on vascular inflammation via promotion of oxidant stress, recruitment of monocytes, and production of proinflammatory cytokines" [12-13]. Essentially, the body would communicate with the brain to create a feedback loop that would promote the role of angiotensin II, which entails plaque deposits in arteries and vasoconstriction. Over time, inflammation of this degree is likely indicative of an active hypertension model and individuals suffering with hypertension will have no physical symptoms that surface. "Reduction in nitric oxide bioavailability, increase in angiotensin II and endothelin coupled with endothelial activation initiate the vascular and cardiac dysfunction and hypertension" [5]. Also, other cautionary effects of hypertension that are easily overlooked are autoimmune dysfunction. Cytokine production, central nervous system stimulation, and renal damage are three mechanisms that are adaptive or innate immune responses linked to hypertension and CVD [5]. To further emphasize the concern of hypertension is the oxidative stress that plays a part in negligence of treatment. Antioxidant deficiency and excess free radical production have been documented in epidemiologic, observational, and interventional hypertension studies [5]. In general, health is widely negligible unless it is urgent through the realms of an emergency room visit. Although these mechanisms are not easily detectable, it is important to be proactive during hypertension management because under the surface many mechanisms are compromised and often disregarded. In turn, this could ultimately foster a lack of adherence to medication for treating hypertension. Therefore, nurturing this inconsistency would ultimately lead to the inaccuracy of diagnosing and proper management of hypertensive patients. Thus, the classification of hypertension is a point of emphasis for the treatment and continued education of such a non-communicable disease.

AHA Defines Hypertension

According to the American Heart Association (AHA), there are multiple ways of classifying hypertension, but none of the classifications reflect the accuracy of the National Heart, Lung, and Blood Institute's definition. Although these classifications affect different subpopulations, they share the same core definition. Resistant hypertension was first classified as a way to help identify high-risk patients that could benefit from specialized care for secondary causes of hypertension [14]. However, this does not provide a clear distinction for individuals with resistant hypertension, as there are multiple types. The AHA does not define hypertension into categories, so a recent study set out to distinguish three separate types: apparent, true, and pseudo-resistant hypertension. This is a very important detail that potentially affects how data for finding prevalence within a population is recorded. The AHA does not attempt or have a separate category to distinguish between resistant and pseudo-resistant hypertension [14]. However, it is noted within this study that there is clinical evidence differentiating between true resistant and pseudo-resistant hypertension. Pseudo-resistant hypertension is when individuals with elevated BPs due to improper BP measurement or nonadherence to medication; therefore, they are not considered to have true resistant hypertension [14-16]. According to this train of thought, this means that individuals that do not adhere to their medication or had an inaccurately measured blood pressure

are defined as having pseudo-resistant hypertension. Epidemiological studies adopted the term apparent resistant hypertension with the intent of not excluding the term, pseudo-resistance, which refers to having BP > 140/90 mmHg while taking ≥ 3 antihypertensive medications [14, 17]. This detail reflects that defining true resistant hypertension is dependent upon the definitions of pseudo-resistant hypertension and apparent resistant hypertension. Therefore, individuals with a blood pressure measured greater than 140/90 mmHg and taking at the least 3 medications to combat hypertension, are considered to have apparent resistant hypertension. It is important to understand that apparent resistant hypertension is a subgroup of the pseudo-resistant hypertension patients and its relation to that group provides a definition for true resistant hypertension. The distinction of true resistance from apparent resistance is demonstrated when pseudo-resistance has been excluded by 24 hour ambulatory BP monitoring, proper BP measurement technique and confirmation of medication adherence [14]. There is a certain level of criteria that an individual must progress through in order to be diagnosed with true resistant hypertension. Essentially, an individual can be diagnosed with true resistant hypertension if there is no margin of error that would lead to a pseudo-resistant or apparent diagnosis, and having a mean blood pressure fall in between 140/90 mmHg and 130/80 mmHg after 24 hours. True resistant hypertension is defined as BP > 140/90 mmHg with a mean 24 hour ambulatory BP > 130/80 mmHg in a patient that is taking ≥ 3 antihypertensive medications [14]. Certainly, there are benefits to distinguishing between each term; this undoubtedly increases the accuracy for diagnosing individuals for their specific health care needs. Moreover, the message to be taken away is to find reliable ways to accurately measure blood pressure, in order to provide proper individual health care.

Hypertension and Gender Differences

Hypertension is one of the more prevalent chronic diseases, not exclusive to any specific gender. However, there are studies that have targeted genders and gender differences to find a correlation to lifestyle and other various factors. There are distinct sex differences in the prevalence, absolute BP, and molecular mechanisms of hypertension [18-22]. In certain circumstances, it has been documented that there is a trend between men having higher blood pressure measures compared to women. Physiologically, men and women are different, so the way hypertension affects each gender will be generally the same, but management of hypertension is not accounted for in the studies of prevalence. It has been reported from numerous studies that the prevalence of hypertension in males and females is not predictive, but is associated with individual awareness and negligence. In essence, what these studies found were a correlation between men being negligent or not caring, and women being proactive and aware in managing hypertension. Additionally, men have more reeling consequences in comparison to women. Men typically have greater organ damage in comparison to women, which suggests that men have greater negative consequences than women in terms of overall cardiovascular health [23]. A connection can be assumed from the information: due to men's negligence of hypertension, it will lead to a much more debilitating health outcome. However, this is not to say that it is directly correlated, merely the statistics predict that it is more probable to result in such a manner. Contrary to what the data indicates, even though men have far worse consequence to women when managing hypertension, its prevalence resides in women over 60 years of age. The National Health and Nutrition Examination Survey III and IV studies proved that hypertension prevalence was greater in women over 60, when compared to men, regardless of ethnicity [24]. This reinforces the fact that it is very difficult to predict prevalence of hypertension between the two genders for reasons that are individualistic to patients. Prevalence can run rampant among certain genders dependent only to the lifestyle and manner in which they manage hypertension. Although there are differences between the genders physiologically, the prevalence of hypertension cannot be predicted by gender. All data can make the case that certain genders have higher risk factors for developing

hypertension because of specific biomarkers that play a role in the functioning human body. Overall, gender differences do not hold a valid argument for the prevalence of hypertension, but understanding that biomarkers are not exclusive to gender can better predict prevalence.

Table 1: Chronic diseases associated with hypertension

Reference	Disease	Prevalence	Complications	Mortalities
WHO, 2016 [25]	Diabetes	The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014	Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation	In 2012, an estimated 1.5 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose
WHO, 2016 [26]	Cardiovascular Disease (CVD)	N/A	Heart attack, stroke, blood clots, aneurysm, heart disease	An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths
CDC, 2013 & 2014 [27-28]	Chronic Kidney Disease	Estimated 20 million people in the United States in 2014 with chronic kidney disease	Kidney failure, CVD, anemia, depression	Number of deaths from nephritis, nephrotic syndrome, and nephrosis: 47,112 in 2013
Flegal, WHO [29-30]	Obesity	Estimated 600 million people worldwide in 2014 with issues of obesity	CVD, diabetes, cancers, musculoskeletal disorders	Grades 2 and 3 (BMI > 35) obesity associated with significantly higher all-cause mortality

Biomarkers of Hypertension

One of the more highly acclaimed and closely followed longitudinal studies about hypertension and cardiovascular disease is known as the Framingham study. This study began back in 1948 to further understand heart health and other factors that may play a significant role in the deterioration of health. In 1948, the Framingham Heart Study was initiated to investigate risk factors for CVD in the community [31-32]. It was a huge success at the time because of the groundbreaking data that was collected and analyzed. Similar to the present research, patients had their blood drawn for analysis. During the study, participants were surveyed for their medical history, physical exams, BP measurements, and assessments of cardiovascular risk factors [31]. Following these visits, the data collected would include samples of each patient’s biomarker levels. However, what is the role of a biomarker in this instance? The Biomarkers Definitions Working Group defines a biomarker as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ [33-34]. The biomarkers measured at examination cycle 6, found that UACR, CRP, ARR, and PAI-1 have been associated with hypertension incidence in this cohort [12, 31,35]. The likelihood that these biomarkers would predict a correlation to hypertension is more than probable, according to the Framingham study. Interestingly, the reason for the association between hypertension and these biomarkers is due to biological pathways that are correlated with blood

pressure. The Framingham Heart Study demonstrated that circulating concentrations of CRP, PAI-1, and UACR predict incident hypertension in nonhypertensive individuals during short-term follow-up [12, 31]. On the surface, the results of the Framingham study provided insight on several factors that are crucial to the mechanism of hypertension. However, research conducted outside of the Framingham study has proven that hypertension is not exclusive to these biomarkers for diagnosis. Primary hypertension has no known cause in 95% of cases, while secondary hypertension may be a result from pregnancy, sleep apnea, Cushing's syndrome, kidney malfunction, and as a side effect of drugs [1]. Still, it is difficult to pinpoint exactly what is the cause of hypertension, as there are many factors that influence its prevalence. More importantly, the Framingham study proved to be a key cog in future research.

CRP

Not only was the purpose of the Framingham study to find links that cause hypertension and cardiovascular disease; it ultimately set a foundation for succeeding hypertension research. The premise for follow-up research on the Framingham study was to check if hypertension was a hereditary disease and could be predicted in offspring of those of who have been diagnosed. Given the critical information from the Framingham study, the follow-up study involving offspring of both hypertensive and nonhypertensive parents demonstrated that there was a connection between the biomarkers evaluated and hypertension to a certain degree. There are higher CRP concentrations in offspring with one or both parents with hypertension in comparison to nonhypertensive offspring of nonhypertensive parents [31]. The principal findings in this study resulted in higher levels of CRP in the offspring of hypertensive parents, in comparison to, non-hypertensive groups. It was concluded that CRP concentrations in nonhypertensive offspring increase in proportion to the number of parents with hypertension [31]. Certainly, this provides a glimmer of data that connects blood pressure and heredity, more so than hypertension through biomarkers. This discovery means that on a biological level, there is minimal predictability between CRP and hypertension. From this analysis, it is proven that CRP is vital to hypertension by affecting the endothelial cell structures. Furthermore, high concentrations of CRP lead to higher PAI-1 expression in human aortic endothelial cells [31, 36]. C-reactive protein's role in the body facilitates several reactions that are predictive of hypertension. In terms of blood pressure, C-reactive protein will increase PAI-1, which would decrease the body's ability to combat blood clots. Thus, higher concentrations of CRP would proportionately lead to increased blood pressure. "In addition, CRP upregulates angiotensin type 1 receptors in vascular smooth muscle cells in vivo and in vitro. Importantly, the BP-modulating effects of the renin-angiotensin-aldosterone system are mediated through this receptor" [31, 37- 38]. Although angiotensin type 1 receptors do not necessarily have a physiological role, its conversion into the type 2 receptor is a factor for increased blood pressure. It can be concluded that a high concentration of CRP is considered a biomarker that could presumably manifest itself as hypertension, which is the reason why many studies test for its concentration levels, as it is a viable indicator for hypertension. Among other biomarkers that are tested for, PAI-1 is accounted for because of its association with CRP.

PAI-1

Findings within the Framingham study documented that PAI-1 has a role in incidental hypertension as well as systolic blood pressure. With current research indicating that, there is not much variance in concentrations of PAI-1 between children and their parents with hypertension. PAI-1 concentrations in offspring based on the hypertension status of their parents did not vary

and did not exclude its role in the development of hypertension [31]. This finding would stipulate that PAI-1 is not a heritable characteristic, nor does it offer a conclusion that it does not play a significant role in hypertension. In a follow up study to the Framingham study, offspring from that research group were the subject of examination. From this follow up research, it was made clear that there was a connection between hypertension and PAI-1. The reason for the connection was assumed that being hypertensive would increase the concentration of PAI-1; however this was misinformation within the community. Elevated PAI-1 levels were found in hypertensive individuals, but it was initially believed that hypertension induced the elevation of PAI-1 levels as a result of stress or endothelial activation [12, 38-40]. Interestingly, this information would suggest why hypertension diagnosis is so often inaccurate and difficult to spot. The misinformation that higher levels of PAI-1 are a result of hypertension generates an inaccurately assumed diagnosis, when PAI-1 is more of a predictor of hypertension. Furthermore, PAI-1 is a biomarker for hypertension because of the consequences that result from an excessively high concentration. Another concern with elevated PAI-1 levels is the development of metabolic abnormalities like insulin resistance or the predisposition to hypertension because of the reduced fibrinolytic potential [12, 41]. Although not truly reflected in the results, PAI-1 is still considered a risk factor for any negative metabolic changes to the body. The final piece of information found from the follow up research found that an excess of PAI-1 floating around might lead to fibrosis, which does not provide any relief for a hypertensive individual. Perivascular and medial fibrosis is accelerated when there is an overproduction of PAI-1 [12, 41]. This would mean PAI-1 would have an influence to the resulting mortality derived from hypertension. Essentially, the expression of overly produced PAI-1 will force blood pressure to rise in an attempt to distribute blood flow through compromised blood vessels. From this perspective, PAI-1 expression in combination with high-density CRP concentrations would reflect what happens internally during hypertension.

UACR

Typically, UACR tests are administered when checking the diagnosis of kidney disease, but there is a lot more information that can be deduced from a simple urine sample. Albumin is a protein that is abundant in the blood and it is not normally found in high amounts excreted by the kidneys through urine. Whereas creatinine, which may be an influencer to gender differences due to muscle mass differences, it is usually excreted by the kidneys and it is released with urine at a consistent rate. When these tests are administered, the creatinine provides a constant to compare the level of albumin concentration. The test results would provide details on the concentration of albumin in urine based on its proportion to a normalized rate of creatinine. UACR concentrations are privy to BP progression and incidence of hypertension in nonhypertensive individuals without diabetes [31, 43]. The UACR results would indicate that there is some association between blood pressure and higher levels of albumin in urine. Urinary albumin excretion is a worse predictor of blood pressure progression in nondiabetic, nonhypertensive individuals over established risk factors compared to microalbuminuria [43]. Granted, these findings for UACR are not the sole indicator for hypertension, but it definitely is something to be mindful of when being assessed. More studies are required to determine if measuring UACR, alone or in combination with other markers, could possibly help with primary prevention of hypertension [43]. With more research being placed on UACR concentrations, the lack of evidence creates ambiguity for the correlation of UACR concentrations being able to predict hypertension on its own or in tandem with other biomarkers. There is no clear-cut evidence that would support this theory. However, this should not discredit its role as a source for predicting hypertension, since there is some level of connection between hypertension and UACR levels. Although there are plenty of drawbacks to UACR analysis, it can be a useful biomarker for predicting the likelihood of developing hypertension [43]. Statistics derived from a regression model that takes into account multiple variables that are known

risk factors, have proven that there is a correlation between hypertension development and UACR levels. In multivariable logistic regressions that adjusted for known risk factors, UACR actually proved to be a significant predictor of incident hypertension [43]. These statistics should provide a better perspective on the significance of UACR levels in regards to the development of hypertension. Still, there is no conclusive evidence to portray UACR levels as a sole source for diagnosing hypertension, but it is a detail to consider at the very least.

ARR

Lastly, the monitoring of ARR is an intriguing association to hypertension; having a higher concentration of ARR demonstrates that there is a greater chance of developing hypertension [44]. Through several decades of research, primary hyperaldosteronism has been linked to the cause of secondary hypertension, which is described as having high or sometimes normal aldosterone levels, inhibited rennin levels, and an elevated ARR [44-47]. The association of aldosterone and hypertension is relevant as this hormone closely regulates the volume and pressure of blood. The analysis of aldosterone alone may lead to devastating consequences because circulating rennin levels must be taken into account, otherwise aldosterone and rennin may contribute to CVD and hypertension development [44]. It is the low level of circulating rennin that would induce an elevated ARR score [44]. One study tried to determine a correlation and relationship between higher concentrations of ARR and hypertension; this study proved to have some promising results. Not only was there an understanding that higher levels of ARR would lead to hypertension, but it was also linked to heredity. In nonhypertensive individuals, an increase in ARR was associated with an increased risk of BP progression and incident hypertension; rennin and aldosterone are better predictors together rather than stand-alone hormones [35]. With respect to the blood pressure outcomes, the evaluation of the two hormones is connected on a genetic level, as there is evidence for linkage in two chromosome regions. “We observed modest evidence of linkage to chromosome 11p with a maximum multipoint LOD score of 1.89 at 2 cM and to chromosome 5p with a maximum multipoint LOD score of 1.60 at 30.8 cM for residuals from multivariable-adjusted models” [35]. This is very important, as an assumption can be made that hypertension is a hereditary disease and it is predicted on the account of ARR. Even with limited conclusions, ARR still yields valuable information that may manifest itself as a foundation for diagnosing hypertension. Being able to fully understand the ramifications of hypertension by evaluating these biomarkers could only lead to managing or even treatment at the molecular level.

Managing Hypertension with Bioactive Compounds

Table 2: The effect of various bioactive compounds on biomarkers of hypertension

Reference	Analysts	n	Subject	Duration	Intervention	Outcome	Study
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Martirosyan, 2007 [48]	Amaranth oil	125 patients 85 main group 40 comparison group	Comparison group: patients with CHD and HP (average age 52) Main group: patients with CHD and HP (average age 59)	3 weeks	Daily dose 18 ml amaranth oil	Reduced total cholesterol by 1.31 mmol/L, triglycerides 0.91 mmol/L, LDL 1.1 mmol/L (P < 0.01)	Clinical trial
Taubert, 2007 [49]	Dark chocolate (polyphenols 30 mg or more)	173 patients	Patients with hypertension	2 weeks (median)	Daily dose 100 grams dark chocolate (polyphenols 30 mg or more)	Reduces blood pressure in humans (P < 0.001)	Meta-analysis
Gu, 2001 [50]	Potassium	150 patients	Patients with high blood pressure (35-64 years, Chinese men and women)	12 weeks	Daily administered 60 mmol KCl dose	Significantly reduces systolic blood pressure by ~ 5.00 mmHg (P < 0.001)	Randomized placebo-controlled trial
Widman, 1993 [51]	Magnesium	60 patients	Patients with essential hypertension	8 weeks	Daily dose magnesium supplementation	Significantly reduces blood pressure 5.6/2.8 mmHg	Crossover study
Mahajan, 2007 [49]	Vitamin C	40 male patients 30-50 years	Patients with essential hypertension	12 weeks	1,000 mg vitamin C and 5 mg amlodipine	Reduces systolic blood pressure	Clinical trial
Paran, 2001 [50]	Lycopene	30 patients	Patients with hypertension (age 40-65) and no current medication	14 weeks	Daily intake 10-20 mg lycopene	Reduced blood pressure by 9 mmHg/7 mmHg (P < 0.01)	Randomized placebo-controlled trial

Now that there is an understanding of which biomarkers have an intricate role in the diagnosis of hypertension; it is time to examine which bioactive compounds are capable of treating hypertension. Based on a research experiment conducted by Martirosyan on the effects of amaranth oil, there was significant evidence that supports the reduction of total cholesterol, triglycerides, and LDL. In the 3-week study, 125 participants diagnosed with coronary heart disease and hypertension were randomly given a daily dosage of 18 ml amaranth oil [48]. In this study, the effects of amaranth oil suggest that there is an effect on the biomarkers of hypertension. The philosophy behind adding a supplementation of amaranth oil into the diet is to change the fatty acid composition of the erythrocyte membrane. However, this was not the only observable change

that was a result of this study. According to Table 2, clinical effects of amaranth oil were related to both the change in fatty-acid composition and squalene content of a diet [48]. These results would suggest that on a chemical level, amaranth oil reduces total cholesterol, triglycerides, and LDL by replacing saturated fats with unsaturated fats to conduct change in composition.

In a meta-analysis of 5 clinical trials by Taubert, 173 patients dealing with hypertension underwent a 2-week median randomized control trial with the dietary supplementation of dark cocoa. The intervention was a daily dose of up to 100 grams of dark cocoa with a polyphenol content of 30 mg or more. From this meta-analysis, it was concluded that there was a reduction of blood pressure, both systolic and diastolic. Cocoa is rich with polyphenols, which has a blood pressure-lowering effect [49, 54]. More importantly, the addition of cocoa in the diet not only reduces total blood pressure, but its improvement of endothelial function is a product of nitric oxide signaling. The polyphenols in cocoa-containing foods, based on this study, are suggested to be responsible for the reduction in blood pressure, improvement of endothelial function, and platelet inhibition because of nitric oxide synthesis [49, 55-56]. The outcome of this study provides evidence that polyphenols, specifically in dark chocolate, will produce a reduction in blood pressure because of improved endothelial function. Meaning, if the endothelium is able to function efficiently, the blood vessels will continue to dilate to increase optimal blood flow.

In Gu's study, it was proposed that potassium deficient hypertensive patients could reduce their systolic blood pressure through the administration of potassium supplementation. Gu's idea of reintroducing potassium into the body will restore the body's ability to efficiently pump blood throughout the body. This study focused on 150 Chinese hypertensive patients with an age range of 35-64 years old. Gu's 12 week study administered a daily total concentration of 60 mmol dose of KCl supplementation intravenously and noticed significant results with a blood pressure measurement within the ranges of 130-159 mmHg over 80-94 mmHg. A possible explanation for why potassium is an effective mediator of increased blood pressure is the stimulation of Na⁺K-ATPase in smooth muscle cells and adrenergic nerve terminals, which immediately triggers vasodilatation [51-53]. According to the study, there was substantial evidence that supports the reduction of systolic blood pressure, however diastolic blood pressure was not affected. Moderate potassium supplementation substantially reduced systolic BP and it is possible that potassium intake may treat hypertension in China [50]. Salt sensitivity hypertension could possibly be treated with an increase in potassium because of its ability to lower blood pressure in both animals and humans [51]. Regardless of the demographic, there is now evidence that would indicate that there is some mechanistic benefit of supplementing a hypertensive patient's diet with potassium.

Earlier research, overseen by Widman, has tested the hypothesis that magnesium supplementation will be helpful in managing bouts of hypertension. Granted this assumption was based on finding the dosage for which it would ultimately make a significant change. Details of this crossover study include: 60 hypertensive patients, 8-week duration study, and a daily magnesium supplement intravenously (total concentration: 15 mmol, 30 mmol, 40 mmol). Given these daily dosages, it was concluded that a daily dose of 30-40 mmol of magnesium is sufficient in producing a reduction in systolic blood pressure. The results of this study had 3 explanations as to why magnesium supplementation is a helpful aide to treating high blood pressure. "First, adding magnesium to patients with prior diuretic treatment restores a diuretic induced potassium and magnesium deficiency, thus making it possible for the diuretic treatment to exert its optimal effect" [54]. Another explanation that supports the assumption of reduced blood pressure is that a higher dosage would optimally aide in reducing blood pressure. High doses of magnesium might have an actual pharmacological effect on blood pressure [54]. This assumption would indicate that magnesium supplementation would be a legitimate form of treatment for hypertension. In Widman's crossover study, it was found that 40 mmol of magnesium was the most effective in reducing systolic blood pressure. Lastly, the effects of magnesium is more likely to result in low

blood pressure, however in this case it would be a treatment for individuals with high blood pressure. Magnesium may induce diarrhea and hypovolemia, which would naturally result in lowered blood pressure [54]. Albeit, there is a side effect to the high dosage of magnesium, the more important aspect to note would be the ability to greatly reduce high blood pressure.

At the time, there were not many studies to support the idea that lycopene, found in tomatoes, is great for treating hypertensive patients. In particular, a study conducted by Paran included participants that did not have or take any medication for hypertension. The premise is to see if there was a direct relationship between lycopene and the management of hypertension. It was Paran's idea to find the most effective way to manage hypertension because of its invariably low adherence to treatment. Natural product therapy may be the solution to improved patient attitude as well as adherence to treatment [56]. Essentially, it would be much easier to get the dosage that is needed by eating tomatoes, more so than adhering to a schedule to administer medication for a disease that does not cause any noticeable physical symptoms. Therefore, Paran decided to take the steps to pioneer research on lycopene's antioxidant properties. Tomatoes contain a natural carotenoid, lycopene, and are considered to be an effective antioxidant; it inactivates free radicals and reduces LDL susceptibility to oxidation [56]. Based on the results of a 14 week study, it was found that 10-20 mg doses of lycopene is sufficient for making a change in systolic and diastolic blood pressure. Much like vitamin C, lycopene's role is to stave off the free radicals in order to improve endothelial function. Ultimately, this would indicate that lycopene may have an indirect impact on hypertension, and more research is required to validate the claims of lycopene having the capacity to treat hypertension.

Rather than taking supplements of the listed bioactive compounds, an easier alternative to ensure that a hypertensive patient is getting the necessary vitamins or bioactive compounds, is to eat foods that contain these compounds. Vitamin D can be commonly found in poultry, fish, beans, and nuts. In a 3 month trial conducted in 2013, Vitamin D was supplemented daily at 1,000 IU to 283 hypertensive patients [60]. Other studies have confirmed the reproducibility of lowering systolic blood pressure due to the specificity of each design to evaluate blood pressure as an endpoint [60-64]. The results of this would lead to a decrease in systolic blood pressure by 1.4mmHg. It is not fully understood why Vitamin D has such an effect on blood pressure; however it is common to see a link for hypertension and Vitamin D deficiency. The most likely explanation for how Vitamin D might produce a desired effect is its role as a negative regulator of the RAS [65]. Vitamin D deficiency will result in high levels of PTH, which is also associated with elevated blood pressure [66-67]. Intuitively, it would make sense to supplement somebody with Vitamin D, if patients are clearly deficient. Although, the idea would also be experimental as there is not enough evidence to show that there is a direct causation of Vitamin D deficiency leading to hypertension. It is within the interest of researchers to navigate and see if there are any insightful results that may come from such a trial.

In comparison, Vitamin C has a much better result for seeing positive change in hypertensive patients. Based on raw numbers alone, Mullan and company conducted a 4-week trial on type 2 diabetics and found that there was a significant change in arterial blood pressure with the daily 500mg supplementation of Vitamin C. "The improvement in arterial stiffness after a relatively short treatment time suggests a functional rather than structural change in the vasculature" [68]. Similar to how the Vitamin D mechanism works, Vitamin C or Ascorbic acid is a very effective free radical scavenger and is useful in protecting nitric oxide from excessive degradation [68]. Although, the results of this study have shown to be promising, the study was prone to confounding variables that affected the outcome. Meaning, there were limitations that allowed for conclusive evidence that Vitamin C can purely reduce arterial blood pressure. Fortunately, these results produced a deeper understanding as to what mechanisms are crucial to arterial stiffness and overall blood pressure. Nitric oxide bioactivity may be the explanation needed to understand changes in

blood pressure and arterial stiffness [68]. Despite the inconclusive evidence that suggests vitamin C plays a major role in the reduction of blood pressure, there is a better understanding for which mechanisms are affected. The most plausible explanation or mechanism for Vitamin C to improve endothelial function in hypertension is by scavenging free radicals within the vasculature [55]. The concept of Vitamin C supplementation is due to the improved immune function, tissue repair, and wound healing capabilities. It was found that the effects of ascorbic acid might help with restoring relaxation of the vessels. It is not accurate to surmise that Vitamin C independent of other factors may be the absolute treatment of hypertension, however along with amlodipine, BP was significantly reduced [55]. Although the effects of vitamin C do not directly result in decreasing blood pressure, moreover it is a byproduct of a much more complicated function. Nevertheless, when supplementing with amlodipine, a combination with vitamin C would produce a more favorable result than amlodipine on its own.

With more research dedicated to the beneficial effects of vitamins, specifically Vitamin E, there seems to be reproducible data that was concluded in a 2012 study. It is known that the benefit of Vitamin E would include tissue protection from free radicals. The abundance of Vitamin E can be found in foods such as: sunflower seeds, spinach, almonds, and other various nuts. Given that there is a connection between diabetic patients as well as hypertensive patients, the 8-week trial supplemented type 2 diabetic patients with a daily dosage of 400mg of Vitamin E. It was found that Vitamin E significantly decreased MAP (mitogen-activated protein, which serve as signalers for cellular response) when comparing the control group with the Vitamin E group, as well as reducing SBP and DBP [69]. Furthermore, there are plenty of studies to reinforce the findings in this study. In cases of mild hypertension, Vitamin E can reduce BP through a long-term process [69-70]. Mechanistically, there are some favorable results that occur with the supplementation of Vitamin E; there may be an increase in intracellular magnesium that would confirm anti-hypertensive properties [69]. "It is proposed that increased oxygen free radical production lowers the intracellular Mg concentration, and, in light of such evidence, vitamin E administration may regulate the intracellular Mg concentration" [69, 71]. More importantly, this study suggests that there was a decrease in both systolic and diastolic blood pressure by 9.87mmHg and 7.37mmHg, respectively. Of these vitamins, the most effective results seem to come from Vitamin E.

Lastly of Table 2, Vitamin B9 or commonly known as, folic acid, was tested in multiple clinical trials at high dosages and a meta-analysis found that there was a positive effect. One of the main benefits that have been studied is the improved endothelial function. "The effects of folic acid supplementation on systolic BP and percentage of FMD (percentage flow mediated dilation referring to endothelial dysfunction) are consistent with epidemiologic observations that there exists an inverse relationship between BP and plasma folate status" [72-73]. It is notable that the changes in blood pressure apply towards systolic blood pressure and not diastolic blood pressure. The reason being, there was not much room for improvement for diastolic blood pressure in the clinical trials. "One possible explanation for folic acid's nonsignificant observable effect on diastolic BP may be because the baseline diastolic BP values were starting below 90 mm Hg, and so there was no considerable room for improvement when subjects were supplemented with folic acid" [71]. Based on the literature, there is plenty of confusion on the effects of folic acid; however, the primary goal of the analysis was providing clarification. Fortunately, there is conclusive evidence based on an average of collected data that would indicate a minimum timeframe and dosage. Based on the studies from the meta-analysis, supplementing 5000 µg/d of Vitamin B9, at a minimum of 6 weeks, can improve endothelial function and slightly lower blood pressure [71]. Although the results are fairly minimal, folic acid does provide a beneficial outcome to hypertensive patients. Claiming that there is no potential benefit to supplementing with any of these vitamins would be discrediting any functionality to bioactive compounds.

Table 3: The effect of vitamins on biomarkers of hypertension

Reference	Vitamin	Benefits	Foods Found In	Dosages	Outcome
Forman, 2013 [60]	D	Bone health, metabolism	Poultry, fish, beans, nuts	3 month trial with 1,000 IU daily supplementation 283 hypertensive patients	Decreased systolic blood pressure by 1.4 mmHg
Mullan, 2002 [68]	C	Immune function, wound healing, tissue repair	Oranges, bell peppers, kiwi, broccoli	4 week trial with 500 mg daily supplementation type 2 diabetic patients	Decreased mean arterial blood pressure of ~10 mmHg
Rafraf, 2012 [69]	E	Tissue protection from free radicals	Sunflower seeds, spinach, almonds	8 week trial with 400 mg daily supplementation 83 type 2 diabetic patients	Decreased systolic blood pressure by 9.87 mmHg and diastolic blood pressure by 7.37 mmHg
McRae, 2009 [72]	Folic Acid (B9)	Vital for new cell creation, prevents brain and spine defects, improves endothelial function	Fortified grains and cereals, asparagus, legumes	Median 6 week trial (meta-analysis) with 5,000-10,000 µg daily supplementation 293 participants	Decreased systolic blood pressure at an estimated effectiveness of 2.03 mmHg

Discussion

Hypertension is a categorization of 3 distinct types: apparent, true, and pseudo-resistant. Each of these categories are not widely used among practitioners; however, the 3 distinctions would be helpful in compartmentalizing hypertensive patients. Not all cases of hypertension are considered identical, so these distinctions would provide a guideline to accurately diagnosing and treating patients. As adherence to medication continues to be a problem with most hypertensive patients, the 3 classes will help practitioners with treatment and management plans because there is more data to rely on, rather than inaccurate perceptions of symptoms. Adherence to treatment can be negatively affected due to thoughts or beliefs of symptoms related to hypertension—improving adherence could be improved through education of development and maintenance [8, 74-81]. With helpful guidelines, doctors and medical professionals will have a much more efficient and effective method for treating patients. These categories provide a measure of accuracy and effectiveness that would ultimately resolve any issues with adherence.

Many questions arise, as there is a concern for how prevalent hypertension is since it is a common chronic disease. Certain qualms that come to mind are: who is more likely to be affected, can it be shown that certain genders will be affected more, and are there any other diseases that cause or are associated with hypertension? Granted such questions are just a small scope for understanding the prevalence of hypertension. It has been observed that there are in fact significant findings that can predict the likelihood of specific genders developing bouts with hypertension. When comparing men and women, women are more likely to develop inflammatory and immunological disorders [18, 82]. However, this does not take into account the factors of age and other diseases that are associated to their conditions. It is important to note that an increase of 10mmHg SBP doubles the risk of developing CVD while a drop of 5 mmHg results in a 14%

decrease in stroke and 9% decrease in coronary heart disease [21, 83]. Still, there is not a clear answer as to how prevalent hypertension is because of the confounding variables that make each individual case unique. Although, there is a trend that would suggest that over the course of a lifetime, both men and women are at risk for developing hypertension due to the association with other diseases. As for the prevalence of hypertension, it can be assumed: if one is already dealing with obesity, diabetes, CVD, or kidney disease, then it is likely hypertension is another disease that may bring everything into perspective.

On a molecular level, understanding which biomarkers are the results of a pathological or functional change for hypertension would also be beneficial for practitioners. Testing and analyzing the values of CRP, ARR, UACR, and PAI-1 would produce valuable insight to diagnosing and treating patients. Those specific biomarkers are responsible for informing doctors of biochemical imbalances throughout the body that are indicative of functional and/or physiological changes. More importantly, heredity and genetics are also valuable pieces of data that can help with determining the probability of diagnosis. It was concluded that CRP concentrations in the nonhypertensive offspring of hypertensive parents are higher, than their nonhypertensive counterparts [31]. It is noted that not all tested biomarkers could prove to be an effective approach to predicting heredity. ARR, UACR, and PAI-1 did not show any significant indication that there would be a genetic predisposition [31]. Aside from the value that could be had from detection, these biomarkers can specifically indicate the pathologic mechanism, severity of the disease, and provide an ideal treatment response for managing hypertension [84]. Furthermore, it is the importance of discovering specific biomarkers that will generate ideas for countering their mechanisms by applying what is known about bioactive compounds.

In regards to those new adaptations, bioactive compounds are available in the form of functional food, which are useful in treating or managing chronic diseases, like hypertension. Granted, the conducted studies gave insight into the mechanisms and affected structures by these compounds. It is important to note, these bioactive compounds allow for a better understanding as to why they result in the desired outcome. However, there is not enough evidence to conclude that there is a correlation to directly treating hypertension. Combating biomarkers with the administration of bioactive compounds, either found in food or supplements, would be a mechanism that garners effective management. Some bioactive compounds that were observed and produced valuable results were: various vitamins, dark chocolate, amaranth oil, magnesium, potassium, and lycopene. In fact, it is more accurate to say that the observed bioactive compounds have anti-hypertensive properties that improve the function of manipulated structures. In essence, it can be concluded that there is most certainly a positive effect for hypertensive patients to supplement or eat functional foods that contain these observed bioactive compounds. To say the least, long-term supplementation with these bioactive compounds will help with hypertension management. On the other hand, it is just as important to assess the level of physical activity.

Many observational studies with significant data suggests that high levels of physical activity are important for the lifestyle management of chronic diseases like CVD and hypertension [85]. It should be noted that the increase in physical activity would lead to better lipid profile composition and BP [85-86]. Most studies would indicate that the best form of physical activity for adults is to engage in aerobic exercise 3-4 times a week [85]. Not only is it important to be physically active when affected by these circumstances, it is appropriate to maintain these positive lifestyle changes by eating heart healthy meals. It is one thing to know what is healthy to eat, but most often overlooked is understanding why certain food options are more favorable in maintaining hypertension than others. The idea of lifestyle management is to ensure that an individual with hypertension is making the right decisions in regards to both nutrition and activity. One such understanding that Eckel suggests is to know why minerals like sodium affect BP and how reducing sodium intake may effect chronic diseases [85]. Overall, these are effective tools for

managing a lifestyle with hypertension and introducing functional foods that are clinically proven to improve endothelial dysfunction is only going to help that cause.

CONCLUSION

The results of numerous clinical trials indicate that managing hypertension by consuming bioactive compounds found in functional foods can lower blood pressure. In addition to increasing physical activity, total cholesterol levels, LDL concentrations and blood pressure have been lowered from the consumption of the bioactive compounds lycopene, potassium, magnesium amaranth oil, dark chocolate, and Vitamins C, D and E. These bioactive compounds found in functional foods should be the focus of additional epidemiological studies for a non-pharmacological modality for managing the chronic disease of hypertension.

List of Abbreviations: AHA, American Heart Association; ARR, aldosterone: renin ratio; BP, blood pressure; CRP, C-reactive protein; DBP, diastolic blood pressure; CVD, cardiovascular disease; PAI-1, plasminogen activator inhibitor-1; SBP, systolic blood pressure; UACR, urinary albumin creatinine ratio; WHO, World Health Organization

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